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REVIEW ARTICLE

Prophylaxis in Kidney Transplantation

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ABSTRACT

Kidney transplantation is the gold standard treatment for end-stage renal disease, improving survival and quality of life compared to dialysis. However, the use of immunosuppressive therapy to prevent allograft rejection renders recipients vulnerable to infections, a major concern in the posttransplant period. Prophylaxis strategies are indispensable in minimizing infectious risks and optimizing patient outcomes. This narrative review synthesizes current prophylaxis strategies across pretransplant, peritransplant, and posttransplant phases, providing a comprehensive overview of indications, timing, dosing, and adverse effects. Pretransplant prophylaxis involves thorough screening for infections, updating immunization status, and managing latent infections. Peritransplant prophylaxis focuses on tailored antimicrobial approaches to mitigate surgical and donor-related infection risks during the perioperative period. Posttransplant prophylaxis is a crucial component against opportunistic infections, particularly focusing on preventing *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection. This discussion encompasses the nuances of prophylactic regimens, highlighting the efficacy and challenges associated with the agents available and used in clinical practice. This review emphasizes the pivotal role of prophylaxis in minimizing infectious risks and optimizing outcomes in kidney transplant recipients, advocating for a proactive and multifaceted approach to infectious disease management in the transplant setting.

Descriptors: Kidney Transplant; Infection; Prophylaxis; Immunosuppression.

Profilaxia no Transplante Renal

RESUMO

O transplante renal é o tratamento de excelência para a doença renal em estágio terminal, melhorando a sobrevivência e a qualidade de vida dos doentes em comparação com a diálise. No entanto, o uso de terapêutica imunossupressora para prevenção da rejeição do enxerto torna os recetores vulneráveis a infeções, uma complicação importante no período pós-transplante. As estratégias de profilaxia são indispensáveis para minimizar os riscos infeciosos e otimizar os resultados obtidos. Esta revisão pretende sistematizar as estratégias de profilaxia nas fases de pré-, peri- e pós-transplante, oferecendo uma visão abrangente das indicações, *timing*, doses e efeitos adversos. A profilaxia pré-transplante envolve a pesquisa meticulosa de infeções ativas, atualização do estado vacinal e tratamento de infeções latentes. A profilaxia peri-transplante concentra-se em abordagens antimicrobianas personalizadas, de forma a reduzir os riscos de infeção cirúrgica e relacionados com o dador durante o período do peri-operatório. A profilaxia pós-transplante é crucial para prevenir infeções oportunistas, com foco na pneumonia por *Pneumocystis jirovecii* e na infeção por citomegalovírus. Esta discussão pretende abranger as diferenças dos diversos regimes profiláticos, destacando a eficácia e os desafios associados aos agentes disponíveis e utilizados na prática clínica. Pretende ainda enfatizar o papel fundamental da instituição de profilaxias na minimização dos riscos infeciosos e na melhoria dos resultados dos recetores de transplante renal, defendendo uma abordagem proativa e multifacetada na gestão de doenças infeciosas nesse contexto.

Descritores: Transplante de Rim; Infeção; Profilaxia; Imunossupressão.

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INTRODUCTION

Kidney transplantation (KT) is the best treatment for selected patients with end-stage renal disease (ESRD), improving survival and quality of life compared to patients on dialysis or those on dialysis awaiting transplantation).[1,2] However, the use of immunosuppression to avoid allograft rejection leads to an increased risk of infection, one of the most frequent and feared complications in the posttransplant period. Prophylaxis is crucial to avoid or minimize the infection risk and preserve kidney function, improving both graft and patient outcomes.[3]

The aim of this review is to describe the prophylaxis strategies currently available, including main indications, timing, dose adjustment, and adverse effects, and provide a systematic view on its management to simplify its use in clinical practice and optimize prophylaxis strategies that are already in place.

METHODS

A non-systematic search of the PubMed database for English-language articles, using the keywords infection, immunosuppression, kidney transplantation, and prophylaxis was performed to construct this narrative review. Case reports and case series deemed relevant by the authors were also included. Additionally, review papers were hand-searched to identify potentially pertinent articles.

KT and the need for prophylaxis

In 1933, Dr. Yuriy Vorony, in Kherson, Ukraine, attempted the first human kidney transplant from a deceased donor. The patient died 2 days after the transplant, as the graft was incompatible with the recipient's blood group.[4] Later, in 1950 in Illinois, United States of America, Dr. Richard Lawler successfully transplanted a kidney from a deceased donor. That kidney was rejected 10 months later. After 2 years in Boston, Dr. Joseph Murray performed the first successful kidney transplant between living patients (twins). This transplant lasted 8 years and the recipient died from an unrelated cause. It became more evident that rejection and immunosuppression were some of the main obstacles to graft survival. In 1962, the same team led the first successful kidney transplant from a deceased donor to an unrelated recipient, using azathioprine as an immunosuppressive drug.[5] During the following decades, new immunosuppressive drugs were discovered, and better methods for matching donors and recipients were found. These advances along with improved surgical techniques led to more transplant surgeries and more satisfying and sustained results. A long way has been traveled and today KT is considered the preferred treatment option for selected patients with ESRD.

