RESEARCH ARTICLE

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Risk factors for infectious complications of ANCA-associated vasculitis: a cohort study

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Abstract

Background: Severe infections are common complications of immunosuppressive treatment for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with renal involvement. We investigated the clinical characteristics and risk factors of severe infection in Chinese patients with AAV after immunosuppressive therapy.

Methods: A total of 248 patients with a new diagnosis of ANCA-associated vasculitis were included in this study. The incidence, time, site, and risk factors of severe infection by the induction therapies were analysed. Multivariate Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CI).

Results: A total of 103 episodes of severe infection were identified in 86 (34.7%, 86/248) patients during a median follow-up of 15 months. The incidence of infection during induction therapy was 38.5% for corticosteroids (CS), 39.0% for CS+ intravenous cyclophosphamide (IV-CYC), 33.8% for CS+ mycophenolate mofetil and 22.5% for CS + tripterygium glycosides, 76 (73.8%) infection episodes occurred within 6 months, while 66 (64.1%) occurred within 3 months. Pneumonia (71.8%, 74/103) was the most frequent type of infection, and the main pathogenic spectrum included bacteria (78.6%), fungi (12.6%), and viruses (8.7%). The risk factors associated with infection were age at the time of diagnosis (HR = 1.003, 95% CI = 1.000–1.006), smoking (HR = 2.338, 95% CI = 1.236–4.424), baseline secrum creatinine (SCr) ≥5.74 mg/dl (HR = 2.153, 95% CI = 1.323–3.502), $CD4^+$ T cell< 281 μl (HR = 1.813, 95% CI = 1.133–2.900), and intravenous cyclophosphamide regimen (HR = 1.951, 95% CI =1.520–2.740). Twelve (13.9%) patients died of severe pneumonia.

Conclusion: The infection rate during induction therapy was high in patients with AAV. Bacterial pneumonia was the main type of infection encountered. Age at the time of diagnosis, smoking, baseline SCr ≥5.74 mg/dl, $CD4^+$ T cell< 281 μl, and IV-CYC therapy were identified as risk factors for infection.

Keywords: Anti-neutrophil cytoplasmic antibody, Vasculitis, Infection, Lung, Risk factors

Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis syndrome including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangitis (EGPA) and renal-limited vasculitis (RLV). The diagnosis of AAV is based on the presence of clinical manifestations with characteristic histopathological findings and the presence of MPO-ANCA or PR3-ANCA [1–7]. AAV may have predominant involvement of the upper respiratory tract, lungs, kidneys, skin, and nervous system. Most patients with AAV achieved remission after appropriate immunosuppressive therapy with corticosteroids and immunosuppressants, including cyclophosphamide (CYC), mycophenolate mofetil (MMF), and rituximab (RTX) [8–11]. Nevertheless, infection after immunosuppressive therapy contributes to the most common cause of death. The burden of infectious disease in patients with AAV has been reported [1–6, 12–15]. Nonetheless, risk infectors reported so far are inconsistent. In this study, we retrospectively analysed the epidemiological and clinical characteristics of Chinese patients with ANCA-associated vasculitis and discussed major infection episodes occurring during immunosuppressive therapy in a single centre.

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Methods

Patient selection

A total of 248 patients newly diagnosed with AAV and renal involvement who met the criteria of the Chapel Hill Consensus Conference [7] between January 1, 1998 and December 31, 2013 at the National Clinical Research Center of Kidney Diseases Jinling Hospital were included, among whom 194 patients had renal biopsies that showed pauci-immune necrotic and crescentic glomerulonephritis. All patients were ANCA-positive. Patients with secondary vasculitis, including Henoch-Schonlein purpura, allergy, autoimmune disease, tumour, cryoglobulinemia and infection, were not included. Patients with end-stage renal disease (ESRD) or who received only non-immunosuppressive treatment for infection at the time of diagnosis of AAV were excluded from the study. Ethical statement: This study was approved by the Institutional Review Board of our hospital and performed in accordance with the ethical standards laid down in appropriate version of the Declaration of Helsinki. All patients signed informed consent.

