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An Approach to a Pulmonary Infiltrate in Solid Organ Transplant Recipients

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Abstract The onset of a pulmonary infiltrate in a solid organ transplant (SOT) recipient is both a challenging diagnostic and therapeutic challenge. We outline the potential aetiologies of a pulmonary infiltrate in a SOT recipient, with particular attention paid to fungal pathogens. A diagnostic and empirical therapy approach to a pulmonary infiltrate, especially invasive fungal disease (IFD) in SOT recipients, is provided.

Keywords Invasive fungal disease · Invasive aspergillosis · Solid organ transplant · Pulmonary infiltrate · Pneumonia · Transplant

Introduction

The differential diagnosis of a new pulmonary infiltrate in the solid organ transplant (SOT) recipient is diverse, ranging from non-infective and immunosuppressant toxicity to invasive opportunistic infection (OI) such as invasive fungal disease (IFD). Approximately two-thirds of pulmonary infiltrates are infective in origin [1]. A prospective prevalence study of European SOT recipients estimated the incidence of pneumonia to be 10.1 episodes per 1000 SOT patients/year and where known, identified the causative pathogen to be bacteria in 87 %, viruses in 29 % and fungi in 6.4 % [2•]. The likely causative organism is dependent on degree of immunosuppression, time post transplantation, local epidemiology and host risk factors. Irrespective of aetiology, the development of a pulmonary infiltrate in a SOT patient is associated with increased mortality (21–35 %), significantly higher if there is nosocomial acquisition or infection is due to IFD [1, 3–6]. A targeted management approach of pulmonary infiltrates in SOT recipients is hence required to reduce patient mortality. We outline an approach to assessment, diagnosis and empirical therapy, with a focus on IFD, including *Pneumocystis jirovecii* pneumonia (PCP).

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Infectious Aetiologies of Pulmonary Infiltrates in SOT Recipients

The infective aetiology of a pulmonary infiltrate falls into the major broad categories of viral, bacterial, mycobacterial and fungal origin. In one mixed population SOT study, there was no difference in aetiology according to type of transplant [1]. The likelihood of certain pathogens can in part be extrapolated from a 'time-post-transplant' assessment (Fig. 1). However, the 'time-post-transplant' concept is dynamic considering the net state of immunosuppression may change (i.e., rejection episode requiring further immunosuppression), resulting in patients brought into a risk category comparable to an 'earlier' transplant period [7]. We briefly outline the major pathogens within these key groups and associated risk factors.

