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REVIEW

Current perspective on infections and mitigation strategies in primary systemic vasculitis

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Abstract

Purpose of Review The purpose of this review is to summarize and evaluate most recent evidence on the epidemiology of infections and associated risk factors in patients with primary systemic vasculitides (PSV), as well as discuss mitigation strategies including the risk of antibiotic prophylaxis.

Recent Findings Infections remain one of the leading causes of mortality in patients with PSV, with rates of severe infection ranging from 16 to 40% in different cohorts. Older age, frailty, renal and pulmonary involvement, and higher burden of comorbidities have been recognized as important patient-associated risk factors. Treatments including higher cumulative doses of glucocorticoids are associated with an increased risk of infections, and recent studies show the potential benefit of interventions such as reduced-dose glucocorticoid regimens. Existing mitigation strategies include screening, vaccination, and infection prophylaxis. The latter remains particularly important for *Pneumocystis jirovecii* pneumonia; however, the benefit-risk ratio seems to be less clear outside of induction phase (i.e., high dose of glucocorticoids) and optimal treatment duration remains less clear.

Summary Patients with PSV are at increased risk of infections, due to disease itself, comorbidities, and treatment side effects. Awareness of the timing and types of infection, as well as mitigation strategies are imperative to ensure treatment success and survival for patients.

Keywords Vasculitis · ANCA-associated Vasculitis · Infections · Prophylaxis · Risk Mitigation

Introduction

The primary systemic vasculitides (PSV) refer to a group of autoimmune rheumatic diseases (AIRDs) characterized by vascular inflammation, leading to ischemic events and end-organ damage [1]. Despite advances in the treatment of these conditions, infections remain an important cause of morbidity and mortality in people living with vasculitis. Mitigation strategies (e.g., antibiotic prophylaxis) are currently employed in clinical care; however, certain aspects such as duration, risk stratification, and optimization of these interventions remain unanswered. In this review, we will summarize recent findings on the epidemiology of infections in adults with PSV, as well as existing evidence on mitigation strategies. For the purpose of this review, and from here onwards, we will refer to severe infections (SI) as those leading to hospitalization, requirement of intravenous antibiotics, and/or death [2].

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Epidemiology of Infections in Primary Systemic Vasculitides

Anti-neutrophil Cytoplasmic Antibody-associated Vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) are the most common form of small vessel

vasculitis. Recent longitudinal cohorts have reported high infection incident rates, particularly during the first year after diagnosis, with decreasing incidence during follow-up (Table 1) [3, 4]. A systematic review and meta-analysis that included pooled data from 21 studies (1,284 individuals with AAV) focused on the incidence of infections primarily during the maintenance period. The cumulative incidence of SI was 15.99% (95% CI: 6.95%-27.53%) during the total follow-up period (induction and maintenance) and 7.62% (95% CI: 4.43%-11.43%) in the maintenance phase [11]. Infections remain a common cause of mortality, accounting for 4.1-22.4% of deaths and the leading cause of excess mortality in individuals with AAV [3, 4, 12, 13] (Table 1).

Other Forms of Systemic Vasculitides

Infections in individuals with giant cell arteritis (GCA) are frequent, particularly during the first year after diagnosis (Table 1) [5, 71) [8]. For individuals with TAK, a systematic review and meta-analysis that included 517 patients on biologics, reported an incidence of infection of 6% (95% CI: 2%-10%) as the most common adverse event [14]. Compared to global infection rates of tuberculosis [15], a high prevalence of tuberculosis of 31.27% (95% CI: 20.48%-43.11%) has been reported in a meta-analysis of observational studies of patients with TAK [16]. Data on the incidence of infections in other forms of vasculitis is scarce (Table 1) [9, 10].

Patient-related Risk Factors for Infection

Age and Frailty

Older age is a risk factor for poor outcomes, including SI, in individuals with PSV [7, 10, 17–19]. In the PEXIVAS study, individuals with AAV who developed a SI within the first year after diagnosis were more likely to be older (68.2 ± 13.6 vs 59.7 ± 15.8 years, p =0.016). A recent multicentric study of 1,004 individuals with GCA showed that SI were more frequent in individuals aged 65-79 (OR 11.90 [95% CI: 1.69-83.63]) and ≥80 years (OR 13.71 [95% CI: 1.59-117.91]), when compared to individuals ≤64 years old [6]. Similar observations were made in a recent nationwide Danish study of 17,773 individuals with GCA. Age ≥70 years was associated with a higher incidence of overall infections, including SI, during the first year of treatment [5, 20]. Older age at disease diagnosis has also been associated with an increased risk of SI in a large cohort of individuals with anti-GBM disease [10].

Although multiple studies have utilized chronological age (i.e., age) as a predictor of outcomes, chronological age might not accurately reflect biological age, which is possibly a better predictor of morbidity and mortality [21]. This is even more important for older adults, as shown in studies of community-dwelling older adults. Frailty, a syndrome characterized by a decline in physiologic reserve and homeostasis with a subsequent increase in vulnerability to stressors, has been shown to provide a holistic assessment in older adults and better predict outcomes. In a large claims data analysis that included two different cohorts of individuals with GCA, moderate/severe frailty (as measured by a claims-based frailty index) had a two- and four-fold increased risk for SI when compared to pre-frail individuals (HR 2.51 [95% CI: 1.38-4.57] in federal and HR 4.54 [95% CI: 1.44-14.29] in commercial database, respectively) [7•]. Using the same claims-based frailty index, frailty was associated with an increased risk of SI (HR 8.62 [95% CI: 2.08-35.66] vs non-frail) in a large cohort of older adults with AAV and appeared to be a stronger risk factor than older age (age ≥75 years HR 3.27 [95% CI: 1.94-5.53], vs age 65-74) [22]. Frailty seems to be prevalent in individuals with multiple forms of vasculitis, even those <65 years old, and associated to a higher frequency of infections [23]. Although further data is needed to better understand the role, assessment, and incorporation of frailty in the care of individuals with AAV, these data highlight the potential use of frailty measurement in risk assessment and the development of personalized interventions toward risk mitigation.

