Risk factors for severe infections during induction therapy of patients with microscopic polyangiitis

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Abstract

Objective

Severe infections contribute to morbidity and mortality in microscopic polyangiitis (MPA). This study aims to investigate the clinical characteristics and identify risk factors for early severe infections in newly diagnosed patients with MPA.

Methods

This retrospective cohort study included patients newly diagnosed with MPA followed up for at least 6 months at two tertiary care centres between January 2013 and December 2023. Clinical data, including demographics, laboratory findings, treatment regimens, and infection details, were collected. Multivariable logistic regression analysis was used to identify risk factors for severe infections within 6 months after the diagnosis in patients with new-onset MPA.

Results

A total of 374 patients with MPA were included, and 25.9% (97/374) experienced severe infections. Compared to the non-infection group, the infection group had a significantly higher daily average dosage of prednisone for remission induction, a higher proportion of patients with a history of chronic lung disease, and a higher proportion receiving rituximab (RTX) therapy ($p<0.05$). In multivariable logistic regression analysis, a history of chronic lung disease, higher daily average dosage of prednisone therapy and RTX therapy for remission induction were associated with an increased risk of severe infections, whereby higher baseline serum IgM levels were associated with a decreased risk. The most common site of infection was the lung (75.23%), and bacteria (43.1%) was the most prevalent pathogen.

Conclusion

MPA is associated with a high risk of severe infections, especially in patients treated with higher dosage glucocorticoid and with a history of chronic lung disease.

Key words

microscopic polyangiitis, severe infections, risk factors, clinical characteristics

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Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of rare autoimmune diseases comprising microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), characterised by inflammation of the walls of small to medium blood vessels leading to tissue and endothelial damage (1). MPA is the most common AAV, affecting a wide spectrum of organs including the kidneys and the lungs. The goal of MPA therapy is to attain remission within 3-6 months and minimise treatment related toxicity and complications without compromising therapy efficacy (2). Immunosuppressive therapy has greatly improved outcomes, however, treatment-associated infections have emerged as a primary cause of early mortality in patients. In addition, the disease which often affects the respiratory tract, plays a role in the progression of severe infections. Infections are the leading cause of death in the first year and a major cause of morbidity and mortality thereafter (3-5). Several risk factors including leukopenia, lymphopenia, lung disease, severe renal impairment, hypoalbuminaemia (6), higher steroid doses and older age have been reported to be associated with severe infections in patients with AAV (7-10). The use of trimethoprim sulfamethoxazole (TMP-SMX) in a prophylactic dose also has been reported to be associated with reduced risk of severe infections in patients with AAV (11). However, studies focusing on risk factors for infections that occur within 6 months of new-onset MPA are rare. This study retrospectively analysed the spectrum of severe infections and their potential risk factors in patients with MPA within the first six months of diagnosis.

Materials and methods

Patients

This was a retrospective cohort study based on two single centres in China. All patients with newly diagnosed MPA at Xiangya Hospital and Zhuzhou Hospital affiliated to Xiangya Medical College between January 2013 and December 2023 were included. The inclusion criteria were: 1) meeting the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for MPA (12); 2) newly diagnosed and with no steroid or immunosuppressant exposure history before enrolment; 3) at least 6 months of follow-up (including patients who died within 6 months but excluding patients lost to follow-up). The exclusion criteria were: 1) without immunosuppressive therapy due to general condition or personal reasons; 2) died after initial treatment; 3) complication of IgA nephropathy, membranous nephropathy and other chronic kidney disease; complication of other autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis; complicated with malignant tumors, organ transplantation, or acquired immune deficiency syndrome (AIDS); 4) with incomplete baseline information and incomplete follow-up data. This study was approved by the Ethics Committee of Xiangya Hospital (approval no.: 202108374) and Zhuzhou Hospital affiliated to Xiangya School of Medicine (approval no.: KY2024089-01). A total of 374 newly diagnosed patients were finally included in the study. All enrolled patients were divided into two groups with or without severe infections according to whether severe infections occurred during the six-month follow-up period.

