COVID-19 and infective complications in renal transplant recipients

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UNIVERSITY OF ZAGREB
FACULTY OF MEDICINE

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COVID-19 and infective complications in renal transplant recipients

GRADUATE THESIS

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Abbreviations

AKI	Acute Kidney Injury
ARSD	Acute Respiratory Distress Syndrome
BKV	BK VIRUS
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitors
COVID-19	Coronavirus disease of 2019
D+/R-	Donor positive/ Recipient negative
DGF	Delayed Graft function
DM	Diabetes Mellitus
EBV	Epstein-Barr virus
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
HIV	Human Immuno-deficiency Virus
HLA	Human Leukocyte Antigen
IPA	Invasive Pulmonary Aspergillosis
KDIGO	Kidney Disease Improving Global Outcomes
KT	Kidney Transplantation
KTR	Kidney Transplant Recipient
LTBI	Latent Infection by Mycobacterium tuberculosis
MRD	Multi-resistant Drug
NNRTI	Nonnucleoside Reverse Transcriptase Inhibitors
PCR	Protein Chain Reaction
PI	Protease Inhibitors
PJP	Pneumocystis Jirovecii Pneumonia
PTLD	Post-transplantation Lymphoproliferative Disorder
RRT	Renal Replacement Therapy
SOT	Solid Organ Transplant
TB	Tuberculosis
TMP/SMX	Trimethoprim/Sulfamethoxazole
UTI	Urinary Tract Infection

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Summary

Title: COVID-19 and infective complications in renal transplant recipients

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Infections after kidney transplantation remain the second cause of complications after cardiovascular events with a high rate of morbidity and mortality. Since the beginning of the COVID-19 pandemic, many have theorized its role in the possible bad outcomes in renal replacement therapy and transplantation, but many studies are still needed and ongoing to confirm the role and the comorbidity linked to Coronavirus disease-19 in kidney transplant recipients. Despite prophylactic use of Antibiotics, urinary tract infections with pathogens such as E. coli remain the main cause of infection after kidney transplantation. Other pathogens such as CMV virus or EBV are also common due to increase immune suppression. Opportunistic infection and fungal infection are also noted in renal transplant recipients with epidemiological predisposition and comorbidities. The COVID-19 infection has the worst outcome in the immunocompromised kidney transplant population and the current pandemic due to this infection greatly influences the management of chronic kidney failure. Through this review, we present the most common infections in KTR, their timeline of presentation, the management according to recent guidelines, and the impact of COVID-19 in renal transplantation.

Keywords: COVID-19, kidney transplantation, Infection in kidney transplantation, Impact of COVID-19 on renal transplantation.

Sažetak

Naslov: COVID-19 I INFEKTIVNE KOMPLIKACIJE NAKON TRANSPLANTACIJE BUBREGA

Autor: Cedric Arol Takou Kuitcheu

Infekcije nakon transplantacije bubrega drugi su uzrok komplikacija nakon kardiovaskularnih događaja s visokom stopom morbiditeta i smrtnosti. Od početka pandemije COVIDA-19, mnogi su teoretizirali njihovu ulogu u mogućem lošem ishodu nadomjesne bubrežne terapije, ali još uvijek su potrebna i traju mnoga istraživanja kako bi se potvrdila uloga i komorbiditet povezan s bolesti Korona virusom 19 u primatelju transplantata bubrega. Unatoč profilaktičkoj upotrebi antibiotika infekcija mokraćnog sustava s patogenima kao što je E. coli ostaje glavni uzrok infekcije nakon transplantacije bubrega. Ostali patogeni poput CMV virusa ili EBV virusa također su česti zbog povećane imunološke supresije. Oportunistička infekcija i gljivična infekcija također su zabilježene kod primatelja s epidemiološkom predispozicijom i komorbiditetom. Infekcija COVID-19 ima najgori ishod u populaciji s imunološki oslabljenim transplantiranim bubregom, a pandemija zbog ove infekcije uvelike utječe na liječenje kroničnog zatajenja bubrega. Ovim osvrtom, predstavljamo najčešći infekcije u KTR-u, njihov vremenski okvir prezentiranja, upravljanje prema nedavnim smjernicama i utjecaj COVIDA-19 na transplantaciju bubrega.

Ključne riječi: COVID-19, Transplantacija bubrega, Infekcija u transplantaciji bubrega, Utjecaj COVID-19 na transplantaciju bubrega.

Introduction

The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2. Since its outbreaks in China, there have been more than 163 million confirmed cases of COVID-19, including more than 3 million deaths worldwide, reported to WHO. More than 1.2 billion vaccine doses have also been administered.[1] Except the Hemodialysis and Peritoneal dialysis, patient with chronic kidney disease need to receive a kidney transplant which is a lifesaving procedure to outlive the complications linked to chronic kidney failure. The Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease proposed a five-stage classification for Chronic Kidney diseases (CKD) based on the glomerular filtration rate (GFR; Table 1).[2] End-stage renal disease (ESRD) correspond to CKD Grade 5, for which lifelong renal replacement therapy (RTT), is necessary for survival and is associated with significant alterations in cardiovascular function; homeostasis of body fluid, electrolytes, and acid-base equilibrium; bone metabolism, erythropoiesis; and blood coagulation.[3]

Table 1. GFR categories in CKD

GFR category	GFR (ml/min/1.73 m2)	Terms
Grade 1	≥90	Normal or high
Grade 2	60-89	Mildly decreased
Grade 3a	45-59	Mildly to moderately decreased
Grade 3b	30-44	Moderately to severely decreased
Grade 4	15-29	Severely decreased
Grade 5	<15	Kidney failure

Taken from KDIGO 2012, Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. [2,3]

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

History of renal transplantation

During the 20th Century, effective organ transplantation is one of the most achievement in the field of medicine. On 23rd, December 1954, the first transplantation of a Kidney in Boston, USA is performed, where, a kidney transplantation is done between two identical tweens. Only 16 years after that, on April 16, 1970, the first kidney transplantation in the Southern part of Europe was performed in Ljubljana, Slovenia. A second kidney transplantation followed on January 30, 1971, in Rijeka, Croatia. In both cases, the mother donated a kidney to the son.[4] Today Croatia is one of the 8 members of the Euro-transplant network including Austria, Belgium, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia. Euro-transplant is an international non-profit organization, which acts as a mediator between donor hospitals and transplant centers for the benefit of patients in need of an organ transplant in all its member states.