Comorbidities

Individuals living with PSV are at increased risk of comorbidities, resulting as a complication of the disease itself or the associated treatments. Renal (i.e., chronic kidney disease) and pulmonary comorbidities (e.g., chronic obstructive pulmonary disease) have been associated with an increased risk of SI [4, 24, 25]. A higher burden of comorbidity, usually characterized by higher counts in cumulative scores such as the Charlson Comorbidity Index (CCI), is associated with an increased risk of SI [26]. In a recent multicentric retrospective study that included 162 individuals with AAV with a mean follow-up of 5.4 years, patients who developed a SI were more likely to have a higher composite Rheumatic Disease Comorbidity Index (median [IQR]: 1 [0 – 2] vs 1 [1–3], p =0.03) [4]. In an analysis of hospitalized patients with GCA due to SI, a CCI ≥2 (present in 50.7% of individuals) was associated with higher in-hospital mortality (OR 1.38 [95% CI: 1.09-1.76]) [8]. Higher CCIs were also associated with an increased risk of incident infections, including SI, in a large national Danish cohort of individuals with GCA [5, 20]. With the increased risk of multimorbidity in individuals with PSV, especially AAV, this data highlights the value of its assessment to identify patients at higher risk for SI and other poor outcomes [27].

Table 1 Cohort studies reporting incidence of infections and associated risk factors in individuals with primary systemic vasculitides

Primary systemic vasculitis	Location (year)	Number; Follow-up	Infection rate (cases per 100 PY)*	Risk factors for SI	Other observations
ANCA-associated vasculitis (GPA and MPA)	Sweden (2021) [3]	325; median 5.9 y	9.1 cases per 100 PY First year: 22.1, Second year: 16.4, Fifth year: 11.4	Older age, higher BVAS**	Mortality associated to SI: 74/129 (57.4%)
	Greece (2021) [4]	162; mean 5.4 y	7.5 cases per 100 PY First year: 18.57, Second year: 6.23, Third year: 5.67, Fourth year: 4.74	Older age, impaired renal function**, treatment with PLEX and/or dialysis	Median time to first infection 1.1 years (range 0.36-4.14). Type of infections (in descending order of frequency): respiratory infections, VZV, GI, bacteremia, urinary
Giant cell arteritis	Denmark (2024) [5]	17,773; 1996-2022	1-year cumulative incidence proportion for infections: 52.4% (95% CI: 51.7-53.2) 1-year cumulative incidence proportion SI: 17.6% (95% CI: 17.1-18.2)	Older age, higher CCI, and higher cumulative glucocorticoid doses	Compared to matched non-GCA controls: Overall infections RR 1.4 (95% 1.38, 1.42) SI RR 2.71 (2.61, 2.82)
	Italy (2024) [6]	1,004; 49 months	48/1004 (6.19%)	Older age, systemic symptoms, higher initial doses of glucocorticoids (i.e., > 50 mg/day)	Infections by age group: ≤ 64 years: 1.88%, 65-79 years: 7.32%, ≥ 80 years: 7.25%
	USA (2022) [7•]	Medicare (2007-2017): 734; MarketScan (2015-2019): 1,022	Medicare: 10.7 cases per 100 PY Marketscan: 6.3 cases per 100 PY	Moderately/severely frail, older age	Type of infections (in descending order of frequency): bacterial, pulmonary, VZV, urinary, skin/soft tissue
	USA (2020) [8]	1998-2016	1998-2000: 11,240.14 per 100,000 hospital claims 2009-2010: 12,317.91 per 100 hospital claims 2015-2016: 18,933.29 per 100,000 hospital claims	NA	In-hospital mortality: 6.96% Risk factor for in-hospital mortality: age ≥ 80 years, CCI ≥2.
IgA vasculitis	Australia (2021) [9]	267; mean 19.5 y	9.57 cases per 100 PY	For mortality: Older age; Higher CCI*; CKD presence	Deaths due to infection: 5.8% Type of infections (in descending order of frequency): skin/soft tissue, urinary, pneumonia, upper respiratory tract, opportunistic, bacteremia
Anti-GBM disease	France (2020) [10]	201; median 6.1 y	58.0 cases per 100 PY	Older age, ANCA positivity	SI during first 3 months associated with increased 3-year mortality (HR 3.13 [95% CI: 1.24, 7.88])

SI Severe infection, *CCI* Charlson comorbidity index, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *GBM* glomerular basement membrane, *VZV* varicella zoster virus, *GI* gastrointestinal, *RR* relative risk, *HR* hazard ratio

*Infection rates reported as cases per 100 PY, unless specified otherwise. **Characteristic at time of diagnosis

Treatments and Risk Factors for Infection

Glucocorticoids

Glucocorticoids remain a main driver of infection, among other associated toxicities. Recent AAV trials have focused on the use of low glucocorticoid regimens, including the use of other immunosuppressive medications for glucocorticoid-sparing effect [28–30]. In the LoVAS trial [28•], individuals with AAV who received a reduced-dose glucocorticoid regimen alongside rituximab induction had a lower incidence (-12.8% [95% CI: -24.2%--1.3%]) of SI, compared to those randomized to high-dose glucocorticoid treatment. Similar observations were made in the PEXIVAS trial [29•]. PEXIVAS randomized 704 individuals with severe AAV through a 2-by-2 factorial design to a standard vs a reduced dose of glucocorticoids along with or without plasma exchange. No difference between the arms of the two different interventions was observed for the primary outcome (i.e., death or occurrence of end-stage renal disease [ESRD]); however, those randomized to the reduced-dose glucocorticoid arm experienced fewer infections during the 52-week study period (incidence rate ratio 0.69 [95% CI: 0.52-0.93]). Similar observations have been reported in recent contemporary observational AAV cohorts [4]. For GCA, a recent Danish national cohort study of 17,773 individuals with GCA reported that a greater cumulative dose of glucocorticoids (>6 g) increased susceptibility to overall infections (OR 1.47 [95% CI: 1.29-1.67]) and infection-related hospitalizations (OR 2.58 [95% CI: 2.02-3.30]), compared to a minor dose (<2 g) [5]. Glucocorticoids remain an important modifiable risk factor for infections in patients with PSV. Although a recent study has raised concern about the applicability of reduced-dose glucocorticoid protocols to some patients with AAV [31], glucocorticoid minimization should be attempted in most cases, as noted by recent treatment guidelines [32, 33].

Rituximab and Hypogammaglobulinemia

A meta-analysis that included 1,434 individuals with AAV receiving treatment with rituximab reported an incidence of SI of 6.5 cases per 100 PY [34••]. The most common infections were bacterial (9.4%) and mortality related to infection was 0.7%. Higher cumulative doses of rituximab were associated with an increase in the prevalence of infections. In a recent post-hoc analysis of the RAVE trial, 18/22 (81.8%) of the SI reported occurred during the first 6 months [35••]. Higher baseline serum IgM levels (HR 1.005 [95% CI: 1.002-1.009]) were associated with an increased risk of SI, while higher baseline CD19+ B cell count (HR 0.995 [95% CI: 0.991-0.9999]) and use of trimethoprim-sulfamethoxazole (TMP-SMX) (HR 0.232 [95% CI: 0.087-0.623]) with a decreased risk of SI.

