ORIGINAL ARTICLE

Pulmonary infections after renal transplantation: a prospective study from a tropical country

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SUMMARY

Pulmonary infection is a leading cause of morbidity and mortality in renal transplant recipients. In a prospective study, we characterized their epidemiology in a tropical country with high infectious disease burden. Adult renal transplant recipients presenting with pulmonary infections from 2015 to 2017 were evaluated using a specific diagnostic algorithm. 102 pulmonary infections occurred in 88 patients. 32.3% infections presented in the first year, 31.4% between 1 and 5, and 36.3% beyond 5 years after transplantation. Microbiological diagnosis was established in 69.6%, and 102 microorganisms were identified. Bacterial infection (29.4%) was most common followed by tuberculosis (23.5%), fungal (20.6%), *Pneumocystis jiroveci* (10.8%), viral (8.8%), and nocardial (6.9%) infections. Tuberculosis(TB) and bacterial infections presented throughout the post-transplant period, while Pneumocystis (72.7%), cytomegalovirus (87.5%) and nocardia (85.7%) predominantly presented after >12 months. Fungal infections had a bimodal presentation, between 2 and 6 months (33.3%) and after 12 months (66.7%). Four patients had multi-drug resistant(MDR) TB. In 16.7% cases, plain radiograph was normal and infection was diagnosed by a computed tomography imaging. Mortality due to pulmonary infections was 22.7%. On multivariate Cox regression analysis, use of ATG (HR-2.39, 95% CI: 1.20–4.78, $P = 0.013$), fungal infection (HR-2.14, 95% CI: 1.19–3.84, $P = 0.011$) and need for mechanical ventilation (9.68, 95% CI: 1.34–69.82, $P = 0.024$) were significant predictors of mortality in our patients. To conclude, community-acquired and endemic pulmonary infections predominate with no specific timeline and opportunistic infections usually present late. Nocardiosis and MDR-TB are emerging challenges.

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Background

Infections after renal transplantation have been conventionally described to follow a temporal pattern stratified as [1] 0–1 months—increased risk of donor derived and nosocomial infections [2] 2–6 months—opportunistic infections are common due to high level of cumulative immunosuppression, and [3] beyond

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6 months—usually community-acquired infections are expected as level of maintenance immunosuppression is lower [1]. Changing immunosuppression protocols have contributed to a significant improvement in short-term graft and patient survival at the risk of a parallel increase in the risk of infections [2,3]. The implementation of multiple prophylaxis strategies over the years has also influenced the timeline of infections.

Pulmonary infections form a major subgroup in the infectious disease spectrum in renal transplant recipients [4–8]. It is the predominant cause of infection-related mortality in these patients. Early diagnosis and treatment are essential for improving the outcome. A wide range of bacterial, mycobacterium, fungal, viral, and parasitic organisms can cause pulmonary infections. Often they present with nonspecific signs and symptoms. Recognizing infectious disease patterns can guide the diagnostic approach and empirical antimicrobial therapy thereby thus improving patient outcomes. There is a dearth of studies describing clinical, radiological, and microbiological features of pulmonary infections in renal transplant recipients particularly in tropical, low- and middle-income countries (LMIC) where the overall burden of infections is high. Most of the literature published till date pertains to data obtained retrospectively or in an era when less potent immunosuppression protocols were in use [9–15].

Therefore, we conducted this prospective observational study aiming to delineate the clinical, radiological, and microbiological profile of pulmonary infections in renal transplant recipients and to develop a diagnostic algorithm for these patients.

Study design

This prospective study was conducted in the nephrology department of a tertiary care public hospital. Around 150 patients undergo renal transplantation annually at our center and we have about 2500 patients on regular follow-up. We included all adult (age ≥18 years) renal transplant recipients who presented with a pulmonary infection between 2015 and 2017. Pulmonary infection was defined as per guidelines as a constellation of suggestive clinical features like fever, cough with or without sputum or respiratory distress, a demonstrable infiltrate on chest X-ray or CT scan with or without supporting microbiological evidence of infection [16].

Demographic details like native kidney disease, comorbidities like pretransplant diabetes, chronic viral infections (hepatitis B, hepatitis C) and other co-current infections, donor details, induction and maintenance immunosuppression, new-onset diabetes after transplantation (NODAT), and transplant vintage were noted from the records. Information was also obtained about the history of treatment with additional immunosuppression for episodes of acute rejection and/or recurrent/ denovo glomerular disease in the 6 months preceding the pulmonary infection.

In our center, we use IL2 receptor blockers (currently basiliximab) or anti-thymocyte globulin (ATG) as induction therapy at the time of transplantation, individualized to patients' immunological risk profile based on cell-dependent cytotoxicity (CDC) and flow cytometry crossmatch tests combined with assays for panel reactive antibodies (PRA) and donor-specific antibodies (DSA). Patients getting a first transplant with a well-matched (at least haplo-match) related donor with no PRA and negative flow crossmatch receive no induction. Basiliximab is used in case of all spousal donors, donors with more than ≥4 HLA mismatch, current moderate PRA or low DSA with well-matched living related transplant, and B-cell-positive flow crossmatch. ATG is used in all deceased donor transplants and with a living donor if current PRA ≥50%, T-cell-positive flow crossmatch, and high historical PRA.

