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REVIEW

Preventing infections in immunocompromised patients with kidney diseases: vaccines and antimicrobial prophylaxis

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic revealed that our understanding of infectious complications and strategies to mitigate severe infections in patients with glomerular diseases is limited. Beyond COVID-19, there are several infections that specifically impact care of patients receiving immunosuppressive measures. This review will provide an overview of six different infectious complications frequently encountered in patients with glomerular diseases, and will focus on recent achievements in terms of vaccine developments and understanding of the use of specific antimicrobial prophylaxis. These include influenza virus, *Streptococcus pneumoniae*, reactivation of a chronic or past infection with hepatitis B virus in cases receiving B-cell depletion, reactivation of cytomegalovirus, and cases of *Pneumocystis jirovecii* pneumonia in patients with anti-neutrophil cytoplasmic antibody–associated vasculitis. Varicella zoster virus infections are particularly frequent in patients with systemic lupus erythematosus and an inactivated vaccine is available to use as an alternative to the attenuated vaccine in patients receiving immunosuppressants. As with COVID-19 vaccines, vaccine responses are generally impaired in older patients, and after recent administration of B-cell depleting agents, and high doses of mycophenolate mofetil and other immunosuppressants. Strategies to curb infectious complications are manifold and will be outlined in this review.

Keywords: glomerulonephritis, immunosuppression, infections, prophylaxis, vaccines

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has dramatically highlighted the profound vulnerability of patients with kidney disease, both acute and chronic, to infection-related morbidity and mortality. However, the impact of other infections on this patient group, particularly those under immunosuppressive therapy, has been well recognized for decades [1]. With the continuous expansion of immunosuppressive therapies, much progress has been achieved in terms of early and sustained disease control, resulting in improved short- and long-term outcomes. However, immunosuppression carries a price of increased susceptibility to opportunistic infections, which have surpassed active primary disease as the prime cause of mortality, such as in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [2]. Such treatment-related toxicity needs to be anticipated and countered.

As a recent perspective article has extensively covered the topic of COVID-19 vaccination in patients with immune-mediated glomerular diseases [3], this review will instead focus on other infections of clinical relevance, also drawing from increasing experience made during the past years, for instance the far-reaching consequences of B-cell directed therapy with regards to immune response following vaccination.

This article focuses on six clinically relevant pathogens, including cytomegalovirus (CMV), varicella-zoster virus (VZV), influenza virus, hepatitis B virus (HBV), *Pneumocystis jirovecii* and *Streptococcus pneumoniae*. While relatively clear recommendations exist regarding vaccination and prophylaxis, respectively, for influenza, HBV and *S. pneumoniae* [4], optimal preventive strategies are lacking for CMV, VZV and *Pneumocystis*; therefore, these will be discussed individually (Tables 1 and 2). Although not considered a typical infectious complication of patients with chronic kidney disease (CKD), prevalence of hepatitis C is high enough in this cohort to warrant screening, especially, as nowadays a curative treatment exists [5]. Other, less frequent opportunistic diseases [such as infections with fungal and mycobacterial pathogens

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Table 1: Risk factors for specific infectious complications encountered in patients with kidney diseases receiving immunosuppression.

Infectious complication	Immunosuppression increasing risk of infection	Disease- and host-specific risk constellations
CMV	GC dose ≥20 mg/day ± other IS	SLE; longer disease duration; lymphopenia; age; Black ethnicity
VZV	GC dose ≥20 mg/day ± other IS, cumulative CYC (14% risk increase per gram; used as induction therapy), peak MMF or mycophenolic acid	SLE; CKD; lymphopenia; female sex; Black ethnicity
Influenza	Not established (likely comparable to CMV and VZV)	Not established
Hepatitis B	Reactivation (RTX; high-dose GC therapy over a longer period of time)	
Pneumocystis jirovecii	GC dose ≥20 mg/day for >4 weeks (± other IS), CYC, RTX	AAV; patients with associated disorders leading to immune-incompetence (lymphopenia); CTD-ILD, CKD; age; Han Chinese ethnicity (uncertainty if a risk factor in other ethnicities) (Testing trial [67])
Streptococcus pneumoniae	Not established	SLE, other systemic autoimmune disease likely also a risk factor; age

CTD-ILD, connective tissue disease–associated interstitial lung disease; GC, glucocorticosteroids; IS, immunosuppression; MMF, mycophenolate mofetil; RTX, rituximab.