Clinical and laboratory data

All clinical and laboratory data were collected retrospectively at diagnosis and during the follow-up period, including the patients' age, gender, medical history, routine blood analysis, 24-h urine protein excretion, urinary sediment red blood cell count, serum albumin and serum creatinine (SCr), liver enzymes, immunoglobulin and T lymphocyte counts, serum ANCAs, lung involvement, Birmingham Vasculitis Activity Score (BVAS) [16], the usage of immunosuppressive agents, methylprednisone pulse therapy, plasma exchange, and adverse events including major infection. Major infections were diagnosed according to common terminology criteria for adverse events (CTCAE) v4.0 in addition to clinical and radiological manifestations and microorganism cultures.

Immunosuppressive therapies

None of the patients had received any immunosuppressive therapy before diagnosis. Patients without contraindication initially received intravenous methylprednisolone pulse therapy (0.5 g, once daily, for 3 consecutive days) after diagnosis of AAV. Patients with severe manifestations of AAV underwent plasma exchange therapy. All patients received oral prednisone at a dose of 0.6–0.8 mg/kg/day for 4 weeks, which was then tapered by 5 mg each week to 10 mg/day. Induction immunosuppressive agents included MMF 1–1.5 g/day orally, monthly intravenous cyclophosphamide (IV-CYC) at 0.75–1.0 g/m^2 body surface area in monthly pulses, tripterygium glycosides (TW, extract from the traditional Chinese herb *Tripterygium wilfordii,* which mainly contains triptolide) and multi-target therapy (prednisone, mycophenolate mofetil and tacrolimus) [8]. Maintenance therapy included prednisone 5 mg/day combined with MMF and azathioprine. Prophylaxis of *Pneumocystis Jirovecii* pneumonia (PJP) with SMZ-CO (trimethoprim-sulfamethoxazole 400/80 0.48 g per day) was used in patients whose CD4$^+$ T cell counts were less than 200/μl, and the doses were tapered in patients with renal dysfunction [17].

Antimicrobial therapy

All immunosuppressive agents, except prednisone, were discontinued in patients with AAV who suffered from major infection during the follow-up period. Antimicrobial therapy was prescribed according to clinical and radiological manifestations and microbiological characteristics. Patients diagnosed with PJP were treated with SMZ-CO and echinocandin together.

Supportive therapy

Patients with weight loss were prescribed enteral nutrition. The patients with severe acute kidney injury or acute respiratory distress syndrome (ARDS) were treated with continuous blood purification.

Definitions

A recorded severe infectious complication was defined as implying the administration of an antimicrobial medication for an observable clinical, microbiological and radiologic suspected infection requiring hospitalization. Immediate dialysis was defined as the clinical necessity of renal replacement therapy on admission. The first immunosuppressive agent used in addition to corticosteroids was termed induction therapy. The immunosuppressive regimen used during follow-up was termed the maintenance agent. The diagnosis criteria for deep fungal infection included clinical manifestations, such as fever, cough, diarrhoea or lower urinary tract symptoms, and the detection of fungi in sputum, urine, stool or tissue specimens. Cytomegalovirus (CMV) infection was diagnosed by CMV polymerase chain reaction (PCR). The range of quantification of this assay was 600–100,000 copies/ml for CMV. CMV pneumonia was defined as the detection of ground glass opacity by chest X-ray film or computed tomography, the detection of CMV in the bronchoalveolar lavage fluid or lung tissue samples, and clinical signs such as fever, cough, dyspnoea and hypoxemia. The diagnosis of PJP was made clinically or by the identification of *Pneumocystis* from sputum, bronchoalveolar fluid, tracheal secretions or lung tissue by special stains or a non-nested PCR, specifically designed to diagnose pneumonia rather than colonization [18]. ARDS was defined as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen $[P_{aO2}/F_{IO2}] \leq 200$ mmHg) with bilateral infiltrates on chest radiographs, without left atrial hypertension. Multiple organ dysfunction syndrome (MODS) was defined as the simultaneous failure of at

least two organs. ESRD was defined as eGFR < 15 ml/min per $1.73m^2$ or requiring renal replacement treatment for > 3 months.

Follow-up and endpoints
The follow-up endpoints included the final date of December 31, 2014, dropping out before the final date, reaching ESRD, or death.