The risk of hypogammaglobulinemia associated with rituximab, especially IgG levels <6 g/L at baseline and after treatment, constitutes one of the primary mechanisms for SI among AIRDs [36, 37]. Different thresholds have been utilized in the literature to define hypogammaglobulinemia. The incidence of hypogammaglobulinemia seems to be more frequent in AAV (<6 g/L in 40% and <5 g/L in 28.1%) [38, 39] compared to other AIRDs (RA: <7 g/L in 20%; systemic lupus erythematosus (SLE): <5g/L in 18.2%) [38, 40]. In a longitudinal observational study [39] of individuals with AIRDs, hypogammaglobulinemia was most frequently observed in individuals with AAV (40.0% vs 7.9%, p =0.008), as well as a greater reduction in IgG levels (11.3 [3.8 – 29.7] vs 2.3 [0–18.2] g/L, p =0.047). In an analysis of 657 individuals with newly diagnosed or relapsing AAV from the national Japanese registry (J-CANVAS), IgG <5 g/L levels were independently associated with the development of SI (HR 1.75 [95% CI: 1.03-3.00]) [41•]. It is important to note that only 37.3% received rituximab in the group of individuals developing hypogammaglobulinemia. These observations are in line with the recent report of the RITAZAREM trial that found no difference in the incidence of hypogammaglobulinemia between rituximab and azathioprine, highlighting the importance of monitoring IgG levels even when using non-B-cell depleting therapies (BCDT) [42]. Interestingly, individuals with sustained B cell-depletion (longer than median time to repopulation of 39 months) post rituximab therapy exhibit a higher risk of SI in the longer term [43]. Sustained B-cell depletion was associated with higher eGFR and female sex in this cohort.

Other Biologics

A systematic review and meta-analysis of the use of biologics (i.e., tocilizumab, abatacept, adalimumab, etanercept) along with glucocorticoids versus glucocorticoids alone for the treatment of individuals with GCA, showed no difference in severe adverse events (including SI) (OR 0.81 [95% CI: 0.54-1.20]) [44]. Reports of infections associated with biologic use in other PSVs are less common. In a trial of tocilizumab in TAK, although infections were more frequent in the treatment arm compared to placebo (9/18 [50%] vs 6/18 [33.3%]), no SI were reported. Few other studies have reported low rates of infections in individuals with TAK on biologic treatment [45, 46].

Plasma Exchange

The PEXIVAS trial [29•] has led to further discussion of the risks and benefits of plasma exchange (PLEX). Although PLEX still has a role in the management of specific subgroups (i.e., high risk of ESRD, severe diffuse alveolar hemorrhage), a recent meta-analysis [47] that included 1,060 participants of 9 clinical trials showed that PLEX increased the risk of SI at 12 months (RR 1.27 [95% CI: 1.08-1.49]). The increase in SI caused by PLEX occurs earlier in the disease (i.e., around time of the intervention) has been attributed to several factors, including the removal of immunoglobulins, the use of blood products, and the need for central venous access and an intensive care unit environment [48]. The increased risk of infections associated with PLEX needs to be weighed against the potential benefits, and this needs to be assessed on a case-by-case basis.

Avacopan

Avacopan, a C5a receptor inhibitor, has been recently approved as an adjunctive treatment in AAV [32]. An analysis combining data from the ADVOCATE, CLASSIC, and CLEAR trials showed that participants in the placebo arms had a higher rate of infections and a more significant decrease in white blood count when compared to those receiving avacopan [30, 49–51]. In a recent safety trial of 30 patients, SI were presumed to be secondary to avacopan in only 3.3% of patients [52]. Although emerging data seems favorable, further studies are needed to better delineate the incidence of infections associated with avacopan use.

Infection Risk Mitigation

Aside from risk assessment and identification of modifiable and non-modifiable risk factors, mitigation strategies include screening, vaccination, and the use of prophylaxis in selected individuals (Fig. 1).

Infection Screening

Individuals with AIRDs receiving treatment with biologics therapies, other immunosuppressive agents, or medium-high dose glucocorticoid (>7.5 mg/day prednisone equivalent) are at higher risk for reactivation of hepatitis B (HBV) or hepatitis C virus (HCV) [53]. With the advent of immunosuppression, reactivation has also been reported in patients previously exposed to HBV or HCV. Use of BCDT (e.g., rituximab, obinutuzumab) carries a risk of reactivation of >20% in individuals who are HBsAg and anti-HBc positive [54]. Viral hepatitis screening should be performed in all patients, ideally prior to starting treatment. HBV vaccination should be given before initiation of treatment to patients with initial HBV testing negative, and adapted regimens have been suggested for those receiving immunosuppressive treatment [54, 55].

The screening of patients for latent and active tuberculosis prior to initiation of biologic or glucocorticoid-sparing immunosuppressive therapies is suggested for patients living in endemic areas or other higher-risk populations such as those with alcohol use disorder, tobacco use, or household TB contacts [53, 56]. Interferon-gamma release assay

