Review

Jingfeng Zhang*

Research status of pulmonary infection after renal transplantation

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Abstract: Recipients with a low immunity are under a high risk of infection due to the extensive use of immunosuppressive drugs after renal transplantation. Pulmonary infection after renal transplantation is a prevalent postoperative complication characterized by a wide range of pathogens and high mortality. If the disease cannot be diagnosed in time, then the therapeutic effect will not be effective. This article reviews susceptible factors, high onset time, common pathogens, clinical manifestations, and therapy of pulmonary infection after renal transplantation to provide reference for disease prevention and treatment.

Keywords: renal transplantation, pulmonary infection, infectious characteristics, medication

Renal transplantation has become one of the most effective and mature methods for treatment of end-stage renal diseases. However, patients who have low immunity can easily have various complications such as rejection, infection, bleeding, and hypertension because of the high dose of immunosuppressive drugs. Pulmonary infection is the main complication after renal transplantation and also the cause of death in patients who underwent renal transplantation. In particular, severe pneumonia rapidly progresses and has high mortality. Within 1 year after renal transplantation, the incidence of pulmonary infection in patients is reported to be approximately 5%–10% abroad [1] and 8.7%–14.96% domestic [2,3]. Moreover, pulmonary infection after renal transplantation often endangers the life of patients, requires treatment in intensive care units, and exhibits very high mortality and disability rates. This article reviews the susceptible factors, high onset time, common pathogens, clinical manifestations, and therapy of pulmonary infection after renal transplantation to provide reference for disease prevention and treatment.

1 Susceptible factors

After renal transplantation, patients encounter many susceptible factors; as such, the incidence of various infections, especially opportunistic pathogen infections, increases significantly [3,4]. Common susceptible factors include the following:

- ① Age of transplant recipients: elderly organ transplant recipients (over 65 years old) may experience significant immune hypofunction and may be prone to post-transplant infection risk.
- ② Underlying diseases of the recipients: patients who underwent renal transplant often acquire a variety of basic diseases, such as diabetes mellitus, hypertension, and hyperlipidemia. The physiological metabolisms of these patients are disordered, and their basic conditions are poor. Some of these patients have history of repeated dialysis, hospitalization, and antibiotic treatment. All these complications result in reduced self-resistance and a high risk of postoperative infection.
- ③ Donor-derived infection: donor-derived pathogens include cytomegalovirus (CMV), Epstein–Barr virus, and *Toxoplasma gondii*. If the latent infection of pathogenic bacteria before the operation or the existing infection of donor is not treated in time, then infectious risk and mortality rate would increase.

- ④ Postoperative catheter insertion: prolonged tracheal intubation, drainage tube, catheter, and central venous catheter provide opportunities for pathogens to invade the body of donors and increase the incidence of infection.
- ⑤ Application of immunosuppressive drugs: after the application of immunosuppressive drugs, patients who underwent renal transplantation have low immunity; the defense abilities of these patients to various pathogens, including many opportunistic pathogens, are obviously reduced, and opportunistic infections can easily occur.
- ⑥ Occurrence of acute rejection: after acute rejection, the application of large dose of hormones and/or lymphocyte antibody produces great aggressiveness against lymphocytes. Given that the recovery time required by acute rejection is long, the opportunity of the patient to be in contact with various pathogenic bacteria in the hospital increases, resulting in the occurrence of infections.

