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Review

The Spectrum of Infectious Diseases in Kidney Transplantation: A Review of the Classification, Pathogens and Clinical Manifestations

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Abstract. *Kidney transplantation is the treatment-of-choice for a significant number of patients with end-stage renal disease. Renal transplant recipients (RTRs) benefit from a longer life expectancy, with a better quality of life. Despite, recent accomplishments in the field of kidney transplantation, both short- and long-term, surgical and medical complications still exist. Among these complications, cardiovascular disease, carcinogenesis and infections are the most important. Infectious diseases constitute the most common complications after renal transplantation and the second most common cause of death among RTRs with a functioning graft. Theoretically, all infectious pathogens could cause disease in immunocompromised RTRs, yet among these, one could identify more important ones, such as the Enterobacteriaceae, causing urinary tract infections; pneumonia due to Pneumocystis jirovecii; Candida species which cause invasive fungal infections; herpes viruses; hepatitis viruses and parasites. Early diagnosis and effective treatment are key elements in salvaging both the allograft and the patient. However, clinical manifestations and diagnosis of such infectious diseases are not easily identified due to the altered state of immune response of the RTR. Thus, apart from possessing a deep knowledge of the etiology and the treatment options in each case, transplant physicians should also always remain alert when dealing with RTRs.*

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In recent years, progress in kidney transplantation has led to better prognosis for patients with end-stage renal disease (ESRD). Yet controversy arises with the increasing success of transplantation and reduced availability from donors resulting in ever smaller organ pools (1, 2). The cumulative experience of transplant surgeons and physicians, advancement of surgical techniques, improvement in organ preservation and development of new immunosuppressive drugs has improved recipient and graft survival and function, even for marginal recipients and organs (1-3). Even though immunosuppressive drugs improve graft survival and function, it has been established that they contribute significantly to all post-transplantation complications. Common complications after renal transplantation are major cardiovascular events, oncogenesis and infectious diseases. The latter complicate renal transplantation frequently and are the second most common cause of death in patients with functioning grafts (2). The aim of this review is to classify the long list of infectious diseases occurring in RTRs and to summarize the variety of etiological causes and specific clinical manifestations in a comprehensive way.

Classification of Infections

Sources of infection (Table I). Considering that living donors are seldom immunocompromised and that deceased donors are usually hospitalized for long periods of time in an intensive care unit (ICU), one can understand that donor-derived infections (DDI) are common in RTRs (4). They accounted for 0.2% of the total infectious disease burden in patients with all types of allografts in the USA between 2005-2011 (4, 5). The incidence of DDI has increased annually since 2007, when it was estimated at around 1% (5). Rare infections have been reported in RTRs with the donor being the source of infection

Table I. *Classification of infections in kidney transplant recipients in relation to infection source.*

Infections of the donor	Infections of the recipient	Nosocomial infections	Community-acquired infections
Bacteremia or fungemia during transplant harvesting	Infections lost to pre-transplant evaluation	Multiresistant bacterial strains	Opportunistic infections
False-negative results for donor CMV/EBV	False_negative results of viral tests	Fungi	
Latent tuberculosis	Latent tuberculosis	Viruses	

CMV: Cytomegalovirus, EBV: Epstein-Barr virus.

(6). There are three categories of DDI in renal transplantation (4, 7, 8): Donor bacteremia or fungemia during organ procurement can lead to infected blood vessels, thus leading to either mycotic aneurysms or rupture of vascular anastomoses; Donor-derived cytomegalovirus (CMV) or Ebstein-Barr virus (EBV) seronegative infection can lead to recipient superinfection (9, 10); Latent DDI, with the most common being tuberculosis (11, 12).

As minimization of ischemia time (both warm and cold) leads to improved graft function (1), graft implantation in some cases is completed before all necessary microbiological tests are performed on the donor. In order to ensure that any infection has been avoided, checking the final microbiological results of the donor is paramount, otherwise bacteremia or fungemia might occur in the early postoperative period.

Another source of infections is the recipient of the graft. Latent infection can progress to a severe infectious disease due to immunosuppression. Meticulous history taking can help avoid these situations. The patient should be asked about long-distance travel, dietary habits, vaccination and personal hygiene (1).

Multiple-drug resistance has become a common problem in transplant units. It is well-established that the risk of infection from multiresistant strains is very high for the recipient. Common infections include Gram-positive and Gram-negative multiresistant bacteria, multiresistant mycobacteria, viruses and fungi. Infections vary with relation to the surgical site, and can be catheter-related, ventilator-related and nosocomial infections (7, 8, 13).