Despite the increasing success rates, complications and challenges are still present and infection is one of the leading causes of decreased graft and patient survival rates. Transplanted patients are more susceptible to infection, and it can occur at any time during the posttransplant period. Most of these infections are caused by opportunistic agents, leading to invasive disease in the immunocompromised host and are associated with the long-term immunosuppressive therapy given to prevent allograft rejection and subsequent loss.[3,6] Given the T-lymphocyte dysfunction inherent to transplant immunosuppression, viral infections are a major contributor to morbidity, resulting in graft dysfunction and rejection, and an increased risk for other opportunistic infections.

It is important to remember that clinical signs of infection in immunocompromised patients are sometimes subtle and nonspecific compared to patients with intact immune system function, making recognition harder. Fever, if present, must include noninfectious causes in its differential diagnosis, such as graft rejection or drug toxicity.[6]

The immunosuppressive state is influenced not only caused by the time, dose, and specific immunosuppressive drug, but also by the loss of mucocutaneous integrity (intravenous [IV] central catheters, drains, or urinary catheters) and metabolic conditions like diabetes or uremia. The pattern of infection and the agents involved typically follow a standard timeline, considering the time after transplantation, immunosuppression regimens, and donor and recipient exposures.

In this review, prophylaxis strategies will be divided by pretransplant, peritransplant and posttransplant periods.

Pretransplant prophylaxis

Screening

Before KT it is important to perform a thorough medical history, discussing the patient's previous infection exposure and history, as well as immunization record, hobbies, animal exposure, and travel records are discussed.[7,8] This is the first step in creating an adequate prophylaxis strategy for each patient.

Every candidate should be tested for human immunodeficiency virus (HIV), hepatitis A, B, and C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), *Treponema pallidum, Toxoplasma* and *Mycobacterium tuberculosis*.[3]

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Some of these organisms can be present in the immunocompetent host and normally do not cause disease. However, with immunosuppression therapy there is an increased risk of reactivation/replication and invasive disease, with high rates of morbidity and mortality.[7]

Besides the standard testing applicable for most candidates and other pathogens may be searched for considering the epidemiological context, such as contact with dogs (*Leishmania* spp.) or cattle (*Brucella* spp.). Patients from Africa, Asia, Latin America, or other endemic areas should also be tested for *Strongyloides*.[7] Dietary habits should be considered, including the use of well water (*Cryptosporidium*), consumption of uncooked meats (*Salmonella, Listeria*, hepatitis E) and unpasteurized dairy products (*Listeria*).[9]

Dental infections should be screened and treated accordingly. Catheter-related infections (hemodialysis and peritoneal dialysis) should be thoroughly searched and treated, if present. If the candidate has a history of recurrent infections (e.g., bronchiectasis infections, urinary tract infections (UTI) with staghorn calculi, tonsilitis), anatomic abnormalities, systemic illnesses, and secondary immune defects should be screened and addressed.

Immunization

The immunization record should be updated according to national guidelines, and it plays an important role in preventing infections in immunocompromised patients.[7] Close contacts of transplant recipients should also be fully vaccinated.[8] Immunization should preferably take place pretransplant (at least 4 weeks before), as the immune response might be compromised after transplant following immunosuppressive regimens. Live vaccines are contraindicated.[8] Inactivated vaccines, if needed after the transplant to complete the series or if the patient remains seronegative, can be administrated after 2 to 6 months after the transplant. Optimal timing is controversial, and it is reasonable to wait at least 3 months and up to 12 months before vaccination. The influenza vaccine can be given as early as 1 month following transplantation, if needed (during outbreaks). After rejection treatment, the timing of vaccination might be different, and it is usually avoided for six months.[10-12]

Immunization for kidney transplant candidates and recipients is shown in Table 1. Hepatitis A and B in seronegative patients, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza (inactivated form), 13-valent pneumococcal conjugate (if not yet received, in a single lifetime dose), and 23-valent pneumococcal polysaccharide (in two doses, 5 years apart) should be administered. Varicella and mumps, measles, and rubella vaccines are live/live attenuated vaccines and should be given before the transplant, if the patient is seronegative. The varicella zoster vaccine should be considered in patients older than 50 years old and the human papillomavirus (HPV) vaccine in patients between 11 and 26 years old. Splenectomized patients (or patients who may require splenectomy or eculizumab) should be vaccinated against *Haemophilus influenzae* and *meningococcus*.[3,11,12]

One of the main concerns with immunization is that vaccination, particularly against influenza, which should be given yearly, can lead to the development of anti-human leukocyte antigen (HLA) antibodies. However, several studies have demonstrated that vaccines are safe in the posttransplant context and are not associated with worse outcomes.[13,14]

Table 1. Immunization for kidney transplant candidates and recipients.