All patients received calcineurin inhibitors (CNI)-cyclosporine/tacrolimus, mycophenolate mofetil (MMF) or azathioprine and prednisolone (20 mg/day). In the initial 1 month, we target tacrolimus trough level (C0) of 10–15 ng/ml and cyclosporine C2 level of 1200–1800 ng/ml. Steroid is tapered to a maintenance dose of 5.0–7.5 mg/day by the end of 3–4 months and MMF to 1.0–1.5 g/day by 6 months. By the end of 6 months, tacrolimus dose is adjusted to target trough level of 3–6 ng/ml and C2 level for cyclosporine is adjusted to 800–1000 ng/ml. For this study, high CNI level was defined as levels higher than defined during the 1 month prior or at the time of presentation with the infection. All patients received cotrimoxazole (trimethoprim: 80 mg and sulfamethoxazole: 400 mg) prophylaxis for at least 6 months after transplant. Till the time of this study, cytomegalovirus (CMV) prophylaxis was given for 6 months to only to D+R− (donor CMV IgG positive and recipient seronegative) transplant recipients or if the induction immunosuppression included ATG. We have subsequently switched to a universal CMV prophylaxis strategy with oral valganciclovir 450 mg once daily for 6 months. We do not have a routine BK virus surveillance protocol. Any patient who presented with fever, cough, breathlessness, chest pain, and/or weight loss was evaluated for pulmonary infection. All patients with clinical suspicion underwent a plain radiograph of the chest. A noncontrast

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high-resolution computerized tomography (HRCT) scan of the thorax was done in most patients unless they had significant clinical improvement within 24 h. If the patient was producing sputum, it was sent for culture analysis. Additionally, basic blood investigations including complete blood counts, renal function tests, liver function tests, and blood cultures were sent and empiric antimicrobial therapy was started. Initial empiric therapy usually comprised of a beta lactam (either piperacillin-tazobactam or cefoperazone + sulbactam) with or without azithromycin. We avoid empiric use of fluoroquinolones due to the high prevalence of tuberculosis (TB).

If patients did not improve or deteriorated in the next 24–48 h, they underwent a detailed procedural evaluation as shown in Fig. 1 for specific microbial identification. Candidiasis was considered as a diagnosis only if identified on broncho-alveolar lavage (BAL) fluid or biopsy analysis in a patient with radiology suggestive of a fungal infection and/or presence of other evidence of disseminated candidiasis. Patients were followed up for outcome till hospital discharge or death. The study was approved by the institute ethics committee and adhered to the guidelines recommended by the Istanbul declaration. Written informed consent was taken from all the patients.

Statistical analysis

Data analysis was performed with STATA 14.1 software. Continuous variables were expressed as mean ± standard deviation or medians with range. Categorical variables were compared with Pearson chi-square test or Fisher exact test. Nonparametric Wilcoxon rank sum test was comparing continuous variables. For risk factors for mortality analysis, two groups were made, episodes resulting in mortality or no mortality. Multivariate Cox regression model was used to evaluate risk factors for mortality due to pulmonary infections.

Results

One hundred and two episodes of pulmonary infections were managed in 88 patients during the study period. Baseline characteristics of study participants are shown in Table 1. The mean age of the patients was 37.7 ± 10.7 years (range 18–63), and 70 (79.6%) were males. All the patients had undergone ABO compatible transplantation, and none had received pretransplant desensitization therapy. None of the patients gave history of smoking after transplantation but their pretransplant smoking status was not known. None of the patients had a history of bronchial asthma, chronic obstructive airway disease, or any other chronic pulmonary illness. 44 patients received induction immunosuppression with IL-2R antagonists (31, 35.2%) or ATG (13, 14.8%). The maintenance immunosuppression is shown in Table S1.

Clinical profile of post-transplant pulmonary infections

Median duration of symptoms prior to presentation to hospital was 7 days (range 1–150 days). Figure 2 enumerates the common presenting symptoms of the