Risk factor predisposing to infection after transplantation

Infections remain the main cause of non-cardiovascular death and hospitalization after kidney transplantation[5,6]. Post-transplantation risks of complication are mostly related to the recipient and the donor characteristics, the surgical procedure, and the immunosuppressive therapy. More potent immunosuppression is generally associated with a higher risk of infection. Older adults are at high risk of infections due to immunosenescence, frailty, functional impairment, and multiple comorbidities[7,8]. For instance Urinary tract Infections (UTI) the most common infection after kidney transplant[9] are significantly more frequent in older recipients than their younger counterparts, even after exclusion of asymptomatic bacteriuria[10]. The origin of the transplant such as transplant from a deceased donor, a higher number of HLA (Human Leukocyte Antigen) mismatches between recipient and donor, and a high risk for cytomegalovirus disease (i.e., donor positive and recipient negative) are associated with infection[8]. Following bacterial infection, viral infections with opportunistic infections such as Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are also common[11]. COVID-19 has been associated with high morbidity and mortality in kidney transplant recipients (KTR). However, risk factors for COVID-19 disease in patients with kidney transplants remain poorly defined.[12] It is worth noting that epidemiological predisposition plays an important role in exposure as some regions of the world are endemic to a certain type of infection.

Timeline of posttransplant kidney infections

Infection as a complication of Kidney transplantation can manifest early or less than a month after the operation and usually, this will be the case of postoperative complications and nosocomial infections, as well as wound infections, either superficial or deep. Central intravenous access, urinary catheterization, pneumonia, and donor-derived infection are also of concern. Anastomotic urinary leaks and strictures can also occur, and peri-transplant hematomas, urinomas, or lymphoceles may become secondarily infected. These early infections are mostly from bacterial pathogens with few viral infections. During the period of the first six (6) months, due to maximum immunosuppression, opportunistic infections may surge, and mostly there is an increase of viral infection in comparison to bacterial infection with CMV and BK viremia, Respiratory virus infection, and community-acquired pneumonia as well as fungal or mycobacterial infections and tuberculosis. Late infection occurs after six months and remains marked with community-acquired and opportunistic persistent infections, and this typical timeline can greatly be modified depending on prior prophylaxis and immunosuppression plan modification.[13,14]

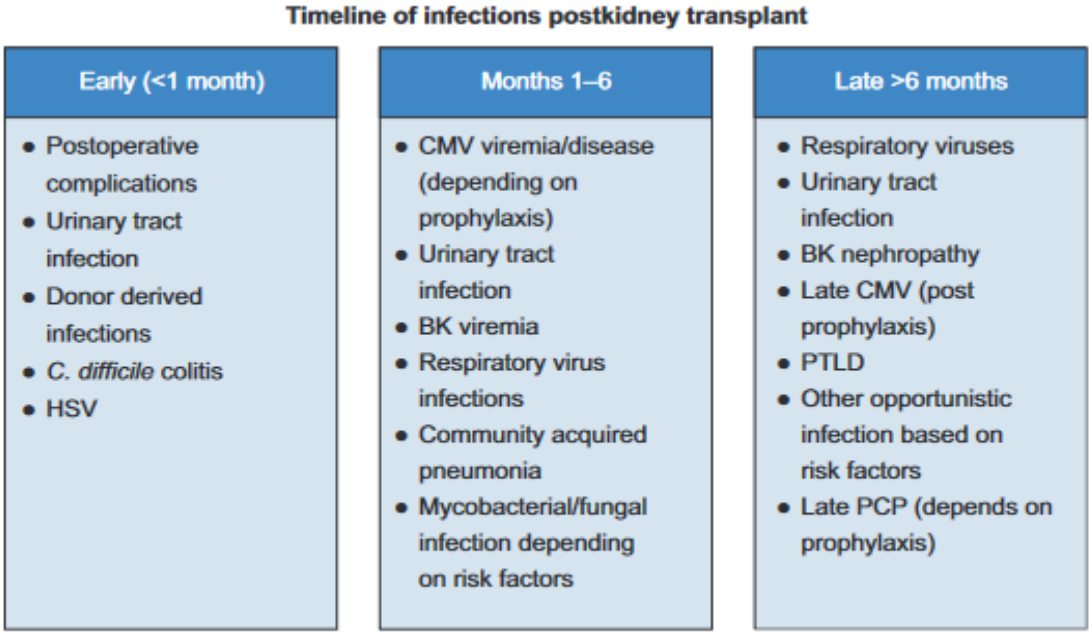

Figure 1: Taken from Kidney Transplantation, Bioengineering and Regeneration, Kidney Transplantation in the Regenerative Medicine Era[13].

Early infection post renal transplantation

Post-operative complications

Surgical procedures are performed safely during transplantation and complication can occur as in any surgery, leading to delayed graft function (DGF) or graft loss. Carvalho et al reported an incidence of surgical complications after KTs varying between 5% to 25%; with most complications being urinary, vascular, or wound-related.[15] Risk factors include surgical technique, immunosuppression, recipient characteristics such as heavier weight, and increased time on dialysis before KT. In contrast, Zrim et al noted that higher BMI was associated with an increased risk of wound complications, early nephrectomy, and DGF, but it was not associated with surgical or urological complications.[16] Urinary complications were associated with longer surgeries and DGF occurred less often when the extravesical Lich-Gregoir technique was used with a ureteric catheter.[15] Wound complications are mostly infections either superficial or deep and hernias. In their study, Humar et al. reported superficial infections (3.8%) to be more common than deeps infections (1%) with risk factors such as recipients with older age, diabetes, obesity, and patients who had more often undergone a retransplantarion.[17] Wound complications can result in significant morbidity with prolonged hospitalization or rehospitalization.

Donor-derived infections

A thorough examination and good medical history of each donor are important to reduce the risk of transmission of infections from the donor to the recipient. Although a donor with HIV-positive infection is a contraindication to transplantation in the non-HIV infected recipients, some donors with a positive infection such as HBV and HCV can still give their kidneys for transplantation.[18] The use of NAT (Nucleic Acid Test), especially in donors with known behavioral risk factors for acquiring HIV, HCV, or HBV, likely diminishes (but does not eliminate) the risk of such transmission events and improves the likelihood of organ utilization in this setting.[13] History of traveling to endemic regions should also be evaluated to take into account the risk of infection with rare pathogens such as Coccidioidomycosis, Strongyloidiasis, West Nile, or rabies. Bacterial infection can also occur and in such cases, antibiotics should be initiated immediately post-transplantation and based upon the culture from the donor. Thus, a multidisciplinary team approach to donor screening is essential to provide appropriate and safe organ allocation.