2 High onset time

Infection after renal transplantation differs from common infection, and the onset time has evident characteristics. Most infections occur within 1 year after the operation, especially 2–6 months after the transplantation. Hoyo *et al.* [1] pointed out that the risk of infection increases for those who have renal transplantation for more than one year due to the long-term use of immunosuppressive drugs. However, the infection and mortality rates are less than those of patients infected within 1 year of renal transplantation. Mawhorter and Yamani [5] reported that infection is most likely to occur in 80–130 days, which is the strongest period of immunosuppression, and opportunistic infections may occur within 6 months after the operation [6]. According to the “Infectious Diseases in Solid Organ Transplantation” [4] publication issued by the American Society of Transplantation in 2013, the infection of renal transplantation can be divided into three phases. Phase 1 (0–30 days after transplantation) is usually associated with pretransplant physical conditions or surgical complications. In this phase, donor-derived or hospital-acquired infections are prone to occur, and most pathogenic bacteria include bacteria and fungi. This phase is closely related to the persistence of pretransplantation infection without effective treatment, use of immunosuppressive drugs, surgical trauma, tracheal intubation, and insertion of various catheters in the operation. Phase 2 (31–180 days after transplantation) consists of reactivation of potential risk factors from donor organs and recipients. This phase has not only the most typical time of infection but also the time of opportunistic infection. Two types of pathogens [7] are prone to cause infection: ① infection caused by a virus with immune regulation function, with the most common one as CMV, and ② infection caused by a variety of opportunistic pathogens, such as *Pneumocystis*, *Mycobacterium tuberculosis*, and fungi. The function of renal organ transplanted in patients is unstable in this period. A large dose of immunosuppressive drugs is used to destroy cellular immune factors and prevent the occurrence of rejection. Most of the patients are in an excessive inhibition state, resulting in obvious cellular immunity defects; thus, opportunistic infections are most likely to occur. In phase 3 (more than 180 days after transplantation), the incidence of opportunistic infections is significantly reduced, and community-acquired infections mainly occur. The main pathogens are *Streptococcus pneumoniae*, respiratory viruses, and *Mycoplasma*. Six months after transplantation, the immune system remodeling in patients is gradually completed, and the function of the transplanted renal organ is basically stable. Immunosuppressive drugs are also gradually reduced to a dose suitable for patients, and the autoimmune abilities of their bodies are restored to a certain extent. The abilities of the patients to resist the invasion of the external environment are enhanced, and the chances of infection are gradually reduced up to the levels similar to those of the general population.

3 Diagnostic criteria for pulmonary infection

According to the “Guidelines for the Diagnosis and Treatment of Community-Acquired Pneumonia” [8] published by the Chinese Society of Respiratory Diseases in 2006 and the “Guidelines for the Management of

Adults with Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia” [9] issued by the American Thoracic Society in 2005, the diagnostic criteria for pulmonary infection after renal transplantation are the same as those for general pneumonia. The diagnostic criteria are as follows: ① recent symptoms of cough or phlegm or original respiratory disease are aggravated and appearance of pyogenic sputum with or without chest pain; ② fever; ③ pulmonary solid variant sign and/or moist rales; ④ white blood cells $>10 \times 10^9/L$ or $<4 \times 10^9/L$ with or without the left shift of the nucleus; and ⑤ chest X-ray examination showing flaky, patchy infiltrating shadow or interstitial change with or without pleural effusion. If any item from ① to ④ appears with item ⑤ and pulmonary tuberculosis, lung tumor, noninfectious interstitial lung disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilia infiltration, and pulmonary vasculitis are excluded, then a clinical diagnosis of pulmonary infection can be established. Marchetti *et al.* [10] pointed out the lack of standardized test value for CMV infection because of differences in organ transplant and test specimens.