Time of infection after transplantation. Several time-related patterns of post-transplant infection owing to the standardization of immunosuppressive regimens have been recognized (Table II). This is attributed to the constant change of balance between the risk factors for infection (induction and maintenance therapy) and the protective factors that avert it (7, 8). Acute or acute-on-chronic hematological disease, acute viral infection, adjustment of immunosuppressive regimen and acute renal failure contribute majorly to postoperative infection. A three-period system has been established to facilitate diagnosis and treatment of post-transplant infections, dramatically improving patient and graft survival (7, 8).

The first period accounts for the first four post-transplantation weeks. There are three types of infectious diseases that prevail during this period: Latent preoperative recipient infections that have not been diagnosed or treated appropriately. Acute infections arise from these latent infections after induction of immunosuppressant treatment; Latent preoperative donor infections that are usually nosocomial infections. Common cases are multidrug-resistant Gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) or *Candida* spp. infections; Infections that occur during transplantation, either in the phase of organ procurement or during organ implantation. These can be ventilator-associated pneumonia (VAP), catheter-related urinary tract infection (UTI), surgical site infection (SSI), or due to unstable anastomoses.

Notably, opportunistic infectious diseases do not occur during this first period, despite the high net weight of induction immunosuppressant treatment. The main reason for this is that it is the cumulative result of immunosuppression that is responsible for opportunistic infections rather than the net weight of immunosuppression itself.

The second period extends from the end of the first post-transplantion month to the end of the sixth month. Infections in this period are a result of (7, 8): Latent or recurrent infections that were not adequately treated during the first period. These could be pseudo-membranous colitis, fungal pneumonia, and abscesses that were not well formed; viral infections from Herpesviridae, human immunodeficiency virus (HIV) and hepatitis viruses. These viruses cause life-long conditions that suppress the immune system and consequently cause targeted graft damage, graft rejection and poor recipient survival. Other viral infections include BK polyomavirus infection and common viral respiratory infections; Opportunistic fungal (*Aspergillus* spp., *Pneumocystis jirovecii*) and protozoal (*Toxoplasma gondii*) infections.

Patients with high maximum panel-reactive antibodies and graft-specific antibodies need higher doses of immunosupression to prevent graft rejection. This amplifies the risk of infection. In

Table II. *Classification of infections in kidney transplant recipients in relation to timing of infection post-transplantation.*

First period (1st postoperative month)	Second period (2nd – 6th month)	Third period (beyond the 6th month)
Donor-related infections (HSV, LCMV, WNV, HIV) – infrequent	Latent infections: *Pneumocystis jirovecii*, *Cryptococcus neoformans,* HSV, HBV, HCV, CMV, EBV, *Mycobacterium tuberculosis, Clostridium difficile*	Urinary tract infections (Enterobacteriaceae)
Recipient-related infections (*Aspergillus* spp., *Pseudomonas* spp.) Nosocomial infections (MRSA, VRE, non- *albicans Candida*)		Pneumonia (Enterobacteriaceae, fungi) CMV, HSV, SARS, PTLD, Kaposi sarcoma

HSV: Herpes simplex virus, LCMV: lymphocyte choriomeningitis virus, WNV: West Nile virus, HIV: human immunodeficiency virus, MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *Enterococcus*, HBV: hepatitis B virus, HCV: hepatitis C virus, CMV: cytomegalovirus, PTLD: post-transplant lymphoproliferative disorder, SARS: severe acute respiratory syndrome.

case of infection, a modification of the immunosuppressant regime and a broad spectrum of antibiotics should be used promptly after obtaining biological fluid samples for testing.

The third period begins from the end of the sixth post-transplantion month and extends typically to the end of the first post-transplantion year (7, 8). Patients might either present with a satisfactory graft function and reduced risk of infection, with chronic infections that complicate graft function and need constant surveillance, or present with poor graft function and graft rejection events, thus leading to prolonged and heavy regimens of immunosuppressive therapy and subsequently high risk of infection. The latter category is in continuous need of chemoprophylaxis against opportunistic infections.