Statistical analysis
Statistical analysis was performed with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Medians and ranges were reported for non-normally distributed data, and means ± standard deviations were reported for normal-distributed data. The Kruskal-Wallis test was applied for the comparison of non-normal distributed data. Differences between means were tested using the Student's t-test. A Mann-Whitney U test was used for non-parametric distributions. Chi-squared tests were used for the comparison of categorical data. To address the independent predictive value of factors associated with the rate of infections, the variables with P values of less than 0.1 in univariate analysis as well as those reported in the literature were selected for multivariate analysis using the Cox regression model. The group with corticosteroids only was used as a reference group in multivariate analysis. Only the time to first severe infection was evaluated. Laboratory values and BVAS used for modelling were from the time of diagnosis. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-offs of SCr, haemoglobin, albumin, CD4+ T cells and BVAS. All tests were two-tailed, and P-values of < 0.05 were considered significant. Confidence intervals (CIs) were calculated at the 95% level.

Results
Characteristics of the cohort
This study identified 248 individuals with ages ranging from 14 to 78 years (median 55 years), including 214 cases diagnosed as MPA, 16 cases diagnosed as RLV, 10 cases diagnosed as GPA and 8 cases diagnosed as EGPA. Seventy-five patients (30.2%) showed lung involvement, 30 (12.1%) had alveolar haemorrhage, and 54 (21.8%) had sinus involvement. MPO-ANCA was more prevalent, and only 21 cases (8.5%) were PR3-ANCA-positive. Fifty-three patients started immediate dialysis. Initial immunosuppressive treatment consisted of pulse methylprednisolone (67.3%), plasma exchange (23.8%), IV-CYC (26.6%), MMF (31.0%) and TW (16.1%). Twenty-six percent of patients received only oral corticosteroids (Table 1). Forty-two patients (16.5%) received SMZ-CO to prevent PJP, and 29 of them were CYC users.

Incidence and location of infection
A total of 103 infectious episodes occurred in 86 patients (34.7%) during follow-up for 1~ 155 months (median 15 months). Fifteen cases experienced a second episode of infection, and one patient experienced a third episode. Seventy-six episodes (73.8%) of infection occurred during induction therapy (median 1.5 months). Twenty-seven episodes (26.2%) occurred during maintenance therapy (median 18 months), and six episodes (5.8%) occurred after 24 months. Pulmonary infections (71.8%, 74/103) were the most frequent type of infection, followed by skin ($n = 7$, 6.8%), digestive tract ($n = 3$, 2.9%), urinary tract ($n = 2$, 1.9%) and central nervous system ($n = 1$, 1.0%) infections. Six patients (5.8%) developed sepsis because of their reported infection.

Pathogens
The pathogens responsible for infection were confirmed in 87 episodes. The whole pathogen spectrum included bacteria, fungi and viruses. Bacterial infection was the most common ($n = 57$, 66%), especially *Acinetobacter baumannii*, followed by fungal ($n = 21$, 24%) and viral infections ($n = 9$, 10%) There were four CMV, seven PJP and 16 unspecified infections (Table 2).

Risk factors for infection
The infectious rate of induction therapy with corticosteroids only was 38.5% (25/65), that for CS + IV-CYC was 39.0% (26/66), CS + MMF was 33.8% (26/77) and CS + TW was 22.5% (9/40). The incidence of smoking (36.0% vs. 17.3%, $P = 0.000$) and diabetes (8.1% vs. 2.5%, $P = 0.032$) was significantly higher among the infected patients. The cutoff level of SCr haemoglobin, albumin, CD4+ T cells, and BVAS were determined as 5.74 mg/dl, 7.75 g/dl, 33.95 g/l, 281/ul, and 25.5 respectively based on ROC curve analysis. Single factor analysis revealed that risk factors for complicated infection in patients with AAV included age, smoking, pulmonary involvement, hemoglobulin, albumin, SCr level, CD4 [+] T cell count, BVAS, and immunosuppressive therapy with MMF, CYC and TW. In adjusted models for the AAV cohort, increased risks of infection were observed in patients who were older at the time of diagnosis (HR = 1.003, 95% CI = 1.000–1.006), smoking (HR = 2.338, 95% CI = 1.236–4.424), with baseline Scr ≥5.74 mg/dl (HR = 2.153, 95% CI = 1.323–3.502), CD4^{+} T cell< 281 μl (HR = 1.813, 95% CI = 1.133–2.900), and users of intravenous cyclophosphamide regimen (HR = 1.951, 95% CI =1.520–2.740) (Table 3).