Urinary Tract Infections (UTI)

Invasion of the Urinary tract by a microorganism can cause a UTI, which is defined as a pathological invasion of the urothelium that results in an inflammatory response, which might present clinically but can also be defined based on microscopy and culture[19]. It can manifest with burning micturition, dysuria, urgency, frequency, and a change in urine appearance or smell of urine in the general population. On the other hand, transplant patients may differ significantly, and typical signs and symptoms may be absent. Despite prophylaxis treatment, UTIs are the most common post-transplantation infections and they are associated with an increased risk of rejection and graft malfunctioning. Allograft tenderness is a tell-tale symptom of graft pyelonephritis.[13] A growth of 10^5 colony-forming units/mL of a single organism from the urine culture of the patient is a laboratory indication of infection (asymptomatic or symptomatic). Epidemiologically, the most frequent microorganisms causing UTI in the Solid organ transplant (SOT) setting are, as in the general population, gram-negative bacilli, mainly Escherichia coli, followed by Klebsiella spp., Pseudomonas aeruginosa, and Enterococcus spp.[20]. The most common isolated organism in UTI after Kidney transplantation (KT) is E. coli, followed by Enterococcus faecalis[18–21]. Due to immunosuppression, UTI can be asymptomatic at the beginning and thus the infection can quickly progress to more complicated forms such as pyelonephritis and urosepsis. The prevalence of UTIs after kidney transplantation is extremely varying among studies, ranging from 23 to 75% and accounting for about 40–50% of all infectious complications. Risk factors include female gender due to anatomical predisposition, some studies included older age as a risk factor while others didn't find a significant correlation. The type of immunosuppression and comorbidities such as diabetes mellitus (DM), uropathies, and poor hygiene are associated with an increased risk of UTI. Transplant-related factors such as the type of donor (living or deceased), delayed graft function, acute rejection, CMV infection, and urological complication (catheterization, stenting, and vesicoureteral reflux) might also be associated with increased risk factors for UTI[9] (figure 2). Management should be done according to guidelines in place in the region. Starting with empiric treatment and once susceptibility data are available, the narrowest spectrum antibiotic should be used to complete the course of therapy. Routine peri-transplant antimicrobial prophylaxis and increased use of antibiotics promotes the development of multidrug resistant organisms[19] and such information on drugs used and epidemiological situation should be taken into account when deciding on the individual therapy scheme. Hamid et al. reported female gender, prolonged Foley's catheterization, coexisting DM, and induction of anti-thymocyte globulin (ATG) therapy to be independently associated with a high risk of multi-resistant drug (MRD) UTI, with E. coli strains being the most resistant pathogen.[22] Recurrence of infection and MRD infections are also highly associated with poor outcomes and possible graft loss.

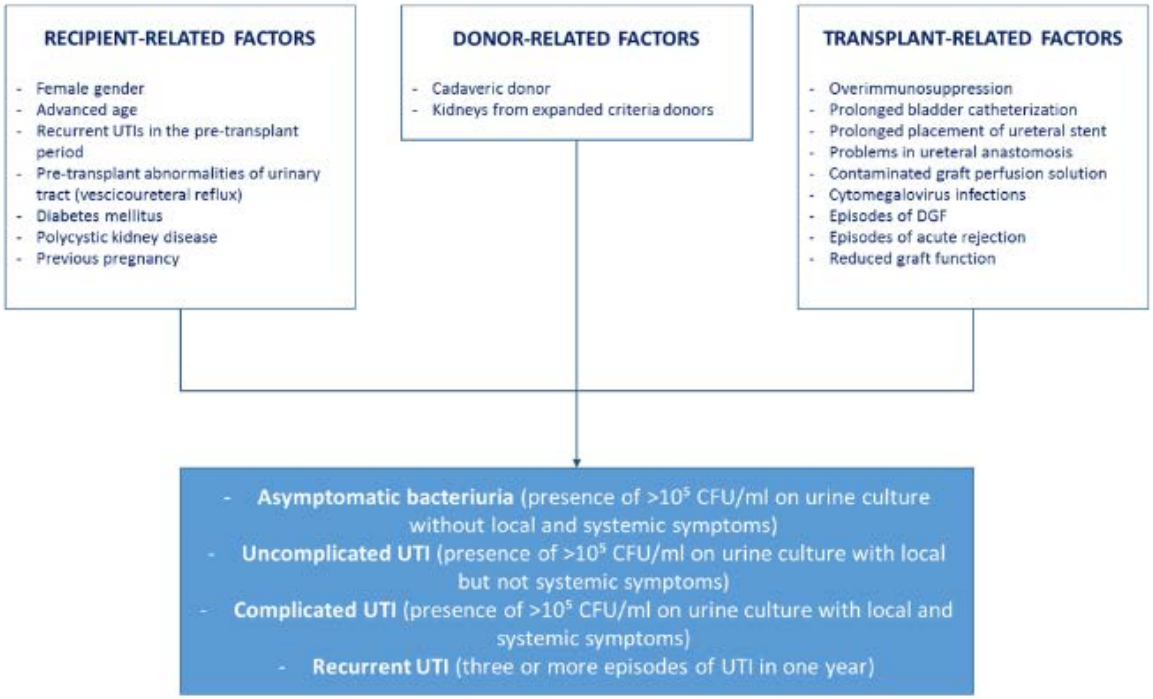

Figure 2: Risk factors for UTI in kidney transplantation[9]

Intermediate and late infection post renal transplantation

Respiratory tract infection and COVID-19

Before the COVID-19 pandemic, bacterial pneumonia was the most common respiratory tract infection in KTR[23]. Either nosocomial due to increased hospitalization and catheterization or community-acquired, with a higher morbidity and mortality rate related to nosocomial infection. Infections are a major complication in KT due to immunosuppression. In a single-center study, Kara and al found that more than half (56%) of the pneumonia episodes developed within the first six months following the transplantation, whereas 44% developed after six months (all > 1 year). 32% of cases were considered nosocomial pneumonia, and 68% were considered community-acquired pneumonia. Bacteria were the most common cause of pneumonia (28%), and fungi ranked second (8%) with A. fumigatus being the causative agent[24]. Significant risk

factors associated with pneumonia episodes are older age, hypertension, cardiac disease, history of acute graft rejection, and the immunosuppression protocol.[25] The most commonly encountered pathogens are gram-negative bacilli (Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa…), but gram-positive coccus such as Staphylococcus aureus or Streptococcus pneumoniae and anaerobic bacteria can also be found. Six months after transplantation, cases of pneumonia are mostly due to community-acquired bacteria with mostly infectious agents such as S. pneumonia, H. influenza, Mycoplasma, Chlamydia, and others).[23]

