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***ABSTRACT.*** ***Objective.*** To compare the rate of severe infections after the onset of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with the rate in the background population, and to identify predictors of severe infections among patients with AAV.

***Methods.*** The study cohort was 186 patients with AAV diagnosed from 1998 to 2010, consisting of all known cases in a defined population in southern Sweden. For each patient, 4 age- and sex-matched reference subjects were randomly chosen from the background population. Using the Skåne Healthcare Register, all International Classification of Diseases codes of infections assigned from 1998 to 2011 were identified. Severe infections were defined as infectious episodes requiring hospitalization. Rate ratios were calculated by dividing the rate in AAV by the rate among the reference subjects.

***Results.*** The rate ratio for all severe infections was 4.53 (95% CI 3.39–6.00). The highest rate ratios were found for upper respiratory tract: 8.88 (3.54–25.9), *Clostridium difficile:* 5.35 (1.54–23.8), nonspecific septicemia 4.55 (1.60–13.8), and skin 5.35 (1.69–19.8). Of the severe infections, 38.4% occurred within 6 months of diagnosis, 30.2% from 7–24 months, and 31.4% after 24 months. High serum creatinine and older age at diagnosis were associated with severe infection ($p < 0.001$). Of those with severe infection, 46.5% died during followup compared to 26% of patients without severe infection ($p = 0.004$).

***Conclusion***. Patients with AAV have markedly higher rates of severe infection compared with the background population, especially patients with older age and impaired renal function. The risk of severe infection is particularly high in the first 6 months following the diagnosis of vasculitis. (First Release August 1 2017; J Rheumatol 2017;44:1468–75; doi:10.3899/jrheum.160909)

*Key Indexing Terms:*

ANCA-ASSOCIATED VASCULITIS | SEVERE INFECTIONS | RATE
POPULATION-BASED STUDY | RATE RATIO | RENAL DYSFUNCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [AAV: granulomatosis with polyangiitis (GPA, Wegener's), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss)] is a group of systemic inflammatory diseases predominantly affecting small and medium blood vessels and resulting in disease manifestations in multiple organs, with associated morbidity and high mortality[1]. Compared to reference populations, patients with AAV have high rates of comorbidities caused by disease-specific organ damage, and the potential longterm effects of widespread inflammation and medications used to treat AAV[2]. While the introduction of cyclophosphamide (CYC) in the 1970s as a treatment for AAV has improved survival[3,4,5], its use in combination with

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glucocorticoids puts patients at risk for severe infections. The current treatment for AAV includes intravenous (IV) pulsed or shorter courses of CYC-based regimens, although other drugs have been shown to be effective in achieving remission[6,7,8,9,10]: methotrexate for non-severe disease, and more recently rituximab (RTX).

One of the most serious and common drug toxicities in vasculitis is the occurrence of infections. Severe infections occurred among 73 of 158 patients (46%) with GPA treated with oral CYC during a followup time of 1229 person-years[11]. Infections were responsible for 50% of deaths during the first 12 months in patients with AAV recruited from 1995 to 2005 into 4 clinical trials conducted by the European Vasculitis Study Group[12].

The aims of our study were to (1) compare the rate of infections among patients with AAV to that among the reference population; (2) study predictors of infections in AAV; and (3) study the outcome of patients with AAV with severe infection.

## MATERIALS AND METHODS

*The study area and population*. The study was conducted in a defined geographical area in southern Sweden, which has been described in detail[13]. The study population is about 701,000 (December 2009) and the study area consists of 2 healthcare districts (central and southwest region of Skåne).

*The Skåne Healthcare Register (SHR)*. This is a central database to which all information on healthcare contacts and diagnostic codes are transferred. The SHR receives data from all levels of healthcare (primary outpatient care, private clinics, and the highly specialized in-hospital care). Each single healthcare consultation at any level (physicians or paramedics) generates data entries by the healthcare provider that are transferred to the SHR[14]. The diagnoses are classified according to the International Classification of Diseases, 10th version (ICD-10).

*The AAV cohort*. A total of 186 incident cases of AAV (95 women) diagnosed during a 13-year period (1998–2010) was studied. Patients were identified from clinical and serology registers at hospitals in the study area. All medical records of patients living in the area at the time of diagnosis were reviewed to establish a diagnosis of small vessel vasculitis. The patients were classified into GPA, MPA, and EGPA according to the European Medicines Agency algorithm (2007)[15]. Demographic, clinical, and laboratory data were collected from time of diagnosis. Information was collected on endstage renal disease (ESRD) at any time during the followup from diagnosis to December 31, 2011. ESRD was defined as either commencement of chronic dialysis or renal transplantation at any time during the followup. The estimated glomerular filtration rate (eGFR) was assessed using the Modification of Diet in Renal Disease Study formula[16]. Patients were followed from the time of diagnosis (earliest January 1, 1998) until December 31, 2011, or death.