Characteristics of pneumonia
The exact pathogen was identified in 44 of 82 episodes of pneumonia. Bacteria were the most common pathogens ($n = 27$, 61.4%), especially *Acinetobacter baumannii*

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Table 1 Clinical characteristics of AAV patients complicated with or without infection

	AAV (n = 248)	Infection group (n = 86)	Non-infection group (n = 162)	P
Age(ys)	55.0 (42.8~ 64.0)	58.0 (46.8~ 66.0)	54.0 (40.0~ 63.0)	0.082
male, n(%)	103 (41.5)	40 (46.5)	63 (38.9)	0.155
smoke, n(%)	59 (23.8)	31 (36.0)	28 (17.3)	0.000**
Diabetes, n(%)	11 (4.4)	7 (8.1)	4 (2.5)	0.032*
MPO-ANCA, n(%)	227 (91.5)	79 (91.9)	148 (91.4)	0.968
PR3-ANCA, n(%)	21 (8.5)	7(8.1)	14 (8.6)	0.968
Hemoglobin (g/dl)	8.5 (7.4~ 9.7)	8.2 (6.7~ 9.2)	8.8 (7.7~ 9.9)	0.004**
White blood cell (/mm3)	7200.0 (5000.0~ 10,000.0)	7600.0 (5900.0~ 11,350.0)	6900.0 (4900.0~ 9750.0)	0.049*
Albumin (g/l)	35.5 (31.6~ 38.7)	33.8 (30.3~ 36.9)	35.9 (32.4~ 39.6)	0.002*
Globulin (g/l)	27.4 (23.4~ 32.2)	26.8 (22.3~ 33.1)	27.6 (23.5~ 31.6)	0.761
Creatinine (mg/dl)	3.3 (1.8~ 5.3)	4.16 (2.5~ 6.9)	2.8 (1.5~ 4.7)	0.000**
eGFR< 60 ml/min per 1.73m^2, n(%)	216 (87.1)	81 (94.2)	135 (83.3)	0.000**
CD4 lympnocyte cell(/ul)	416.0 (234.5~ 589.8)	399.0 (207.5~ 552.0)	428.0 (258.0~ 662.0)	0.027*
IgG (g/l)	13.3 (10.4~ 16.4)	13.4 (10.4~ 16.5)	12.9 (10.3~ 16.3)	0.570
C3 (g/l)	0.9 (0.8~ 1.1)	0.9 (0.8~ 1.2)	0.9 (0.8~ 1.1)	0.569
Lung involvement, n(%)	75 (30.2)	34 (39.5)	41 (25.3)	0.011**
BVAS	14 (12~ 16)	15 (12~ 17)	14 (12~ 16)	0.009**
MP pulse therapy, n(%)	167 (67.3)	56 (65.1)	111 (68.5)	0.929
Plasma exchange, n(%)	59 (23.8)	25 (29.1)	34 (20.9)	0.109
Induction therapy				
corticosteroids only, n(%)	65 (26.2)	25 (29.1)	40 (24.7)	0.349
corticosteroids+CYC, n(%)	66 (26.6)	26 (30.2)	44 (27.2)	0.938
corticosteroids+MMF, n(%)	77 (31.0)	26 (30.2)	47 (29.0)	0.245
corticosteroids+TW, n(%)	40 (16.1)	9 (10.5)	31 (19.1)	0.052

**P < 0.01; *P < 0.05, *IgG* Immunoglobulin G, *BVAS* Birmingham vasculitis activity score, *MP* Methylprednisone, *CYC* Cyclophosphamide, *MMF* Mycophenolate mofetil

(n = 6, 13.6%), *Staphylococcus aureus* (n = 5, 18.5%) and *Pseudomonas aeruginosa* (n = 3, 6.0%). Thirteen cases were diagnosed as fungal infections, and most were caused by *C. albicans* (n = 8, 61.5%). CMV was identified in all four cases with viral pneumonia.