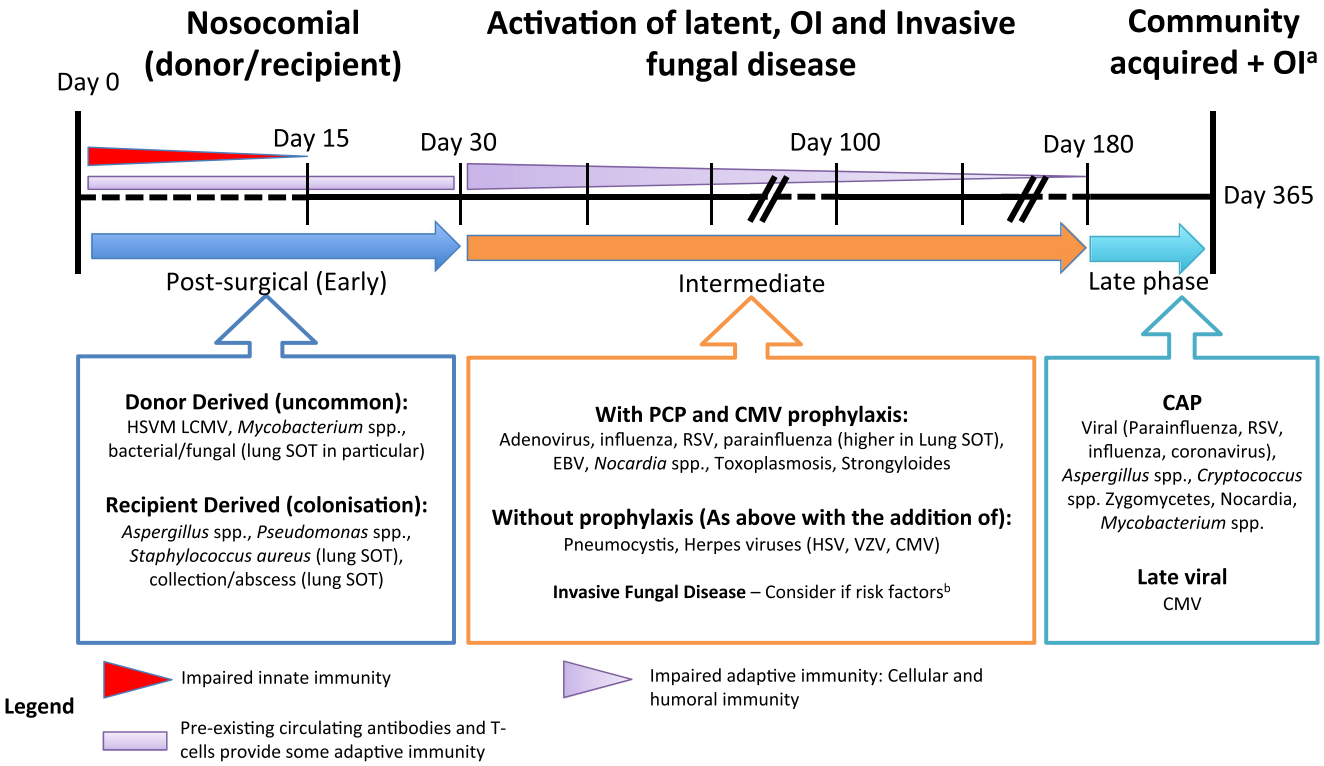

Fig. 1 The correlation between infection risk and 'time-post-transplant', in regards to specific immunological deficits. *OI* opportunistic infection, *SOT* solid-organ transplantation, *PCP Pneumocystis jiroveci*, *CMV* cytomegalovirus, *CAP* community-acquired pneumonia, *EBV* Epstein-Barr virus, *RSV* respiratory syncytial virus, *VZV* varicella zoster virus, *HSV* herpes simplex virus. Adapted from [7, 8]. [a]Opportunistic infections may arise in the late phase if there are increases in immunosuppression in the setting of rejection, graft failure, re-transplantation, etc. [b]Risk factors—recurrent bacterial infection, CMV disease, renal failure requiring dialysis

Viral

Viral pathogens should be considered as the primary insult in many pneumonic processes in SOT recipients. Respiratory syncytial virus (RSV) is a common cause of community-acquired pneumonia (CAP) especially in the intermediate and late transplant period (Fig. 1) [2•, 9, 10]. CMV is more commonly encountered as isolated viraemia, colitis or hepatitis in SOT recipients, and pneumonitis is uncommon outside of lung SOT cohorts; pneumonitis incidence is further reduced in patients with sirolimus-based immunosuppression [11]. Influenza is associated with significant morbidity and mortality, especially if occurring early post-transplant and/or in lung transplant recipients [12–14]. The risk of influenza infection is consistent across the post transplant period, additional risks being pulse steroids, rejection and lymphocyte depletion [15]. Of note, the clinical presentation may be atypical; in the 2009 pandemic, cough (91 %) and myalgia (50 %) were common symptoms [12].

Bacterial

In a prospective multicentre point prevalence study in Europe, pneumonia was identified as primarily a late complication (70 %), community acquired (40 %) and bacterial in origin (87 %) [2•]. The rate of bacterial pneumonia in SOT is upward of 40 % [10]. The most common bacteria isolates reported are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* and *Stenotrophomonas maltophilia* [2•, 3, 10], and mortality in modern cohorts is 1.9–20 % [3, 4, 16]. Empirical therapy should be targeted towards local epidemiology and routine microbiology [17, 18]. Less frequently, nocardiosis can present as bronchopneumonia, however, classical descriptions are of a nodular radiological appearance with or without cavitation or "halo sign" [19–21]. *Nocardia* affects 0.7–3.5 % of SOT recipients, traditionally in SOT other than lung [18, 22, 23] but with growing infection rates in lung SOT (3.5 %), and with rates in heart, intestine, kidney and liver recipients 2.5, 1.3, 0.2 and 0.1 %, respectively [20]. Infection typically occurs within the first or second year post transplantation (median time to infection 34–38 months) [17, 20, 24]. Risk factors are similar to other OIs, namely increased immunosuppression, corticosteroids and high plasma calcineurin levels in the preceding 30 days [18, 20, 24]. *Legionella* spp. is another bacteria that can present with a lobar, reticular, nodular or cavitary pulmonary disease in the SOT recipient. Concurrent bacteraemia is rare and if *Legionella* spp. is suspected then specific, sputum/BAL culture or PCR should be requested [25–28].