(Table 3), nocardiosis, or strongyloidiasis] are beyond the scope of this review or will be addressed only briefly. Likewise, infections in kidney transplant recipients have been extensively discussed elsewhere [6].

In this review, screening strategies for identification of latent infection and targeting antimicrobial prophylaxis, where appropriate, are recommended. The role of various immunosuppressants on infection risk is discussed, emphasizing the overarching principle of glucocorticoid minimization [7].

INFECTIONS—RELATED TO DISEASE OR THERAPY?

Overall the risk of infection in the immunocompromised patient is predominantly determined by a complex interaction between host and environmental factors, as well as the mode and intensity of immunosuppressive therapy, type of kidney disease, degree of CKD [8] and involvement of other organs. Age and comorbidities, particularly diabetes and chronic pulmonary disease, are further co-determinants of infectious adverse events. In clinical practice, however, it is often not possible to differentiate the various risk factors involved.

A substantial proportion of patients exhibit disease- or treatment-related lymphopenia, which is associated with an increased risk of infection, including *Pneumocystis*. In systemic autoimmune disorders, concomitant pulmonary involvement renders patients particularly vulnerable to respiratory infections [9]. Likewise, nephrotic syndrome and its associated renal losses of immunoglobulins is linked to serious infectious complications [1]. Although usually well tolerated, important adverse effects, including hypogammaglobulinemia, have become apparent with the increasing and prolonged use of rituximab and other B-cell depleting agents [10]. Low baseline immunoglobulin levels predict the risk for secondary immunoglobulin deficiency, but are also related to underlying disease and previous therapies. While hypogammaglobulinemia *per se* is not a contraindication to the continuation of anti-B-cell therapy, immunoglobulin replacement therapy may be indicated in patients with infectious complications; however, currently there is no clear consensus and guidelines in that sense [11]. Hematotoxicity is an anticipated adverse effect of cyclophosphamide (CYC), and leukopenia correlates with infectious risk. CYC dose needs to be adapted for age and degree of kidney dysfunction, and white cell counts must be monitored during therapy [12]. The combination of immunosuppressants or host risk factors contribute to the overall immunocompetence, the "net state of immunosuppression," a concept originating from the field of organ transplantation [13]. The connection between primary immunodeficiency, infection and autoimmunity, with glomerulonephritis representing a prime example, adds another layer of complexity. Recently, the term "Secondary Immunodeficiency Related to Kidney Disease (SIDKD)" has been proposed in this context [14].

CONCEPTS TO MITIGATE RISK OF INFECTION

Infections in immunocompromised hosts may have a bacterial, viral or fungal cause [1], and may also include reactivations in addition to *de novo* infections. In selected cases, coinfections do occur [15, 16]. The risk of opportunistic and chronic infections is an important consideration before initiating immunosuppressive treatment. The recent European Alliance of Associations for Rheumatology (EULAR) recommendations for screening and prophylaxis of such adverse events in adults with autoimmune disease also apply to the field of nephrology and provide guidance for patient management [17].

Fundamental preventive strategies encompass prophylaxis, preemptive therapy and vaccination (Fig. 1), all of which are initiated under various circumstances, as discussed below [18]. All patients facing intense and/or prolonged immunosuppressive treatment should be screened for active or previous infection with HBV, as there is a substantial risk of reactivation [19]. In patients with past HBV infection, prophylactic antiviral therapy is compulsory at the time of anti-CD20 therapy administration, but also warranted if glucocorticoids are used at a dose of >20 mg prednisolone per day (or equivalent) for longer than 4 weeks (Tables 1 and 2). The duration of prophylaxis varies depending on the respective immunosuppressive agents but should be continued for at least 12 months following anti-CD20 treatment [19]. Close liaison with hepatologists or infectious disease specialists is advised in such scenarios.

In endemic areas, screening for latent infection with *Mycobacterium tuberculosis* (LTBI) by chest X-ray and interferon-gamma

Table 2: Primary strategies to mitigate risk of infections in immunocompromised patients with glomerular diseases.