Vaccine type	Vaccine target	Notes/indications
Nonlive (inactivated, killed, subunit, or recombinant)	Hepatitis B virus	All recipients nonimmune based on serologic testing
	Hepatitis A virus	High-risk patients if not previously vaccinated or immune (travel to or residence in an endemic area)
	Meningococcus (serotypes A, B, C, W, and Y)	At-risk patients not previously vaccinated: treatment with eculizumab; impaired splenic function
	H. influenzae	
	HPV	All recipients not previously vaccinated if age-based indication is met (11-26 years old)
	Pneumococcal vaccines	All recipients not previously vaccinated or who need booster doses (according to national guidelines)
	Seasonal influenza virus	All recipients annually
	SARS-CoV-2	All recipients according to national guidelines
Live, attenuated (pretransplant)	VZV	All recipients > 50 years old
	Measles, mumps, rubella	Patients not previously vaccinated and/or without evidence of immunity

Source: Elaborated by the authors.

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Treatment of latent infections

Infections are more difficult to diagnose and harder to treat once the patient is immunocompromised, and it is important to treat both active and latent infections before transplantation. Moreover, drug interactions with immunosuppressants may limit treatment options and enhance toxicities.

Tuberculosis (TB) in transplant recipients could result from allograft or nosocomial transmission or be community-acquired, but in this population, it is mostly seen as a reactivation of a latent infection. Considering this epidemiology, systematic screening is warranted in patients before starting immunosuppressive therapy. All patients should be screened through a chest radiograph and tuberculin skin testing (TST) or interferon-gamma release assay (IGRA). In candidates with ESRD, IGRA is preferred, as it seems to have a higher sensitivity and distinguishes between infection and immune response from Bacillus Calmette-Guerin (BCG) vaccination.[7,15] Anti-TB prophylaxis should be provided for candidates with a history of inadequately treated TB, positive IGRA, tuberculin reactivity ≥ 5 mm or a history of reactivity without adequate prophylaxis, and close contact with active pulmonary TB. Treatment regimens that include rifampin should be completed up to two weeks before transplantation, as rifampin will significantly reduce the serum levels of calcineurin inhibitors and glucocorticoids, even weeks after cessation of therapy. Patients who receive a kidney from a donor known to have untreated TB, should be treated posttransplant (if the donor was fully treated, further treatment is not necessary).[15]

Peritransplant prophylaxis (within 30 days after KT)

There is no individualized data regarding colonization or infection, thus standard perioperative antimicrobial prophylaxis should be administered to all KT recipients. Generally, a first-generation cephalosporin (e.g., cephazolin) offers adequate protection in the first 24 hours and it is used intra-operatively.[16] If specific pretransplant colonization or infection status is known, the prophylaxis strategy should be adjusted.

During the 1st days after surgery, as with other types of surgeries, there is a high risk of surgical-related infections. Each transplant center is responsible for the protocol regarding antibacterial and/or antifungal peritransplant prophylaxis, according to susceptibility patterns and epidemiologic records. Generally, antifungal prophylaxis is not required in KT recipients, but it should be adapted according to individual risk factors and colonization status.[17] *Candida* spp. prophylaxis is warranted in pancreas transplants because of the high risk of contamination or anastomotic leaks at exocrine drainage sites (relevant for simultaneous kidney-pancreas transplantation). Fluconazole is commonly used.[18]

Infections known from the donor should also be covered when choosing the right prophylaxis regimen.

Skin and soft tissue infections

KT recipients have the lowest rate of skin and soft tissue infections (SSI) among solid organ transplants (4-11%).[19,20] However, it remains an important complication in the early posttransplant period, impacting the length of hospital stay, and cost.

SSI include bacterial infections such as cellulitis, abscesses, and wound infections. Risk factors include recipient diabetes mellitus or obesity, surgeries with several anastomoses (vascular and ureteric) which predispose to leaks, and hematomas considered potential sites of infection. Moreover, some immunosuppressive agents frequently used are known to impair wound healing, such as glucocorticoids, antithymocyte globulin, and mammalian target of rapamycin inhibitors.[17]

Preventive measures to reduce the risk of these infections include thorough wound care, optimized sterile techniques, and avoidance of infection sources.[17]

It is important to remember that some viral infections, including herpes simplex virus (HSV) and VZV, may manifest as skin lesions and should be recognized and treated.