Definition of severe infections

Severe infections were defined as a grade >2 according to the WHO classification (*e.g.* hospitalisation and/or intravenous treatment for infection and/or death). Infectious episodes were self-reported, but verified by the treating doctor, and information on infection events were collected from medical records.

Data collection

The following clinical data at baseline were collected: age, gender, comorbidities (chronic lung disease and diabetes), Birmingham Vasculitis Activity Score at baseline, organ involvement (kidney, skin, eye, subglottic, lung, ear,

nose and throat, heart, nervous system, sensorineural deafness), with or without severe infections at baseline. Laboratory data included red blood cell count, haemoglobin, leukocytes, neutrophils, lymphocytes, platelets, neutrophil-lymphocyte ratio (NLR), serum creatinine, estimated glomerular filtration rate (eGFR), serum albumin, serum immunoglobulins (IgG, IgA and IgM) and complement (C3 and C4), C reactive protein (CRP) were collected. eGFR was calculated using the Kidney Disease Improving Global Outcomes-Epidemiology Collaboration equation.

Treatment regimen

Renal replacement therapy (RRT), medical induction strategy (glucocorticoid (GC)+rituximab (RTX), GC+cyclophosphamide (CYC), GC+ mycophenolate mofetil (MMF)), and TMP-SMX prophylaxis were recorded. In addition, we aimed to assess more precisely the association between prednisone dosage and the risk of infection. For these analyses, average daily prednisone dose was collected from the date of treatment initiation (= T0') until the date of the first infection during treatment (which did not include severe infection at baseline), death or last follow-up (6 months), whichever occurred first. Information on infection events including the number of infections (times), the time of infection, infection site (such as respiratory infection, bloodstream infection, urinary infection, etc), associated pathogens were collected from medical records. Depending on the causative pathogens, infection was categorised as bacterial, viral, fungal or others.

Statistical analysis

The Kolmogorov-Smirnov test was used to verify the normality of the measurement data of the demographic and clinical characteristics of the participants. The measurement data with a normal distribution were presented as mean ± standard deviation, and the comparison between the two groups was performed by t-test. Non-normal measurement data were presented as median and IQR, and Mann-Whitney U-test was used for comparison between the two groups. The categorical variables were presented as counts (percentages), and the chi-square test or Fisher's exact probability test was adopted for the comparison between the two groups. All parameters with a $p<0.05$ in univariable analysis were included in the multivariate logistic analysis to analyse the risk factors of severe infections, and backward selection was used in the final model. All analyses were carried out by using SPSS25.0 software.

Table I. Baseline characteristics of patients without and with severe infections.