Infection	Primary prevention	Specific considerations	Secondary measures
CMV	Limited data to prescribe preventive measures; valganciclovir 900 mg/day, or valaciclovir 500–1000 mg twice daily If prevention is prescribed, the duration depends on the intensity of immunosuppression (i.e. during management with CYC, or in AAV during the first 6 months when RTX is used with high doses of steroids)	- Adjustments to kidney function needed - Gastrointestinal side effects common - Leukopenia/pancytopenia	
VZV	HZ vaccine (recombinant), 2 doses (2–6 months apart) recommended in adults ≥19 years and older who are immunocompromised	Immune response impaired by commonly used immunosuppressants (B-cell depletion, MMF, high doses of steroids)	
Influenza	Seasonally adjusted influenza vaccine	Immune response impaired by commonly used immunosuppressants (B-cell depletion, MMF, high-doses of steroids)	
Hepatitis B	Vaccination: - Hepatitis B recombinant vaccine ("HepB"): 4 doses (initial, after 1 month, after 2 months, after 1 year), or - Twinrix (combined with hepatitis A): 4 doses (initial, after 1 week, after 1 month, after 1 year), or - Hepatitis B surface antigen ("HepB-CpG"): initial dose and after one month	Regular monitoring of anti-HBs in the blood, and respective re-administration of hepatitis B vaccine (especially in those under immunosuppression) Immune response impaired by commonly used immunosuppressants (B-cell depletion, MMF, high doses of steroids) Response rates might be higher when HB recombinant vaccine is used [71], and HB recombinant vaccine can be administered in pediatric and adult populations	
	Prevention of reactivation: - Tenofovir alafenamide 25 mg once daily - Entecavir 0.5 mg once daily	In RTX-treated patients, continue antiviral prophylaxis for 12 months after the last RTX dose Side effects (include): - Gastrointestinal symptoms - Skin issues (including severe pruritus and maculopapular rash) - Kidney function monitoring is necessary, as worsening kidney function is common	Tenofovir disoproxil 300 mg once daily Lamivudine 100 mg once daily
Pneumocystis jirovecii	Prevention using TMP/SMX 400/80 mg thrice weekly; alternative approaches common (800/160 mg thrice weekly, or daily prescription)	- Dose adjustments to kidney function - Allergic reactions/drug hypersensitivity - Liver function abnormalities - Hyperkalemia - Hypoglycemia - Tubulointerstitial nephritis	- Dapsone 100 mg daily (50 mg may be possible as well) - Atovaquone 1500 mg daily - Aerosolized pentamidine 300 mg, once a month
Streptococcus pneumoniae	Vaccination with vaccines eliciting immune response to several serotypes (i.e. Pneumococcal Vaccine Polyvalent against 23 serotypes, PPV23)	- "Mix&Match," i.e. the use of PCV15 or PCV20 (polyvalent vaccine against 15 or 20 serotypes, respectively) followed by PPV23 (≥ 8 weeks–1 year and subsequent "booster doses") may elicit a better response - Immune response impaired by commonly used immunosuppressants (B-cell depletion, MMF, high-doses of steroids)	

MMF, mycophenolate mofetil; RTX, rituximab.

release assay is also recommended. While isoniazid prophylaxis was included in the study protocol of the MINTAC trial (assessing tacrolimus versus prednisolone for *de novo* minimal change disease in adults) for patients considered to be at high risk of LTBI [20], no such recommendations exist for individuals receiving anti-CD20 therapy. Given the great variation worldwide, the EULAR recommendations advise to adhere to the respective national guidelines and drug regimens if preventive chemotherapy of LTBI is considered [17]. Recommendations for LTBI are summarized in Table 3.

Vaccination is a key factor in curbing infection risk and severity in immunocompromised individuals. Although vaccine hesitancy has received much attention in the wake of the COVID-19 pandemic, it is not an entirely new trend and has been identified as a major threat to global health by the World Health Organization prior to the appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Approaches to overcome this phenomenon are urgently needed [21]. Several types of vaccines are recommended by KDIGO for patients with kidney disease [22]. Likewise, the US Centers for Disease Control and Prevention