Nosocomial infections

Nosocomial infections are of increasing importance in transplant recipients, as patients have higher vulnerability in the early posttransplant period.

UTI are the most common bacterial infection in KT recipients, with an incidence as high as 80% in some series.[19] Risk factors include bladder catheterization, surgical trauma, immunosuppressive therapy, and immunological trauma associated with allograft rejection. Agents causing UTIs are similar to those in the general population. However, in the hospital setting multidrug-resistant (MDR) bacteria must be considered, as they present a demanding and growing public health issue. The increasing incidence of MDR pathogens challenges conventional treatments and needs more complex and tailored approaches to avoid their progressive spread and impact on both kidney and patient outcomes. Infections with MDR agents complicate treatment protocols, leading to longer hospital stays, increased healthcare costs and higher morbidity and mortality rates. Antibiotic resistance is growing in clinical practice, with treatment of asymptomatic bacteriuria and misuse of antibiotics posing as important risk factors. Antibiotic selection should be guided by the results of microbiology tests and duration of therapy should be tailored and reduced to the minimum effective dose. The most common MDR agents causing ITU in KT recipients include, but are not limited to,

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extended-spectrum beta-lactamase (ESBL)-producing bacteria (such as *Escherichia coli* and *Klebsiella*) and carbapenem-resistant Enterobacteriaceae.[21]

Viral or bacterial respiratory infections of different severities are also very common and may be acquired from visitors and hospital staff.

To minimize the risk of infection, drains, bladder catheters, and central venous catheters should be removed as soon as possible. Organisms such as vancomycin-resistant *Enterococcus* (VRE), *Candida* spp., or *Staphylococcus aureus* from colonized skin are often associated with biofilms, leading to an increased risk for bacteremia and should be treated promptly if present.[9]

Another important infection during this period is *Clostridium difficile* colitis (incidence of 0.5-16% in KT recipients), and it should be included in the differential diagnosis of diarrhea in transplant recipients. Antimicrobial exposure is the most important risk factor and every antimicrobial agent may predispose to *C. difficile* colitis, but clindamycin, cephalosporins, ampicillin, and fluoroquinolones are the most frequently implicated.[22]

Donor derived

Asymptomatic or latent infections from donors can be transmitted to the recipient including CMV, HIV, HCV, HBV, EBV, HSV, and human T-lymphotropic virus (HTLV-1/2). Donor screening for these viruses is warranted, and knowledge of their presence is useful to develop preventative or monitoring strategies for recipients.

Syphilis should be tested. Transmission of syphilis through renal transplantation is rare and only described in case reports.[23] It is not a contraindication for organ donation if the recipient receives posttransplant treatment with an adequate regimen of penicillin.

Due to the shortage of organs and the efficacy of direct-acting antivirals, some centers have started to use hepatitis C viremic donors for noninfected kidney transplant recipients if antiviral therapy can be guaranteed after transplant.[7,24] HIV-infected individuals are also considered as donors for HIV-infected recipients, generally under research protocols and the outcomes have been progressively better.[25] While this option is promising for HIV-positive recipients, it is still not available in Brazil. Donors with positive hepatitis B core antibody are also considered safe as long as the recipient is given antiviral prophylaxis.[26]

In living donation, the screening range should be widened and testing for toxoplasmosis and *M. tuberculosis* should be performed.[7] Considering TB, donor transmission accounted for up to 15% of reported posttransplant cases, with the prevalence decreasing with the use of isoniazid prophylaxis. Donors with active disease should not be considered.[27] *Trypanosoma cruzi* and *Strongyloides* transmission by transplantation has been described and testing should be performed based on epidemiologic risk factors. Renal transplantation is not contraindicated in affected donors.[7]

Bacterial infections in the respiratory or urinary tract and bloodstream infections should be diagnosed before transplantation. Evidence of adequate treatment and infection control should be documented, and the recipient should be treated accordingly.

Stent removal

Ureteral stents are commonly placed across the ureteral-vesical anastomosis during KT surgery to reduce the risk of urologic complications such as urinary leak or ureteral stenosis, but seem to be associated with a higher risk of UTI. Early ureteral stent removal (within 4 weeks of KT) may help prevent posttransplant UTI and this should be pursued when possible.[28]

Posttransplant prophylaxis

During the early period after transplant, patients are susceptible to nosocomial and opportunistic infections, especially within the first 6 months when the immunosuppression dose is higher. Prophylaxis plays a key role, and it is crucial to avoid significant morbidity and mortality.