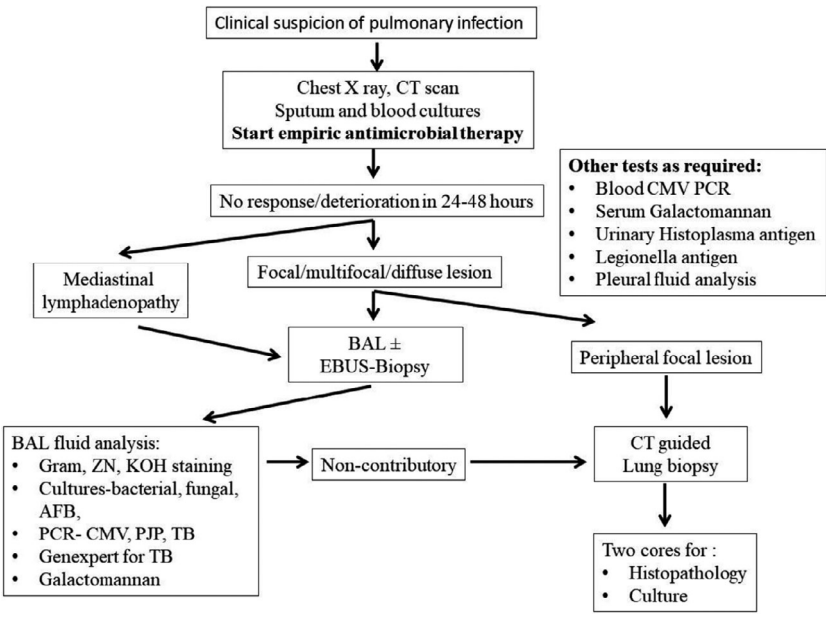

Figure 1 Diagnostic approach to renal transplant recipients with pulmonary infections.

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Table 1. Baseline characteristics of study participants.

Characteristics	*N* = 88
Age (in years), mean ± SD (range)	37.7 ± 10.7 (18–63)
Male gender (%)	70 (79.6)
Living donor (%)	81 (92.1)
Live related (%)	53 (60.3)
Spousal (%)	20 (22.7)
Live unrelated (authorized) (%)	8 (9.1)
Deceased donor (%)	7 (7.9)
Second transplant (%)	2 (2.3)
HLA Mismatch ≥ 4/6 (%) (*n* = 80)	28 (35.0)
Pretransplant diabetes (%)	5 (5.7)
Hypertension (%)	78 (88.6)
Basic kidney disease	
Diabetic kidney disease (%)	4 (4.5)
Structural abnormalities (%)	4 (4.5)
Glomerular diseases (%)	3 (3.5)
Tubulointerstitial diseases (%)	4 (4.5)
Others* (%)	3 (3.5)
Unclassified (%)	70 (79.5)
Dialysis vintage in months (*n* = 83), median (range)	10 (1–120)
Pretransplant tuberculosis (%)	11 (12.5)
Pretransplant HCV infection (%)	14 (15.9)
Treated (%)	8 (53.3)
Pretransplant HBV infection (%)	4 (4.5)
Induction	
No induction (%)	44 (50.0)
IL-2R antagonists (%)	31 (35.2)
Anti-thymocyte globulin (%)	13 (14.8)
Acute rejection (%)	21 (23.9)
Acute cellular rejection (%)	15 (17.1)
Antibody-mediated rejection (%)	3 (3.4)
Mixed rejection (%)	3 (3.4)
Additional immunosuppression for rejection or recurrent disease (%)	24 (27.3)
New (%)	26 (29.6)
Cotrimoxazole prophylaxis (%)	88 (100.0)
Antiviral prophylaxis (%)	20 (22.7)
Previous infection-related hospitalization (%)	44 (50.0)
Previous CMV viremia/infection	14 (15.9)

*Acute cortical necrosis(n=1) and acute kidney injury progressing to CKD(n=2).

patients with fever (84.3%) and cough (72.6%) being the most common complaints. Mean serum creatinine at presentation was 2.9 ± 2.1 mg/dl, and hemoglobin was 9.9 ± 2.3 g/dl. 25.5% of the infectious episodes were associated with leukocytosis (total leukocyte count >10 000/cu.mm^3) and 16.7% with leukopenia (total leukocyte count <4000/mm^3). Thrombocytopenia (platelet counts <150 000 cu.mm) was present in 40.2% patients.

Timeline of clinical presentation

Median time to occurrence of post-transplant pulmonary infection (PTPI) was 35.5 months (range 0.5–281 months). The time of clinical presentation is shown in Fig. 3. Three episodes (2.9%) occurred in the first month following transplant. Thirty episodes (29.4%) occurred between 2 and 12 months post-transplant, of which 19 (18.6%) occurred between 2 and 6 months and 11 (10.8%) between 7 and 12 months post-transplant. 32 (31.4%) and 37 (36.3%) episodes occurred 1–5 and >5 years post-transplant, respectively.

Microbiological profile of infections

Microbiological diagnosis was established in 71 (69.6%) episodes, of which a single causative agent was identified in 46 (64.8%) and 25 (35.2%) had polymicrobial etiology. 102 microorganisms were identified in these patients. Bacterial infection was the most frequent, seen in 30 (29.4%) cases. Fungal infections were diagnosed in 21 (20.6%) and TB in 24 (23.5%) cases. *Pneumocystis jiroveci* was detected in 11 (10.8%), viral in 9 (8.8%), and nocardial infections in 7 (6.9%), cases respectively. Figure 4 shows the timeline of presentation of the infections identified. The clinical characteristics of these infections are shown in Table S2.