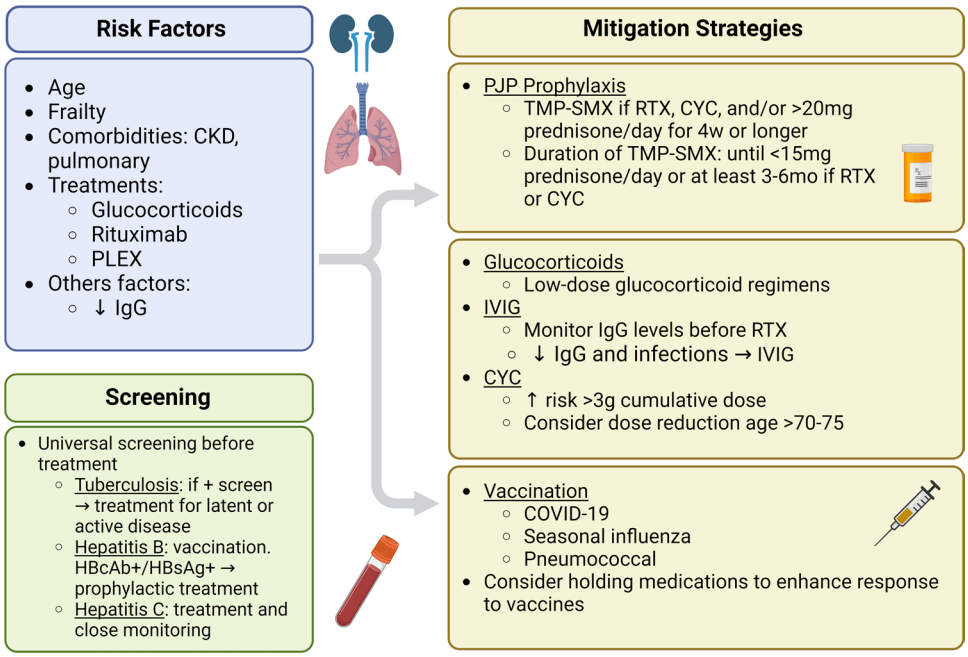

Fig. 1 Risk factors for infection and mitigation strategies in patients with primary systemic vasculitis (Created with Biorender.com). CKD = chronic kidney disease; PLEX = plasma exchange; IgG = immunoglobulin G; HBcAB = hepatitis B core antibodies; HBsAG = hepatitis B surface antigen; PJP = *pneumocystis jirovecii* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole; RTX = rituximab; CYC = cyclophosphamide; IVIG = intravenous immunoglobulin

(IGRA) has been shown to have a lower false-negative and false-positive rate compared to tuberculin skin test (TST), in patients with rheumatic diseases before starting biologic therapy, particularly in patients treated with glucocorticoids [57]. Different cut-offs for TST are recommended for immunosuppressed individuals (e.g., >15 mg/day prednisolone equivalent for >1 month, use of tumor necrosis factor-alpha inhibitor [TNFi]). In the occurrence of latent or reactivated tuberculosis, patients should be treated before starting a biologic or glucocorticoid-sparing immunosuppressive therapy. Immunosuppressive treatment may be commenced after at least 1 month of anti-tuberculosis treatment with adequate monitoring every 3 months thereafter [53].

Vaccination

COVID-19

Adequate vaccination for people living with AIRDs remains challenging primarily due to differences in seroconversion observed in patients receiving different immunosuppressive drugs, especially rituximab and certain anti-metabolites (e.g., cyclophosphamide, methotrexate, azathioprine) [58•]. Vaccination should be encouraged in all patients with AIRDs, including PSV, although in several instances, including but not limited to life-threatening disease, AIRD's treatment should be started swiftly, regardless of vaccination status. Despite the fact that flares of disease after vaccination have been reported, these are rarely severe, and the benefits of vaccination outweigh the potential risks, especially in this higher-risk population [58•]. The American College of Rheumatology (ACR) guidelines recommend that patients with AIRDs receive 3 doses of the primary COVID-19 vaccination series and 2 boosters (a total of 5 doses) [59•]. Holding off specific immunosuppressive treatments for 1-2 weeks after each COVID-19 dosage is recommended to enhance vaccine response, and in the case of rituximab, it is recommended that vaccine series are started 4 weeks before the next rituximab dose [59•].

Influenza

Yearly influenza vaccination with either high-dose or adjuvanted influenza vaccination is recommended for all patients with AIRDs 65 years or older and those 18 years or older on immunosuppressive treatments [59•]. If disease allows, methotrexate should be held for 2 weeks after vaccination to enhance vaccine response [60, 61]. For patients receiving rituximab, influenza vaccine should be given on schedule given its seasonal occurrence, and rituximab should be delayed for at least 2 weeks after vaccination. Rituximab is known to decrease the response to influenza vaccination [62, 63]. All other immunosuppressive treatments should be continued per the usual schedule [59, 64, 65]. Influenza vaccine should be recommended irrespective of disease activity [59•].

Pneumococcal Pneumonia

Pneumococcal vaccination is strongly recommended to all individuals with rheumatic diseases with less than 65 years of age on immunosuppressive treatments. All adults above 65 years of age, irrespective of comorbidities, are recommended pneumococcal vaccine [59•]. Current recommendations include a combination of different existing vaccines (i.e., PCV15 or PCV13 followed by PPSV23 or PSV20, or PCV20 followed by PPSV23) [65]. Methotrexate and rituximab may reduce vaccine response [62, 63], which is a concern in individuals with PSV such as AAV, who are at higher risk for infection due to immunosuppression and comorbidities (i.e., lung disease). A recent multicenter randomized label study compared two "reinforced" pneumococcal vaccine regimens to standard regimens in individuals with AAV receiving treatment with rituximab [66•]. Preliminary results of this study showed that one of the "reinforced" regimens that consisted of a double dose of PCV13 followed by a single dose of PPSV23 7 days after yielded a significantly improved antibody response. Although further studies are needed, these results in combination with those for COVID-19 vaccination highlight the need for innovative regimens in individuals with PSV on chronic immunosuppressive therapy.

Role of Prophylaxis Treatment

Pneumocystis Jirovecii

Individuals with PSV, especially AAV, have been associated with a high incidence of *Pneumocystis jirovecii* pneumonia (PJP) of up to 12.14 cases per 100 PY and a high associated mortality [67, 68, 69••]. More recent studies, including a recent systematic review and meta-analysis of 1,434 patients, have reported incidence rates as low as 1.1 per 100 PY [34••]. However, the risk of PJP might vary during different phases of treatment, even despite the use of maintenance medications, and this might be possibly associated with the use of high-dose glucocorticoids. In a recent retrospective study of 1,461 patients with AAV, only 10 cases of PJP were observed during the induction phase (incidence rate 1.50 cases per 100 PY) and 5 cases during the maintenance phase (0.21 cases per 100 PY) [70•]. Although glucocorticoid doses were not captured, dosing differences between induction and remission phases could explain the difference in PJP incidence. PJP prophylaxis use was only observed in 30% of rituximab or cyclophosphamide dosing episodes.

A retrospective multicenter study from South Korea reported that trimethoprim-sulfamethoxazole (TMP-SMX) was associated with a significant reduction in the incidence (HR 0.07 [95% CI: 0.01-0.53]) and mortality (HR 0.08 [95% CI: 0.0006-0.71]) in patients with rheumatic disease receiving prolonged, high-dose steroids. The number needed to treat (NNT) (52 [33–124]) for preventing one PJP case was lower than the number needed to harm (NNH) (131 [55–∞]), indicating that the benefit of TMP-SMX was greater than the risk of potential harm to the patient [68]. More recently, a retrospective study from South Korea that included 818 patients receiving treatment with rituximab reported a significant reduction in the risk of PJP infection associated with TMP-SMX (HR 0.11 [95% CI: 0.03-0.43]), giving an NNT of 146 [69••]. Although this number was higher than the NNH of 86, NNT decreased to 20 in those patients receiving high-dose glucocorticoids (i.e., prednisone ≥30 mg/day), aligning with the observations of differences in incidence rates during induction and maintenance phases. Finally, a recent post-hoc analysis of the Rituximab versus Cyclophosphamide for ANCA vasculitis (RAVE) study, not only showed a decreased risk of PJP infections associated with TMP-SMX use but also showed an overall lower frequency of SI (HR 0.30 [95% CI: 0.13-0.69]) [25].