Infections follow a relatively consistent pattern considering the time elapsed since transplantation and the duration of immunosuppression, reflecting the change in risk factors over time (hospitalization, surgery, immunosuppression, rejection and consecutive treatment, latent infection, and exposures).[3]

Pneumocystis jirovecci pneumonia

Pneumocystis jirovecci pneumonia (PJP) is a severe and life-threatening fungal opportunistic infection that affects immunocompromised hosts. Colonization with *P. jirovecci* is common in the adult population, but the primary infection is generally asymptomatic. Symptomatic, invasive disease is rare and limited to immunocompromised individuals, usually in the form of PJP.[29]

PJP incidence in most centers was 10 to 15% before the regular use of prophylaxis regimens, which significantly reduced its occurrence to less than 2%.[30] Among solid organ transplant recipients, KT recipients have the lowest rate of PJP, but it remains an important consideration. Current recommendations suggest all patients receive prophylaxis.[31,32]

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Trimethoprim-sulfamethoxazole (TMP-SMX) is considered the first-choice regimen for PJP prophylaxis, as it is a convenient, widely available, highly effective, and affordable antibiotic combination.[33,34] Additionally, it has a broad-spectrum action, preventing many hospital and community-acquired infections caused by Gram-positive and Gram-negative bacteria, such as *S. aureus, E. coli, Pseudomonas aeruginosa* and *Enterococcus* species. Its effects extend to *Toxoplasma, Nocardia*, and *Listeria* species and some methicillin-resistant *S. aureus* (MRSA) community-acquired strains. This is particularly important considering respiratory and UTI, common in the posttransplant infection that cause of high morbidity, costs, and extended hospital stays.[32]

The prophylactic dose of TMP-SMX is one single-strength (SS) tablet (400 + 80 mg) daily or one double-strength (DS) tablet (800 + 160 mg) three to seven times a week, taken orally. No difference has been found between the daily versus thrice weekly dosages.[34] This regimen should last 6 to 12 months, when the risk is considered highest, but it should be adjusted individually, as the optimal duration is unknown. Additional prophylaxis is generally recommended at times of increased immunosuppression, such as the during treatment for graft acute rejection, CMV infection or flares of autoimmune disease.[32]

Some potential side effects are allergic reactions (ranging from mild to moderate skin rash to Stevens-Johnson syndrome or toxic epidermal necrolysis), gastrointestinal disturbances, increased serum creatinine levels, and bone marrow suppression (with subsequent leukopenia and thrombocytopenia, especially when used concurrently with other myelosuppressive agents like valganciclovir and mycophenolate mofetil). While generally well-tolerated, these side effects might lead to drug cessation. Alternatives to PJP prophylaxis include atovaquone or dapsone, but these do not provide the same broad-spectrum benefits as TMP-SMX and are more expensive. Dapsone is contraindicated in patients with documented glucose-6-phosphate dehydrogenase (G6PD) deficiencies. Daily doses and kidney adjustment are shown in Table 2.

For the presumed or established PJP diagnosis, TMP-SMX is the first-line agent and drug of choice, with no other agent showing better outcomes.[32]

Table 2. Prophylaxis and treatment of PJP: drug dose and renal impairment adjustment.

Drug	Daily dose	Renal impairment adjustment
Prophylaxis		
TMP-SMX	1 SS or 1 DS (three times a week)	CrCl 15-30 mL/min: 50% of the usual dose CrCl < 15 mL/min: 25-50% of the usual dose
Atovaquone	1,500 mg	No adjustment needed
Dapsone	50-100 mg	No adjustment needed
Treatment		
TMP-SMX	15-20 mg/kg IV (of trimethoprim)	CrCl 15-30 mL/min: 50% of the usual dose CrCl < 15 mL/min: 25-50% of the usual dose
Pentamidine	4 mg/kg IV	CrCl < 10 mL/min: 4 mg/kg every 24 to 36 hours
Atovaquone	750 mg bid	No adjustment needed

Source: Elaborated by the authors. CrCl = creatinine clearance.

