Original Article

Study of the pattern of lower respiratory tract infection within the first year in renal transplant patients

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Keywords
Renal transplantation; Pneumonia

Abstract
Renal transplantation is the most common type of solid organ transplantation, although immunosuppressive therapy is essential for the viability of the graft it leads to increased incidence of infection, especially urinary tract and respiratory tract infections.

The aim of the present study: To study the pattern of lower respiratory tract infection within the first year in renal transplant patients.

Subjects: Sixty patients receiving renal transplantation because of end stage renal disease were followed up for one year to detect any episode of lower respiratory tract infection.

Methods: On suspicion of respiratory tract infection patients were subjected to sputum and blood examination together with doing bronchoscopy and BAL in the first 24 h after presentation, all samples were subjected for microbiological examination including quantitative culture for diagnosis of the etiologic organism.

Results: Thirteen patients had episodes of pneumonia (21.66%), the most common cause of pneumonia was single organism bacterial infection (46.1%) followed by mixed bacterial infection (23.1%), then TB and cytomegalo virus infection (15.4% each), etiologic organism was identified in 100% of cases, 11 patients had good response to anti-microbial therapy and showed no signs of rejection or impaired graft function and 2 patients died because of pneumonia.

Conclusion: Lower respiratory tract infection is a serious complication after renal transplantation. Bacterial and mixed bacterial infections are the most common etiologies, proper diagnosis using all tools of diagnosis especially bronchoscopy and quantitative culture can help in diagnosis and prevent the overuse of antibiotics.

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Renal transplantation is the most common type of organ transplantation. It has become the treatment of choice for most patients with end-stage renal disease (ESRD). Marked improvements in early graft survival and long-term graft function have made kidney transplantation a more cost-effective alternative to dialysis. Before the advent of immunosuppression, renal transplantation was limited to human leukocyte antigen (HLA)-identical (HLA-ID) siblings and was not applicable to the vast majority of patients with ESRD [1]. The introduction of combined azathioprine-steroid therapy in 1963 produced encouraging results and became the mainstay of immunosuppression. Although this therapy improved the results of transplantation, acute rejection and complications associated with steroid therapy persisted [1]. The introduction of cyclosporine in 1983 significantly improved the outcomes of all solid-organ transplants by reducing the risk of rejection. Further innovations, including anti-T cell antibodies (both monoclonal and polyclonal preparations), as well as other maintenance immunosuppressants (e.g., tacrolimus, mycophenolate, and sirolimus), have made a significant impact on both maintenance immunosuppression and the introduction of combined azathioprine-steroid therapy in 1963 produced encouraging results and became the mainstay of immunosuppression. Although this therapy improved the results of transplantation, acute rejection and complications associated with steroid therapy persisted [1]. The introduction of cyclosporine in 1983 significantly improved the outcomes of all solid-organ transplants by reducing the risk of rejection. Further innovations, including anti-T cell antibodies (both monoclonal and polyclonal preparations), as well as other maintenance immunosuppressants (e.g., tacrolimus, mycophenolate, and sirolimus), have made a significant impact on both patient and graft survival [2]. Currently, 1-year patient and graft survival rates exceed 90% in most transplant centers [1]. Although much progress has been made in the survival of the grafted kidney; infection is still a major complication among renal transplant recipients, including pneumonia, one of the most frequent life-threatening complications of long-term immunosuppression [3]. A broad range of potential pathogens are involved, of which the most common are bacterial and opportunistic infections [4–6]. Early diagnosis and accurate treatment are important in curing such an infection.

The aim of the present study

To study the pattern of lower respiratory tract infection within the first year in renal transplant patients in Kuwait.