Bacterial infections

Median time to occurrence of bacterial infection from the time of transplant was 28.5 months (range 1–147 months). Klebsiella (*n* = 12) and *Pseudomonas aeruginosa* (*n* = 10) were the most common agents. *Escherichia coli* (*n* = 4), Citrobacter spp. (*n* = 2), Acinetobacter spp. (*n* = 2), Enterobacter species (*n* = 2), and methicillin-resistant *Staphylococcus aureus* (*n* = 1) were the other organisms detected. Sputum culture was positive in five episodes, BAL culture in 16 cases, both sputum and BAL culture in six episodes, and blood culture in three episodes. In 3 of the 6 episodes in which both sputum and BAL cultures were positive, same organism was cultured, while the other three were mixed infections (*E. coli* + Citrobacter, Klebsiella + Citrobacter, Psuedomonas + *E. coli*).

Tuberculosis

There were 24 cases of TB, of which four were multidrug-resistant (MDR). Median time to occurrence of TB from the time of transplant was 49 months (range

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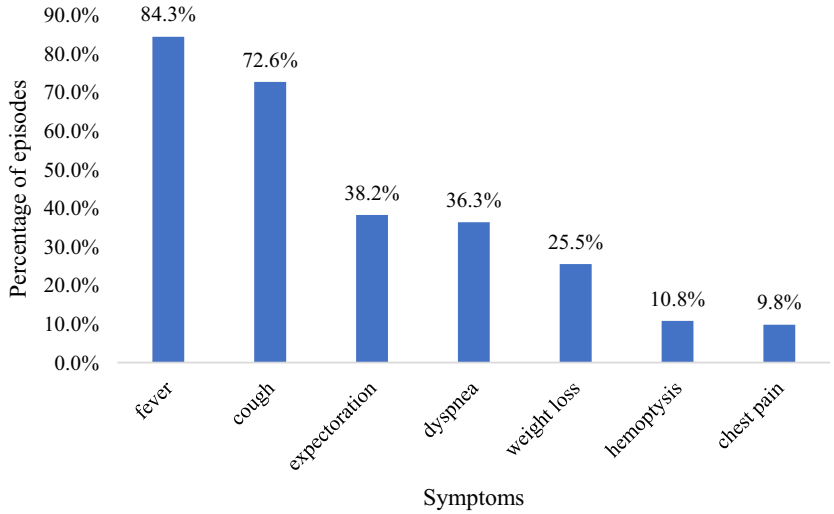

Figure 2 Presenting features of post-transplant pulmonary infection symptoms.

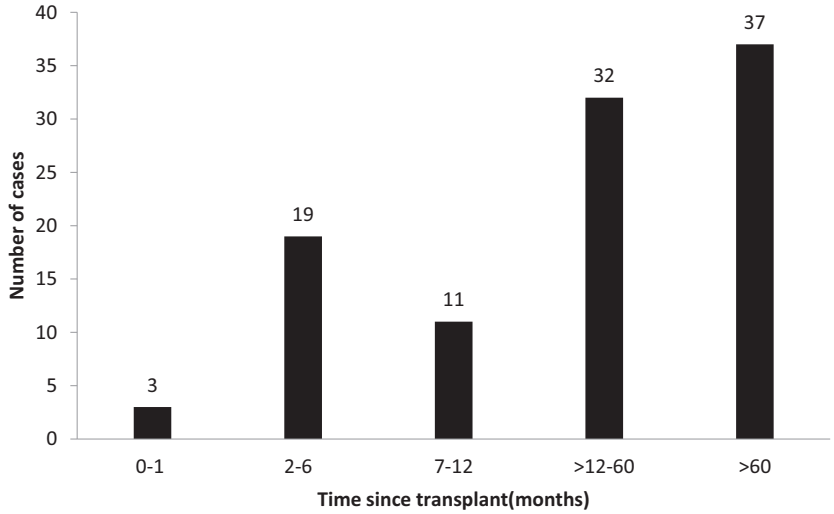

Figure 3 Timeline of onset of pulmonary infections.

3–281 months). Of the 24 cases, four were sputum positive, 11 were BAL fluid positive, and two were both sputum and BAL positive. TB was diagnosed by lung biopsy in three cases, pleural fluid analysis in 2, and endobronchial ultrasound-guided transbronchial node aspiration (EBUS-TBNA) in one case. Both lung biopsy and BAL were positive in one patient.

Fungal infections

Twenty-one cases showed a fungal etiology. Median time to occurrence of fungal infection from the time of transplant was 21 months (range 2–206 months). 7 (33.3%) presented 2–6 months and 14 (66.7%) beyond 12 months after transplantation. Nine (42.5%) were due to Aspergillus species, and 8 (38.1%) were Candida species; there were 2 (9.5%) cases of pulmonary mucormycosis and 1 (4.7%) each of Histoplasmosis and Cryptococcosis. Two cases of pulmonary Mucormycosis and one each of Cryptococcosis and Histoplasmosis were identified by lung biopsy.