As in the general population, KT patients with COVID-19 infection mostly present with fever and respiratory symptoms such as cough, as leading symptoms (Figure 3). In some KT patients, fever may be absent.[26] Non-white ethnicity, obesity, diabetes, and asthma/chronic pulmonary diseases are risk factors independently associated with COVID-19 disease in patients with kidney transplants and immunosuppression modulation.[12] Symptoms such as cough, shortness of breath, myalgia, headache, sore throat, and gastrointestinal symptoms are more common in KT patients than the typical COVID-19 presentation. Additionally, several unreported symptoms like chest tightness and pain, coryza, dehydration, conjunctivitis, dizziness, and weight loss appeared in the COVID-19 positive KTR. Acute Kidney Injury (AKI), proteinuria, and hematuria have all been reported in COVID-19 KT patients as well. The mortality rate of COVID-19 in kidney transplant patients is at least 4 times higher than in the normal population infected with COVID-19.[26] The management is mostly done in patients presenting with severe symptoms such as dyspnea and requiring mechanical ventilation, wherein most patients a reduction of the of immunosuppression is done and supportive therapy is implemented.[12,27]

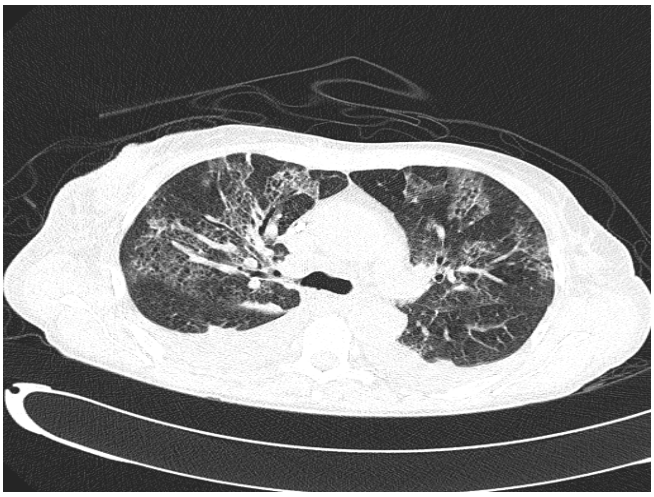

Figure 3: COVID-19 pneumonia

Cytomegalovirus infection and disease

Cytomegalovirus (CMV) is a DNA virus of the human herpesvirus HHV family. It is one of the most common viral opportunistic infections after kidney transplantation. The donor and the recipient could be already infected and with different strains before transplantation. Risk factors for infection reactivation include the type and the degree of immunosuppression, donor positive (D+) and recipient negative (R-), the host immune response, and a greater HLA mismatch. CMV direct infection and immunomodulators effect increased opportunistic infection and thus higher morbidity and mortality.[13,18] The disease manifests in the non-immunocompromised individual asymptomatically, or as a mononucleosis-like clinical picture. Immunosuppressed patients will have unexplained fever, leukopenia, and end-organ manifestations. CMV infection describes the presence of virus as detected by culture (throat swab, urine), molecular techniques (PCR: protein chain reaction, antigenemia), and/or serological status changes.[28] Symptomatic patients are classified as having CMV disease, which presents as a viral syndrome (fever, malaise) or as tissue-invasive diseases, such as hepatitis or pneumonitis.[13] (Figure 4) Prevention and treatment are mainly done with antiviral treatment. Ganciclovir is the most used agent in many centers as recommended by guidelines. Consensus recommendations direct the duration of prophylaxis based on the serostatus of the donor and recipient. For CMV D+/R- patients, 3-6 months of prophylaxis with oral ganciclovir or valganciclovir is recommended. For CMV R+ patients, 3 months is recommended but 6 months should be considered if anti-lymphocyte induction is used. No prophylaxis is recommended in the CMV D-/- patients.[11]

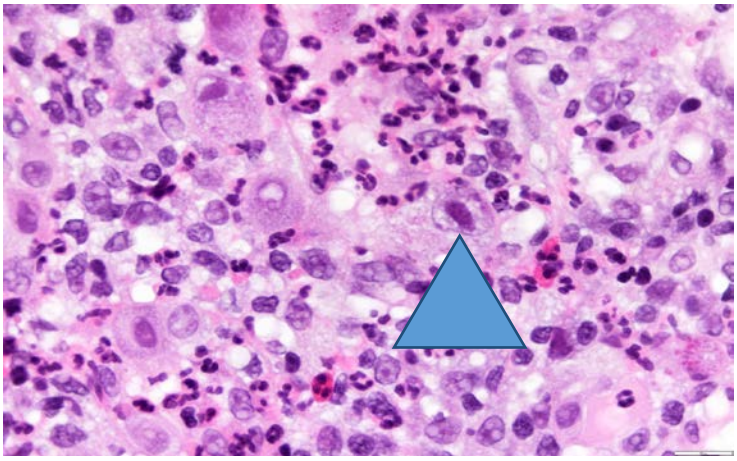

Figure 4: Brown staining, CMV colitis.

Epstein Barr Virus

Epstein Barr virus (EBV) is a double-stranded DNA virus from the herpes virus family that targets oropharyngeal epithelial cells and B-lymphocytes causing B-cell activation and proliferation. Primary infection usually happens in childhood and remains asymptomatic in immunocompetent individuals.[28] However in Immunocompromised hosts such KTR, both acute infection and reactivation of latent infection may lead to pathology, with clinical syndromes associated with non-neoplastic viral replication on the one end, and EBV-mediated neoplastic transformation, including post-transplantation lymphoproliferative disorder (PTLD), on the other.[29] PTLD is a serious complication following a solid organ transplant and hematopoietic stem cell transplant, with the highest incidence rate occurring in heart-lung transplantation at 2-10% and the lowest rate in renal transplant recipients estimated at 0.46-5% in the first post-transplant year.[29,30] The risk of developing PTLD depends on allograft type, exposure to lymphocyte-depleting therapies, and the serologic status of the donor and recipient, Caucasian race, and male sex.[11,28] The highest risk is in EBV-seronegative recipients of EBV-seropositive donor organs (D+/R-). Older or younger age, number of transplants (first vs. later), the intensity of immunosuppression, treatment of acute rejection with depleting antibodies within the first year after transplantation, simultaneous pancreas-kidney transplantation, HLA mismatches (especially HLA B and DR mismatch) were also included as risk factors in a review made by Le and al[29] confirming what was found in other studies as well.[30] The spectrum of EBV-PTLD clinical presentations range from infectious mononucleosis-like syndrome with fever, sore throat, malaise, and fatigue, to more constitutional “B” symptoms consistent with lymphoma such as fever, night sweats, weight loss. The use of antivirals treatment as prophylaxis remains controversial. Some studies suggested that the introduction of ganciclovir in the prophylactic management reduced the incidence of EBV infection post-transplantation. On the other hand, another study contradicted those results on the efficacy of antiretroviral in prophylaxis use, proposing that only patients at high risk for, or experiencing de novo EBV infection, such as unexposed pediatric patients, should be considered candidates for antiviral therapy.[28–30] Prevention strategies to reduce PTLD include serial monitoring of EBV PCRs in high-risk KTR during the first year post-transplantation. With increasing EBV viral loads or persistently elevated viral loads in patients with mononucleosis-like symptoms, the first approach is to reduce immunosuppression while being aware that rejection may occur if immunosuppression is lowered too aggressively.[29,30] Management strategies vary across institutions and guidelines and many centers choose the multimodal treatment strategy based on reduction of immunosuppression, immunotherapy with rituximab (for CD20 positive PTLD), chemotherapy, radiation therapy, or a combination of these treatment modalities.