	Patients without severe infections (n=277)	Patients with severe infections (n=97)	*p*-value
Age (years)	64 (54, 71)	64 (56.5, 72)	0.425
Female sex	142 (51.26)	41 (42.27)	0.127
Baseline BVAS Score	15 (12, 18)	16 (12, 19)	0.046
History of chronic lung disease	47 (16.97)	29 (29.90)	0.006
History of diabetes	29 (10.47)	6 (6.19)	0.213
Use of TMP-SMX	47 (17.09)	11 (11.34)	0.179
With severe infections at baseline	140 (50.54)	58 (59.79)	0.116
Organ involvement			
Kidney	247 (90.15)	86 (89.58)	0.874
Lung	159 (58.03)	57 (59.38)	0.818
Heart	17 (6.20)	5 (5.21)	0.722
Ear, nose and throat	26 (9.49)	6 (6.25)	0.331
Mucous membranes and eyes	16 (5.84)	8 (8.33)	0.393
Cutaneous	4 (1.46)	2 (2.08)	0.652
Nervous system	57 (20.80)	17 (17.71)	0.514
Laboratory results			
RBC	2.945 (2.49, 3.46)	2.74 (2.40, 3.25)	0.070
Hb	83 (70, 97)	83 (68, 94)	0.452
WBC (/μL)	8.2 (5.9, 12.1)	7.5 (5.65, 10.2)	0.257
Lymphocytes (/μL)	1.1 (0.7, 1.5)	1.1 (0.7, 1.45)	0.889
Neutrophils(/μL)	6.4 (4.3, 9.5)	5.8 (4.39, 8.28)	0.281
N/L	6.36 (3.44, 9.43)	5.36 (3.70, 8.21)	0.274
PLT	260 (192, 351)	234 (182.5, 311)	0.026
IgG (g/L)	14.86 (11.9, 17.5)	14.5 (11.55, 17.6)	0.393
IgA (mg/L)	2560 (1830, 3600)	2495 (1820, 3130)	0.313
IgM (mg/L)	980.5 (750, 1440)	914 (780, 1260)	0.030
C3	826 (705, 971)	817 (703.5, 984.5)	0.240
C4	240 (193, 290)	236.5 (215.5, 310)	0.103
CRP	21.1 (5.13, 86.3)	15.5 (5.06, 62.2)	0.545
Albumin	31.5 (27.4, 36.5)	31.45 (27.55, 35.2)	0.985
Creatinine (mg/dL)	3.80 (2.01, 6.29)	3.93 (2.43, 4.82)	0.371
Urea	16.71 (10.71, 24.1)	16.95 (10.79, 22.40)	0.076
eGFR	16.52 (10.08, 31.13)	17.60 (10.63, 29.09)	0.670
Remission induction treatment			
GC+CYC	238 (85.92)	74 (76.29)	0.028
GC+RTX	19 (6.86)	13 (13.40)	0.047
GC+MMF	20 (7.22)	10 (10.31)	0.335
Renal replacement therapy at baseline	66 (23.83)	17 (17.53)	0.199
Average daily dosage of prednisolone	20.64 (14.85, 27.5)	32.05 (22.5, 42.9)	< 0.0001

GC: glucocorticoid; RTX: rituximab; CYC: cyclophosphamide; MMF: mycophenolate mofetil.

Results

Baseline patient characteristics stratified by infectious complications

A total of 374 patients who met the inclusion criteria were enrolled in our study. There were 97 patients with at least one severe infection within the 6 months after the diagnosis. Characteristics of patients are summarised in Table I. Baseline characteristics between patients in the two groups were similar; however, compared with those in the non-infection group, the patients in the infection group had higher BVAS score at baseline ($p=0.046$), and more of them had chronic respiratory disease ($p<0.001$). The non-infection group had relatively higher platelet levels ($p=0.026$) and serum IgM levels ($p=0.03$). Regarding therapy and medication use for remission induction, the infection group had a larger proportion of patients that underwent

Table II. Multivariable logistic regression analysis of predictors of severe infections.

Covariate	OR	95% CI	*p*-value
History of chronic lung disease	2.188	1.060 to 4.514	0.034
GC+RTX	4.898	1.834 to 13.079	0.002
IgM	0.999	0.999 to 1.000	0.009
Higher average daily dosage of prednisolone	13.427	7.038 to 25.616	<0.0001

prednisone in combination with RTX (13.4% *vs*. 6.86%, p=0.028) and had a lower proportion of patients that underwent prednisone in combination with CYC (76.29% *vs*. 85.92%, p=0.047). Furthermore, patients in the infection group had a higher average dose of prednisone (p<0.0001) during the first 6 months.

Predictors of severe infections

We further analysed the risk factors for severe infections in MPA patients within 6 months after the diagnosis. Univariate analysis of demographics, comorbidities, laboratory examinations at baseline and medication use were examined. Variables with a p-value <0.05 (in the univariate analysis) were entered into multivariate analysis and factors associated with the risk of severe infection within 6 months after the diagnosis are described in Table II. In multivariate logistic analysis (after adjustment for previously identified factors), history of chronic lung disease (OR 2.188; 95% CI 1.060 to 4.514; p=0.034), GC + RTX for remission induction (OR 4.898; 95% CI 1.834 to 13.079; p=0.002) and higher average daily dosage of prednisolone (OR 13.427; 95% CI 7.038 to 25.616; p<0.0001) were independent predictive factors for severe infections, while serum IgM levels was still associated with a reduced risk of infection (OR 0.999; 95% CI 0.999 to 1.000; p=0.009). Notably, severe infection at baseline was not significantly associated with an increased risk of severe infection.