Infectious Pathogens

Bacterial infections. Common Gram-positive bacteria causing infectious disease after transplantation are *S. aureus*, *Enterococcus* spp. and *N. Nocardia asteroids*. Community-derived infections can be caused by Gram-positive bacteria of the alimentary (*Listeria monocytogenes*) or respiratory tract (*Streptococcus pneumonia*) (7).

The most alarming Gram-positive bacterium is *S. aureus*. It is associated with 25% incidence of bacteremia in RTRs. Additionally, new methicillin and vancomycin-resistant strains are frequently being isolated. A recent trend regarding infection from multidrug-resistant strains is that the reduction of the incidence of nosocomial infections is followed by an increase in community-derived infections. Current research suggests that vancomycin resistance is transferred from one strain to another by other transformed vancomycin-resistant Enterococcusstrains through plasmids with the *vanA* gene (14). Another Gram-positive bacterial genus with multidrug-resistant strains that cause infections in the abdominal viscera is *Enterococcus*, which are mainly transmitted through contact with infected instruments and material. The genes which cause these strains to become vancomycin-resistant are vanA and vanB (15).

Another important genus of Gram-positive bacteria causing infection after renal transplantation is *Mycobacterium* spp., either *Mycobacterium tuberculosis* or other non-tuberculous mycobacteria. These infections are difficult to diagnose due to their common extrapulmonary sites of infection in RTRs and are difficult to treat because of interactions between immunosuppressive and antitubercular drugs. The relative risk of infection is 20-75-times higher in RTRs. Risk factors for tuberculosis include country of origin, diabetes mellitus, smoking and contact with people who carry the disease (11).

Common Gram-negative bacteria causing infection are *Pseudomonas aeruginosa* and Enterobacteriaceae such as *Escherichia, Klebsiella,* and *Salmonella* species. Nosocomial infections are usually caused by *Neisseria meningitidis*, *Moraxella catarrhalis, Legionella pneumophila, Acinetobacter baumannii, Haemophilus influenzae* and nonsporogenous anaerobic bacteria. Particularly, *P. aeruginosa* complicates approximately 15% of renal transplants during the first period after transplantation and it accounts for 10% of UTI events (16). Recently, concerns have arisen due to the appearance of new Enterobacteriaceae strains resistant to ciprofloxacin and carbapenems that produce extended-spectrum beta-lactamase (ESBL) (16). Community-acquired infections are often caused by *Salmonella, Haemophilus, Campylobacter, Mycoplasma, Pseudomonas, Chlamydia* and *Treponema* species (7, 8, 13).

Recently the increasing incidence of the *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, A. baumannii, P. aeruginosa* and *Enterobacter* spp. multidrug-resistant (rESKAPE) microorganisms has inflicted worry on nephrologists, especially when the source of infection is detected in the community (13). Patients that become infected by these bacteria usually present with a set of common traits such as viral infections, multiple ICU admissions, poor graft function, therapy with cell-depleting antibodies and calcineurin inhibitors, recent history of infection and treatment failure (13).

Viral Infections

Common viral pathogens complicating renal transplantation are herpesviridae [CMV; EBV; herpes simplex virus 1 and 2 (HSV); human herpes virus 6, 7 and 8 (HHV); varizella zoster virus (VZV)], hepatitis viruses (HBV, HCV, HEV) and retroviruses (HIV, HTLV1 and -2). Common community-derived pathogens include hepatitis A virus, Respiratory Syncytial Virus (RSV), Human Metapneumovirus (hMPV), influenza and parainfluenza viruses, B19 parvovirus, rotaviruses, polyomaviruses and papillomaviruses (7).

The most common viral infection in RTRs is CMV, which usually manifests as pneumonia. Risk factors for CMV-associated pneumonia include a seropositive graft in a seronegative recipient, antilymphocyte antibodies, elderly donor, treatment with calcineurin inhibitors, lower estimated glomerular filtration rate and multiple episodes of graft rejection (9, 17). Prophylaxis with vagancyclovir and treatment with intravenous ganciclovir should be rigorous and meticulous. Primary infection with CMV is associated with reduced survival and poor graft function (18). Tapering the dose of the immunosuppressive drugs does not improve the clinical outcome of CMV infection (17, 18).

Recently the pool of HIV-positive recipients has grown larger (19-21). It has been established that seropositive recipients can safely undergo transplantation without jeopardizing their state of disease, albeit their graft function has proven to be lower, with concomitant higher rates of rejection (22-24). Case series of seropositive grafts implanted to seropositive recipients show much promise as far as survival and infection rates are concerned (25).