Pneumocystis jiroveci pneumonia

There were 11 cases of *Pneumocystis jiroveci* pneumonia (PJP) and they were diagnosed by PCR testing of BAL fluid or lung biopsy. Median time of occurrence of PJP from the time of transplant was 18 months (range 10–89 months). 8 (72.7%) cases presented 12 months after transplantation. There were four cases of PJP and CMV co-infection.

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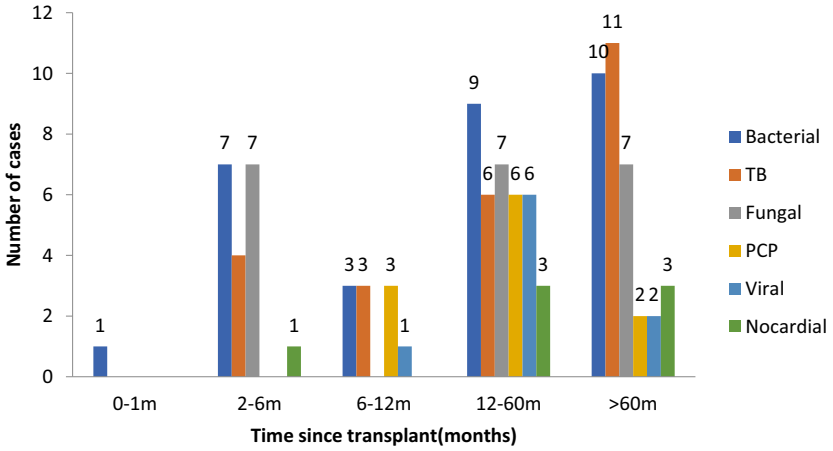

Figure 4 Timeline of infections according to etiology.

Viral infections

A viral etiology was identified in nine cases (8.8%), of which eight were due to CMV and one was due to Varicella. Median time to occurrence of viral pneumonia from the time of transplant was 19 months (range 10–102 months). 7 (87.5%) cases with CMV infection presented more than 12 months after transplantation. All cases of CMV pneumonia were detected by CMV PCR testing of BAL fluid. Blood CMV PCR was also positive in 6 of the 8 episodes. The single case of Varicella pneumonia was associated with classical skin lesions showing viral inclusion bodies on Tzanck smear.

Nocardiosis

Nocardiosis was diagnosed in 7 (6.9%) cases. Median time to occurrence from the time of transplant was 44 months (range 3–204 months). 6 (85.7%) cases presented after the first year of transplantation. Diagnosis was established in three cases by BAL fluid analysis and in four cases by lung biopsy.

Mixed (polymicrobial) infections

In 25 cases, more than one etiological agent was isolated. Out of these, four etiological agents were detected in one episode, 3 in 8 episodes, and 2 in 18 episodes (Table S3).

Radiological features of pulmonary infections

The chest X-ray showed evidence of infection in 83.3% episodes and was noncontributory in 16.7% cases where a noncontrast high-resolution computed tomography (HRCT) scan of thorax was required for diagnosis. HRCT was performed in 97 out of the 102 episodes (95.1%) and all showed abnormality. The type of lesions seen on CT scan is mentioned in Table S4. None of the radiological patterns were specific for any underlying microbial infection.

Diagnostic yield of various modalities

Out of the 39 cases in which sputum analysis was possible, there was a diagnostic yield in 20 (51.3%). Bronchoscopy with BAL fluid analysis was performed in 77 (75.4%) cases, with a positive yield in 49 (63.6%). Lung biopsy was done in 17 (16.7%) with no complication, and it was diagnostic in 11 (64.7%). Endobronchial ultrasound with transbronchial node aspiration (EBUS-TBNA) was diagnostic in 1 out of the 4 cases in which it was performed.

Outcome of pulmonary infections in renal transplant recipients

Shock requiring inotropic support developed in 26 (21.5%) and mechanical ventilation was required in 18 (17.7%) episodes. In 21 (20.6%) cases, the patients needed dialysis due to acute graft dysfunction. Both the patients with pulmonary mucormycosis underwent surgical intervention, lobectomy, and wedge resection, respectively.

Twenty of the 88 patients died due to the pulmonary infection (22.7%). A single infectious agent was detected in 9 (Bacteria-4, Tuberculosis-4, *Pneumocystis jiroveci*-1), 7 had polymicrobial etiology, and no microbial diagnosis could be established in four cases (Fig. 5). Hypotension requiring inotropic support was observed in 18 (17.6%), mechanical ventilation was required in 21 (20.5%), and hemodialysis in 21 (20.5%) infection episodes. 18

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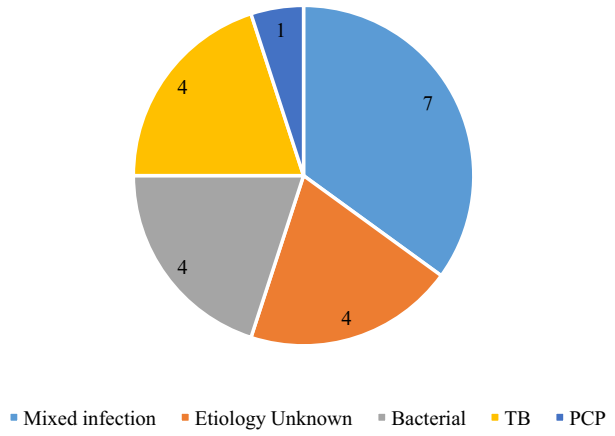

Figure 5 Mortality due to pulmonary infections as per etiology.