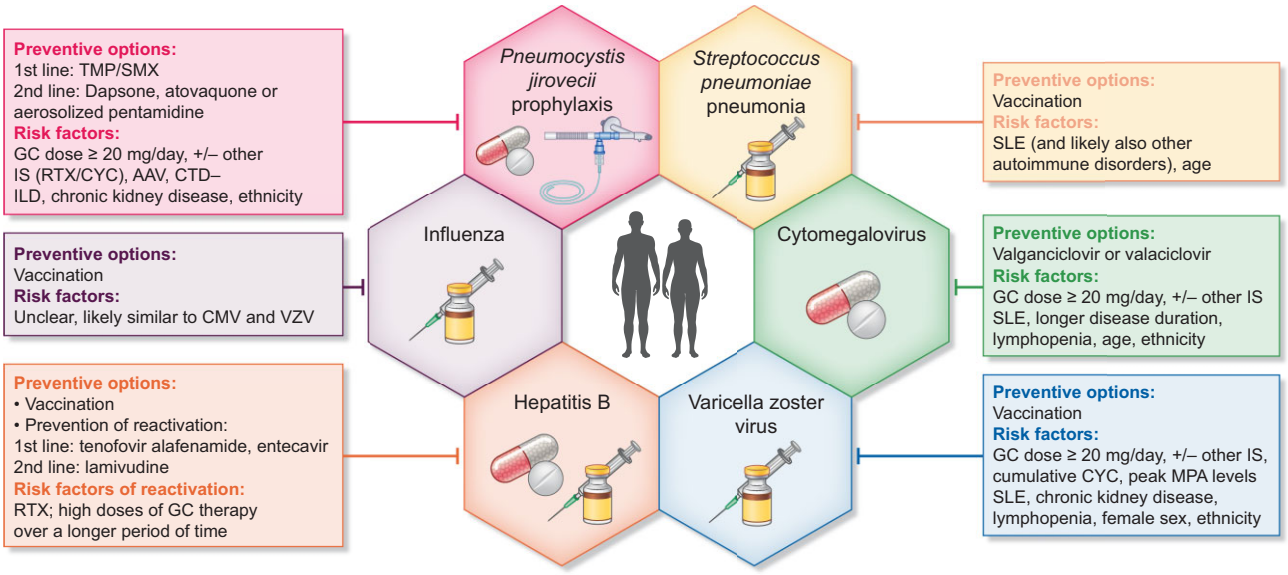

Figure 1: Preventive options for immunocompromised patients with glomerular diseases are highlighted. These include the intake of oral therapies, nebulized pentamidine to prevent *Pneumocystis jirovecii* pneumonia and the administration of vaccines. Risk factors for infection and/or reactivation are given for each infection.

Advisory Committee on Immunization Practices (ACIP) provides detailed instructions for sequential administration of vaccines among immunocompromised adults, with vaccination protocols varying according to the degree of immunosuppression. Recommended vaccinations are summarized in Table 2. However, response rates to vaccinations are frequently blunted, especially in patients treated with B-cell depleting agents. Glucocorticoid therapy at a dose of >20 mg daily and a duration of more than 2 weeks, as well as any anti-CD20-targeted therapies are categorized as high-level immunosuppression, a state associated with suboptimal seroconversion rates [23]. Therefore, ideally, immunization should be completed prior to the start of immunosuppressive therapy. However, this is not possible in conditions mandating swift and effective therapy, especially if vaccine schedules are more complex (for instance, hepatitis B vaccines) or advocated seasonally.

Annual influenza vaccines are universally recommended for all immunocompromised persons and their close contacts. High-dose compounds were shown to be linked with lower rates of hospitalization after infection in dialysis patients [24]. Given the high burden of pulmonary infections in patients under immunosuppression, pneumococcal vaccination is also warranted [23]. Two types of inactivated pneumococcal vaccines are available, a polysaccharide vaccine including 23 serotypes (PPV23) and conjugated agents (PCV13, PCV15 and PCV20). Recommended approaches vary across countries. Usually, a conjugated vaccine (nowadays predominantly PCV15 or PCV20) is recommended initially [25], followed by PPV23 at an interval between ≥8 weeks up to 1 year, depending on the extent of immunosuppression. Recently, a French open-label phase 2 study Innovative Anti-pneumococcal Vaccine Strategies in Patients With ANCA-associated Vasculitis Receiving Rituximab Therapy (PNEUMOVAS); NCT03069703), involving 95 patients with active AAV, assessed the effects of higher-dose ("reinforced") pneumococcal vaccines on immune response in the context of rituximab-based induction therapy. A protocol using double dose PCV13 7 days apart, followed by a dose of PPV23 5 months later, yielded the highest antibody levels [26]. Whether this concept will also curb infection rates remains to be seen.