4 Common pathogenic bacteria and therapy of pulmonary infection

4.1 Bacterial infection

Pulmonary bacterial infection after renal transplantation accounts for 44% of the total infection rate [3], which is significantly higher than the overall incidence of hospital-acquired pneumonia by 2.33%. Infections within 1 month after transplantation are mostly hospital acquired and caused by Gram-negative bacilli, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. Six months after transplantation, pneumonia is mainly community acquired and caused by Gram-positive bacteria, such as *S. pneumoniae*, *Moraxella catarrhalis*, and *Legionella* [4]. According to the “Guidelines for the Management and Adults with Hospital Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia” [9] issued by the American Thoracic Society in 2005, the initial empirical antimicrobial therapy for patients receiving immunosuppressive drugs, broad-spectrum antimicrobial agents, or even multi-drug combination should be selected. The treatment of early infection should cover Gram-negative bacteria [11]. In mild infection, broad-spectrum penicillin + enzyme inhibitor, third-generation cephalosporin + enzyme inhibitor, or fluoroquinolone can be used. In severe infection, antimicrobial agents should cover most g-resistant bacteria, g + *Staphylococcus*, and fungi; carbapenems against *P. aeruginosa*; or β -lactamase/ β -lactamase inhibitor combined with fluoroquinolone. A combination of teicoplanin, linezolid, or vancomycin is required for the existence of methicillin-resistant *Staphylococcus aureus* infection risk factor. When choosing antimicrobial agents, the function of transplanted kidney should be accurately estimated according to patient age, weight, sex, and serum creatinine level, and the dosage should be adjusted according to drug instructions. Moreover, antibiotics that have no obvious nephrotoxicity to renal metabolism, such as penicillins and cephalosporins, as well as sulfonamides and quinolones, should be selected. Antibiotics with obvious nephrotoxicity to renal metabolism, such as aminoglycosides and polypeptide drugs, should be avoided; the dosage should be strictly reduced according to the degree of renal damage, and blood concentration should be monitored.

4.2 Fungal infection

The incidence of fungal infection after renal transplantation is 5% [12]. Fungal infection mostly occurs within 2–6 months after transplantation and rarely occurs within 1 month after transplantation. This incidence is often due to the long-term usage of broad-spectrum antibiotics, the most common of which is *Candida* (*Candida albicans*), followed by *Aspergillus*. The initial clinical symptoms have no evident specificity, and cough and phlegm, chest tightness, shortness of breath, and dyspnea could be found along

with the progress of the disease. Xu [13] pointed out that the incidence of invasive pulmonary aspergillosis increases, and the mortality rate is 30%–100%. At present, commonly used antifungal drugs in clinics are composed mainly of four categories: triazole, polyene, fluorocytosine, and echinocandin [14]. Triazole is widely used in clinical practice and can cover most sources of infection. Amphotericin B causes significant nephrotoxicity and is mainly considered a second-line drug. Echinocandin is also widely used in clinical practice, but it has no inhibitory activity for *Cryptococcus neoformans* and *Fusarium*; hence, its usage is also limited to some extent.

4.3 Virus infection

The incidence of viral pneumonia after renal transplantation is approximately 12%. Common viruses are CMV, hepatitis virus [hepatitis B virus (HBV) or hepatitis C virus (HCV)], and BK virus. CMV infection is the most common viral infection after renal transplantation. The incidence of this infection is as high as 8%–32%, most of which occur in the first to sixth months after the operation. The proportion of CMV carriers in the general population is extremely high, reaching 50.0%–92.2%. When the body immune function is normal, although the CMV genome exists in the human body, it is in a latent state, neither producing the virus nor causing clinical symptoms [15]. Renal transplant recipients may have CMV infection by receiving donor kidney or latent viral activation. The cellular immune function of patients after renal transplantation is inhibited due to the treatment of immunosuppressive drugs, and latent CMV is easily activated into active infection stage [16]. CMV infection is mainly manifested as fever, atypical lymphocytosis, neutropenia or thrombocytopenia, and fatigue. Some patients may also experience cough, acute respiratory distress syndrome, and other clinical manifestations [17]. Currently, CMV infection can be treated by five available drugs, namely, ganciclovir, valganciclovir, cidofovir, foscarnet, and leflunomide. High doses of acyclovir and valacyclovir have also been used for CMV prevention in transplant recipients but not in the treatment of acute CMV disease [18]. Ganciclovir is a new-generation nucleoside antiviral drug with broad-spectrum antiviral effects and is recognized as an effective anti-CMV drug.