The data were divided into 2 groups based on the period during which AAV was diagnosed: between 1998 and 2003 (the early cohort) and between 2004 and 2009 (the recent cohort). To have a comparable time of followup, for the early cohort, time of followup ended on December 31, 2003, and for those diagnosed after 2004, time of followup ended on December 31, 2009. Data collection was carried out retrospectively using the same data collection form for both the recent and early cohort.

*Treatment*. The majority of patients included in the study were treated with oral CYC (2 mg/kg body weight/day) or IV CYC pulse therapy (10 pulses, each 15 mg/kg over 6 mos), adjusted to renal function and age according to the CYCLOPS protocol[17]. The induction regimen with CYC was gradually changed to IV infusions at the beginning of 2004. CYC was given in combination with prednisolone (starting at 1 mg/kg/day). Patients with s-creatinine ≥ 500 μmol/l or life-threatening pulmonary hemorrhage received plasma exchange. Patients with severe or life-threatening disease received additional IV methylprednisolone (3000 mg). On achieving remission, patients received maintenance treatment with azathioprine for at least 24 months. As an alternative to CYC, from the beginning of 2007, RTX (1 g × 2) has been used for induction of remission. The oral prednisolone dosing was consistent throughout the study period.

*The reference population*. The population from the study area seeking healthcare is referred to as the reference population. The inclusion criteria and selection of the reference population have been described elsewhere[2,18]. All subjects chosen had at least 1 clinic visit during the study period with a diagnosis (any) by a physician in the SHR. The reference person could not have the disease under study (no ICD codes for AAV). For each patient with AAV, 4 reference persons matched for age, sex, and area of residence were randomly chosen. In addition, each person had to live in the study area at the time of the index year. The index year is the end of December the year before the diagnosis year for the case. The date of entry to the cohort is the date of diagnosis of AAV and for the reference person is the first assigned diagnosis code at the index year.

*Linking of data sources*. Using personal identification numbers, the cohorts of the AAV and reference populations were linked to the SHR to identify all healthcare visits with their assigned ICD codes. The time period searched was from January 1, 1998, to December 31, 2011. The resulting data include all healthcare contacts for AAV and their reference populations since diagnosis (and index year). The data include the type of contact (inpatients or outpatients), healthcare provider (hospital and specialized ward), and assigned ICD-10 diagnostic codes (up to 8 codes at each healthcare contact).

*Infections*. The diagnosis of infection was classified according to the ICD-10 codes as listed in Appendix 1. For the infection episode to be registered as present, patients or the reference person should have had assigned the corresponding ICD-10 code for the given infection after the date of AAV diagnosis for cases and index date for reference subjects. In our study, only the first episode of severe infection was registered and analyzed. Severe infections were defined as infectious episodes requiring hospitalization.

*Statistical analyses*. The rates of infection were calculated by dividing the number of patients or reference persons diagnosed with the infection of interest by the sum of person-time during the followup period. The person-time was defined as the number of days each person was followed from the date of the diagnosis of AAV or index date for the reference subject to the end of followup, as described[18]. The followup time was calculated from the date of diagnosis or index date for reference until the earliest of the following: (1) date of infection; (2) death; (3) date when case or reference person moved outside the study area; or (4) December 31, 2011, the ending date of the study. The rate ratio of infections was calculated by dividing the infection rate for patients by that of reference population. The test of interaction [ratio of relative risk (RRR)] has been used to compare rate ratios of infections among patients from the recent versus the early cohort[19]. For continuous normally distributed variables, data are presented as means (± SD), and Student t test is used for comparison between groups. Continuous not normally distributed data are presented as median and interquartile ranges (IQR), and the Mann-Whitney U test is used for comparison. The chi-square test compared categorical variables. Infection-free survival (followup time from date of diagnosis of AAV to the occurrence of infection, death, or last followup) and patient survival were studied using the Kaplan-Meier method. A p value of $< 0.05$ was considered significant. By Cox regression, the following factors were investigated in a univariable analysis as potential predictors of severe infection: ESRD (including only ESRD events that occurred before infection event), age at diagnosis, sex, s-creatinine, ENT involvement, ANCA specificities (proteinase 3 and myeloperoxidase), hemoglobin level, and diagnosis period. A multivariable analysis was performed on all the variables used in first analysis. Statistical Analysis System (SAS) has been used to calculate the person-year time of followup and the rates of severe infections. Statistical analysis was

performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (IBM SPSS Statistics). The Regional Ethical Review Board for southern Sweden approved the study (2010-517 and 301-2007).