Specific vaccine recommendations exist for patients receiving particular therapies that are associated with susceptibility for certain infections. For instance, compounds blocking complement C5 and upstream, such as eculizumab or ravulizumab, used in the treatment of C3 glomerulopathy, complement-mediated thrombotic microangiopathy and in randomized clinical trials for other glomerulonephritis, necessitate vaccination against *Neisseria meningitidis*. Importantly, the risk for invasive meningococcal disease remains elevated despite receipt of meningococcal vaccine. This is partly due to the agents' interference with complement-mediated bactericidal activity; moreover, available vaccines do not cover all serogroups [27]. Therefore, additional antimicrobial prophylaxis is warranted for the duration of anti-complement therapy [27]. In mice lacking C3 or C5, the susceptibility to developing meningococcal disease was enhanced by >1000-fold or 100-fold via the C5a receptor 1 (C5aR1), but C5aR1 blockade by either knocking out the receptor or pharmacological inhibition reduced the inflammatory response and increased survival rates [28]. This explains why there is no requirement for antibiotic prophylaxis or vaccination when avacopan, a small molecule targeting C5aR1, is prescribed. For details regarding the modes of action of the various agents, we would like to refer to other articles published in this supplement.

CYTOMEGALOVIRUS

Primary infection with CMV, a highly prevalent herpes virus, usually causes a self-limited illness in immunocompetent individuals but results in life-long viral persistence, predominantly in hematopoetic progenitor cells and endothelial cells [29]. Reported anti-CMV immunoglobulin G (IgG) seroprevalence varies globally, approaching 90% in resource-limited countries, but also surpassing 50% in industrialized nations in non-selected adult cohorts [30].

Table 3: Less evidence exists on antifungal and antimycobacterial prophylaxis/preventive chemotherapy and risk factors of systemic diseases in patients with kidney diseases. These infections are more endemic and most reports originate from the Indo-Pacific region. Some of the risk factors are adopted from kidney transplant recipient literature.

Infection/disease	Primary prevention	Specific considerations/risks
Oropharyngeal candidosis	Limited data to prescribe preventive measures; mouthwash might be considered when GC dose is high, encourage patients to comply with basic hygiene measures and use of over-the-counter mouthwash products	No specific recommendation on the agent can be made and practices differ (i.e. in the UK, the use of triple mouth wash is popular when thrush is present, comprising a mix of flixonase nasules, nystatin oral suspension and doxycycline soluble tablets) Oral candidosis is a risk factor for severe infections (overall), but this might be related to prescription of higher cumulative GCs [72]
Invasive fungal infections	Not warranted; more data needed	The risk increases with the dose of GCs (≥20 mg/day) and the prescription of other immunosuppressants, pre-existing respiratory disease or respiratory disease manifestations, lymphopenia, concurrent infections or secondary to viral/bacterial pneumonia; in KTR, age ≥65 years, diabetes and the presence of an urinary tract infection were the main risk factors [73]
Latent tuberculosis	Different approaches are possible: (i) The Centers for Disease Control and Prevention (CDC) (applicable for low TB incidence) recommends a short-course, rifamycin-based, 3- or 4-month regimen for preventive chemotherapy of latent TB infection: for details please see https://www.cdc.gov/tb/topic/treatment/ltbi.htm (ii) World Health Organization guidelines recommend various regimens for management of LTBI: for details please see https://www.who.int/publications/i/item/9789241548908	Screening of patients with risk factors; general screening and preventive chemotherapy in areas with low tuberculosis incidence are not necessarily needed Patients receiving immunosuppressive therapy were less likely to have a positive IGRA (OR 0.66) and a lower rate of positive tuberculin skin test result (OR 0.51) [74]. A screening method with a better predictive value for active TB is needed
Tuberculosis	Not warranted, more data needed	

GC, glucocorticoid; IGRA, interferon-gamma release assay; IS, immunosuppression; KTR, kidney transplant recipients; OR, odds ratio; TB, tuberculosis.