The main pulmonary radiologic findings included consolidation (n = 38, 51.4%), diffuse interstitial pneumonia (n = 21, 28.4%) and multiple nodules (n = 13, 17.6%). Bacterial pneumonia presented with consolidation (n = 24, 32.4%), nodules (n = 9, 12.2%) and a diffuse reticular pattern (n = 6, 8.1%). CMV pneumonia mainly presented with ground-glass opacities (4, 5.4%), diffuse reticular thickening (n = 3, 4.1%) and nodules (n = 1, 1.4%) on bilateral lungs. Fungal pneumonia was characterized by consolidation (n = 14, 18.9%), nodules (n = 4, 5.4%), halo (n = 4, 5.4%) and air crescent sign (n = 2, 2.7%). Thirteen cases were complicated by ARDS, and 10 were complicated by MODS. Nine patients required mechanical respiration (5 BiPAP and 4 endotracheal intubation).

Treatment and outcome of infectious episodes

All 103 episodes were treated with intravenous antibiotics. Twelve (11.7%) of 103 patients died and all due to severe pneumonia. The time to death was from one to sixteen months after the initiation of immunosuppressive therapy. None died due to AAV (Table 4).

Discussion

A link between vasculitis and infection has long been suspected. Bacterial infections can trigger the production of various autoantibodies, including ANCA [19]. Infection is a major concern in the management of AAV and is the most common cause of death, especially in patients with malnutrition or immunosuppressive therapy [1–3]. Immunosuppressive therapy is performed with consideration of the disease activity, which is comprehensively evaluated based on the BVAS score [20]. Nonetheless, even in patients with severe ANCA-associated vasculitis, secondary infection, rather than active AAV, is the leading cause of death [21]. There still remains no firm

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Table 2 Pathogens of infection

	Pathogens (n = 87)	N (%)
Bacterium	Acinetobacter baumannii	6 (7)
	Staphylococcus aureus	5 (6)
	Pseudomonas aeruginosa	3 (4)
	Escherichia coli	2 (2)
	Klebsiella pneumoniae	2 (2)
	Neisseria	2 (2)
	M.tuberculosis	2 (2)
	Viridans Streptococci	1 (1)
	Streptococcus	1 (1)
	Salmonella enteritidis	1 (1)
	CitrobacterWerkmanandGillen	1 (1)
	A.juniiBouvetandGrimont	1 (1)
	Stenotrophomonas maltophilia	1 (1)
	Enterobacter cloacae	1 (1)
	Nonspecific infection	28 (32)
Fungus	C.albicans	9 (11)
	Pneumocystis jiroveci	7 (8)
	Aspergillus fumigatus	3 (4)
	Candida tropicalis	2 (2)
Virus	Varicella-zoster virus	5 (6)
	Cytomegalovirus	4 (5)

conclusion about the burden and characteristics of major infections in patients with AAV.

We retrospectively reviewed the clinical charts of 248 Chinese patients with AAV. Major infections were reported in 34.6% of our single-centre cohort. Approximately 64.1% of these infections developed in the first three months of induction therapy. In the reported

studies, corticosteroids contributed to 89% of infections of patients with AAV, and the infection rate decreased when the corticosteroids were tapered [1–4]. Corticosteroid treatment leads to an immunocompromised status in patients by inhibiting cytokines, neutrophils, and immunologic response and by exerting anti-inflammatory and immunosuppressive effects [22]. Infection is suspected when fever (≥37.3 °C) persists for no less than three days and C-reactive protein increases after remission of AAV [22]. The evaluation of infection is based on the presence of organ manifestations. Identifying methods of causative microorganisms, such as common bacteria, viruses, and fungi, include mycological, histological, and genetic tests [20].