Characteristics of severe infections

During the follow-up period within 6 months, 97 patients in the infection group had 101 infections; 3 patients (3.09%) had two or more infections. The first episode of infection occurred a median of 77.4 (range: 15-180) days after diagnosis of MPA. The most common sites of infection were bronchopulmonary infections (75.23%), followed by skin infections (11.01%), bloodstream infections (6.42%), urinary tract infections (4.59%), abdominal cavity infections (1.83%) and central nervous system infections (0.93%), with 8 patients having concurrent infections in two different sites simultaneously (Table III). Microbiological confirmation was obtained in 54 episodes (51 patients) of the reported cases, mainly derived from the culture results of sputum, urine, blood and cerebrospinal fluid, and 11 samples had cultured out multiple (two or more) pathogens at the same time. There were 31 (25 persons) bacterial infections, 19 (15 persons) fungal infections, 17 (15 persons) viral infections, 3 *Mycobacterium tuberculosis* infections, 1 (1 person) with Mycoplasma infection and 1 (1 person) with Rickettsial infection. Bacteria (31 episodes) were the main pathogens, with 8 episodes (25.8%) of *Klebsiella*, 5 episodes (16.1%) of *Pseudomonas aeruginosa*, 4 episodes (12.9%) of *Enterococcus*, 2 episodes each (6.4%) of *Escherichia coli*, *Nocardia*, *Haemophilus influenzae*, and *Staphylococcus*. The most common cause of fungal infections was *pneumocystis jirovecii* (8 episodes), followed by *Candida* (5 episodes), and *Aspergillus* (4 episodes). Of note, 8 pneumocystis infections occurred without cotrimoxazole prophylaxis, including 4 patients treated with prednisone in combination with CYC, 3 patients treated with prednisone in combination with MMF, and 1 patient treated with prednisone in combination with RTX. The most common cause of viral infections was Varicella zoster virus (9 episodes), followed by Epstein-Barr virus (2 episodes), cytomegalovirus (2 episodes), and SARS-CoV-2 virus (2 episodes). We also recorded three episodes of *Mycobacterium tuberculosis* and one episode of *Coxiella burnetii* and *Mycoplasma pneumoniae*. Unfortunately, one of the patients passed away due to severe pneumonia.

Table III. Characteristics of severe infections (n=97).

Characteristics	Number
Number of infections (times)	
1	94 (96.9%)
2	2 (2.06%)
3	1 (1.03%)
Infection site	
Lung	82 (75.23%)
Skin/soft tissue	12 (11.01%)
Blood	7 (6.42%)
Urinary tract	5 (4.59%)
Abdominal cavity	2 (1.83%)
Central nervous system	1 (0.93%)
Pathogen type	
Bacteria	31
Klebsiella	8
Pseudomonas aeruginosa	5
Enterococcus	4
Escherichia coli	2
Nocardia spp.	2
Haemophilus influenzae	2
Staphylococcus	2
Ralstonia mannitolilytica	1
Corynebacterium striatum	1
Legionella	1
Citrobacter	1
Fungus	19
Pneumocystis jirovecii	8
Candida spp.	5
Aspergillus spp.	4
Cryptococcal	1
Trichosporon	1
Virus	17
Varicella zoster virus	11
Epstein-Barr virus	2
Cytomegalovirus	2
SARS-CoV-2	2
Others	5
Mycobacterium tuberculosis	3
Coxiella burnetii	1
Mycoplasma pneumoniae	1

Note: Some patients were infected in two sites simultaneously, and some were infected with multiple pathogens at the same time.

Discussion

With the use of corticosteroids and immunosuppressive therapies, the outcome of AAV patients has significantly improved. However, disease activity and treatment-induced infections remain major challenges. A study of 489 patients shows a high rate of severe infections in AAV with incidence rates of severe infections at 1, 2 and 5 years being 22, 23 and 26%, respectively (13). Infection is not only the leading

cause of mortality in the early stage of remission-induction treatment among AAV patients but is also a crucial factor related to poor long-term prognosis. Therefore, it is essential to focus on infection-related factors, and early detection of infection can provide clinicians with more opportunities to reduce mortality. This study aims to analyse the clinical characteristics and risk factors associated with infections in MPA patients, with the goal of prompt and effective therapeutic measures against infection to improve patient outcomes.