BK Polyoma Virus

The BK Virus (BKV) is a circular, double-stranded DNA virus belonging to the polyomavirus family, which also includes the JC virus and SV40. The BKV was first isolated from the urine of a renal transplant recipient with ureteric stenosis in 1971, but it was not until 20 years later that BK was recognized as a cause of interstitial nephritis and allograft failure in renal transplant recipients. After primary infection, the virus establishes latency in the uroepithelium and renal tubular epithelial cells. In the setting of immunosuppression, the virus reactivates and begins to replicate, triggering a cascade of events starting with tubular cell lysis and viruria.[18,31] BKV replication after kidney transplantation can lead to nephropathy (elevated serum creatinine, interstitial inflammation) and accelerated renal allograft (Figure 5). Loss BKV nephropathies occur in 1 to 5% of patients and risk factors include heavy immunosuppression regimens.[11] Other hypothesized risk factors for BKV and BKV Nephropathy include male gender, older recipient age, rejection episodes, degree of HLA mismatching, prolonged cold ischemia, BK serostatus, and ureteral stent placement, but these have not been uniformly observed in all studies.[31] The early diagnosis is made by the regular follow-up of the BKV in the year after the transplantation, and the diagnosis of certainty is made by a biopsy of the renal graft. Up to date, reduction of immunosuppression is the only recommended and useful treatment and there is no guideline for prophylaxis management. Other potential therapies include cidofovir, leflunomide, Intravenous immunoglobulin (IVIG), and potentially quinolones. [28]

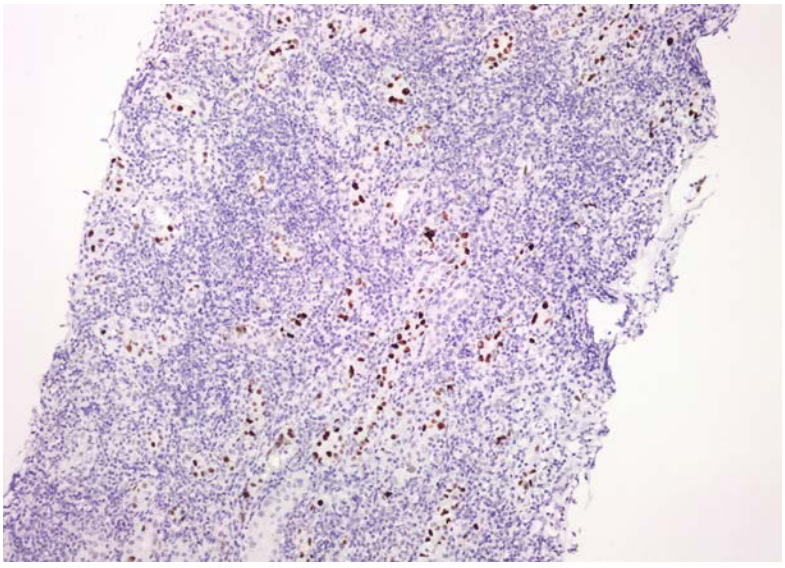

Figure 5: Brown staining, BKV nephropathy.

HIV (human immune deficiency virus)

The human immune deficiency virus (HIV) is a single-stranded RNA virus from the retrovirus family, which targets T cells and destroys the host immune system. Before the antiretroviral era, HIV infection was an exclusion criterion for transplantation, and dialysis was preferred for that population. Today, with combine antiretroviral therapy, a prolonged lifespan is achievable in patients with HIV infection, and more specifically it is possible to limit viral replication to a threshold below the limit of detection in peripheral blood by standard viral load assays, making kidney transplantation feasible with HIV positive recipients. The survival rates of patient and graft between HIV-infected recipients and non-infected is reported to be the same.[13,32] In a study Alsharidi et al. noted that the progression of HIV disease was not seen posttransplant, but the major challenge was a significantly increased risk of graft rejection among HIV-infected recipients. Infection remains the major post-transplant complication with an incidence as high as 54% in HIV infected recipients with mostly pathogens such as gram-negative bacteria like E. coli and Enterobacter spp.[32]. Thus, we can say with other authors that the long-term patient and graft outcome is not influenced by HIV status but is adversely influenced by infections, as survival was diminished in patients having at least one infection.[32,33] Another issue after transplantation is the drug-to-drug interactions between antiretrovirals and immunosuppressive therapies. Specifically, between calcineurin inhibitors (CNIs) and protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). Patients using a PI-containing regimen require a lower dose of CNI while those on an NNRTI-containing regimen need higher doses.[13] Despite appropriate CNI dose adjustments, variations of drug serum levels are difficult to control and have been linked to increased graft rejection in HIV+ KTR.[33] Thus, with careful selection of patient, (relevant criteria include CD4>200 cells/mm3, HIV viral load<50 copies/mL, stable antiretroviral regimen, and no active opportunistic infections[13]), an appropriate choice of immunosuppression regimen, a multidisciplinary evaluation and a practical follow up, KT in HIV infected recipients can be performed with a good outcome.