Complications after primary CMV infection or reactivation from latency predominantly occur in states of immunodeficiency, either due to an underlying disease (e.g. AIDS or malignancy), or because of immunosuppressive therapy. This may result in the development of CMV syndrome or CMV disease, which is defined as evidence of active viral replication with symptomatic organ involvement, such as pneumonitis, hepatitis and gastrointestinal involvement, amongst others [16]. CMV is an important cause of early infectious complications in transplant recipients, where two strategies are recommended to prevent reactivation in CMV-positive individuals. Universal prophylaxis with valganciclovir may be applied for a duration of 3 to 6 months, with lymphopenia and late-onset CMV reactivation constituting the main limitations. Alternatively, a pre-emptive approach may be applied, which involves monitoring of viral load to target antiviral therapy once viral replication is detected. This approach necessitates stringent monitoring, which may be logistically demanding in an outpatient setting [31]. Of note, valganciclovir displays significant myelosuppressive activity and resistance may develop. Recently, new treatment options have emerged, such as maribavir, which received European Medicines Agency approval for the treatment of resistant or refractory post-transplant CMV infection in 2022 [32]. Moreover, letermovir was recently tested as alternative antiviral drug for antiviral prophylaxis in donor-positive/recipient-negative transplant recipients [33].

There is growing recognition of CMV as an important opportunistic pathogen in individuals with immune-mediated kidney diseases. In this context, most experience stems from systemic lupus erythematosus (SLE) cohorts, where severe CMV infection is increasingly recognized as an emerging problem [34]. A systematic review of SLE patients found longer disease duration, and higher glucocorticoid doses as risk factors for active CMV disease [35]. CMV infections in glomerular diseases might indicate a state of "overimmunosuppression" and may guide reduction of immunosuppression. CMV flares are also associated with an increased risk for thromboembolic complications. Indirect consequences of CMV infection include increased cardiovascular risk and adverse modulation of the immune system (for instance in AAV), the latter being a matter of active research [36].

Recently, Lim *et al.* applied an individualized approach to administer anti-CMV prophylaxis for 3 months for seropositive patients with active glomerulonephritis and three or more of the following risk factors: severe kidney impairment, use of methylprednisolone, CYC, mycophenolate mofetil, rituximab or plasma exchange. Among patients satisfying these criteria ($n = 21$), CMV disease occurred more frequently in the group without prophylaxis (8.3% versus 0%). This single-center study is limited by its retrospective nature and its small sample size, but could provide the framework for a prospective study [37].

Generally, efforts to curb CMV-related morbidity are hampered by the lack of standardized CMV DNA quantification [polymerase chain reaction (PCR)] across different laboratories [16]. Moreover, tissue-invasive disease can occur in the absence of positive serum PCR, especially in cases of CMV gastrointestinal tract disease [38].

Several candidate CMV vaccines, including mRNA platforms, are currently being investigated in phase 1 and 2 trials, but are limited to transplant cohorts and women of childbearing age. Therefore, it appears doubtful that these agents will become available for other entities of interest in the near future.

Altogether, CMV continues to adversely affect outcomes in patients with immune-mediated kidney disease. A controlled trial of CMV prophylaxis in this setting would be worthwhile.

VARICELLA-ZOSTER VIRUS

Herpes zoster (HZ) or shingles is a secondary infection caused by the reactivation of a latent VZV infection. Primary infection typically affects children causing varicella disease (chickenpox)—a highly infectious contagious but mostly mild, self-limited disease. However, patients receiving immunosuppression might require hospitalization, mainly due to secondary bacterial complications [39], and case fatalities have been reported in individuals after kidney transplantation [40]. Following primary infection, the virus establishes latency entering the ganglionic neurons where it may stay dormant for decades. Reactivation of the virus leads to HZ, typically presenting with a painful rash in the distribution of dermatomes which may last for 2–4 weeks. Possible complications include post-herpetic neuralgia (PHN), eye involvement (HZ ophthalmicus), facial palsy or, in more severe cases, encephalitis, cerebral vasculopathy, pneumonia and visceral zoster. Individuals above the age of 60 years with waning immunity, patients with impaired cellular immunity and patients under immunosuppression are at greater risk of developing disseminated HZ.

The incidence rate of HZ in the general population varies between 3.2 and 6.3/1000 person-years (py), increasing up to 20-fold in patients with malignancy, solid organ transplantation, autoimmune diseases and those receiving immunosuppression. Similarly, patients with CKD are more susceptible to HZ, however, data on the risk and frequency of HZ in immunocompromised patients with kidney disease are lacking [41–43]. Indirect evidence mainly extrapolated from patients with SLE and lupus nephritis suggest an increased risk of HZ (8.84–32.5/1000 py), although it is unsure whether this is attributed to the disease *per se* or to treatment-related factors [44–46]. For instance, in the Safety and Efficacy of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Proliferative Lupus Nephritis (TULIP-LN) trial, herpes zoster in patients with proliferative lupus nephritis ($n = 145$) was twice as likely in the anifrolumab group as in the placebo group (16.7% vs 8.2%) [47]. In a maintenance therapy trial of AAV patients, a total of 18 patients (10% of the cohort) developed HZ. Most cases occurred between 6 and 36 months, which implies that the risk of HZ is elevated even during periods of less intensive immunosuppression. Risk factors to develop HZ included female sex and serum creatinine ≥1.5 mg/dL [48].