Our study is a large retrospective MPA cohort, a total of 101 infections were recorded among 97 patients (25.9%) in the infected group. Several risk factors for AAV infection have been reported in the literature, including older age, diabetes, impaired renal function, lymphopenia, immunosuppressive therapy and a high cumulative dose of steroids (7, 8). Partially consistent with these findings, our results revealed that MPA patients with infection within the first six months had a larger proportion of a history of chronic lung disease, a higher BVAS, lower platelet and serum IgM levels at the time of diagnosis, and received a higher dose of prednisone, compared with patients without infection. Further, in the multivariable analysis, the higher average daily dosage of prednisolone, the use of RTX for induction, and history of chronic lung disease was independently associated with an increased risk of severe infections, whereas serum IgM levels were found to be protective.

Therapeutic management has been identified as a major contributor to the risk of infection. Rapid control of AAV in the early stage of disease usually requires heavy immunosuppressive therapy. However, high-dose glucocorticoid and immunosuppressant therapy increase the risk of severe infections. In this study, we found that patients with infections were treated with higher average daily doses of glucocorticoids during follow-up. This result is consistent with other literature. Namely, studies including PEXIVAS (14) and LoVAS (15) trials showed patients in the steroid reduced-dose group experienced less severe infections compared with patients in the standard-dose group, with a non-inferior remission rate at 6 months. In addition, a meta-analysis enrolled 1145 participants from three randomised controlled trials and two observational studies, of whom 543 were assigned to the low-dose GC group and 602 to the high-dose GC group. This meta-analysis showed no difference in remission or relapse rates between two groups, while significant reduction in the risk of infection (RR 0.60, p=0.02) on low-dose GC group compared with high-dose GC group (16). Now current guidelines recommend a more rapid steroid taper during induction treatment with CYC or RTX (17). And avacopan has emerged as an effective GC-sparing agent in AAV(18).

We have observed that the use of RTX is associated with an increased risk of severe infections compared with CYC. The results of our study contrast with previous studies showing that a numerically higher cumulative incidence of severe infections among patients treated with CYC than patients treated with RTX for both induction and maintenance therapy (19). This discrepancy may be explained by a potential selection bias as clinicians might have been more likely to prescribe the RTX regimen to patients perceived to be at higher risk of infection. Additionally, due to economic reasons, patients with more severe conditions in China tend to be prescribed RTX more frequently, and the severity of AAV is also a contributing factor to susceptibility to infection. Furthermore, in our cohort, the low use of TMP-SMX prophylaxis is also a factor influencing the results. Although RTX is now recommended for remission induction and maintenance in patients with AAV, severe infections remain and should be of concern (20).

A recent study from the RAVE cohort showed that TMP-SMX reduces the risk of severe infections (not only PJP infection) in patients treated with either GCs and RTX or CYC/AZA, especially within the first 6 months after initiation of therapy (11). In addition, available data from Waki *et al*. and Arielle *et al*. reported similar protective effects of TMP-SMX on severe infections (21, 22). However, there was no difference on the data of the use of TMP-SMX prophylaxis between the two groups in our study.

It may be related to the small number of patients in both groups receiving TMP-SMX.

The prophylaxis rate observed in our cohort (15.5%) was notably lower than the rates reported by Waki *et al*. for AAV patients receiving similar immunosuppressive regimens (21). Several factors likely contribute to this underuse, including clinician concerns about adverse effects, drug interactions, and uncertain treatment duration, as well as patient challenges such as poor adherence due to drug intolerance.