Mycobacterial

Mycobacterial infections can occur at any time point following SOT, occurring most frequently in lung SOT [29, 30]. The frequency of *Mycobacterium tuberculosis* (TB) causing a pulmonary infiltrate is dependent on locale (0.53–6.4 % in developed countries), the risk nonetheless still 20- to 74-fold higher than in the general population and associated with 30 % mortality [1, 10, 30–34]. Lung infiltrates are the primary TB manifestation in 50 % of SOT recipients. TB infection following pre-transplant treatment of latent TB is rare, as most cases are due to reactivation rather than de novo acquisition. Donor-derived TB (<5 % of TB in SOT) with modern screening practices is also infrequent [34, 35]. Pulmonary TB generally presents with a protracted period of symptoms prior to diagnosis (median 30 days). Although TB in SOT can occur in the first year post transplant, typically it is a late manifestation (median 64 months in a Spanish SOT cohort) [30]. Empirical therapy for TB without microbiological confirmation (by culture or PCR tests) should not occur without a high probability of disease considering the toxicity associated with therapy (41 % in liver SOT, 4.5 % in heart/lung SOT, 2.5 % in renal SOT) and potential rifampicin-induced disruption to immunosuppressant regimens [36].

Pneumocystis jirovecii

Although the causative pathogen is a fungus, the diagnostic approach to PCP is discussed separately. PCP in SOT in the early transplant period is considered rare due to the almost universal uptake of prophylaxis [37], predominately with trimethoprim-sulfamethoxazole which reduces the risk by 91 % [38, 39]. PCP occurs most frequently in heart SOT recipients (7.3 per 1000 patient-years), followed by kidney (2.7 per 1000 patient-years) and liver transplant recipients (2.6 per 1000 patient-years) [40, 41]. Risk factors in the era of universal prophylaxis were evaluated in one retrospective case control study that identified most cases occurred in the second year post transplant (33 %) and that age, total lymphocyte count and CMV infection were established risk factors [37]. The finding of CMV infection and lymphocyte count as risk factors has been previously demonstrated, as has graft rejection [37-39, 42, 43] Despite the second year post SOT being the most common time for PCP, it can present at any time post transplant [41, 44].

In contrast to that in HIV populations, disease in SOT recipients is more acute and severe fulminant respiratory failure is common as is fever and hypoxia out of proportion to physical findings. Lymphadenopathy is uncommon [45, 46, 47]. Secondary cases irrespective of secondary prophylaxis are relatively uncommon [48]. Isolated cases or outbreaks are described in SOT patients without obvious risk factors for PCP [49–51]. PCP should remain a considered differential in patients with pneumonia late post transplant, especially if known risk associations are present or a concurrent outbreak is evident.

Invasive Fungal Disease (IFD)

Epidemiology

Estimation of the incidence of IFD in SOT recipients is problematic due varied definitions and interpretations of colonisation vs. invasive disease. Invasive aspergillosis (IA) remains the most common cause of pulmonary IFD with the incidence estimated broadly at 2.7–60 % [1, 10, 33, 52]. The most common infecting species is *Aspergillus fumigatus* but infections due to *Aspergillus niger*, *Aspergillus terreus* and *Aspergillus flavus* are also encountered [53•]. In one retrospective study, IA accounted for 65.1 % of IFD [54]. The overall incidence for IFD among lung, kidney, liver, and heart transplant recipients was 49, 2, 11 and 10 per 1000 person-years in a single transplant centre 10-year review [54]. The incidence of pulmonary IA was estimated at 0.4–5 % in renal, liver 1–8 %, heart 1–14 % and 6–16 % in lung SOT [1, 6, 10, 54–62]. In lung SOT recipients, IA is estimated to account for almost 50 % of IFD [53•].