In 2006, the Food and Drug Administration approved a single-dose live-attenuated vaccine (LZV) (Zostavax®) for HZ which proved to be effective both for HZ prevention and PHN protection. However, it was contraindicated in patients with a "high-level" of immunosuppression. Another two-dose adjuvanted recombinant (non-live) subunit HZ vaccine (RZV) (Shingrix®) has recently been approved for immunocompetent adults aged ≥50 years and for adults of any age at increased risk of HZ including patients under severe immunosuppression. Both vaccines have proven to be effective in preventing HZ in CKD patients. In a recent meta-analysis including 404 561 individuals with CKD, vaccination with either RZV or LZV reduced the risk of HZ by 45% (hazard ratio 0.55) [49]. In immunocompromised patients, two *post hoc* efficacy analyses of patients with hematological malignancies and self-reported immune-mediated diseases, the efficacy of the RZV vaccine against HZ was 87.2% and 90.5%, respectively [50, 51]. In a recent network meta-analysis, RZV provided an additional 36%–45% protection compared with LZV against HZ [52]. Data on clinical efficacy in certain states of immunosuppression other than malignancy and transplantation are sparse and the indication for RZV in these states is mainly based on immunogenicity and safety studies [53, 54]. Based on safety and efficacy estimates, we would recommend the use of the recombinant HZ vaccine in immunocompromised individuals.

Antiviral prophylaxis with aciclovir or valaciclovir is not routinely recommended for immunocompromised patients except for patients with hematologic malignancies and/or individuals receiving proteasome inhibitors, such as bortezomib; in this context, prophylaxis is justified by high VZV reactivation rates [55]. However, immunocompromised patients without known VZV immunity exposed to a person with varicella or HZ may benefit from a post-exposure prophylaxis either with antiviral agents or with intravenous varicella-zoster immunoglobulins [17, 56, 57].

PNEUMOCYSTIS JIROVECII

Pneumonia due to *Pneumocystis jirovecii* (PJP), an atypical fungal pathogen, is a common complication in patients with HIV but is also an important cause of infection-related illness in other immunodeficiency conditions, especially hematologic malignancies or following organ transplantation. Prophylaxis with trimethoprim–sulfamethoxazole (TMP/SMX) is effective in preventing infectious complications and is nowadays included in most transplant protocols in the first 6 months after transplantation [58].

An early European Vasculitis Study Group (EUVAS) study, conducted between 1995 and 2002, established *Pneumocystis* as a relevant opportunistic pathogen in AAV [59]. Although infection rates have declined subsequently, prophylaxis is advocated during the induction period for AAV [60]. Recent UK guidelines recommend a duration of at least 6 months, acknowledging a weak evidence base [61]. In cases of rituximab-based maintenance therapy, prophylaxis is recommended by the 2022 EULAR AAV recommendations [62]. Prophylaxis is strongly advised for older persons, in cases of lung disease, or severe lymphopenia. Of note, TMP/SMX prophylaxis also appears to reduce infectious complications unrelated to *Pneumocystis* [63].

Somewhat surprisingly, the risk of PJP in patients with SLE and other glomerular diseases seems considerably lower than in AAV and the risk/benefit ratio of universal prophylaxis is less clear [64]. Prolonged high-dose glucocorticoid treatment is consistently linked with an increased risk for PJP [58] and guidelines advocate *Pneumocystis* prophylaxis if steroids are used for more than 4 weeks at a daily dose of ≥20 mg prednisolone equivalent (Table 1) [17]. However, a recent literature review including a total of 1787 patients with minimal change disease (an entity where high-dose steroids are frequently used), found only one reported case of PJP in a dialysis-dependent patient, although prophylaxis was not routinely established [65]. This could be partly explained by the patients' younger age at disease onset and subsequent fewer comorbidities, but also argues for disease-specific risk factors. In a recent cohort study of individuals with giant cell arteritis, not a single case of PJP was reported during 547 py of follow-up. This is surprising, as the mean age was 73 years, and patients had accrued comorbidities similar to individuals with AAV [66]. Renal-limited conditions such as IgA nephropathy can