Cytomegalovirus

CMV, like other herpes viruses, becomes latent following primary infection, but reactivates and causes disease in the immunocompromised setting. Seroprevalence in the general population reaches 60% in developed countries and up to 100% in developing countries. Immunocompromised patients are susceptible to CMV infection, either through reactivation of a latent infection or as a primary infection due to donor-derived transmission.[34]

CMV serostatus of the donor and recipient is key to predicting the risk of infection after transplantation. It is the most frequent infection after solid organ transplantation, with an incidence of up to 50% in high-risk patients (KT recipients with an organ from a CMV seropositive donor, especially after T-lymphocyte depletion).[35,36] CMV can impact patient and allograft outcomes through direct and indirect effects. Direct effects include CMV syndrome, commonly categorized as a viral syndrome (febrile illness often accompanied by leukopenia, neutropenia, atypical lymphocytes, thrombocytopenia, or elevation of liver enzymes) or CMV tissue-invasive disease, which may manifest as colitis, hepatitis, pneumonitis, esophagitis and, more rarely, retinitis or myocarditis.[36]

Described for the first time in 1989 by R. Rubin, the indirect effects include upregulation of HLA and adhesion molecules, leading to acute and chronic rejection, arteriosclerosis and cardiovascular disease, opportunistic infections, malignancies, and

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diabetes mellitus.[37] These effects result from the immune response over long periods of low level of virus replication and are independent of a high viral load. Considering these effects, prophylactic strategies are essential.[35,37]

There are two main approaches to CMV prophylaxis (universal prophylaxis versus pre-emptive therapy), and their use and duration depend on the population considered, donor, and recipient CMV serostatus and individual risk factors.[38,39] Universal prophylaxis consists of administering of an antiviral drug for a predetermined period after the transplant (3 to 6 months considering the serostatus and type of immunosuppression) while pre-emptive involves monitoring CMV viral replication on a scheduled protocol and initiating of antiviral treatment when the viral load increases above a specific threshold. However, these thresholds have not been standardized between centers. The first approach has a higher risk of drug toxicity (such as valganciclovir-induced neutropenia and leukopenia) and increased costs. The second approach requires rigorous surveillance, and its impact on the indirect effects of low-level CMV replication is uncertain. Around 90% of European centers use the universal prophylaxis in high-risk patients, which seems to be the preferred regimen. Pre-emptive strategies are useful in low-risk (D-/R-patients), given their low risk of infection and disease.[36,38,39]

Valganciclovir is the antiviral drug of choice for CMV prophylaxis as it is taken orally and has high efficacy and oral bioavailability. It also helps prevent infections caused by other herpes viruses (HSV, VZV, and HHV-6).[38,40] It should be started in the immediate posttransplant period. Dose and duration depend on the patient's kidney function (Table 3) and CMV serostatus between donor and recipient (Table 4). The optimal duration is unknown and it should be individualized.

Ganciclovir (5 mg/kg per day) can also be used as a first-line treatment, but its IV administration is inconvenient for ambulatory prophylaxis. It is reserved for patients unable to take oral medication.

Some centers use valacyclovir (2 g orally every 6 hours), but neurotoxicity limits its use, and it seems less effective than valganciclovir.[38,40]

Table 3. Prophylaxis and treatment of CMV: drug dose and renal impairment adjustment

Drug	Daily dose	Renal impairment adjustment
Prophylaxis		
Valganciclovir	900 mg daily	ClCr 40-60 mL/min: 450 mg ClCr 25-40 mL/min: 450 mg every 2 days ClCr 10-25 mL/min: 450 mg twice weekly ClCr < 10 mL/min: not recommended
Ganciclovir	5 mg/kg IV	ClCr 50-70 mL/min: 2.5 mg/kg ClCr 25-50 mL/min: 1.25 mg/kg ClCr 10-25 mL/min: 0.625 mg/kg ClCr < 10 mL/min: 0.625 mg/kg Three times weekly
Valacyclovir	2 g q6 hours IV	ClCr 30-50 mL/min: 1 g q6 hours ClCr 10-30 mL/min: 500 mg q6 hours ClCr < 10 mL/min: 500 mg (single dose)
Letermovir	480 mg	No adjustment needed
Treatment		
Valganciclovir	900 mg bid	ClCr 40-60 mL/min: 450 mg bid ClCr 25-40 mL/min: 450 mg daily ClCr 10-25 mL/min: 450 mg every 2 days ClCr < 10 mL/min: not recommended
Ganciclovir	5 mg/kg bid IV	ClCr 50-70 mL/min: 2.5 mg/kg bid ClCr 25-50 mL/min: 2.5 mg/kg ClCr 10-25 ml/min: 1.25 mg/kg ClCr < 10 mL/min: 1.25 mg/kg Three times weekly
Foscarnet	60 mg/kg q8 hours or 90 mg/kg bid IV	Adjustments needed, consult elsewhere
Cidofovir	5 mg/kg once weekly IV (concurrent use of probenecid)	If AKI develops, reduction to 3mg/kg; If more severe AKI or proteinuria develops, discontinuation is warranted
Maribavir	400 mg bid	No adjustment needed

Source: Elaborated by the authors. AKI = acute kidney injury; q6 hours = *quaque* 6 hours (every 6 hours).