Tuberculosis

Tuberculosis (TB) is a multisystemic disease caused by the bacillus Mycobacterium tuberculosis, and infection is mostly through exposure to infected aerosols. Tuberculosis is a rare complication occurring after SOT, but it remains much more frequent than in the general population with a high mortality and morbidity rate.[34] The incidence depends

on whether the region is endemic or non-endemic with a higher incidence in SOT, estimated to be 20 to 74 times higher than in the non-transplanted population.[28] Pulmonary tuberculosis after kidney transplantation is caused mainly by reactivation of latent infection by Mycobacterium tuberculosis (LTBI) and unrecognized LTBI can lead to fatal disseminated disease due to the immunosuppressive therapy.[23] A study by Eswarappa et al. reported an incidence of tuberculosis infection in India, an endemic region, high as 8.6% which is in correlation with other studies in that region, where the incidence was found to be up to 13.3% in KTR.[28,35] In contrast, Gras et al. reported an overall prevalence of 0.83% in KTR in low-endemic countries, which is close to those previously described in other low-endemic countries.[34] Risk factors include older age, DM type 2, type of immunosuppression, co-infection(CMV, HCV), chronic liver disease in KTR, immunomodulating viral infections, and previous TB exposure.[23,28,35] Although pulmonary tuberculosis with symptoms such as coughing, was reported to be the most presenting form, the occurrence of extrapulmonary tuberculosis with atypical presentation is also alarming. The most common clinical manifestation is moderate to permanent fever, more often seen in disseminated disease and impairment of the general state with night sweats and weight loss.[23] Most clinical practice guidelines recommended screening for LTBI in patients starting immunosuppression or who are highly likely to start immunosuppression, and patients who are immunosuppressed due to concurrent illness, including patients with HIV.[28,36] Gold standard therapy for the non-transplant patient with TB is isoniazid, rifampin, pyrazinamide plus the addition of ethambutol and/or streptomycin. Unfortunately, there are major issues related to this regimen in transplant recipients.[28] For treatment in KTR, most recommendations suggested the use of isoniazid-based therapies for LTBI, and despite discrepancies in the duration and timing of commencing treatment, nine months of isoniazid-based therapy appeared to be the preferred therapy for LTBI and most agreed that treatment of LTBI should be initiated before the commencement of immunosuppressive therapies[36].

Pneumocystis jiroveci

Pneumocystis jirovecii is a unicellular parasitic fungus and an opportunistic pathogen that causes severe pulmonary infection in immunocompromised hosts.[37,38] Pathogenesis of pneumocystis is via aerosolization of small inoculation and the incidence of P. jirovecii pneumonia (PJP) varies from 0.6 to 14% among KTR without prophylaxis, with a mortality of up to 50% despite aggressive antibiotic therapy.[37,39] Reactivation of latent infection, from previous colonization, in the severely immunocompromised host is also a pathogenetic mode of infection. In kidney

transplantation, PJP is a profoundly serious risk factor for graft loss and patient mortality. Kim et al. reported that the occurrence of PJP was significantly associated with overall graft failure.[37] Risk factors associated with pneumocystis infection are still under investigation as some risk factors reported in some studies have not been confirmed in others. Thus, the overall load of immunosuppressive therapy, the older age of donor and recipient, lymphopenia, previous CMV infection, or treatment used for episodes of graft rejection have been reported as risk factors for PJP in kidney transplant patients.[39,40] Clinical presentation usually mimic common pneumonia symptoms such as fever, dyspnea, and a dry cough, often over a few days and may frequently progress to acute respiratory failure more frequently. The most commonly reported radiological finding related to PJP has been the diffuse interstitial pattern.[38,40] In the absence of appropriate treatment, the mortality rate of PJP is 90–100%, and therefore, several guidelines such as the KDIGO guideline, the European Renal Best Practice guideline, and other reports usually recommend PJP prophylaxis by using trimethoprim/sulfamethoxazole (TMP/SMX) for 3–6 months after renal transplantation.[39] In contrast, other studies suggested that since acute graft rejection, CMV infection, and regimens used in the acute graft rejection could be the risk factors for PJP, further PJP prophylaxis is suggested in patients with those risks for 6–12 month following either an episode of acute graft rejection or CMV infection.[39]

Fungal infections in the renal transplant recipient

Candida

Fungal infections are opportunistic infections and they are estimated to be around 2-5% of infections in KTR, with a predominance of candida, aspergillosis, and cryptococcosis infections.[18,41] There is increased susceptibility to fungal infection among renal transplant recipients, especially during the first six months due to increased immunosuppression, with their incidence varying, based on their geographical area. Candida albicans, Candida glabrata, and Candida parapsilosis are the most common species among opportunistic infections due to fungi.[42] Risk factors predisposing to increased fungal infections include excessive use of corticosteroids, multiple episodes of rejection and treatment with anti-rejection therapy, poorly controlled glycemic status, poor graft function, leukopenia, elderly age, recipient of multiple organs, chronic or recurrent viral infection, as well as environmental factors.[41] The disease can present as invasive candidiasis or localized to the urinary tract. In a study by Shekar M, Elumalai R, Elayaperumal I, et al. invasive candidiasis was most commonly associated with

candidemia (59.1% of cases), followed by urinary tract involvement (25%). Despite the frequency of predisposing factors such as diabetes and urinary tract devices, and the high level of immunosuppression, candiduria remained rare. The predominance of C. glabrata (48% in a study by Denis B, Chopin D, Piron P, et al) was already reported in KTR, which contrasts with the findings in the general population, where C. albicans is the most common pathogen identified, accounting for 50 to 70% of isolates.[42,43] The Infectious Diseases Society of America (IDSA) guidelines for the treatment of invasive candidiasis recommend Echinochandin as first-line treatment, alternatively, management with Fluconazole is recommended for patients not severely ill and with a candida non-resistant strain.[42,44] In the same study by Denis B, Chopin D, Piron P, et al, antifungal therapy did not impact the likelihood of candida urine clearance. This is consistent with the findings of previous studies in KTR and the general population.[43] Initial empiric antifungal treatment depends on knowledge of the colonization by the fungi and the general susceptibility pattern of the suspected fungi.[41]

Aspergillosis

Aspergillus species are ubiquitous molds found in organic matter and primarily affect the lungs. However, in patients who are severely immunocompromised, aspergillus may hematogenous disseminate beyond the lungs. Invasive aspergillus, although it remains rare, is the 3rd leading cause of fungal infection in KTR after candida infection and cryptococcosis, with an estimated prevalence of 0.5% to 40% and a high mortality rate, ranging from 40% to 70%.[45] Leitheiser et al. reported older age, a diagnosis of bacterial pneumonia or UTI preceding the onset of invasive fungal infection, and the presence of DM to be the major risk factors for the development of any invasive fungal infection, and specific to aspergillus infection risk factors include bacterial pneumonia, candida colonization, diabetes and coinfection with hepatitis C, prolonged corticosteroid therapy, graft failure requiring hemodialysis, duration of dialysis, leukopenia and potent immunosuppressive therapy.[46,47] During this time of the pandemic COVID-19, SARS-CoV-2 might increase the risk of invasive pulmonary aspergillosis (IPA), Trujillo et al. presented a case report of an invasive aspergillus infection suggesting that IPA may appear as a major event complicating the course of COVID-19 in KTR.[48] Clinical presentation typically involves pulmonary manifestation, with symptoms such as fever, cough, dyspnea, pleuritic chest pain, and, sometimes, hemoptysis (Figure 6). Management of aspergillosis is done with voriconazole and surgery, and sometimes graft-nephrectomy if needed, and the recommendation is that in all immunocompromised hosts and organ transplant recipients should have been tested with the Galactomannan test.[47]