Subjects

The study was conducted at the Kuwait Center of Organ Transplantation in association with Chest Disease Hospital and Al-Rashid Center for Allergy and Respiratory Diseases. The study was done in the period between January 2012 and June 2014. The study included 60 patients with ESRD who underwent renal transplantation and followed up for one year to detect any episode of pneumonia, all patients were on combination immunosuppressive therapy and all received trimethoprim–sulphamethoxazole for prophylaxis. Patients were classified into 3 groups:

- Group 1: including 20 patients received living – related kidney transplantation.
- Group 2: including 20 patients received living – unrelated kidney transplantation.
- Group 3: including 20 patients received cadaveric kidney transplantation.

Written informed consent was taken from all patients before sharing in the study and before bronchoscopy.

Methods

All patients were followed for one year after transplantation and on occurrence of respiratory symptoms the patients were subjected to the following:

1- History taking and clinical examination.
2- Complete blood count.
3- Blood culture and blood sample sent for organism specific anti-body titers [7].
4- Liver and kidney functions.
5- Urine and stool analysis and culture.
6- Chest X Ray.
7- HRCT chest with contrast.
8- Sputum study for [8]:
   - Direct microscopic examination.
   - Gram stain and Ziehl–Neelsen stain.
   - Culture and sensitivity.
   - Special test for viral, fungal elements and for Pneumocystis carinii pneumonia (PCP)
9- Bronchoscopy and Bronchoalveolar lavage [9]: Bronchoscopy was performed according to a standardized protocol within 24 h of admission in all patients (60 patients). An Olympus BF260 videobronchoscope (Olympus Medical Systems Corporation; Tokyo, Japan) was used to perform airway evaluation and BAL was done for all cases, according to radiologic assessment if the disease is localized BAL was done from the affected segment and if the infiltrate is generalized in the whole lung field BAL was done from the middle lobe or lingula, BAL was done using 120 ml of sterile saline in 6 equal aliquots and samples were sent for cytological and microbiological examination including PCR for TB and common viruses associated with infection in this group of patients ex. Cytomegalo virus and Epstein Bar virus.
10- Diagnosis of pneumonia was done according to the following criteria [10]:
   - Respiratory symptoms as cough, sputum production or chest pain with or without fever not explained by other causes including lung congestion and upper respiratory tract infection or oesophageal reflux.
   - Newly developed infiltrates in the CXR with exclusion of cases of pulmonary oedema.
   - Positive culture with more than 10^5 colony forming unit (CFU)/ml from sputum or BAL sample in case of bacterial pneumonia.
   - Positive special stains in sputum or BAL in case of PCP (Gomori methenamine silver stain) or mycobacteria (Ziehl–Neelsen stain).
   - Elevated IgM titer in case of atypical pneumonia (Mycoplasma, Chlamydia or legionella).
   - Presence of hyphae and positive fungal culture from sputum or BAL in case of fungal pneumonia.
   - Elevated IgM titer of specific virus or positive PCR of virus in sputum or BAL.

Statistical analysis

All statistical analyses were conducted using the software package SPSS 20.0 for Windows® (SPSS Inc., Chicago, IL, USA). Data are presented as frequencies for categorical
variables, and by mean ± standard deviation for numerical variables. Categorical variables were compared using a chi-square test, and continuous variables were compared using an independent unpaired t-test. P-values less than 0.05 were considered significant.

Results

From Table 1 there was no significant difference between the 3 groups of patient as regards the age, male to female ratio or the presence of co-morbidity, co-morbidity in the present study indicates the presence of any chronic disease like diabetes, hypertension, chronic heart disease but it did not include any chronic pulmonary disease or chronic infectious disease. The number of patients was 20 in each group.

From the 60 patients included in the present study 13 (21.66%) patients 7 males and 6 females suffered from attacks of pneumonia in the first year after transplantation, with mean age of 45.2 ± 7.1 years, in all cases definite etiology was identified.

In group 1: five patients had attacks of pneumonia (25%), three of which had bacterial pneumonia with one of them developed empyema, one patient had pulmonary tuberculosis (TB) and one patient had cytomegalo virus pneumonia (CMV) Table 2.