The 2021 ACR and Vasculitis Foundation guidelines for the management of AAV conditionally recommend PJP prophylaxis for those patients who are treated with rituximab or cyclophosphamide and receiving moderate-dose glucocorticoids (>20 mg/day) or higher in combination with other immunosuppressive therapy [33]. The 2022 update EULAR recommendations for the management of AAV also recommends the use of TMP-SMX as PJP prophylaxis in patients receiving rituximab, cyclophosphamide and/or high-dose glucocorticoids [32]. This is also in line with prescribing information for rituximab that recommends prophylaxis for PJP for equal or more than 6 months after the last rituximab dose for patients with GPA or MPA [33].

While there is not enough information to guide the total duration of PJP prophylaxis, these observations and the risk of potential harm associated with TMP-SMX need to be taken into consideration to guide risk assessment and shared decision making. PJP prophylaxis during the first 6 months of therapy has been associated with a higher risk of adverse events including, rash, nephropathy (e.g., acute kidney injury, renal failure), and hyperkalemia [70•]. Although most of these studies have focused on TMP-SMX, alternative therapies such as dapsone, atovaquone, and pentamidine can also be associated with potential side effects. While benefit of PJP prophylaxis will certainly outweigh risk in certain individuals (e.g., ≥30 mg/day of prednisone equivalent, hypogammaglobulinemia, structural lung disease), the risk/benefit ratio needs to be reassessed in all patients [32].

For non-AAV PSV, the risk and benefit of PJP prophylaxis remain unclear. Existing studies have shown differences in the risk of PJP infection among systemic rheumatic diseases, and this difference might also apply to individuals with distinct PSV. Recent studies in individuals with GCA have shown a low risk of PJP infection, with an incidence rate from 0-0.08 cases per 1,000 PY, despite the concerns for older age and high doses of glucocorticoids. These studies show that the risk of PJP is not the same across individuals with PSV [71•].

Antivirals

Prophylactic antiviral therapy for HBV with tenofovir or entecavir is strongly recommended for all individuals positive for HBV core antibody (HBcAb) and HBsAg receiving immunosuppressive treatment [72]. Treatment should be started 1–2 weeks before starting therapy. Patients should be monitored for up to 12 months after cessation of anti-HBV therapy. If the patient is positive for HBcAb and negative for HBsAg, frequent monitoring every 1–3 months with ALT, HBV DNA, and HBsAg can be performed for evidence of reactivation. Risk of reactivation might be higher with rituximab compared to cyclophosphamide. Prophylactic therapy over frequent monitoring is favored for patients initiating rituximab who are HBcAb positive, regardless of HBsAg status [73]. Prophylaxis is not routinely recommended in individuals receiving other immunosuppressive treatments (i.e., methotrexate, mycophenolate mofetil, and azathioprine) due to lower risk of reactivation [74]. The exact duration of prophylaxis in patients with rheumatic diseases remains unclear; current guidelines recommend continuing it for at least 6 months (or for at least 12 for patients receiving anti-CD20 therapies) after cessation of immunosuppression [73]. If HBV reactivation occurs during antirheumatic therapy, immunosuppression may be continued if there is only mild hepatitis; however, for patients with moderate to severe hepatitis, immunosuppressive therapy may need to be held [75].

Intravenous immunoglobulin

Hypogammaglobulinemia has been observed in individuals with AAV, most commonly but not exclusively associated with rituximab use. Deficiency of IgG is a more important risk factor for infection, as compared with IgA or IgM deficiency [76•]. The determining factors for the development of clinically significant hypogammaglobulinemia during or BCDT include a pre-existing low IgG level and previous or concomitant immunosuppressive therapy [76•]. The decision to start immunoglobulin replacement therapy (IGRT) should be guided by the degree of hypogammaglobulinemia, serious or recurrent infections, demonstration of impaired

antibody responses to polysaccharide antigens, and poor response to antibiotic prophylaxis. Immunoglobulin levels should be checked prior to initiation of BCDT and repeated every 6–12 months for the duration of BCDT and a minimum of one year after stopping treatment. Initial dosing of IGRT should be 0.4 g/kg/month, then it can be adjusted according to IgG trough levels, infection frequency, and clinical response, as well as the decision to continue IGRT should be reviewed annually based on clinical and laboratory parameters. Co-management with an immunologist is recommended [32, 76

Conclusion and Future Research Directions

Infection remains to be one of the main causes of morbidity and mortality among patients with PSV, highlighting the importance of risk assessment, and the implementation of mitigation strategies (Fig. 1). Glucocorticoid reduction, either through the use of reduced-dose regimens or adjunctive therapies (i.e., avacopan) is an important modifiable risk factor for infection. Future efforts should be focused on improving efforts for risk stratification and implementation of mitigation strategies in clinical practice, to better guide individualized shared decision-making process in the care of individuals with PSV. To date, most existing information on infections comes from the AAV literature, and information on other forms of PSVs is needed, given the limitations of extrapolating observations from AAV to individuals with other forms of PSV.