Recipient-derived infections may relate to exposure to endemic fungi (e.g. *Histoplasma capsulatum, Coccidioides immitis* and *Paracoccidioides brasiliensis*) or activities/travel (e.g. raising pigeons for *Cryptococcus neoformans* or marijuana use for *Aspergillus* spp.) [63]. In a Transplant-Associated Infection Surveillance Network (TRASNET) study, histoplasmosis was the most commonly reported endemic pathogen (0.102 % incidence) with a bimodal presentation similar to that seen in smaller studies (40 % first 6 months, 34 % 2–11 years post SOT) [63–66]. IFD other than IA is less frequently reported. Invasive *Scedosporium apiospermum* and *Scedosporium prolificans* donor-derived infection from donors with a near-drowning episode prior to death has been reported, however *Scedosporium* spp. infection is more commonly diagnosed in lung transplant recipients with evidence of previous colonisation. *Scedosporium* spp. IFD is infrequent in liver and heart transplant recipients [67]. *Scedosporium* spp. infection is associated with high mortality early post SOT (median 80.5 days) and presents as isolated pulmonary or disseminated disease in over 85 % of cases [67–69]. Mucormycosis is reported to affect more commonly liver and lung SOT patients, overall contributing approximately 2–8.5 % of IFDs and associated with T-cell depleting immunosuppressive regiments [67, 70–72]. The most common pathogens in order are *Rhizopus, Mucor, Rhizomucor and Cunninghamella* spp. [67, 71].

Cryptococcus neoformans incidence in SOT recipients is 0.3–5 %, causing 7–8 % of IFD in SOT recipients, more

frequently occurring in kidney and liver SOT. Infection typically presents as disseminated disease, occurring 16–24 months post transplantation [70, 73, 74]. A pulmonary infiltrate occurs in 54 % of cases [74]. *Fusarium* spp. also causes IFD. The TRANSNET study reported that 38.9 % of *Fusarium* IFD had a pulmonary only presentation and 22 % had disseminated disease [67].

Risk Factors

Universal risk factors for IFD amongst SOT recipients include environmental exposure and net state of immunosuppression [75, 76]. Overall, risk factors for early (<3 months post SOT) pulmonary IA include recurrent bacterial infection, a complicated post-operative period, renal failure requiring dialysis and CMV disease [6, 75, 77, 78]. In late onset IA (>3 months), risk factors have been identified to be advanced age (age >50 years), recurrent bacterial infection, increased immunosuppression, chronic graft rejection, immunosuppression-related lymphoma and renal failure [5, 6, 77]. Certain SOT cohorts have specific additional risk factors for IA, for example *Aspergillus* spp. colonisation (within 6 months of transplant) in lung SOT recipients and hepatitis C infection and pre-transplant fulminant hepatic failure in the liver recipients [6, 76, 77]. In renal transplant patients, the universal risk factors include prolonged immunosuppression (i.e. with corticosteroids) and graft failure requiring dialysis [79–81]. For heart SOT, in addition to the above risk factors, the presence of an IA episode in the heart transplant program 2 months before or after is an additional risk [59]. Other studies have reported in lung SOT recipients that cystic fibrosis, bronchiolitis obliterans, airway ischemia, hypogammaglobulinemia, bronchial stent and single lung transplant are IA risk factors [53•, 55, 78, 82, 83]. From a matched case control study, zygomycosis in SOT was associated with diabetes, renal failure and prior voriconazole or caspofungin use [84].

Clinical Presentation

The clinical presentation of IFD varies depending on type of SOT. This ranges from asymptomatic colonisation to tracheobronchitis (especially in lung SOT), locally invasive disease, empyema or dissemination [83]. Fungal tracheobronchitis can lead to local ulceration, airway obstruction or stent occlusion. Disseminated IFD is more likely in liver and lung transplant patients [6]. The onset of IFD is reportedly occurring later in modern cohorts, commonly greater than 3 months post SOT [5, 33]. Gavalda et al. in a retrospective case control study demonstrated that 57 % of IA were in the first 3 months post transplant, the mean time 234 days (range 2–3025) with no difference in mortality if IA was early (<3 months) or late (>3 months) post SOT [6]. This description of earlier onset IA compared to previous reports may be related to centre-specific antifungal prophylaxis, as a recent global survey of lung transplant centres indicated that universal prophylaxis was used in the first 6 months post transplant [85]. Early pre-emptive/prophylaxis therapy in colonised patients is known to reduce IFD incidence and IFD-related mortality [86]. In some cohorts, renal IA has been reported later than other SOT, whilst liver and lung typically early [55, 57, 62]. Unique to lung SOT, IA is further reported to occur at the site of anastomosis [87].

For mucormycosis, a pulmonary presentation occurs in 53–56 % of cases, with the risk of dissemination 5-fold higher in liver SOT recipients [84, 88, 89••]. Liver transplant patients are also more likely to have disease earlier after transplant than other SOT recipients [84]. The median time from transplant to mucormycosis infection in all SOT is 5.5 months [88]. The pulmonary presentation can be consolidation/mass (29 %), nodularity (25 %) or cavitation (23 %) [88]. For cryptococcosis, although a pulmonary presentation occurs in >50 % of patients, 33 % are fungaemic (usually concurrent) and 53–72 % have disseminated disease or CNS involvement. The risk of disseminated disease is 6-fold higher in liver SOT recipients [74, 90].