Fungal Infections

Fungal infections usually manifest as a systemic infectious disease. Common pathogens are *Aspergillus* and *Candida* species. Other less common infectious pathogens include *C. neoformans, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *P. jirovecii fungitis*. Fungal infections can be attributed to any source of pathogen, and even though they are quite rare, mortality is high, especially in patients with invasive fungitis, with a survival rate approximately of 40% (7, 26, 27).

The most common pathogen, in approximately 50% of cases, responsible for invasive fungal infections is *Candida albicans*. Risk factors for *Candida* infection include older age, treatment of bacterial infections with extended-spectrum antibiotics, use of venous catheters, neutropenia, long-term ICU hospitalization, graft rejection episodes, recent CMV infection and diabetes mellitus (28). Invasive aspergillosis accounts for fewer than 1% of fungal infections in RTRs but it is the most deadly infection (29). Risk factors for aspergillosis include corticosteroid-based regimens for maintenance therapy, acute rejection episodes and need for dialysis after transplantion (27). A recent study showed that longer duration of renal replacement therapy before transplantation and the occurrence of leukopenia were risk factors for early-onset infection, whereas donor seropositivity for CMV increased the risk for late-onset invasive aspergilliosis (30). A common cause of community-derived opportunistic fungal infections is *P. jirovecii*. Higher incidence rates of infection have been associated with the use of heavy immunosuppressive regimens (31).

Helminthic and Protozoal Infections

Protozoal infections are observed only in endemic regions. They are usually DDIs, latent-recipient preoperative infections or endemic community-acquired infections. The most common threadworm in RTRs is Strongyloides stercoralis followed by *Toxoplasma gondii, Cryptosporidium partum, Naegleria fowleri, Acanthamoeba* species*, Giardia lamblia, Trypanosoma cruz* and *Leishmania* species. Careful history recording and physical examination can help diagnose and prevent the spread of infections, which are very difficult to treat after transplantion (1, 8).

Clinical Manifestations of Infection in RTRs

It is important to highlight that the immunosuppressive regimens used in renal transplantation lead to altered immune response and subtle clinical manifestations of infectious diseases.

Urinary tract infections. Bacterial UTIs are mainly caused by Enterobacteriaceae of the recipient or nosocomial *Pseudomonas* or *Enterobacter* species (32). Their pathogenic action is amplified in the state of immunosuppression and they can cause chronic, recurrent or non-recurrent infections that are associated with poor surgical technique. The most common example is chronic obstructive infective pyelonephritis caused by vesicoureteral or pyeloureteral reflux, frequently complicated by bacteremia. They can also cause acute, regional, recurrent or non-recurrent infections that are usually complicated by bacteremia during the first post-transplant period. These include urethritis, cystitis and acute pyelonephritis. If these infections occur during the third period after transplantation, they usually become chronic and are not complicated by bacteremia.

UTIs are the most common type of infection following renal transplantation (33), accounting for 50-75% of post-transplant infections (32), and 30% of post-transplant ICU admissions due to sepsis (34). UTIs are usually ascending infections, SSI (bacterial transfer from the retroperitoneum to the incised urinary bladder) or lymphogenous (8, 32).

Common clinical manifestations include dysuria, hematuria, suprapubic or lumbar pain, bacteriuria and, less frequently, fever. Recurrent UTI may be the only manifestation of leakage in the vesicoureteral anastomosis (8, 32). Severity of infection varies among individuals according to the differences in immunosuppressive therapy and strain infectivity (7, 35). If appropriately treated, UTIs rarely recur.

An important clinical syndrome is the uremic hemolytic syndrome which is caused by the serotonin-producing strain of *Eschericia coli*. Clinical manifestations include acute renal failure, microvascular hemolytic anemia and thrombocytopenia. Recurrent disease is frequent in renal graft recipients, especially when it is the cause of ESRD (36).

Asymptomatic bacteriuria is a common complication following renal transplantation. It is believed to be caused either by reduced immune response because of faulty expression of toll-like receptor 4 (TLR4) or by reduced infectivity of certain bacterial species. Persistent asymptomatic bacteriuria has been associated with acute rejection and pyelonephritis in the allograft (37). The efficacy of antibiotic prophylaxis with trimethoprim/ sulphametho-xazole is ambiguous due to recorded resistance of certain strains to sulfamide antibiotics (37, 38).