Cukuranovic *et al.* [19] indicated that if HBV or HCV is present in patients before operation, then the reactivated infection occurs more often within 1–3 months after the operation. The incidence is 2%–10%, and the recommended therapeutic drug is interferon. Newly acquired HBV or HCV infection occurs mostly within 1 year after the operation, and the recommended therapeutic agents are lamivudine, adefovir dipivoxil, and entecavir.

BK virus can also cause damage to renal function, especially when the immune function of the human body is low. This infection occurs frequently within 3–12 months after the operation, and the incidence is 1%–10%. Patients with severe condition develop BK viral nephropathy, resulting in renal failure. Huang *et al.* [20] conducted a 1-year prospective study on patients who underwent renal operation and reported that the incidence of BK viral nephropathy is 5.6%. Recommended therapeutic agents include cidofovir, leflunomide, and intravenous immunoglobulin [19].

4.4 Other pathogen infections

4.4.1 Tuberculosis infection

The risk of tubercle bacillus infection in patients after renal transplantation is 50–100 times higher than that of healthy people. Pulmonary tuberculosis accounts for approximately 2% and highly occurs within 2–4 months after the operation [4]. The main clinical symptom is fever, occasional dry cough or expectoration, and unobvious pulmonary signs. Tuberculosis may spread after renal transplantation in high-risk population. The recommended therapeutic agents are isoniazid and rifampicin [4].

4.4.2 *Pneumocystis carinii* infection

The incidence of *P. carinii* infection is approximately 3% to 10% and highly occurs within 3–6 months after the operation. The mortality rate could be as high as 100% without timely treatment [4]. Fever, dry cough, and progressive dyspnea are known as the “triple sign” and are typical clinical symptoms of *P. carinii* infection. The recommended therapeutic drugs include compound trimethoprim–sulfamethoxazole and pentamidine [4].

4.4.3 Atypical *Mycobacterium*

Ho *et al.* [21] reported that the main pathogens of pulmonary atypical mycobacteria infection are *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium avium* complex and highly occur within 2–120 months after the operation; this infection is characterized by high incidence and low mortality. The recommended therapeutic drugs are rifampicin, ethambutol, and clarithromycin.

5 Conclusion

Pulmonary infection seriously affects the recovery of renal transplant patients. After pulmonary infection, effective examination of various pathogens should be timely considered to identify the types and characteristics of pulmonary infection after renal transplantation. The dose of therapeutic drugs should be adjusted, and the antibiotics should be selected according to the results of the pathogen examination. Immunosuppressive drugs should be rationally used. The entire body should be strengthened to support the treatment. The symptomatic treatment should be taken, and the balance between water and electrolyte and nutritional support treatment should be maintained. Timely and effective diagnosis and treatment of infection can improve the outcome and guarantee the final success of renal transplantation.

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References

- [1] Hoyo I., Linares L., Cervera C., Almela M., Marcos M.A., Sanclemente G., et al., Epidemiology of pneumonia in kidney transplantation, *Transplant. Proc.*, 2010, 42(8), 2938-2940.
- [2] Luo X.H., Xue W.J., Tian P.X., Ding X.M., Yan H., Xiang H.L., et al., Clinical analysis of 98 cases of pulmonary infection in renal transplant recipients, *J. Mod. Urol.*, 2011, 16(6), 490-492.
- [3] Wang J.M., Bao H., Feng W., Prognosis and clinical features of different pathogens pulmonary infection caused by kidney transplantation, *Pract. Clin. Med.*, 2007, 8(6), 31-33.
- [4] The American Society of Transplantation. Infectious diseases in solid organ transplantation, *Am. J. Transplant.*, 2013, 13(Suppl. 4), S1-S371.
- [5] Mawhorter S., Yamani M.H., Hypogammaglobulinemia and infection risk in solid organ transplant recipients, *Curr. Opin. Organ Transplant.*, 2008, 13(6), 581-585.
- [6] Kupeli E., Ulubay G., Colak T., Ozdemirel T.S., Ozyurek B.A., Akcay S., et al., Pulmonary complications in renal recipients after transplantation, *Transplant. Proc.*, 2011, 43(2), 551-553.
- [7] Bonatti H., Pruett T.L., Brandacher G., Hagspiel K.D., Housseini A.M., Sifri C.D., et al., Pneumonia in solid organ recipients: spectrum of pathogens in 217 episodes, *Transplant. Proc.*, 2009, 41(1), 371-374.
- [8] Chinese Society of Respiratory Diseases. Guidelines for the diagnosis and treatment of community-acquired pneumonia, *Chin. J. Tuberc. Respir. Dis.*, 2006, 29(10), 651-655.