In group 2: four patients had attacks of pneumonia (20%), two of which had bacterial pneumonia, one patient had mixed infection with bacterial and fungal microorganisms being isolated, and one patient had cytomegalo virus pneumonia Table 2.

In group 3: four patients had attacks of pneumonia (20%) with one patient having bacterial pneumonia and two patients had mixed infection with one having bacterial infection plus non-tuberculous mycobacteria infection (MOTT) and the other had mixed bacterial and fungal infection, the last patient in this group had pulmonary TB Table 2.

There was no significant difference between the 3 groups as regard the number of patients suffered from pneumonia.

In the present study definite etiologic agent was identified in all cases of pneumonia:

Bacterial pneumonia: was the most common etiology, it was identified in 6 cases (46.1%); pneumococci was isolated in 2 patients, *Pseudomonas aeruginosa* was isolated in 2 patients, *Klebsiella pneumoniae* was isolated in one patient and lastly *Acinetobacter baumannii* was isolated in one patient, all patients had good response to antibiotic therapy, with no effect on the graft kidney or the patient life.

The second etiologic agent was mixed infection which was diagnosed in 3 patients (23.1%); 2 patients had mixed bacterial and fungal infection with one of them having *K. pneumoniae* and *Candida albicans* infection and the patient was improved on the anti-microbial drugs while the second one had *Acinetobacter baumannii* infection and *Aspergillus fumigatus* infection and the patient entered into respiratory failure and was put on mechanical ventilation and died after 10 days of diagnosis, the other kind of mixed infection was found in one patient who had pneumococcal infection plus *Mycobacterium kansasi* infection (proved by 2 positive cultures from sputum and BAL), patient responded well to antimicrobial drugs.

The third etiologic agent was *Mycobacterium tuberculosis* which was isolated in 2 (15.4%) patients. One of them had sputum positive for Acid-Fast Bacilli and started the treatment and the patient was improved clinically after 2 weeks of therapy and completed the course of anti-tuberculous for 9 months, while the other one had sputum and BAL negative for Acid-Fast Bacilli and the patient deteriorated in spite of the empirical anti-biotic therapy and was put on mechanical ventilation and died, the patient was diagnosed from the culture which came positive for TB after 6 weeks.

The last etiologic agent for pneumonia was the cytomegalo virus infection which was diagnosed in 2 (15.4%) patients through marked elevation of IgM for cytomegalo virus with negative culture for other organisms, the 2 patients improved on the anti-viral therapy.

The radiologic presentation of pneumonia was not specific in the present study, consolidation was the most common presentation, occurred in 8 patients followed by pulmonary infiltrates which was present unilateral in 3 patients and bilateral in 3 patients, the third presentation was the presence of cavitary lesion which was present in 3 patients, lastly one patient developed empyema Table 3.

Except for these 2 patients who died the presence of pneumonia did not affect the function of the graft kidney and the other 11 patients had good response to therapy and until the end of the study none of them died or showed signs of rejection.

Discussion

Infection is the main cause of death after renal transplantation and pulmonary infections have a significant proportion of the infection episodes following transplantation, the lung appears
to be particularly vulnerable to unusual or opportunistic organisms which produce serious complications in the immunosuppressed subjects, the combination of reduced lung defenses, general anesthesia during transplantation and the hospital environment leads to invasion of the lungs by these organisms [11]. The aim of the present study was to study the pattern of lower respiratory tract infection within the first year after renal transplantation, the incidence in the present study was 21.6% (13 cases out of 60 patients), the most common etiology was bacterial and mixed bacterial infection (about 69.2% of cases) followed by TB and Cytomegalo virus infection which were identified in the rest of cases (15.4% for each), fungal infection was not present alone but was present combined with bacterial infection.