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Declarations

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kitching AR, Anders H-J, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. Nat Rev Dis Primer. 2020;6:71. https://doi.org/10.1038/s41572-020-0204-y.
2. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) v5.0 [Internet]. 2017 [cited 2024 Mar 30]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
3. Rathmann J, Jayne D, Segelmark M, Jönsson G, Mohammad AJ. Incidence and predictors of severe infections in ANCA-associated vasculitis: a population-based cohort study. Rheumatol Oxf Engl. 2021;60:2745–54. https://doi.org/10.1093/rheumatology/keaa699.
4. Thomas K, Argyriou E, Kapsala N, Panagiotopoulos A, Chalkia A, Hadziyannis E, et al. Serious infections in ANCA-associated vasculitides in the biologic era: real-life data from a multicenter cohort of 162 patients. Arthritis Res Ther. 2021;23:90. https://doi.org/10.1186/s13075-021-02452-8.
5. Therkildsen P, de Thurah A, Nielsen BD, Faurschou M, Baslund B, Hansen IT, et al. The one-year infection risk among patients diagnosed with giant cell arteritis: use of antibiotics and hospitalisations. Rheumatol Oxf Engl. 2024:keae107. https://doi.org/10.1093/rheumatology/keae107.
6. Monti S, Milanesi A, Klersy C, Tomelleri A, Dagna L, Campochiaro C, et al. Age at diagnosis influences the clinical phenotype, treatment strategies and outcomes in patients with giant cell arteritis: results from the observational GCAGE study on a large cohort of 1004 patients. Ann Rheum Dis. 2023;82:1098–106. https://doi.org/10.1136/ard-2023-223895.
7•. . Tedeschi SK, Jin Y, Vine S, Lee H, Pethoe-Schramm A, Yau V, et al. Giant cell arteritis treatment patterns and rates of serious infections. Clin Exp Rheumatol. 2022;40:826–33. https://doi.org/10.55563/clinexprheumatol/uonz1p. **Large national analysis of treatment patterns and infection in individuals with GCA**.
8. Singh JA, Cleveland JD. Serious infections in people with polymyalgia rheumatica (PMR) or giant cell arteritis (GCA): a time-trend national US study. Clin Rheumatol. 2020;39:3427–38. https://doi.org/10.1007/s10067-020-05129-w.
9. Nossent J, Raymond W, Isobel Keen H, Preen D, Inderjeeth C. Morbidity and mortality in adult-onset IgA vasculitis: a long-term population-based cohort study. Rheumatol Oxf Engl. 2021;61:291–8. https://doi.org/10.1093/rheumatology/keab312.
10. Caillard P, Vigneau C, Halimi J-M, Hazzan M, Thervet E, Heitz M, et al. Severe Infection in Anti-Glomerular Basement Membrane Disease: A Retrospective Multicenter French Study. J Clin Med. 2020;9:698. https://doi.org/10.3390/jcm9030698.
11. Vassilopoulos A, Vassilopoulos S, Kalligeros M, Shehadeh F, Mylonakis E. Incidence of serious infections in patients with ANCA-associated vasculitis receiving immunosuppressive therapy: A systematic review and meta-analysis. Front Med. 2023;10:1110548. https://doi.org/10.3389/fmed.2023.1110548.
12. Steinberg AW, Wechsler ME, Fernández Pérez ER. Trends in Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis-Related Mortality in the United States, 1999 to 2017. Ann Intern Med. 2020;172:160–3. https://doi.org/10.7326/m19-1564.

13. Wallace ZS, Fu X, Harkness T, Stone JH, Zhang Y, Choi H. All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type. Rheumatol Oxf Engl. 2020;59:2308–15. https://doi.org/10.1093/rheumatology/kez589.
14. Shuai Z-Q, Zhang C-X, Shuai Z-W, Ge S-L. Efficacy and safety of biological agents in the treatment of patients with Takayasu arteritis: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25:250–62. https://doi.org/10.26355/eurrev_202101_24391.
15. World Health Organization. Global tuberculosis report 2022 [Internet]. Geneva: World Health Organization; 2022. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022
16. Li L, Zhou F, Li F, Chen J, Xie X. Prevalence of tuberculosis infection among patients with Takayasu arteritis: a meta-analysis of observational studies. Sci Rep. 2023;13:22481. https://doi.org/10.1038/s41598-023-49998-y.
17. England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. Arthritis Care Res. 2015;67:865–72. https://doi.org/10.1002/acr.22456.
18. Thietart S, Karras A, Augusto J-F, Philipponnet C, Carron P-L, Delbrel X, et al. Evaluation of Rituximab for Induction and Maintenance Therapy in Patients 75 Years and Older With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. JAMA Netw Open. 2022;5:e2220925. https://doi.org/10.1001/jamanetworkopen.2022.20925.
19. Bloom JL, Pickett-Nairn K, Silveira L, Fuhlbrigge RC, Cuthbertson D, Akuthota P, et al. The Association Between Age at Diagnosis and Disease Characteristics and Damage in Patients With ANCA-Associated Vasculitis. Arthritis Rheumatol Hoboken NJ. 2023;75:2216–27. https://doi.org/10.1002/art.42651.
20. Osman M, Pagnoux C, Dryden DM, Storie D, Yacyshyn E. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. PloS One. 2014;9:e115026. https://doi.org/10.1371/journal.pone.0115026.
21. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, et al. Frailty in Older Adults: A Nationally Representative Profile in the United States. J Gerontol A Biol Sci Med Sci. 2015;70:1427–34. https://doi.org/10.1093/gerona/glv133.
22. Sattui S, Fu X, Cook C, Srivatsan S, Zhang Y, Wallace Z. The Impact of Chronologic versus Biologic Age on the Risk of Severe Infection, End-Stage Renal Disease, and Death in Older Adults with ANCA-Associated Vasculitis. In: ACR Meet Abstr [Internet]. San Diego, CA; 2023. Available from: https://acrabstracts.org/abstract/the-impact-of-chronologic-versus-biologic-age-on-the-risk-of-severe-infection-end-stage-renal-disease-and-death-in-older-adults-with-anca-associated-vasculitis/.
23. Sattui S, Stadler J, Borchin R, Burroughs C, Yeung C, Merkel P, et al. The Association of Frailty with Outcomes in Patients with Vasculitis. In: ACR Meet Abstr [Internet]. San Diego, CA; 2023. Available from: https://acrabstracts.org/abstract/the-association-of-frailty-with-outcomes-in-patients-with-vasculitis/.
24. Uslu Yurteri E, Sezer S, Torgutalp M, Yayla ME, Sahin Eroglu D, Okatan IE, et al. The factors predicting development of serious infections in ANCA-associated vasculitis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG. 2023;40:e2023015. https://doi.org/10.36141/svdld.v40i2.13243.
25. Kronbichler A, Kerschbaum J, Gopaluni S, Tieu J, Alberici F, Jones RB, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2018;77:1440–7. https://doi.org/10.1136/annrheumdis-2017-212861.
26. Haris Á, Polner K, Arányi J, Braunitzer H, Kaszás I. Incidence and clinical predictors of infections in patients treated with severe systemic ANCA-associated vasculitis. Physiol Int. 2021; https://doi.org/10.1556/2060.2021.00006.
27. Sarica SH, Gallacher PJ, Dhaun N, Sznajd J, Harvie J, McLaren J, et al. Multimorbidity in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Results From a Longitudinal, Multicenter Data Linkage Study. Arthritis Rheumatol Hoboken NJ. 2021;73:651–9. https://doi.org/10.1002/art.41557.
28•. . Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, et al. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. JAMA. 2021;325:2178–87. https://doi.org/10.1001/jama.2021.6615. **RCT comparing standard vs low-dose glucocorticoid regimens in AAV showing lower risk of incident infections.**
29•. . Walsh M, Merkel PA, Peh C-A, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med. 2020;382:622–31. https://doi.org/10.1056/nejmoa1803537. **RCT showing lower risk of incident infections and similar outcomes with low-dose glucocorticoid regimen in individuals with severe AAV**.
30. DRW J, Merkel PA, Schall TJ, Bekker P, ADVOCATE Study Group. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med. 2021;384:599–609. https://doi.org/10.1056/nejmoa2023386.
31. Nagle S, Nguyen Y, Puéchal X, Titeca-Beauport D, Crépin T, Mesbah R, et al. Real-life Use of the PEXIVAS Reduced-dose Glucocorticoid Regimen in Granulomatosis with Polyangiitis and Microscopic Polyangiitis. In: ACR Meet Abstr [Internet]. San Diego, CA; 2023. Available from: https://acrabstracts.org/abstract/real-life-use-of-the-pexivas-reduced-dose-glucocorticoid-regimen-in-granulomatosis-with-polyangiitis-and-microscopic-polyangiitis/.
32. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2024;83:30–47. https://doi.org/10.1136/ard-2022-223764.
33. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Care Res. 2021;73:1088–105. https://doi.org/10.1002/acr.24634.
34••. . Thery-Casari C, Euvrard R, Mainbourg S, Durupt S, Reynaud Q, Durieu I, et al. Severe infections in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides receiving rituximab: A meta-analysis. Autoimmun Rev. 2020;19:102505. https://doi.org/10.1016/j.autrev.2020.102505. **Meta-analysis analyzing incidence of severe infections and risk factors in individuals with AAV receiving treatment with rituximab.**
35••. . Odler B, Riedl R, Gauckler P, Shin JI, Leierer J, Merkel PA, et al. Risk factors for serious infections in ANCA-associated vasculitis. Ann Rheum Dis. 2023;82:681–7. https://doi.org/10.1136/ard-2022-223401. **Post-hoc analysis of RAVE study showing decreased risk of infections associated to use of antibiotic prophylaxis.**
36. Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, et al. Predicting Severe Infection and Effects of Hypogammaglobulinemia During Therapy With Rituximab in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol Hoboken NJ. 2019;71:1812–23. https://doi.org/10.1002/art.40937.
37. Habibi MA, Alesaeidi S, Zahedi M, Hakimi Rahmani S, Piri SM, Tavakolpour S. The Efficacy and Safety of Rituximab in