- [9] American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia, *Am. J. Respir. Crit. Care Med.*, 2005, 171(4), 388-416.
- [10] Marchetti S., Santangelo R., Manzara S., D'Onghia S., Fadda G., Cattani P., Comparison of real-time PCR and PP65 antigen assays for monitoring the development of cytomegalovirus disease in recipients of solid organ and bone marrow transplants, *New Microbiol.*, 2011, 34(2), 157-164.
- [11] Ai-Hasan M.N., Razonable R.R., Eckel-Passow J.E., Baddour L.M., Incidence rate and outcome of gram negative bloodstream infection in solid organ transplant recipients, *Am. J. Transplant.*, 2009, 9(4), 835-843.
- [12] Shen Y.B., Feng F., Xie Y.C., Clinical analysis of pulmonary fungal infection after renal transplantation, *Zhonghua Yi Yuan Gan Ran Xue Za Zhi*, 2011, 21(12), 2461.
- [13] Xu X., Advances in the study of pulmonary infection after renal transplantation, *Chongqing Med.*, 2013, 42(1), 82-84.
- [14] Liu D., Cai S.X., Liu Y.G., Guo Y., Factors affecting the prognosis of invasive pulmonary fungal infections after kidney transplantation: analysis of the ten-year single-center data, *Nan Fang Yi Ke Da Xue Xue Bao*, 2011, 31(5), 882-885.
- [15] Fornara O., Odeberg J., Khan Z., Stragliotto G., Peredo I., Butler L., et al., Human cytomegalovirus particles directly suppress CD4 T-lymphocyte activation and proliferation, *Immunobiology*, 2013, 218(8), 1034-1040.
- [16] Xiao P., Xu Z.H., Lu X., Yang H.M., Advances in the study of cytomegalovirus infection after renal transplantation, *J. Clin. Urol.*, 2012, 27(10), 796-800.
- [17] Cordero E., Casasola C., Ecarma R., Danguilan R., Cytomegalovirus disease in kidney transplant recipients: incidence, clinical profile, and risk factors, *Transplant. Proc.*, 2012, 44(3), 694-700.
- [18] 18. Gao C., Peng L.K., Advances in the diagnosis and treatment of cytomegalovirus infection following renal transplantation, *Fudan University. J. Med. Sci.*, 2011, 38(2), 172-177.
- [19] Cukuranovic J., Ugrenovic S., Jovanovic I., Visnjic M., Stefanovic V., Viral infection in renal transplant recipient, *Sci. World J.*, 2012, 2012, 820621, DOI: 10.1100/2012/820621.
- [20] Huang G., Chen L.Z., Qiu J., Wang CX, Fei JG, Deng SX, et al., Prospective study of polyomavirus BK replication and nephropathy in renal transplant recipients in China: a single-center analysis of incidence, reduction in immunosuppression and clinical course, *Clin. Transplant.*, 2010, 24(5), 599-609.
- [21] Ho T.A., Rommelaere M., Coche E., Yombi J.C., Kanaan N., Nontuberculous mycobacterial pulmonary infection in renal transplant recipients, *Transpl. Infect. Dis.*, 2010, 12(2), 138-142.