The main areas of infection included the lungs and skin. The lung infection rate was as high as 79.6% in this cohort. Most AAV patients had impaired renal function, and lung involvement and diffuse alveolar haemorrhage injure the local protective barrier. Renal injury also increases the risk of severe infection and is closely associated with a poor outcome [6, 18]. According to the literature, the most common causative pathogens are bacteria, such as *Streptococcus pneumonia* and *Haemophilus influenza* [23, 24], followed by fungi and viruses. In our cohort, the main bacteria included *Acinetobacter baumannii*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (Table 2), and our rates of infections with fungi and viruses were higher and lower, respectively, than those of previous reports [25]. Characteristics of AAV, such as global inflammation, renal injury, lung involvement, malnutrition, and immunosuppressive therapy, contribute to infections by opportunistic pathogens [26]. CMV, PJP and 13 cases of pneumomycosis developed during induction therapy. It is also possible that a PJP diagnosis may have been

Table 3 COX regression for AAV complicated infection

varium	Single factor analysis		Multiple factor analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.004 (1.001–1.007)	0.008	1.003 (1.000–1.006)	0.030
gender	1.444 (0.938–2.221)	0.095	0.723 (0.394–1.328)	0.296
smoking	2.293 (1.465–3.588)	0.000	2.338 (1.236–4.424)	0.009
Diabetes	1.504 (0.651–3.474)	0.339		
Hemoglobin< 7.75 g/dl	2.079 (1.358–3.182)	0.001	1.362 (0.827–2.243)	0.224
Albumin< 33.95 g/l	1.902 (1.243–2.910)	0.003	1.178 (0.740–1.874)	0.490
baseline creatinine higher than 5.74 mg/dl	3.190 (2.053–4.957)	0.000	2.153 (1.323–3.502)	0.002
CD4$^+$T cell< 281/ul	02.021 (1.316–3.105)	0.001	1.813 (1.133–2.900)	0.013
BVAS at the time of diagnosis > 25.5	1.883 (0.815–4.349)	0.138		
corticosteroids+MMF	1.945 (1.156–3.272)	0.012	1.004 (0.571–1.765)	0.989
corticosteroids+CYC	1.906 (1.073–3.383)	0.028	1.951 (1.520–2.740)	0.042
corticosteroids+TW	1.519 (1.110–2.715)	0.042	0.572 (0.262–1.250)	0.161

MP Methlyprednisone, *MMF* mycophenolate mofetil, *CYC* cyclophosphamide, *TW* Tripterygium wilfordii

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Table 4 ESRD and Death

	Infection group	Non-infection group
ESRD	21	13
Time to ESRD, (months)	2.5 (1~ 7)	12 (5~ 32.5)
Death	12	0
Time to Death, (months)	3 (2~ 12)	
Cause of Death		
Acinetobacter baumannii	1	
Staphylococcus aureus	1	
Stenotrophomonas maltophilia	1	
C.albicans	1	
Pneumocystis jiroveci	1	
Aspergillus fumigates	1	
Nonspecific infection	1	

ESRD end-stage renal disease

missed, especially earlier in the study period when our microbiology laboratory used Pneumocystis stains. Some clinical studies have concluded that *Streptococcus pneumonia* and influenza vaccines are safe and effective [27–29]. Thus, improving the vaccination coverage against streptococcus pneumonia and influenza in high-risk populations could play an important role in pulmonary prevention [30].

The most common computed tomography findings were ground-glass attenuation, reticular pattern, and fibrous bands with infiltration. In cases of bacterial, fungal and viral pneumonia, a consolidation and reticular pattern, patchy consolidation and glass-ground attenuation were most commonly observed, respectively. These characteristics are predominantly seen in pneumonia patients with AAV.