(20.5%) patients had progressive worsening of graft function following pulmonary infection. Six patients (6.8%) returned to dialysis though five of them had pre-infection S. creatinine >3.0 mg/dl. Eight patients (9.1%) died with a functioning graft. On multivariate Cox regression analysis, use of ATG (HR-2.39, 95% CI: 1.20–4.78, $P = 0.013$), fungal infection (HR-2.14, 95% CI: 1.19–3.84, $P = 0.011$), and need for mechanical ventilation (9.68, 95% CI: 1.34–69.82, $P = 0.024$) were significant predictors of mortality in our patients.

Discussion

Infections are a major cause of morbidity and mortality after renal transplantation [2,3,6,8]. The use of CNI- and MMF-based immunosuppression protocols has helped in improving short-term graft survival in the last few decades. However, there has been a corresponding increase in the risk of infections which is further amplified in tropical and low- and middle-income countries where the overall infectious disease burden is high. A plethora of microorganisms can cause pulmonary infections in renal transplant recipients and are associated with varied presentations. In 27.3% cases, our patients had been treated for either acute rejection or recurrent/denovo glomerular disease during the 6 months preceding the pulmonary infection. This was significantly higher than our overall acute rejection rate of around 11% [8] clearly indicating the increased susceptibility to infections in patients requiring additional immunosuppression at any time after the transplantation. Diabetes is an established risk factor for infections. Though only 5.7% of our patients had pretransplant diabetes, 29.6% were diagnosed with NODAT before developing pulmonary infection. History of at least one previous infection-related hospitalization was present in 50.0%, whereas history of previous CMV infection which is known to increase the risk of opportunistic infections was present in 15.9 % (Table 1).

Infections are common in the first 6–12 months after transplantation [1–8], and in earlier studies, almost half of the pulmonary infections occur during this period. 10–25% of post-transplant pulmonary infections have been found to occur in the first month after surgery being attributed to the risk of nosocomial transmission and initial high level of immunosuppression [13–15]. However, this temporal pattern has changed [17] which was also observed in our cohort. Median time to onset of infection was 35.5 months (range 0.5–281 months) which was much later as compared to our previous study (11.6 months, range: 0.03–166 months) [15]. Only 2.9% cases in our study presented in the first month after transplantation. More than 60% of the cases presented beyond the first year after transplantation with 36.3% presenting >5 years after transplantation. This change in timeline of infections may be due to higher level of cumulative immunosuppression attributed to MMF and tacrolimus-based maintenance immunosuppression and concomitant use of prophylaxis protocols which delays the incidence of some opportunistic infections in the early post-transplant months. This may be further potentiated in geographies where the overall exposure to infections is high in the community and the population density leads to increased risk even in the late post-transplant period. We are a government-aided public hospital which predominantly caters to patients with a weak socioeconomic background as described previously [8] that may translate to crowded and unsanitary living conditions which may further impact the incidence and spectrum of the infections. 84% of our cases had fever, 72% had cough, and only 38% were producing sputum. About 25% patients had other nonspecific features like chest pain and weight loss. Transplant patients should be evaluated for a pulmonary infection when they present with only fever and/or weight loss even in the absence of specific pulmonary symptoms. Plain radiograph of the chest did not reveal any obvious abnormality in 16.7% of cases which were subsequently diagnosed with CT scan. If the index of clinical suspicion is high, we should proceed with a CT scan in a patient with normal chest X-ray [18] as a delay in diagnosis may lead to a fatal outcome. Wide variety of findings were noted on CT, and the variety and complexity of radiological findings have been described previously [18,19]. However, CT manifestations of pulmonary infections caused by different pathogens were diverse and lacking any characteristic signs. We could establish a microbiological diagnosis in 69.6% cases which is similar

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to other studies [13–15,17,18]. Using our diagnostic approach (Fig. 1), more than 80% of our patients underwent an invasive diagnostic procedure with no significant procedural complication. It would be prudent to practice a low threshold for early invasive diagnostic evaluation as a delay in diagnosis can lead to rapid deterioration and poor outcomes in immunocompromised patients. Bacterial infections are the predominant cause of pneumonia in renal transplant recipients [10,12–15] and this was also evident in our study (29.4%). They occurred throughout the post-transplant course highlighting the susceptibility of immunocompromised patients to community-acquired infections. Gram-negative bacteria were the commonest subtype in our study, which is similar to most other reports [12–15]. 23.5% of our cases were diagnosed with TB which was significantly higher than other studies from developed countries where TB is not endemic [13–15,20]. Like bacterial infections, TB did not show any temporal distribution. This high prevalence of TB presenting in the late post-transplant period has also been reported from other centers in India and Brazil [4,10,12,21–23] and reflects the endemicity and high burden of this infection in these communities. There were four cases of MDR-TB, probably the highest number reported in any transplant series till date. The emergence of drug-resistant TB in the transplant population [24] poses a unique challenge as most drugs used for treatment have significant nephrotoxicity. Use of fluoroquinolones for empiric treatment of infections should be avoided to prevent emergence of MDR-TB.