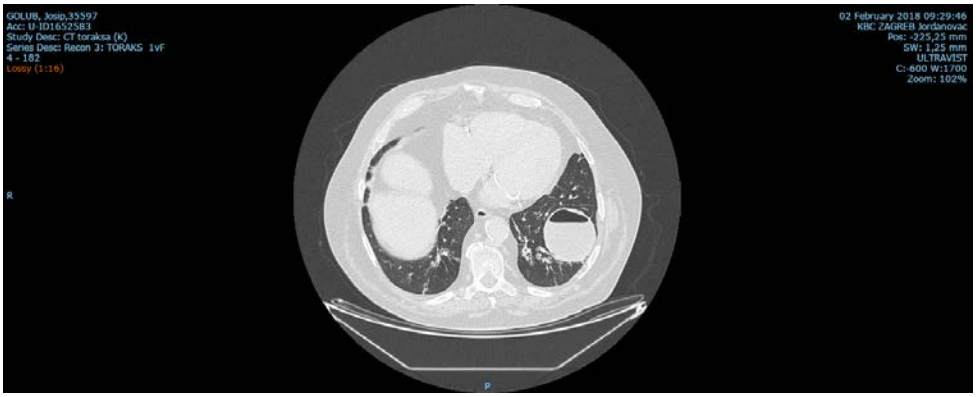

Figure 6: Lung aspergillosis (cavity with a fluid level)

Coronavirus disease 19 in the kidney transplant population

End-Stage Renal Disease (ESRD) and COVID-19

ESRD is considered when chronic injury to the kidney leads to decreased functioning of the organ with a GFR below 15 ml/min/1.73 m2.[2] At this level, RRT is the only option left with peritoneal dialysis, hemodialysis, and kidney transplantation optimally when possible. In a review study, Valeri reported an infection rate of COVID-19 between 11%-26% among patients with end-stage renal disease, with a mortality rate up to 24-27% which is 6-7 times higher than the rate of 4% reported in the global population.[49] Thus, given the immunocompromised nature of ESRD and the high comorbidity burden seen in patients with kidney failure, patients with ESRD are among the most vulnerable populations to COVID-19. Similar to the general population, the most common presenting symptoms in ESRD patients are fever and cough.[50,51] In contrast, Ferrey et al. described an atypical presentation with symptoms of gastroenteritis in ESRD patients.[52] Adapa et al. reported AKI to be an independent risk factor for mortality in COVID-19 patients, with an incidence of about 3-15%; and in patients with severe infection requiring care in the intensive care unit, the rates of AKI increased significantly from 15% to 50%.[53] Another concern is the high incidence of AKI in patients infected with COVID-19 requiring hospital resources that strain not only intensive care units and ventilator capacity, but also renal replacement resources.[49] In COVID-19 patients with

severe AKI and with established ESRD, the continuation of their RRT is vital for survival. It is recommended that healthcare personnel should follow what the CDC recommended for personal protective equipment (PPE) and safety guidelines during their interactions with those patients to decreases the spread of infection and nosocomial acquisition in RRT centers.[53]

Influence of COVID-19 pandemic on renal transplant programs

The COVID-19 pandemic has pushed the world to rethink, reshape and adapt in the way everything works. Regarding renal transplant programs, the fear of allegedly increased susceptibility to infections in KTR, due to immunosuppression, has forced many centers either to shut down their transplantation unit or either to change the paradigm and thus the routine of workflow. The reduction in transplantation volume during this time is partly due to concerns over potential increased susceptibility and worsened outcomes of COVID-19 in immunosuppressed recipients.[54] Loupy et al. reported a strong association between rising coronavirus infections and a marked reduction in the overall number of solid-organ transplantation, even in geographic regions with low infection prevalence.[55] In a national survey conducted in the United States linked to COVID-19 and transplantation, Boyarsky et al. reported a complete suspension of living donor kidney by 71.8%, whereas a majority of the deceased donor programs continued to function with some restrictions, especially in regions with a higher incidence of COVID-19.[56] In contrast to the United Kingdom, whereby kidney transplant programs had to suspend temporarily, both the deceased and living donor transplantation. The underlying reasons were to release/create more intensive care beds, to liberate the workforce to support the intensive care unit, and more importantly, because of the increased mortality due to COVID-19 in immunosuppressed individuals.[57] Concerning transplant procedures, SARS-CoV-2 infection could be missed in both donors and recipients who are asymptomatic, owing to the sensitivity issues with the RT-PCR test. Additionally, in the immediate postoperative period and after hospital discharge, transplanted patients have increased susceptibility to SARS-CoV-2 infection owing to induction therapy and immunosuppressive treatment.[58] Up until today, insufficient evidence is available to consider kidney transplantation as a safe procedure in COVID-19 pandemic areas. In emergency situations—e.g. in cases of no vascular access, unfeasible dialysis, or a hyperimmune state—the benefits might outweigh the risks of a kidney transplant.[58] Kidney organs are not readily available and the number of patients on the waiting list keeps growing. All around the world guidelines are being set to increase the safety peri, during, and post-transplantation procedures during the current pandemic and specially to avoid nosocomial COVID-19 infections.