Our study showed baseline serum IgM levels were independently associated with a decreased risk of severe infections in the multivariable analysis. IgM is the first antibody secreted mainly by B1 cells following exposure to foreign antigens and plays a regulatory role in the development of humoral immunity. Deletion of selective IgM significantly reduced immune protection against numerous infectious agents (23, 24). Furthermore, patients suffering from selective IgM deficiency are more susceptible to infections and autoimmune conditions. In addition, previous studies have demonstrated that RTX treatment for AAV increased the risk of infection (25), and serum IgM concentrations decreased after RTX treatment in patients with AAV (26, 27), indirectly suggesting that IgM may have a protective role against AAV infection. The protective effect of elevated baseline IgM levels may be attributed to several biological mechanisms: enhancing antigen presentation to germinal centre B cells, thereby supporting T-dependent antibody production; enhancing the development of IgG responses; mediating antigen opsonisation by facilitating complement C1q-dependent uptake by macrophages; contributing to pathogen neutralisation by blocking cellular entry or inducing pathogen aggregation; activating the classical complement pathway, leading to the formation of the membrane attack complex and subsequent pathogen lysis (24). Nonetheless, in another cohort, a higher serum

level of IgM was associated with the risk of severe infections, which is contrary to our conclusion (11). Further studies are necessary to characterize the correlation between serum IgM levels and infection in AAV. Our data might further emphasise the importance of closely monitoring of patients with AAV who initially have low IgM serum levels at baseline and may help to tailor immunosuppression.

Our study showed that the platelet value was higher in the non-infection group, but it was not associated with severe infections in the multivariable analysis independently. A platelet count >250 x 10^9/L was found to be a protective factor for survival in the study by Sánchez Álamo *et al*. (4). A Swedish cohort of 93 GPA patients by Bligny *et al*. also showed that patients with higher levels of platelets at baseline were correlated with better survival (28). Lower platelets count in AAV patients may be due to immune complex formation, tuberculosis, decreased bone marrow activity, thrombotic microangiopathy. However, the specific mechanisms underlying the association between higher platelet counts and better prognosis need further study.

Notably, the most prevalent infection type in this study was bronchopulmonary infections (75.23%), almost unanimous in all studies, followed by skin/soft tissue infection, bloodstream infection and urinary tract infection. Respiratory infection is intimately linked to MPA-induced lung injury. Activated neutrophils induced by ANCA release reactive oxygen species, proteolytic enzymes and proinflammatory cytokines, contributing to endothelial damage and inflammation. This damage compromises the vascular integrity, leading to erythrocyte extravasation and subsequent alveolar haemorrhage. Additionally, plasma protein extravasation contributes to the formation of fibrinoid necrosis, ultimately causing pulmonary interstitial fibrosis. Furthermore, AAV patients often suffer from underlying lung conditions such as bronchiectasis, interstitial pneumonia, and chronic obstructive pulmonary disease (COPD), which alter the structure of the airways and lung parenchyma. These factors make patients more susceptible to respiratory infections.

In this study, the most frequently identified pathogenic microorganisms were *Klebsiella*, *Pseudomonas aeruginosa*, *Pneumocystis jirovecii*, *Candida* spp. and Varicella zoster virus, resembling the opportunistic pathogens associated with iatrogenic infections (*e.g.*, infections resulting from the long-term use of immunosuppressive drugs). Therefore, in the absence of bacterial culture and drug sensitivity results, it is recommended to administer antibiotics that provide coverage against these microbial species. This approach can help mitigate the risk of infection and improve patient outcomes in MPA patients. Additionally, increased vaccination compliance including pneumococcal vaccine and influenza vaccination, recombinant varicella-zoster virus (VZV) vaccination is required to reduce the risk of infection in patients with rheumatic and musculoskeletal diseases (29). Notably, eight cases of *Pneumocystis jirovecii* pneumonia were identified who did not receive TMP-SMX prophylaxis. Recent European League against Rheumatism guidelines stress the significance of antibiotic prophylaxis against *Pneumocystis jirovecii* infection in patients with AAV receiving RTX, CYC and/or high doses of GCs (30).

Our study has some limitations. First, this was a retrospective study that included data from two independent single-centre cohorts, which may have led to unavoidable bias. Second, the number of MPV patients in this study was relatively small. Therefore, further studies are required using a large cohort of patients to validate these results. In conclusion, MPA is associated with a high risk of severe infections, especially in patients treated with higher dosage GC. These results should prompt clinicians to consider a more rapid steroid taper during induction treatment, especially in patients with a history of chronic lung disease.

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