We found an increase in fungal infections from 9% [12] to 20.6% which may be indicative of increase in the net of level of maintenance immunosuppression. Fungal isolates in pulmonary infections vary from 17% to 30% cases in other centers from India. Aspergillus and Candida species were the most frequent infections in our study [19,25–27]. Fungal infections were seen in the 2- to 6-month period when the patient is profoundly immunosuppressed and then in the late post-transplant period (beyond 12 months) probably due to environmental exposures.

The incidence of PJP has decreased from 27.3% [12] to 10.8% at out center. Universal prophylaxis with cotrimoxazole was introduced from April 2002, initially for 3 months and then extended to 6 months. Currently, it is given for 12 months and continued lifelong in patients who have received potent induction therapy, require higher level of maintenance immunosuppression or anti-rejection treatment. So the incidence of this infection has not only decreased but it also presents late after cessation of prophylaxis with only three cases presenting in the first 12 months which has also been observed at other centers [26–29]. CMV was the most common etiology for viral infections and predominantly presented late (beyond 12 months). We had seven cases of nocardial infection which has been rarely reported from other centers [15,30]. They presented in the late post-transplant period. Pulmonary infection is the most common clinical manifestation of nocardiosis. Nocardia spp. is recognized as one of the most under-diagnosed and emerging opportunistic pathogens in the world. Use of immunosuppression is a risk factor, and low-dose cotrimoxazole does not prevent infection. The mortality rate in our patients was 22.7%. Pulmonary infections are associated with a high risk of mortality in immunocompromised patients and this has been seen in all transplant cohorts [6–8]. Use of ATG, fungal infection, and the need for mechanical ventilation were significant predictors of mortality in our study. Despite being a prospective study, it had some limitations. The most important was the lack of a control group. Hence, risk factors for pulmonary infections could not be ascertained. Long-term outcomes of pulmonary infections could not be assessed due to the study design. The incidence of TB was high compared to developed countries probably since TB is endemic in India. Despite these limitations, this study gives a comprehensive overview about pulmonary infections in the current era. Transplant recipients may not always present with lung-specific findings and presence of fever and weight loss should prompt an evaluation for a pulmonary infection. The timeline and epidemiology of pulmonary infections have changed with the current immunosuppression protocols and prophylaxis strategies. Majority of the pulmonary infections present beyond the first year after transplantation. Community-acquired bacterial and endemic infections like TB predominate and they do not follow a specific timeline. Infections like PJP and CMV commonly present late after cessation of prophylaxis therapy. Under-diagnosed opportunistic infections like nocardiosis are being increasingly identified. MDR-TB is an emerging challenge in endemic geographies. We should follow a step-wise diagnostic approach incorporating invasive diagnostic modalities for timely etiological diagnosis in these patients.

Authorship statement

SM: conducted the study, monitored the patients did the analysis and wrote the manuscript, KM- helped in planning the study and provided the pulmonology specialist consultation, CJD- helped in planning and analysing the study and provided radiology diagnostic consultation,

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GS,IX and SS- microbiological diagnosis, HS-study analysis, RKY, DB- monitoring and patient care, SKA- monitoring the study patients, helped in conceptualizing the study and writing the manuscript, SB-conceptualized and supervised the study, monitored the patients, helped in analysis and wrote the manuscript.

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Conflict of interest

None of the authors have any conflict of interest to declare.

Data availability statement

The data underlying this article are available in the article. Any reasonable additional data required will be provided by the corresponding author as required.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Maintenance immunosuppression (N=88 patients).

Table S2. Presenting features of post-transplant pulmonary infections as per etiology.

Table S3. Organisms causing mixed infections.

Table S4. Pattern of CT- Thorax findings (N=97).