Given the high incidence of infections in patients with AAV, risk factors need to be defined in order to increase surveillance and prescribe prophylactic antibiotic therapy. Many studies have reported that age, female gender, diabetes, impaired renal function, clinical grade category of rapidly progressive glomerulonephritis (RPGN), lymphopenia and immunosuppressive therapy are risk factors for infection in AAV [6, 12–14, 20, 31]. However, there remains no consensus about the infectious risk factors in Chinese patients with AAV. In this cohort, BVAS and the frequency of diabetes in the infectious group were higher than that in the control group, indicating that higher BVAS and diabetes are potential risk factors of infection. Age at the time of diagnosis (HR = 1.003, 95% CI = 1.000–1.006), smoking (HR = 2.338, 95% CI = 1.236–4.424), baseline Scr ≥5.74 mg/dl (HR = 2.153, 95% CI = 1.323–3.502), CD4$^+$ T cell< 281 ul (HR = 1.813, 95% CI = 1.133–2.900), and use of intravenous CYC were independent risk factors of infection. Whether or not the

use of CYC was a risk factor for developing infection in AAV patients remains controversial [9, 10, 14]. Masaharu [20] also reported that the use of CYC was a risk factor for developing infection in AAV patients, but no difference was observed in renal failure between those with or without infection. On the other hand, CYC showed similar adverse events when compared to Rituximab in two randomized controlled trials [9, 10].

In our study, the infection-related mortality (11.7%) was less than that reported in most of the literatures [4, 13, 14, 32]. Half of these cases died within the first month after diagnosis. Thus, clinicians should consider adaptive immunosuppressive agents to avoid life-threatening infection.

Limitations
There are some limitations in this retrospective study. First, the treatment protocols were not uniform and lack of data on Rituximab. Only a minority of patients were given SMZ-CO prophylaxis because of the insufficient awareness. None of these patients received prophylaxis for fungal infection. In addition, some cases with pulmonary or central nervous system infection failed to show a definitive pathogen. The frequency and severity of pneumonia should be lowered by prophylactic treatment and early diagnosis.

Conclusion
Infections can develop during every stage of AAV, primarily in the lungs and skin. The pathogens identified in this study mainly consisted of bacteria, candidiasis, CMV and herpes simplex virus, and age at the diagnosis, smoking, baseline SCr higher than 5.74 mg/dl, CD4$^+$ T cell< 281 μl, and CYC therapy were independent risk factors for infection in patients with AAV.

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Availability of data and materials

The dataset used and analysed during the current study is not publicly available due to patient-related confidentiality, but it is available from the corresponding author on reasonable request.

Author's contributions

YL, XHL, LZZ, CYH, WJQ, GYC, ZHT, HWX: contributed to the design of study, performed the data collection and interpretation. YL and XHL wrote the first draft. LZZ, CYH, WJQ, ZHT, GYC and HWX revised the manuscript. All authors are accountable for all aspects of the work and have approved the final manuscript.

Ethics approval and consent to participate

This study was approved by Ethics Committee of Jinling Hospital (Nanjing, China). Written consent was obtained from each participant. Declaration of Helsinki was followed while conducting this analysis.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing of interests.