be complicated by serious infections due to *Pneumocystis*. During the original part of the Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING) trial, three cases of PJP were reported [67] and *Pneumocystis* prophylaxis was introduced after a temporal halt with concomitant reduction of steroid dose, with no further cases reported. Of note, there appears to be substantial variation in the incidence of PJP-related infections depending on ethnicity, with a higher risk in individuals of Chinese ethnicity.

In recent glomerulonephritis trials using anti-CD20 monotherapy, PJP prophylaxis was often co-administered [68]. For instance, in the MEmbranous Nephropathy Trial Of Rituximab (MENTOR) trial (rituximab versus cyclosporine for membranous nephropathy) [69], daily single-strength TMP/SMX was prescribed for the rituximab arm for the duration of the study (12 months) and until B-cell repletion.

A large retrospective Korean study ($n = 3524$) tried to establish the efficacy of primary PJP prophylaxis in a large cohort of patients treated with rituximab for a variety of diseases (mostly hematologic malignancies, but also including 99 patients with AAV and 47 with SLE) [70]. The authors concluded that TMP/SMX prophylaxis is effective and shows a tolerable safety profile. However, adverse effects such as allergic reactions (attributable to the sulfa component), hepatotoxicity, hyperkalemia and cytopenias are well recognized. In case of contraindications, dapsone, atovaquone or pentamidine remain alternatives.

To conclude, precise recommendations for *Pneumocystis* prophylaxis in patients with autoimmune kidney disease are lacking. Arguably, neither glucocorticoid-based nor rituximab-based therapy on its own should unconditionally trigger TMP/SMX prescription. Likewise, the optimal timing and duration of any prophylaxis remains uncertain. An individualized approach appears prudent and prophylaxis should be seriously considered if multiple risk factors for PJP coexist, such as combined immunosuppressive therapy including steroids, rituximab or CYC, lymphopenia, and multi-organ disease with pulmonary involvement.

CONCLUSION

Infectious complications will continue to occur in the course of prolonged and often intense immunosuppression for immune-mediated kidney diseases. However, their frequency and impact can be reduced by multimodal strategies, as outlined in this review. When selecting immunosuppressive treatment, we advocate an individualized approach, including careful assessment of risk factors, taking into account the patient's age, kidney function, comorbidities and cumulative immunosuppressive therapy. Particular attention should be given to concomitant lymphopenia and hypogammaglobulinemia, which should be regularly monitored. Prevention of infection through timely vaccination is of great importance. Ongoing refinement of treatment protocols according to individual risks such as ANCA-vasculitis subtypes, avoidance of unnecessary treatment in cases of secondary or "genetic focal segmental glomerulosclerosis," minimization of glucocorticoid doses through new compounds and substantial progress in the field of vaccine development represent prime examples of promising avenues that will hopefully lead to improved outcomes for our patients.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial or non-financial potential conflicts of interest to declare related to this project. M.W. received honoraria or consulting fees from Otsuka, CSL Vifor, AstraZeneca and Delta4. M.K. received honoraria or consulting fees from GlaxoSmithKline, AstraZeneca and Amgen. R.C. received honoraria or consulting fees from Roche, Sanofi, Janssen, Abbvie, Galapagos, Viatris, Fresenius Kabi; funding for participation in clinical trials from Abbvie; Grant/Research Support from Janssen, Celltrion, Nordic Pharma; and conference/educational support from Abbvie, Janssen. I.B. has no conflicts of interest to declare. A.B reports honoraria or consulting fees from AstraZeneca, Bayer, ChemoCentryx, Fresenius and Vifor. M.J.S. reports honorarium for conferences, consulting fees and advisory boards from AstraZeneca, NovoNordisk, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Janssen, ICU Medical, Fresenius, Travere therapeutics and Boehringer. M.S. received honoraria or consulting fees from Biotest, Novartis, Qiagen, Moderna, Takeda and support for investigator-initiated research from Astellas and Biotest. A.K. received honoraria or consulting fees from Otsuka, CSL Vifor, Catalyst Biosciences, Walden Biosciences and Delta4.

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