REFERENCES

1. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; **338**: 1741.
2. Kinnunen S, Karhapää P, Juutilainen A, Finne P, Helanterä I. Secular trends in infection-related mortality after kidney transplantation. *Clin J Am Soc Nephrol* 2018; **13**: 755.
3. van Delden C, Stampf S, Hirsch HH, et al. Swiss Transplant Cohort Study. Burden and timeline of infectious diseases in the first year after solid organ transplantation in the Swiss transplant cohort study. *Clin Infect Dis* 2020; **71**: e159–e169.
4. John GT. Infections after renal transplantation in India. *Indian J Nephrol* 2003; **13**: 14.
5. Alangaden GJ, Thyagarajan R, Gruber SA, *et al*. Infectious complications after kidney transplantation: current epidemiology and associated risk factors. *Clin Transplant* 2006; **20**: 401.
6. Snyder JJ, Israni AK, Peng Y, Zhang L, Simon TA, Kasiske BL. Rates of first infection following kidney transplant in the United States. *Kidney Int* 2009; **75**: 317.
7. de Sousa SR, Galante NZ, Barbosa DA, Pestana JOM. Incidence of infectious complications and their risk factors in the first year after renal transplantation. *J Bras Nefrol* 2010; **32**: 77.
8. Gopalakrishnan V, Agarwal SK, Aggarwal S, Mahajan S, Bhowmik D, Bagchi S. Infection is the chief cause of mortality and non-death censored graft loss in the first year after renal transplantation in a resource limited population: a single centre study. *Nephrology* 2019; **24**: 456.
9. Munda R, Alexander JW, First MR, Gartside PS, Fidler JP. Pulmonary infections in renal transplant recipients. *Ann Surg* 1978; **187**: 126.
10. Jha R, Narayan G, Jaleel MA, *et al*. Pulmonary infections after kidney transplantation. *J Assoc Physicians India* 1999; **47**: 779.
11. Kupeli E, Akcay S, Ulubay G, Ozyurek BA, Ozdemirel TS, Haberal M. Diagnostic utility of flexible bronchoscopy in recipients of solid organ transplants. *Transplant Proc* 2011; **43**: 543.
12. Kalra V, Agarwal SK, Khilnani GC, *et al*. Spectrum of pulmonary infections in renal transplant recipients in the tropics: a single center study. *Int UrolNephrol* 2005; **37**: 551.
13. Hoyo I, Linares L, Cervera C, *et al*. Epidemiology of pneumonia in kidney transplantation. *Transplant Proc* 2010; **42**: 2938.
14. Pazik J, Durlik M, Lewandowska D, *et al*. Pneumonia in kidney allograft recipients. *Transplant Proc* 2003; **35**: 2202.
15. Dizdar OS, Ersoy A, Akalin H. Pneumonia after kidney transplant: incidence, risk factors, and mortality. *Exp Clin Transplant J Middle East Soc Organ Transplant* 2014; **12**: 205.
16. Mandell LA, Wunderink RG, Anzueto A, *et al*. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; **44**(Supplement_2): S27.
17. Gandhi SP, Kute V, Patel KN, Sutariya H, Pandya V. Role of high resolution computed tomography of chest in posttransplant pulmonary infections. *Indian J Transplant* 2017; **11**: 49.
18. Jiang T, Xue F, Zheng X, *et al*. Clinical data and CT findings of pulmonary infection caused by different pathogens after kidney transplantation. *Eur J Radiol* 2012; **81**: 1347.
19. Dizdar OS, Ersoy A, Akalın H. Epidemiology and clinical and radiographic characteristics of pneumonia in kidney transplant recipients; 24-year experience. *Turk Nephrol Dial Transplant* 2017; **26**: 275.
20. Aguado JM, Herrero JA, Gavaldá J, *et al*. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation* 1997; **63**: 1278.
21. Jha V, Sakhuja V, Gupta D, *et al*. Successful management of pulmonary tuberculosis in renal allograft recipients in a single center. *Kidney Int* 1999; **56**: 1944.
22. Meinerz G, da Silva CK, Goldani JC, Garcia VD, Keitel E. Epidemiology of tuberculosis after kidney transplantation in a developing country. *Transpl Infect Dis* 2016; **18**: 176.
23. Huaman MA, Brawley R, Ashkin D. Multidrug-resistant tuberculosis in

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transplant recipients: case report and review of the literature. *Transpl Infect Dis Off J Transplant Soc* 2017; **19**: e12672.
24. Tharayil John G, Shankar V, Talaulikar G, *et al*. Epidemiology of systemic mycoses among renal-transplant recipients in India. *Transplantation* 2003; **75**: 1544.
25. Patel MH, Patel RD, Vanikar AV, *et al*. Invasive fungal infections in renal transplant patients: a single center study. *Ren Fail* 2017; **39**: 294.
26. Sharifipour F, Rezaeetalab F, Naghibi M. Pulmonary fungal infections in kidney transplant recipients: an 8-year study. *Transplant Proc* 2009; **41**: 1654.
27. Eitner F, Hauser IA, Rettkowski O, *et al*. Risk factors for *Pneumocystis jiroveci* pneumonia (PcP) in renal transplant recipients. *Nephrol Dial Transplant* 2011; **26**: 2013.
28. Jairam A, Dassi M, Chandola P, Lall M, Mukherjee D, Hooda AK. *Pneumocystis jiroveci* outbreak in a renal transplant center: lessons learnt. *Indian J Nephrol* 2014; **24**: 276.
29. Iriart X, Challan Belval T, Fillaux J, *et al*. Risk factors of Pneumocystis pneumonia in solid organ recipients in the era of the common use of post-transplantation prophylaxis. *Am J Transplant* 2015; **15**: 190.
30. Coussement J, Lebeaux D, van Delden C, et al. Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. *Clin Infect Dis*. 2016; **63**: 338.

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