The results of the present study are in agreement with the results of many researchers: Torres in year 2000 [12] studied 50 patients with liver transplantation who were admitted to hospital with pulmonary infiltrates and infection was proved in 33 patients, the most common cause of infection was gram negative bacteria especially in the early period after transplantation followed by fungal infection then viral infection, etiology was identified in 34% of cases in spite of doing BAL and protected specimen brush (PSB) samples for all patients. Rano in the year 2001 [13] evaluated 200 consecutive non-HIV immunocompromised patients admitted to the hospital with pulmonary infiltrates, Patients included in the study belonged to four different groups: group 1: solid organ transplant (21 renal, 11 cardiac, 14 liver, and six pancreatocerebral) recipients; group 2: haematopoietic stem cell transplant (HSCT) recipients (n = 53); group 3: patients with hematological malignancies treated with chemotherapy (n = 68); and group 4: patients requiring chronic treatment with corticosteroids (minimum 30 mg prednisone daily for the previous 30 days before inclusion) or immunosuppressive agents (azathioprine or cyclophosphamide; n = 27), in the group of solid organ transplantation pneumonia was diagnosed in 40 patients. Bacteria were the most frequent microorganisms causing pulmonary infiltrates, followed by fungi and viruses. While the etiology of pneumonia was undetermined in 5 cases, there were no statistically significant associations between the specific underlying immunosuppressive state and the etiology of the pulmonary infiltrates. Chang in year 2004 [14] had retrospective study by reviewing 565 patients with renal transplantation over the period between March 1984 and August 2001, 92 patients developed pneumonia from which 71 patients had definite etiology (about 76%) and 21 patients had pneumonia of undetermined etiology (24%), the most common cause of pneumonia was bacterial and mixed bacterial infection followed by TB and fungal infection. Hoyo in the year 2010 [15] retrospectively reviewed 610 patients with renal transplantation, they have diagnosed 60 episodes of pneumonia with an incidence of 8.8%, the most common cause of pneumonia was bacterial infection followed by fungal and viral causes, they could not reach a definite etiology in 34% of cases with nosocomial pneumonia and 54% of cases with community acquired pneumonia. Hoyo in year 2012 [16] reviewed 1656 cases of solid organ transplantation for the occurrence of opportunistic infection, infection occurred in 163 cases from which 40 cases occurred in the lung in the period between the first and sixth month after transplantation, the most common organism isolated was Aspergillus species followed by P. carinii, they concluded that the incidence of opportunistic infection is considerable and the outcome of these infections is usually fatal, in the present study Aspergillus was isolated in only one patient and was associated with bacterial infection and the patient died after 10 days from diagnosis. Kawecki in year 2014 [17] reviewed 295 cases of renal transplantation from 2001 to 2007 and followed the cases for early infection in the first 4 weeks after the procedure, the number of sputum samples were 13 and they showed Gram-positive bacteria (57.1%), Gram-negative bacteria (14.3%) and fungi were isolated in 28.6%, they concluded that number of resistant organisms to multiple antibiotics is increasing regardless of the type of infection after transplantation there is need for more strict adherence to infection control procedures in these patients. In comparison to the above mentioned studies the number of patients in the present study was small but it is worth noting that definite etiology was identified in all cases of pneumonia in the present study, this may be attributed to the use of sputum plus doing bronchoscopy and BAL in the first 24 h associated with the use of quantitative culture in all patients, this policy had a great impact on the diagnosis of etiologic organisms and can aid to prevent overuse of antibiotics and prevent the emergence of resistant organisms. In the present study there was no significant difference in the incidence of infection in relation to the type of transplantation whether the donor was related to the patient or not and whether the donor was alive or cadaveric, this indicates that infection is related mainly to the circumstances of transplantation and the state of immunosuppression and not related to the donor criteria, this necessitates the prophylactic antibiotic therapy in the recipient to be prolonged to reach up to six months to one year after transplantation as this is the most common period in which infection can occur.

**Conclusion**

Lower respiratory tract infection is a serious complication after renal transplantation. Bacterial and mixed bacterial infections are the most common etiologies, proper diagnosis using all tools of diagnosis especially bronchoscopy and quantitative culture can help in diagnosis and prevent the overuse of antibiotics.

**Conflict of interest**

None declared.
References