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Table 4. Serologic status and duration of CMV prophylaxis.

Donor/recipient serologic status	Duration of prophylaxis
Polyclonal antibodies induction therapy	6 months
D+/R+	3 months
D-/R+	3 months
D+/R-	6 months
D-/R-	No prophylaxis needed

Source: Elaborated by the authors.

Valganciclovir-induced myelotoxicity is the main side effect reported. Neutropenia (absolute neutrophil count < 1,000/μL) may lead to the reduction or discontinuation of myelotoxic drugs, including but not limited to valganciclovir. Stopping valganciclovir can increase the risk of CMV infection (especially in high-risk patients) and requires close monitoring of viral replication. Dose reduction should be avoided as it may lead to drug resistance and the addition of granulocyte colony-stimulating factor should be considered first.[41,42]

Recently, letermovir is being tested by many groups as prevention of CMV infection in KT recipients. It is approved in the U.S. and EU for prophylaxis of CMV reactivation and disease in R+ patients who received an allogeneic hematopoietic stem cell transplant. In a Phase 3 trial with 601 patients, letermovir was considered noninferior to valganciclovir in preventing CMV infection and showed fewer side effects.[43] However, there is a considerable drug interaction with tacrolimus, necessitating a dose reduction of 40-50% upon its initiation and close monitoring of tacrolimus serum levels to avoid toxicity.[44] If letermovir is used, a second drug is required to prevent other herpes viruses (HSV, VZV). Letermovir may become a valuable option for prophylaxis and eventual treatment in KT patients with drug resistant CMV infections. Centers worldwide are currently testing its efficacy and side effects, but more studies are still needed to safely change current strategies.[43]

For the treatment of refractory CMV (with or without resistance), antiviral therapies include maribavir, foscarnet, and cidofovir. However, in resistant CMV, there are few therapeutic choices and maribavir plays an essential role. It is an oral drug that inhibits UL97 protein kinase, consequently inhibiting of CMV DNA. It has a multimodal anti-CMV activity, not depending on UL54 DNA polymerase or UL97 protein kinase to be activated. Mutations in CMV genes at these specific locations confer resistance to first-line drugs. Studies show that maribavir is very effective in clearing viremia and controlling symptoms at week 8. Its advantages include less bone marrow and kidney toxicity compared to the other mentioned agents.[45]

After the treatment of CMV infection or disease, secondary prophylaxis is not generally recommended. Very rare cases of early CMV replication/infection occur. However, delayed-onset CMV disease after the end of prophylaxis is common and many clinical studies suggest measurements of CMV cell-mediated immunity may be a useful guide to predict its risk.[38]

Special considerations

Rituximab

Rituximab is a monoclonal anti-CD20 antibody used in several settings after kidney transplant, such as in the treatment of chronic active antibody-mediated rejection, recurrent glomerulonephritis (e.g., membranous nephropathy) or posttransplant lymphoproliferative disorders (PTLD). Rituximab is generally well-tolerated, but as with other immunosuppressive drugs, the main concern is the higher risk of infection and polyomavirus JC or hepatitis B reactivation might occur.[46] Rituximab should not be used if a chronic viral infection is active (hepatitis B or C or HIV).

Hepatitis B reactivation risk is especially important in the setting of a positive hepatitis B surface antigen (HbsAg) or hepatitis B core antibody (anti-HbcAb), and all patients should be tested before starting the treatment. Most experts consider that anti-CD20 agents confer the highest risk of hepatitis B reactivation among immunosuppressive therapies. Antiviral prophylaxis should be started in this setting with either lamivudine, entecavir, or tenofovir and for at least 12 to 18 months after the last administration. Patients with a history of hepatitis B infection should be closely monitored during treatment with Rituximab.[47,48]

TMP-SMX should also be restarted as some studies suggest an increased risk of PJP and the effectiveness of prophylaxis.[49,50]

Reactivation of polyomavirus JC can lead to progressive multifocal leukoencephalopathy (PML), and immunosuppression is known to be a major risk factor. PML is a severe demyelinating disease affecting the central nervous system, and symptoms range from altered mental status or motor deficits to death. This diagnosis in patients treated with Rituximab is extremely rare and normally associated with the impairment of cellular immunity, but it should be considered in any patient with new neurologic manifestations.[50,51]

Low-dose Rituximab therapy in KT recipients appears to have no influence on the incidence of CMV infection and seroconversion. However, considering its high incidence, anti-CMV prophylaxis should be considered (especially in CMV-seronegative recipients).52 EBV infection has not been associated with Rituximab to date.[52]