Outcomes

In SOT recipients with IA, hepatic insufficiency, malnutrition, liver and lung SOT, prior antibiotic therapy, mechanical ventilation, transfusion therapy and CNS involvement are associated with increased risk of death [6, 33, 52]. Nonetheless, survival is still greater in SOT within those with stem cell transplants [6, 52]. The mortality rate of mucormycosis in SOT has been demonstrated to be between 38 and 48 % with renal failure and disseminated disease associated with poorer outcomes [71, 84]. The mortality of cryptococcal disease ranges from 33 to 42 %, and if respiratory failure is present, the prognosis is grave [74, 90].

IFD Diagnostics for a Pulmonary Infiltrate in SOT Recipient

The definitions used for IFD in SOT are extrapolated from those routinely used in cancer and stem cell transplant settings assigned by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections and Mycoses Study Group (EORTC/MSG) [91]. Whilst revised definitions for colonisation, invasive disease and tracheobronchitis have been proposed in lung SOT, there remains a lack of consensus guidelines for IFD and IA in SOT [92].

The absence of microbiological confirmation for a pulmonary infiltrate in SOT is estimated at just over 50 % [10]. Delayed diagnosis of IFD in SOT is associated with graft loss and mortality [93••]. To this end, the combined use of

radiological, microbiological and molecular diagnostics are central to an approach to a pulmonary infiltrate in a SOT recipient.

Although molecular methods are superior to culture, routine culture remains central to any IFD diagnostic schematic. It is important to note that upper respiratory tract specimens lack both sensitivity and specificity for IFD, the positive predictive value (PPV) of a sputum culture for *Aspergillus fumigatus* only 67 % [94, 95]. Whilst lower respiratory tract sampling (BAL or lung tissue) may also lack relative sensitivity for IFD when compared with molecular methods, it remains more specific than upper respiratory tract sampling [96]. The PPV for IFD of a lower respiratory tract fungal culture is however significantly reduced in the SOT when compared with stem cell transplant cohort [97].

A 'suggested' algorithm for routine and advanced respiratory diagnostics, including a stepwise approach to investigating a pulmonary infiltrate in SOT recipient including empirical therapy, is outlined in Fig. 2. Evidence supporting the practice of the more commonly used diagnostics is outlined below.

Tissue Biopsy and Histopathology

The use of tissue biopsy for investigation of a pulmonary infiltrate has only been evaluated in a small number of studies, primarily for pulmonary nodules or masses. Although histopathology may offer the only method of diagnosis, it cannot differentiate within the fungus genus/class [99–101]. In a retrospective single centre review of lung, liver, renal and heart SOT recipients, a percutaneous lung biopsy was performed in 3 %, the procedure yielding a diagnosis in 45 % of cases. The diagnostic yield was increased if a core biopsy was performed in addition to a fine needle aspirate, for IA [102, 103]. The combination of lung biopsy and culture was demonstrated to diagnose 52.6 % of mucormycosis from 116 SOT patients with IFD [71].

Radiology

The most predominant thoracic CT radiological findings in SOT with a pulmonary infiltrate are consolidation (49.4 %), pleural effusion (12 %), nodular infiltration (5.6 %), lymphadenopathy (3.4 %) or cavitation (1.1 %) [1]. Whilst the classical teachings of "halo" and "air crescent" signs are pathognomonic for IA in stem cell transplant patients, they are less strongly associated with IA in SOT recipients [58]. Radiological findings thus cannot be relied upon in SOT transplant with a suspicion of IFD. Bronchoscopy should be employed early to further evaluate the possibility of IFD in high risk patients. In a small study of heart SOT with IA, patients with the CT findings of airway-invasive (AIR) disease (peribronchial consolidation or tree-in-bud pattern) were compared with angio-invasive disease (ANG), 'AIR patients' having later onset presentation, higher rates of haemodialysis, more frequent intercurrent bacterial pneumonia and greater IA attributable mortality [104].