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References

1. Charlier C, Henegar C, Launay O, Pagnoux C, Berezne A, Bienvenu B, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann Rheum Dis. 2009;68(5):658–63.
2. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis-long-term outcome in 155 patients. Arthritis Rheum. 2000;43(5):1021–32.
3. Gavraud M, Guillevin L, Le Toumelin P, Cohen P, Lhote F, Casassus P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. Analysis of four prospective trials including 278 patients. Arthritis Rheum. 2001;44(3):666–75.
4. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis. 2011; 70(3):488–94.
5. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. AnnRheum Dis. 2009;68(3):310–7.
6. Harper L, Savage CO. ANCA-associated renal vasculitis at the end of the twentieth century-a disease of older patients. Rheumatology. 2005;44(4): 495–501.
7. Jennette JC, Fallc RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclaure of systemic vasculitides: the proposal of an international consensus conference. Arth Rheum. 1994;37(2):187–92.
8. Hu W, Liu C, Xie H, Chen H, Liu Z, Li L. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. Nephrol Dial Transplant. 2007;23(4):1307–12.
9. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211–20.
10. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):221–32.
11. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771–80.
12. Kronbichler A, Jayne DR, Mayer G. Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis. Eur J Clin Investig. 2015;45(3):346–68.
13. McGregor JC, Negrete-Lopez R, Poulton CJ, Kidd JM, Katsanos SL, Goetz L, et al. Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function. Nephrol Dial Transplant. 2015;30(Suppl1):i171–81.
14. Kitagawa K, Furuichi K, Sagara A, Shinozaki Y, Kitajima S, Toyama T, et al. Risk factors associated with replapse or infectious complications in Japanese patients with microscopic polyangiitis. Clin Exp Nephrol. 2016;20(5):703–11.
15. Mohammad AJ, Segelmark M, Smith R, Englund M, Nilsson JA, Westman K, et al. Severe infection in antineutrophil cytoplasmic antibody-associated vasculitis. J Rheumatol. 2017;44(10):1468–75.
16. Flossmann O, Bacon P, de Groot K, Jayne D, Rasmussen N, Seo P, et al. Development of comprehensive disease assessment in systemic vasculitis. Ann Rheum Dis. 2007;66(3):283–92.
17. Katsuyama T, Saito K, Kubo S, Nawata M, Tanaka Y. Prophylaxis for pneumocystis pneumonia in patients with rheumatoid arthritis treated with biologics, based on risk factors found in a retrospective study. Arthritis Res Ther. 2014;16:R43.
18. Wilson JW, Limper AH, Grys TE, Karre T, Wengenack NL, Binnicker MJ. *Pneumocystis jirovecii* testing by real-time polymerase chain reaction and direct examination among immunocompetent and immunosuppressed patient groups and correlation to disease specificity. Diagn Microbiol Infect Dis. 2011;69(2):145–52.
19. Konstantinov KN, Ulff-Moller CJ, Tzamaloukas AH. Infections and antineutrophil cytoplasmic antibodies: triggering mechanisms. Autoimmun Rev. 2015;14(3): 201–3.
20. Haris Á, Polner K, Arányi J, Braunitzer H, Kaszás I, Rosivall L, et al. Simple, readily available clinical indices predict early and late mortality among patients with ANCA-associated vasculitis. BMC Nephrol. 2017;18:76.
21. Li ZY, Ma TT, Chen M, Zhao MH. The prevalence and management of anti-neutrophil cytoplasmic antibody-associated vasculitis in China. Kidney Dis(Basel). 2016;1(4):216–23.
22. Yoshida M. Strategy of infection control in immunosuppressive therapy for ANCA-associated vasculitis. Ann Vasc Dis. 2013;6(1):9–15.
23. Bonaci-Nikolic B, Andreievic S, Pavlovic M, Dimcic Z, Ivanovic B, Nikolic M. Prolonged infections associated with antineutrophil cytoplasmic antibodies specific to proteinase 3 and myeloperoxidase: diagnostic and therapeutic challenge. Clin Rheumatol. 2010;29(8):893–904.
24. Koselj-Kajtna M, Koselj M, Rott T, Kandus A, Bren A. Infectious complications of immunosuppressive treatment for anti-neutrophil cytoplasm antibody-related vasculitis. Transplant Proc. 2002;34(7):3001–2.
25. Moosig F, Holle JU, Gross WL. Value of anti-infective chemoprophylaxis in primary systemic vasculitis: what is the evidence? Arthritis Res Ther. 2009; 11(5):253.
26. Sowden E, Carmichael AJ. Autoimmune inflammatory disorders, systemic corticosteroids and pneumocystis pneumonia: a strategy for prevention. BMC Infect Dis. 2004;4:42.
27. Stassen PM, Sanders JS, Kallenberg CG, Stegeman CA. Influenza vaccination dose not result in an increase in relapses in patients with ANCA-associated vasculitis. Nephrol Dial Transplant. 2008;23(2):654–8.
28. Holvast A, Stegeman CA, Benne CA, Huckriede A, Wilschut JC, Palache AM, et al. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. Ann Rheum Dis. 2009;68(6):873–8.
29. 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(3):414–22.
30. Launay O. Improving the vaccination coverage against influenza and streptococcus pneumonia in the populations at risk: the role of pulmonary care services. Rev Mal Respir. 2013;30(9):741–2.
31. Ozaki S, Atsumi T, Hayashi T, Ishizu A, Kobayashi S, Kumagai S, et al. Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study. Mod Rheumatol. 2012;22(3):394–404.
32. Wall N, Harper L. Complications of long-term therapy for ANCA-associated systemic vasculitis. Nat Rev Nephrol. 2012;8(9):523–32.