Considering bacterial infections, upper and lower respiratory tract infections are the most common infections described, but further data is needed to establish this association.[52] TB reactivation has not been strongly associated with Rituximab therapy.[52]

Baseline immunoglobulins (Ig) should be checked. Patients with a low baseline level of IgG are at particular risk for infection and Rituximab should be used with caution in these patients, particularly if IgG is less than 500 mg/dL or other risk factors are present (older age and glucocorticoid use).[50]

Response to vaccination might be impaired until B cell recovery, and it is recommended that immunization records are updated to up to 4 weeks before treatment to guarantee protection during the period of B cell depletion. There is no safety data regarding live vaccines, and these should not be used.[48]

Eculizumab

Eculizumab is a humanized monoclonal antibody against complement component C5a. It is used in the prevention or treatment of relapsing or *de novo* atypical hemolytic uremic syndrome after KT, and its role is being studied in the treatment of antibody-mediated rejection or its prevention in KT with a positive crossmatch against living donors. Treatment with eculizumab increases the risk of infections caused by encapsulated agents, and patients should be vaccinated against *H. influenzae* and meningococcus.[53] Antimicrobial prophylaxis for meningococcal infection with penicillin (500 mg orally twice daily) should be given for 2 weeks if urgent treatment is needed and vaccination was not possible or was administered within the previous 2 weeks. Some centers recommend that antibacterial prophylaxis be maintained for the duration of eculizumab therapy.[53]

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that binds to CD52 leading to the lysis of targeted cells. In solid organ transplantation, it is used as induction therapy (rarely) and as part of the treatment of acute T cell-mediated rejection. Patients have a higher risk of infection, especially by opportunistic agents, as alemtuzumab induces a severe depletion of peripheral blood lymphocytes (both T and B cells). Infection risk is dose-dependent.[48,54]

Patients receiving treatment with alemtuzumab should restart CMV and PJP prophylaxis, as explained earlier. Patients with low CMV risk, should receive anti-herpesvirus prophylaxis with acyclovir (200-400 mg *bis in die* [bid]). Testing for anti-VZV antibodies is recommended and vaccination should be considered if patients are seronegative.[55]

The duration of prophylaxis is not well established, but it should be continued up to 6 months after the completion of therapy or until the $CD4^+$ T cell count > 200 μL.

Female patients should be screened annually for HPV, as its incidence is higher in this population.[48,55]

Case reports describe reactivation of hepatitis B and C, listeriosis and TB, but their association and real incidence are yet to be studied. Antiviral therapy should be given to patients with a positive HbsAg and is suggested for patients with a positive HbcAb.[48]

Rabbit antithymocyte globulin

Rabbit antithymocyte globulin (thymoglobulin) is a polyclonal immunosuppressive agent used as induction therapy in high immunological risk patients or in the treatment of acute T cell-mediated rejection graded Banff II or higher. Patients treated with thymoglobulin should restart antimicrobial and antiviral prophylaxis for at least three months with an identical regimen to that administered in the immediate posttransplant period, namely against CMV and PJP. Antifungal prophylaxis varies by center.[56]

Belatacept

Belatacept is a fusion protein composed of a fraction of a human IgG1 and the extracellular domain of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), blocking the co-stimulatory signals and resulting in T cell inhibition. It is used as immunosuppressive therapy when calcineurin inhibitors are not tolerated or nonadherence is suspected (IV administration).[57]

A higher rate of opportunistic infections (such as CMV disease and PJP) has been reported after conversion to belatacept.[58] Monitoring CMV, polyomavirus BK and EBV replication during therapy is recommended.57 There is no need for specific prophylaxis.

Belatacept use in seronegative KT recipients has been associated with atypical EBV infections and posttransplant lymphoproliferative disorder and its use in these patients is not recommended.57

CONCLUSION

The implementation of prophylactic strategies over the past decades has played an important role in optimizing outcomes and reducing infectious complications in kidney transplantation. With an individualized approach to immunosuppression and

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prophylaxis therapies, transplant centers can effectively minimize the risk of infection and rejection while maximizing graft and patient survival. However, infectious diseases and immunological responses require ongoing research and a better tailoring to ensure the continuous evolution in the field of KT. This necessitates a collaborative effort between clinicians and researchers in various areas to develop future strategies in the standard of care for kidney transplant, ultimately achieving the shared goal of enhancing the well-being of transplant recipients worldwide.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Cardoso C, Bravo P, Messias A, Martins J, Oliveira C; **Conception and design:** Cardoso C, Bravo P, Messias A, Martins J, Oliveira C; **Article writing:** Cardoso C; **Critical revision:** Bravo P, Messias A, Martins J, Oliveira C; **Final approval:** Cardoso C.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study

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