Outcomes of COVID-19 in kidney transplant recipients

Studies have found COVID-19 to be associated with high morbidity and mortality among kidney transplant recipients.[12,26] As in the immune-competent population, fever and respiratory symptoms such as cough and dyspnea remain the most common clinical presentation of COVID-19 infection in KTR. Gastrointestinal symptoms have also been reported in few cases. Comorbidities include diabetes, hypertension, smoking, obesity, chronic pulmonary diseases, and cardiovascular disease.[12,59] Coronavirus pandemic is too recent and currently, data on the clinical course, imaging features, and outcomes in KTR are still being described and fully understood. Abrishami et al. in a study on 12 patients, where ten were admitted to an intensive care unit, nine were intubated, eight died of severe COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), and four were discharged after complete recovery, reported that the most common pattern of lung involvement was bilateral involvement with a diffuse pattern and a posterior segmental distribution. Ground glass opacity, a feature highly suggestive of COVID-19, was observed in all cases and consolidation in the majority of cases (Figure 3). They concluded that interlobular septal thickening, multilobar patterns, consolidative lesions, and a high score for lung involvement were more frequent among the patients with poor outcome and complicated cases with ARDS.[60] Jawdeh reported an elevated incidence of AKI and a mortality rate between 13-30%, which is higher than that of the general population (~5%). This could be attributed to the increased comorbidities in addition to the immunosuppressed state -all of which have been associated with severe COVID-19.[59] Other studies have also found the male gender to be associated with high mortality in COVID-19 infected KTR.[54,59] Craig-Schapiro et al. also reported that there was a need in RRT in hospitalized patients and that high inflammatory markers such as D-dimer, procalcitonin, and C-reactive protein were associated with high mortality.[54]

Vaccination of Renal transplant recipients

Vaccine-preventable disease can cause adverse patient and allograft outcomes in KTR. Patients should be vaccinated pre-transplantation when possible and for those patients who are unable to obtain vaccinations pre-transplant, inactivated vaccines are considered safe when administered after kidney transplant. Live-attenuated vaccinations (LAV) are contraindicated in KTRs due to the risk of infection.[61] Pediatric kidney transplant candidates should be fully immunized according to routine childhood schedules using age-appropriate guidelines. With the exception of influenza, hepatitis B,

pneumococcal, and meningococcal vaccinations which are usually administered by transplant physicians.[62] Influenza is a common viral disease post-transplant and is associated with higher morbidity and mortality. Although generally recommended to administer vaccination 3-6 months after KT, the influenza vaccine may be given earlier than this time period if the transplantation occurs during the influenza season. Influenza vaccination within the first year after transplant is associated with a lower risk of allograft loss and death, thus a yearly vaccination can be safely offered to KTR.[61] Guidelines including those by KDIGO also recommend that influenza vaccine can be given as early as 1-2 months post-transplant.[63] For Hepatitis, current guidelines suggest a three-dose series of HBV vaccine ideally given pre-transplant, or post-transplant if the series was not completed pretransplant.[64] Those who are immune to hepatitis B, either through vaccination or previous infection, can be considered for HBsAg positive organs if the recipients' anti-HBs titters are above 10 IU/mL.[61] Regarding HPV, current recommendations are that all patients with a history of primary or secondary immunocompromising conditions, including SOT recipients, should receive a three-dose series of HPV vaccine at months 0, 1-2, and 6 mo.[63,65] The Centre for Disease Control and Prevention (CDC) estimates that each year there are roughly 40000 cases and 4000 deaths attributable to invasive pneumococcal disease, which occurs in organ transplant recipients at a rate 25 times greater than in the general population.[66] The CDC currently recommends administering PCV 13 followed by PPSV23 (Pneumovax®) eight weeks later for immunocompromised patients including those with CKD, nephrotic syndrome, and SOT.[63,67] This should be followed by a booster dose of PPSV-23, a minimum of 5 years later.[63] Meningococcal vaccine is recommended for KTRs traveling to highly endemic areas such as Sub-Saharan Africa, Saudi Arabia, or patients with a history of splenectomy.[61] Guidelines now recommend immunization against both meningococcus serotype B in addition to serotypes A, C, Y, and W-135 prior to eculizumab immunosuppression use.[63] Anti-viral therapy currently used for CMV prophylaxis in SOT recipients is associated with adverse events including neutropenia. ASP0113 is a first-in-class bivalent DNA-based vaccine developed for preventing CMV infection in immunocompromised transplant recipients. Currently, an ongoing phase III study is evaluating the safety and efficacy of ASP0113 in CMV-seropositive allogeneic hematopoietic cell transplant recipients (NCT01877655).[61] With the current COVID-19 pandemic, Ikizler et al. provided data suggesting that full vaccination protocols should be implemented in patients receiving maintenance hemodialysis and KTRs.[68] In the absence of an observed association between natural SARS-CoV-2 infection and acute allograft rejection in kidney transplant recipients,[69,70] it is unlikely that vaccine antigens would precipitate clinically significant immune responses to renal allografts. Thus, recommendations are to administer COVID-19 pre-transplantation when possible or at least 3-month post-transplantation. Nevertheless, future evaluations of SARS-CoV-2 vaccine platforms in kidney transplant recipients are imperative to confirm safety and immunogenicity.[69]

Conclusions

Since the first successful kidney transplantation up until today, KT remains a successful treatment method that prolongs life and improves exponentially the quality of life of patients with ESRD and kidney failure. Although transplantation procedures are safe, complications after the transplantation can occur at any time with infections being most common after cardiovascular problems. Infections in KTR are associated with high morbidity and mortality and risk factors are numerous. Especially, COVID-19 infection which has the worse outcome in immunocompromised. Thus, it is important to adopt a multidisciplinary approach in order to tackles these issues. Immunosuppressive therapy should be individualized and adapted to the characteristic of the recipient, to provide optimal protection against transplant rejection or graft failure, while reducing the incidence of infections in the meantime. Following guidelines, prophylaxis treatment, and infection prevention contribute to survival after transplantation, but an increase use of drug can also lead to the emergence of multidrug-resistant pathogens, and thus each recipient should be carefully followed to prevent colonization with MRD microorganisms. An insight on the timeline of infection emergence can help provide a better preventive and management plan. Despite the poor outcomes of COVID-19 infection in KTR, all over the world, strategies including, guidelines, vaccination, triage, and personal protectives equipment are being set up in order to continue with transplantation programs during this current pandemic.

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Bibiography

Born in October 1991, Cedric Arol Takou Kuitcheu, is the only boy in a family of 4, he grew up in a small town in Cameroon Called Bafoussam, where he completed his primary education by the end of 2010, before joining Douala, the economical City of his Country of origin. He started university study then with a bachelor's in biology and Chemistry as Majors, before leaving for Europe where he was admitted at Medical School of Zagreb in 2015. He is graduating Medical school in July 2021 with an average score min of 4.2/5. He is regularly active in the student bodies and has been member of the Croatian Student association and surgical association, as well as the sport association as the team leader of the futsal section of the Medical School in English in Zagreb for the past 3 year. Co-chair of Incision Croatia, an association aiming at providing equal surgical care in the World, since 2020 and co-founder and president of the Pan-African association in Croatia since 2021, an association representing African minority in Croatia. He is passionate by football, reading, travel and music and plays music as a DJ on the Croatian scene for 4 years already. He has a good understanding of Microsoft tools and internet search.