ANCA-Associated Vasculitis: A Systematic Review. Biology. 2022;11:1767. https://doi.org/10.3390/biology11121767.
38. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun. 2015;57:60–5. https://doi.org/10.1016/j.jaut.2014.11.009.
39. Padoan R, Felicetti M, Gatto M, Polito P, Doria A, Schiavon F. Rituximab-associated hypogammaglobulinaemia in ANCA-associated vasculitis and connective tissue diseases: a longitudinal observational study. Clin Exp Rheumatol. 2020;38(Suppl 124):188–94.
40. Opdam MAA, Campisi LM, de Leijer JH, Ten Cate D, den Broeder AA. Hypogammaglobulinemia in rheumatoid arthritis patients on rituximab: prevalence and risk factors. Rheumatol Oxf Engl. 2024;63:e1–2. https://doi.org/10.1093/rheumatology/kead326.
41●. . Omura S, Kida T, Noma H, Sunaga A, Kusuoka H, Kadoya M, et al. Association between hypogammaglobulinaemia and severe infections during induction therapy in ANCA-associated vasculitis: from J-CANVAS study. Rheumatol Oxf Engl. 2023;62:3924–31. https://doi.org/10.1093/rheumatology/kead138. **Longitudinal study showing association between hypogammaglobulinemia and incident infections in individuals with AAV.**
42. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Al-Jayyousi R, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. Ann Rheum Dis. 2023;82:937–44. https://doi.org/10.1136/ard-2022-223559.
43. Mescia F, Salviani C, Tonoli M, Affatato S, Moratto D, Tedesco M, et al. Sustained post-rituximab B-cell depletion is common in ANCA-associated vasculitis and is affected by sex and renal function. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2024;39:683–93. https://doi.org/10.1093/ndt/gfad197.
44. Dua AB, Husainat NM, Kalot MA, Byram K, Springer JM, James KE, et al. Giant Cell Arteritis: A Systematic Review and Meta-Analysis of Test Accuracy and Benefits and Harms of Common Treatments. ACR Open Rheumatol. 2021;3:429–41. https://doi.org/10.1002/acr2.11226.
45. Alibaz-Oner F, Kaymaz-Tahra S, Bayındır Ö, Yazici A, Ince B, Kalkan K, et al. Biologic treatments in Takayasu's Arteritis: A comparative study of tumor necrosis factor inhibitors and tocilizumab. Semin Arthritis Rheum. 2021;51:1224–9. https://doi.org/10.1016/j.semarthrit.2021.09.010.
46. Tian X, Li M, Jiang N, Zhao Y, Li J, Zhou Y, et al. Comparative Efficacy of Secukinumab Versus Tumor Necrosis Factor Inhibitors for the Treatment of Takayasu Arteritis. Arthritis Rheumatol Hoboken NJ. 2023;75:1415–23. https://doi.org/10.1002/art.42496.
47. Walsh M, Collister D, Zeng L, Merkel PA, Pusey CD, Guyatt G, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ. 2022;376:e064604. https://doi.org/10.1136/bmj-2021-064604.
48. Walsh M, Casian A, Flossmann O, Westman K, Höglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int. 2013;84:397–402. https://doi.org/10.1038/ki.2013.131.
49. Merkel PA, Niles J, Jimenez R, Spiera RF, Rovin BH, Bomback A, et al. Adjunctive Treatment With Avacopan, an Oral C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. ACR Open Rheumatol. 2020;2:662–71. https://doi.org/10.1002/acr2.11185.
50. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. J Am Soc Nephrol JASN. 2017;28:2756–67. https://doi.org/10.1681/asn.2016111179.
51. Bekker P, Merkel P, Jayne D. Safety of Avacopan in ANCA-Associated Vasculitis: Combined Data from Three Clinical Trials. In: ACR Meet Abstr [Internet]. Philadelphia, PA; 2022. Available from: https://acrabstracts.org/abstract/safety-of-avacopan-in-anca-associated-vasculitis-combined-data-from-three-clinical-trials/.
52. van Leeuwen JR, Popov T, Obergfell A, Rabelink TJ, Teng YKO. Preliminary Assessment of Safety and Tolerability of Avacopan During the Early Access Program for ANCA-Associated Vasculitis. Biol Targets Ther. 2023;17:11–4. https://doi.org/10.2147/btt.s394843.
53. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary. Rheumatol Oxf Engl. 2019;58:220–6. https://doi.org/10.1093/rheumatology/key207.
54. Karadağ Ö, Kaşifoğlu T, Özer B, Kaymakoğlu S, Kuş Y, İnanç M, et al. Viral hepatitis screening guideline before biological drug use in rheumatic patients. Eur J Rheumatol. 2016;3:25–8. https://doi.org/10.5152/eurjrheum.2015.150072.
55. Kim DK, Bridges CB, Harriman KH, Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), ACIP Adult Immunization Work Group. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older--United States, 2015. MMWR Morb Mortal Wkly Rep. 2015;64:91–2.
56. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345:1098–104. https://doi.org/10.1056/nejmoa011110.
57. Ruan Q, Zhang S, Ai J, Shao L, Zhang W. Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis. Clin Rheumatol. 2016;35:417–25. https://doi.org/10.1007/s10067-014-2817-6.
58●. . Sattui SE, Wallace ZS. Managing Immunosuppression in Vasculitis Patients in Times of Coronavirus Disease 2019. Rheum Dis Clin North Am. 2023;49:695–711. https://doi.org/10.1016/j.rdc.2023.03.007. **Review on incidence, risk and mitigation strategies for COVID-19 infection in individuals with vasculitis.**
59●. . Bass AR, Chakravarty E, Akl EA, Bingham CO, Calabrese L, Cappelli LC, et al. 2022 American College of Rheumatology Guideline for Vaccinations in Patients With Rheumatic and Musculoskeletal Diseases. Arthritis Care Res. 2023;75:449–64. https://doi.org/10.1002/acr.25045. **Guidelines for vaccination in individuals with rheumatic diseases.**
60. Park JK, Lee MA, Lee EY, Song YW, Choi Y, Winthrop KL, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis. 2017;76:1559–65. https://doi.org/10.1136/annrheumdis-2017-211128.
61. Abhishek A, Peckham N, Pade C, Gibbons JM, Cureton L, Francis A, et al. Effect of a 2-week interruption in methotrexate treatment on COVID-19 vaccine response in people with immune-mediated inflammatory diseases (VROOM study): a randomised, open label, superiority trial. Lancet Rheumatol. 2024;6:e92–104. https://doi.org/10.1016/s2665-9913(23)00298-9.

62. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70:414–22. https://doi.org/10.1136/ard.2010.137216.
63. Bingham CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum. 2010;62:64–74. https://doi.org/10.1002/art.25034.
64. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatol Oxf Engl. 2012;51:695–700. https://doi.org/10.1093/rheumatology/ker389.
65. Ribeiro ACM, Guedes LKN, Moraes JCB, Saad CGS, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis. 2011;70:2144–7. https://doi.org/10.1136/ard.2011.152983.
66•. . Terrier B, Richert L, Pugnet G, Aumaitre O, Moranne O, Diot E, et al. Innovative Anti-pneumococcal Vaccine Strategies versus Standard Vaccination Regimen in Patients with ANCA-associated Vasculitides Receiving Rituximab Therapy: A Multicenter Randomized Controlled Trial (PNEUMOVAS). ACR Meet Abstr [Internet]. Philadelphia, PA; 2022 [cited 2024 Mar 14]. Available from: https://acrabstracts.org/abstract/innovative-anti-pneumococcal-vaccine-strategies-versus-standard-vaccination-regimen-in-patients-with-anca-associated-vasculitides-receiving-rituximab-therapy-a-multicenter-randomized-controlled-trial/ **RCT on different regimens of pneumococcal vaccination in individuals with AAV receiving treatment with rituximab.**
67. Ghembaza A, Vautier M, Cacoub P, Pourcher V, Saadoun D. Risk Factors and Prevention of Pneumocystis jirovecii Pneumonia in Patients With Autoimmune and Inflammatory Diseases. Chest. 2020;158:2323–32. https://doi.org/10.1016/j.chest.2020.05.558.
68. Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis. 2018;77:644–9. https://doi.org/10.1136/annrheumdis-2017-211796.
69••. . Park JW, Curtis JR, Choi SR, Kim MJ, Ha Y-J, Kang EH, et al. Risk-Benefit Analysis of Primary Prophylaxis Against Pneumocystis Jirovecii Pneumonia in Patients With Rheumatic Diseases Receiving Rituximab. Arthritis Rheumatol Hoboken NJ. 2023;75:2036–44. https://doi.org/10.1002/art.42541. **Large national study assessing risk of incident PJP infection in patients receiving treatment with rituximab, including NNT and NNH calculations.**
70•. . Nettleton E, Sattui SE, Wallace Z, Putman M. Incidence of Pneumocystis Jiroveci Pneumonia in Patients With ANCA-Associated Vasculitis Initiating Therapy With Rituximab or Cyclophosphamide. Arthritis Care Res. 2024;76:288–94. https://doi.org/10.1002/acr.25222. **Large contemporary study assessing incidence of PJP in individuals with AAV.**
71•. . Anumolu N, Henry K, Sattui SE, Putman M. Is there a role for Pneumocystis jiroveci pneumonia prophylaxis in giant cell arteritis or polymyalgia rheumatica? Semin Arthritis Rheum. 2023;58:152154. https://doi.org/10.1016/j.semarthrit.2022.152154. **Large contemporary study assessing incidence of PJP in individuals with GCA and polymyalgia rheumatica.**
72. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res. 2021;73:924–39. https://doi.org/10.1002/acr.24596.
73. Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatol Baltim Md. 2018;67:1560–99. https://doi.org/10.1002/hep.29800.
74. Koutsianas C, Thomas K, Vassilopoulos D. Reactivation of hepatitis B virus infection in rheumatic diseases: risk and management considerations. Ther Adv Musculoskelet Dis. 2020;12:1759720X20912646. https://doi.org/10.1177/1759720x20912646.
75. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:215–9. https://doi.org/10.1053/j.gastro.2014.10.039.
76•. . Wijetilleka S, Jayne DR, Mukhtyar C, Ala A, Bright PD, Chinoy H, et al. Recommendations for the management of secondary hypogammaglobulinaemia due to B cell targeted therapies in autoimmune rheumatic diseases. Rheumatol Oxf Engl. 2019;58:889–96. https://doi.org/10.1093/rheumatology/key394. **Guidance on use of IVIG in individuals with hypogammaglobulinemia secondary to BCDT.**