Common causes of viral UTI are CMV and type 1 human Polyomavirus (BKV). Clinical manifestations include fever, acute graft rejection, tubulointestitial nephropathy, bone marrow depression and renal vascular disease (39, 40). Latent infection from BKV or type 2 human Polyomavirus (JCV) leads to recurrent post-transplant infections. Manifestations of BKV-associated nephropathy include sterile pyuria, eosinophiluria and hematuria, and occur in 1-10% of RTRs (40). Risk factors for BKV-associated nephritis are a high number of mismatches, female donor, high concentration of donor BKV antibodies, male recipient and certain induction therapy protocols (41). BKV infection can also lead to ureteral cell hyperplasia and ureteral obstruction, which can appear even in the first year postoperatively (41, 42).

Respiratory Tract Infections

There exists a large number of pathogens that cause respiratory tract infections in RTRs. Lower respiratory tract infections compromise patient survival rates and reduce graft function. Severe pneumonia in RTRs during the first year after transplantation is a more serious condition compared to later onset pneumonia and is associated with longer duration of mechanical ventilation, and increased length of hospital stay (43). All sources of pathogens contribute to the pool of respiratory infections (7, 44).

The usual clinical manifestations of respiratory disease might be absent. Nonetheless, it is pneumonia should be properly diagnosed when the patient presents with some of the following symptoms: cough, pleural effusion, pleural pain, dyspnea, fever and hemoptysis. Evaluation with chest X-rays is required to confirm diagnosis. Atypical pneumonia might present with cough, fever or dyspnea.

In a study with 610 RTRs, 54 presented with 60 events of pneumonia, of which 23 were nosocomial infections and 37 were community acquired. Among these cases, 44% were attributed to bacteria, 7% to fungi and 3.5% to viruses. Nosocomial infections were predominantly caused by drug-resistant *P. aeruginosa*, whereas community-derived infections were mainly caused by S. pneumoniae. Twenty-one of these patients were admitted to the ICU and eight of them died. In 54% of the patients, blood and broncoalveolar lavage cultures did not confirm disease (44).

Severe respiratory disease can be caused by *S. aureus*, MRSA, *Streptococcal* species, VRE, Gram-negative drug-resistant strains, *Legionella* species, *Chlamydophila pneumoniae*, CMV, RSV, influenza and parainfluenza viruses (43). Fungal infections are very rare and difficult to diagnose. Some of the fungi causing pneumonia or pneumonitis are *P. jirovecii*, *Candida albicans, Aspergillus fumigatus, Blastomycus, Histoplasmum* and *Coccioeides* species (43, 45).

CMV-associated pneumonia usually appears with dry cough, fever, neutropenia and pleural effusions on the chest X-ray, and is usually attributed to latent graft infection. CMV pneumonia has been associated with HHV6, -7 and -8, and delayed graft function, and is a risk factor for fungal pneumonia (7, 17).

Invasive aspergillosis is caused by *Aspergillus fumigatus*, *Aspergillus flavus* or rarely by amphotericin-resistant *Aspergillus terreus*. It manifests as severe sepsis with a rapidly progressive systemic infection, hemorrhage, fungemia and tissue necrosis (29, 30). *Pneumocystis jirovecii*-associated pneumonia usually coexists with CMV, HIV or EBV, and it has a slow clinical evolution (31). HIV-positive patients present with fever, cough, and dyspnea. Seronegative patients might be asymptomatic. If left untreated, it leads to severe hypoxia and massive bleeding from the respiratory tract (20). Several cases of *P. jirovecii*-associated pneumonia after recurrent CMV infections have been reported (46, 47).

Less common causes of respiratory infection should not be omitted from the differential diagnosis such as hMPV (48) or *Burkholderia pseudomallei* (49).

Gastrointestinal Infections

Diarrhea is a common post-transplantation complication. Pathogens causing diarrhea include *E. coli*, *C. difficile, Shigella, Salmonella* and *Yersinia* species, CMV, Rotaviridae, *Cryptosporidia, Isospora belli, Cyclospora, Microsporidia,* and *Strongyloides stercoralis* (50). There are some less common endemic pathogens causing diarrhea (51). Diagnosis is usually difficult to establish.

Gastrointestinal infections can either be nosocomial or community-derived, bacterial or viral, and are usually

complicated by electrolyte disorders, hematochesia and nutritional deficits.