Galactomannan Enzyme-Linked Immunospot Assay (GM-ELISA)

The commercial *Aspergillus* GM-ELISA assay (Bio-Rad, UK) detects galactomannan (GM), a cell wall polysaccharide of most *Aspergillus* spp. and *Penicillium* spp. that is released in serum during growth into tissue. The GM-ELISA assay has been less well validated in SOT than haematology cohorts and appears to have inferior performance in the SOT cohort [105]. Clancy et al. described the use of GM-ELISA from bronchoalveolar lavage (BAL) fluid in a cohort of 81 SOT patients and found the sensitivity, specificity, PPV and NPV to be 100, 90.8, 41.7 and 100 % using a cut-off of 1 [106]. In the same study, 5 of 12 false positives were found in lung SOT, when utilising a GM cut-off of 0.5 [106]. In an earlier prospective study of GM in lung SOT, a high rate of false positives was also noted, particularly amongst cystic fibrosis patients early post transplant, with a sensitivity of 30 % and specificity of 95 % with a cut-off of 0.66 subsequently reported [107]. In liver and lung transplant cohort studies, the sensitivity and specificity were reported as 30–56 % and 87–95 %, respectively [107, 108]. A pooled meta-analysis examining serum GM-ELISA in SOT recipients illustrated poor sensitivity and specificity for proven and probable IFD—41 % and 81 %, respectively [105].

Aspergillus PCR (ASP PCR)

The utility of ASP PCR in SOT recipients and isolation of *Aspergillus* spp. from BAL specimens are poorly defined. Furthermore, panfungal PCR on BAL or pulmonary tissue in SOT recipients or molecular assays directed at detecting specific fungi or groups of fungi has only been reported sporadically for the investigation of IFD [109–111]. Zarrinfar et al. demonstrated poor correlation between molecular and conventional methods for diagnosing IA from BAL and higher rates of false positives with a nested PCR in a pilot study of liver, lung and renal SOT recipients [112]. Buess et al. in a study of nested ASP-PCR from BAL of immunosuppressed patients (13 % SOT) demonstrated again low sensitivity for probable-proven IFD (36 %), with higher specificity (72 %) [113]. Nonetheless, higher sensitivity of ASP PCR from BAL has been demonstrated particularly in lung SOT (80–100 %) [114, 115].

In a comparative study of ASP-PCR and GM-ELISA in lung transplant patients, the sensitivity and specificity were 100 and 88 % and 93 and 89 %, respectively. In lung transplant patients that are colonised with *Aspergillus* spp., BAL GM-ELISA compared with ASP-PCR had higher specificity (92 % vs. 50 %) [114]. GM-ELISA using a cut-off of 0.5–1