Pseudomembranous colitis and ESBL infections are life-threatening for RTRs (52-54). In a prospective clinical trial conducted from 2008 to 2010, among 603 RTRs, 37 presented with *C. difficile* and it was estimated that they had poor graft function (52). Pseudomembranous colitis manifests clinically with bloody, watery, purulent stools, abdominal pain, fever, nausea and dehydration, which can lead to fatal potassium disorders.

HBV and HCV are the primary causes of chronic liver disease in RTRs in the Mediterranean and the USA, respectively (55). HCV contributes largely to RTR morbidity as it reduces the immune response (56), increases the risk for bacterial infections, induces new-onset diabetes after transplantation (57), and extrahepatic tumors (post transplant lymphoproliferative disorder) (58). HCV-positive recipients present with membranous or membrano-proliferative glomerulonephritis due to marked cryoglobulinemia (59). These conditions affect graft function. HCV-positive grafts have been implanted successfully in HCV RNA-positive recipients (58, 60).

Infections of the Central Nervous System (CNS)

Even though they are not vey common, CNS infections can be fatal for RTRs. Mortality from CNS infections has not decreased, but the burden of disease has changed due to early diagnosis and effective treatment (7).

As in any patient, in RTRs, CNS infections may be associated with fever, headache, meningismus, new-onset seizure, altered sensorium, or focal neurological deficit. Because any or all of these clinical manifestations may be subtle or absent as a result of the anti-inflammatory effects of immunosuppressive therapy, the threshold should be lower for suspecting CNS infection in the RTR who presents with one or more of the above symptoms. The most reliable features that suggest CNS infection are unexplained fever with headache.

Focal brain lesions and brain abscesses are attributed mainly to fungal infections (61). Invasive aspergillosis seems to be the most common culprit, with clinical manifestations including altered level of consciousness and seizures. *Candida* spp. less frequently enter the CNS *via* hematogenous spread. Brain imaging in CNS-related aspergillosis reveals multifocal lesions, which are usually located at the grey and white matter junction, affecting mainly the temporal lobes, whereas CNS-related candidiasis is associated with multiple, diffuse, small lesions, located both in the white and grey matter (62).

Bacterial infections are usually caused by *N. asteroides*, which enters the body through the lungs and subsequently invades the CNS *via* hematogenous dissemination (61). The resulting abscesses are small and multiple. Other bacterial pathogens which may rarely cause CNS infections include *K. pneumoniae, S. aureus, P. aeruginosa, Haemophilus influenzae, L. monocytogenes* and *VRE* (61). Toxoplasmosis, caused by *T. gondii*, can be a serious, albeit rare, cause of CNS infection mainly during the first post-transplantation trimester, with clinical manifestations such as headaches, seizures and altered level of consciousness (7, 8).

The most frequent viral pathogens associated with meningitis and meningoencephalitis are herpes viruses, mainly HHV-6, causing disorders of consciousness. Clinical manifestations of herpetic meningoencephalitis in order of decreasing frequency include impaired consciousness, seizures, headaches, disordered speech and fever. Other types of herpes viruses which cause CNS infections are CMV and HSV1 and -2, as well as JVC polyoma virus, which is responsible for a rare disease in RTRs called progressive multifocal encephalopathy (63). The importance of CNS infection due to *Cryptococcus* cannot be too strongly emphasized to the clinician. The most common clinical manifestation of cryptococcal infection is the presence of an asymptomatic lung nodule, whereas chronic infection is associated with pneumonia and meningitis, which are usually also complicated by skin lesions. Cryptococcal meningoencephalitis should be considered in the differential diagnosis of RTRs who present with headache of unknown origin, depressed level of consciousness, skin lesions and impaired renal function which does not improve (64).

Conclusion

In conclusion, infections represent a significant factor of morbidity and the second most common cause of death in RTRs. Recognition of the clinical manifestations, which are frequently mild and atypical due to concurrent immuno-suppressive treatment, as well as a high index of suspicion for specific infections in relation to their source, along with timing post-transplantation lead to prompt diagnosis and potentially successful treatment. Moreover, appropriate immunization of RTRs according to respective guidelines makes a significant reduction in the possible infection rates (60, 65). The necessity for continuous research in the field of infectious diseases is immense nowadays, considering the rapid emergence of new and multiresistant pathogens highly dangerous for RTRs.

Conflicts of Interest

The Authors have no conflict of interest to declare in regard to this article.

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