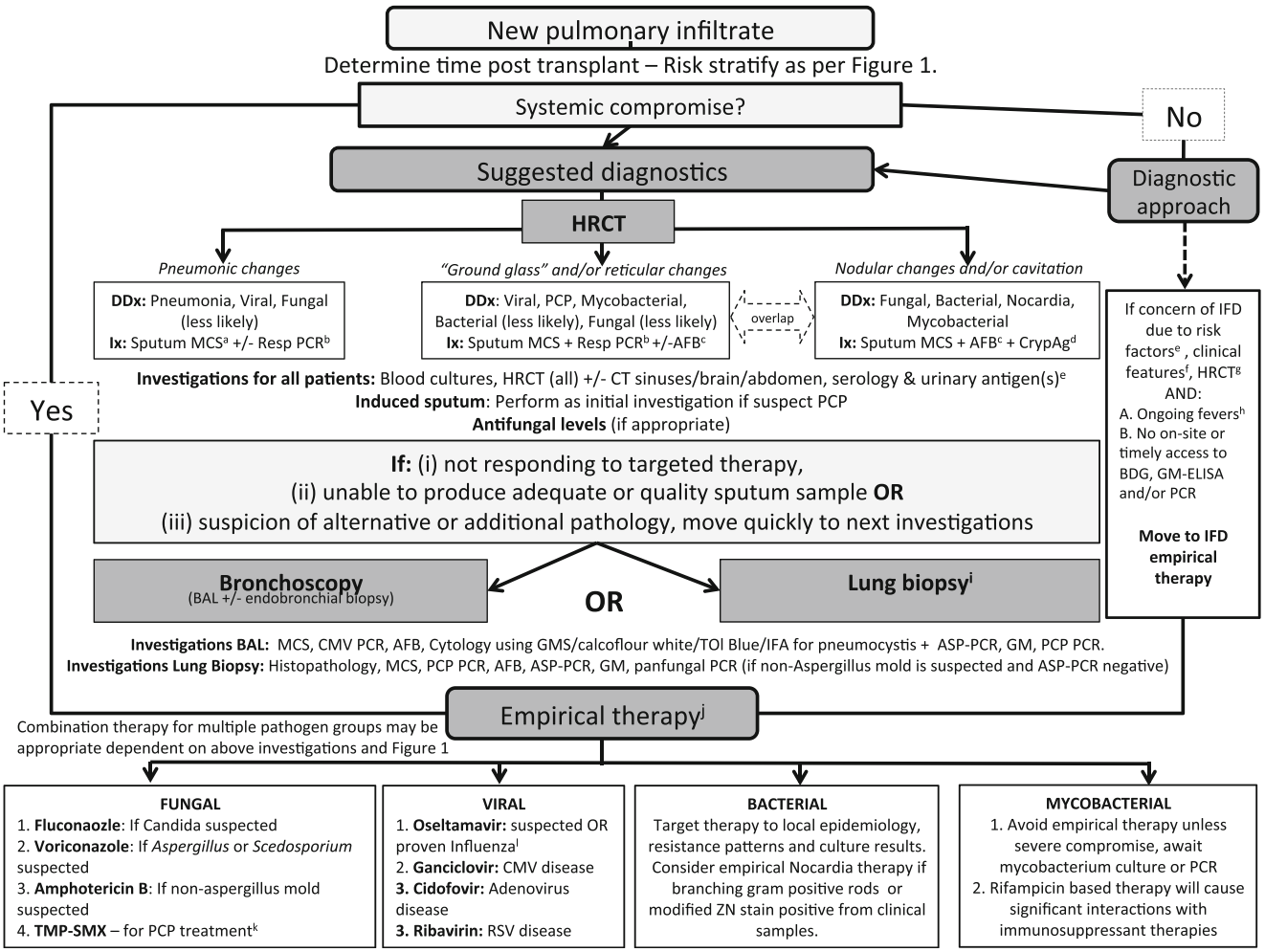

Fig. 2 A flow diagram approach to the diagnosis and empirical management of a pulmonary infiltrate in a SOT recipient. *BAL* bronchoalveolar lavage, *MCS* microbiology, culture and sensitivity, *HRCT* high-resolution computer tomography, *PCR* polymerase chain reaction, *GM-ELISA* galactomannan enzyme-linked immunosorbent assay, *ASP Aspergillus* spp., *AFB* acid fast bacilli, *CrypAg* cryptococcal antigen, *TMP-SMX* trimethoprim-sulfamethoxazole, *PCP Pneumocystis jirovecii* pneumonia, *BDG* (1-3)-β-D-glucan, *GMS* Grocott's methenamine silver, *IFA* immunofluorescence. [a]Sputum MCS—-including Legionella culture (or PCR if culture not routine) and routine fungal culture. [b]Respiratory PCR pathogens: RSV, influenza (A&B), parainfluenza (1,2,3), rhinovirus/enterovirus, coronavirus, *Bordetella pertussis*. [c]AFB and/or mycobacterial PCR should be considered in the setting of appropriate epidemiology and changes consistent with 'miliary' or cavitatory mycobacterial infection. When 'AFB' requested, AFB culture should also be routinely performed not just AFB smear. Consider mycobacterial PCR of GeneXpert if smear positive OR high clinical suspicion of TB. [d]Cryptococcal antigen (serum) should be employed if suspicion of cryptococcus. Note that this test is not validated on BAL specimens, and serum is frequently negative in the setting of low burden disease (e.g. nodular disease). [e]Serology: *Legionella* spp., *Mycoplasma pneumonia* and *Chlamydia* spp. Urinary antigens: *Legionella pneumophila* serogroup 1 antigen, pneumococcal antigen. [e]Risk factors—neutropenia ($<0.5\times10^9$/L), corticosteroids (.2 mg/kg prednisolone equivalent for >2 weeks or >1 mg/kg prednisolone equivalent with neutropenia $<1\times10^9$ for >1 week). [f]Clinical features—cough, chest pain, haemoptysis, dyspnoea, pleural effusion or rub, rhinorrhoea, epistaxis, ulceration or eschar of nasal septum. [g]HRCT findings—as per EORTC/MGS IFD radiological criteria. See description in text [91]. [h]Refractory fevers—persistent (daily for 3–5 days) or recurrent (after an afebrile period of 48 h) fevers despite broad-spectrum antibiotics and negative microbiological investigations. [i]Consider lung biopsy if predominate lesion that is amendable to biopsy (endobronchial or percutaneous preferred) due to increased diagnostic yield. Panfungal PCR from tissue specimen is preferred to BAL panfungal PCR if high suspicion of IFD. [j]For empirical therapy, please refer to local institutional guidelines. For empirical antifungal therapy for presumed IFD, consider consensus guidelines [98]. [k]Due to the high mortality and severe respiratory compromise associated with PCP in non-HIV patients, empirical TMP-SMX therapy should be considered in outbreak settings, absence of PCP prophylaxis or high index of clinical suspicion. [l]Empirical treatment for viral pathogens should primarily be oseltamavir use for suspected influenza, as greatest benefit is obtained closer to initial symptom onset. The remaining listed therapy should be employed if the presence of viral pathogen is confirmed

from bronchoalveolar lavage (BAL) of SOT recipients with suspected IFI offers more promising results with a sensitivity and specificity of 60–90 % and >90 %, respectively [106, 107, 114]. The use of serum and BAL GM-ELISA was compared in a small cohort (n=17) of predominately lung SOT recipients using a cut-off of 0.5; the sensitivity and specificity were

100 % in probable or proven IA, compared to serum which had a sensitivity and specificity of 77 and 100%, respectively [116].

The true utility of both GM-ELISA and ASP PCR is combination testing in BAL, improving sensitivity (97 %) whilst retaining specificity (93 %) [114]. Hoenigl et al. demonstrated that the combination of GM and ASP PCR had a sensitivity of 100 % and specificity of 95–98 % from BAL in a cohort of immunocompromised patients, including SOT [117]. Nonetheless, variability in sensitivity of GM-ELISA and ASP PCR in the SOT recipients compared with stem cell transplant cohort means these investigations should be employed as adjuncts, not as a sole "rule in" or "rule out" test.

Aspergillus Lateral-Flow Device (LFD)

The *Aspergillus* LFD is a point-of-care test that can be used on serum or BAL to diagnose IFD via detection of an extracellular glycoprotein secreted by *Aspergillus* spp. during growth [118]. This device had a sensitivity and specificity of 100 and 81 % when compared with a GM-ELISA result of >1 in a mixed study of haematology and SOT recipients with suspected IA [119]. Its sensitivity (81 %) for IA in a study of haematology patients appeared lower than *Aspergillus* PCR (96 %) yet higher than GM-ELISA (78 %) in isolation [120]. Nonetheless, it has the potential as a rapid beside test and larger clinical evaluations are the device this context are awaited.

(1-3)-β-D-Glucan

The use of the (1-3)-β-D-glucan assay has been the least extensively studied of the mentioned investigations for pneumonia in SOT recipients. The major limitation is that this test generally requires repeat investigations and although may return a positive test in infections caused by Aspergillus spp., *Candida* spp., *Trichosporon* spp., *Fusarium* spp., *Penicillium* spp., *Saccharomyces*, *Acremonium* and *Pneumocystis jirovecii*, is very insensitive in mucormycosis and cryptococcosis [121] This test is therefore not currently recommended for the investigation of a pulmonary infiltrate in a SOT recipient. The potential utility may lie in centres where this test is readily available and invasive methods of PCP diagnosis (i.e. bronchoscopy) cannot be performed, as (1-3)-β-D-glucan is elevated in cases of confirmed PCP and the sensitivity reported at 88–100 % [122, 123]. The use of (1-3)-β-D-glucan in SOT recipients with proven, probable and no IFD was evaluated in a prospective study of BAL specimens, with low sensitivity 79.2 % and poor specificity 38.5 % [124].

Empirical Therapy

The empirical therapy for a new pulmonary infiltrate is dependent on the risk factors, clinical presentation and prior antifungal exposure (prophylaxis and empirical therapy). An approach to empirical therapy in the setting of a diagnostic algorithm is outlined in Fig. 2.

Conclusions

The approach to a pulmonary infiltrate in a SOT recipient is challenging process due to the wide range of potential pathogens. The presence of a pulmonary infiltrate is associated with inferior outcomes irrespective of aetiology IFD having the highest associated morbidity and mortality. The use of molecular diagnostics in SOT for IFD is less well validated than in stem cell transplant populations. A stepwise approach, including multipronged investigation streams tailored to the pre-test organism probability, time post transplant, IFD risk factors and local epidemiology should be employed.

Compliance with Ethics Guidelines

Conflict of Interest Jason A. Trubiano declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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