## RESULTS

*The AAV cohort and reference population*. The study included 186 patients (95 women). Ninety-two (49.5%) were classified as GPA, 83 (44.6%) MPA, and 11 (5.9%) EGPA. A total of 744 reference subjects were sampled according to the study criteria. The total time of followup was 1101 person-years for the patients and 4975 person-years for the reference subjects. The median time of followup was 4.8 years (mean 5.9) for patients with AAV and 6 years (mean 6.7) for the reference subjects. Eighty-six patients (46%) of the AAV cohort had at least 1 severe infection during followup (Table 1). The median time from diagnosis of AAV to first episode of severe infection was 8.3 months (IQR 3.6–31.3), mean 23.7 months (range 0–152, SD 31.3). The 1-, 5-, and 10-year infection-free survival for all patients was 71%, 57%, and 42%, respectively (Figure 1A) and was lower for patients diagnosed with AAV after the age of 68 years, which was the median age for diagnosis (Figure 1B). It was during the first 6 months after diagnosis that 33/86 (38.4%) of infections occurred. There were 26/86 (30.2%) of infections 7–24 months after the diagnosis, and 27/86 (31.4%) of all severe infections occurred after 24 months from the diagnosis of AAV. Among 92 patients with GPA, 36 (39%) had upper respiratory tract infections, influenza, or pneumonia, compared to 20 of 83 with MPA (24%; p = 0.03).

*Rate of first severe infection*. During the followup period, 86 patients (46%) and 118 reference subjects (16%) were diagnosed with at least 1 severe infection. The rate of severe infection among patients was 116.2 per 1000 person-years (95% CI 92.6–143.5) compared to 25.6 per 1000 person-years among references (95% CI 21.2–30.7), giving a rate ratio of 4.53 (95% CI 3.39–6.00; p < 0.001). The rates and rate ratios of a number of severe infections among patients and reference subjects are shown in Table 2.

Eighty-eight patients were diagnosed with AAV between 1998 and 2003 (the early cohort) and 90 between 2004 and 2009 (the recent cohort). There were no significant differences in demographic, clinical, or laboratory characteristics between the 2 cohorts (data not shown). However, ESRD was more frequent among the early compared to the recent cohort (20% vs 8%, p = 0.01). Severe infection occurred in 44 (50%) of patients from the early cohort compared to 38 (42%) of those from the recent cohort (p = 0.2). When analysis was limited to the 52 severe infection events that occurred during first 12 months after diagnosis of AAV, 23/88 (26%) were from the early cohort compared to 29/90 (32%) among patients from the recent cohort (p = 0.04). During the first 12 months after AAV diagnosis, the rate ratio of all severe infections in the early cohort was 4.91 (95% CI 2.68–8.86) and in the recent cohort was 5.65 (95% CI 3.24–9.74; Table 3). When comparing the 2 estimates of rate ratios for all severe infections between the 2 cohorts, no increase in the RRR between the recent/early cohorts was found (1.15; 95% CI 0.51–2.59).

*Risk factors for severe infections*. The mean age at diagnosis for those with severe infection was 68.8 years (± 13.5) versus 60.8 (± 16.8) for those with no infection (p < 0.001; Table 1). Patients with severe infection had a higher median s-creatinine at diagnosis (238 vs 117 µmol/l; p = 0.01) compared with patients without severe infection. The incidence of severe infection was higher among patients with GFR < 50 (ml/min/1.73 $m^2$) at diagnosis (52/99, 52.5%)

*Table 1*. Comparison between patients with ANCA-associated vasculitis with and without severe infection. Results are given as mean (± SD) for normally distributed variables and median (IQR) for not normally distributed variables.

| Characteristics | Severe Infection, n = 86 | No Severe Infection, n = 100 | p |
|---|---|---|---|
| Age at diagnosis, yrs, mean ± SD | 68.8 ± 13.5 | 60.8 ± 16.8 | < 0.001 |
| Sex, F:M | 41:45 | 54:46 | 0.4 |
| Diagnosis: GPA/MPA/EGPA | 47/36/3 | 45/47/8 | |
| PR3 + ANCA: MPO + ANCA, n = 92: n = 78 | 41:38 | 51:40 | 0.5 |
| Laboratory data at diagnosis | | | |
| Serum creatinine, µmol/l | 238 (75–350) | 117 (73–256) | 0.01 |
| Hemoglobin concentration, g/l | 106 ± 20 | 113 ± 18 | 0.03 |
| White blood cell count | 11 (9–14) | 11 (8–14) | 0.9 |
| Platelet count | 370 ± 133 | 391 ± 136 | 0.2 |
| C-reactive protein, mg/l | 101 ± 86 | 92 ± 77 | 0.4 |
| ESR, mm/h | 66 ± 34 | 67 ± 33 | 0.9 |
| *Patients with GFR < 50 ml/min/1.73 $m^2$ | 52/75 (69%) | 47/89 (53%) | 0.03 |
| Deaths | 40 (46.5%) | 26 (26%) | 0.004 |
| ESRD | 22 (25.6%) | 10 (10%) | 0.002 |

* At diagnosis. ANCA: antineutrophil cytoplasmic antibody; IQR: interquartile range; ESR: erythrocyte sedimentation rate; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; PR3: proteinase 3; MPO: myeloperoxidase; GFR: glomerular filtration rate; ESRD: endstage renal disease.

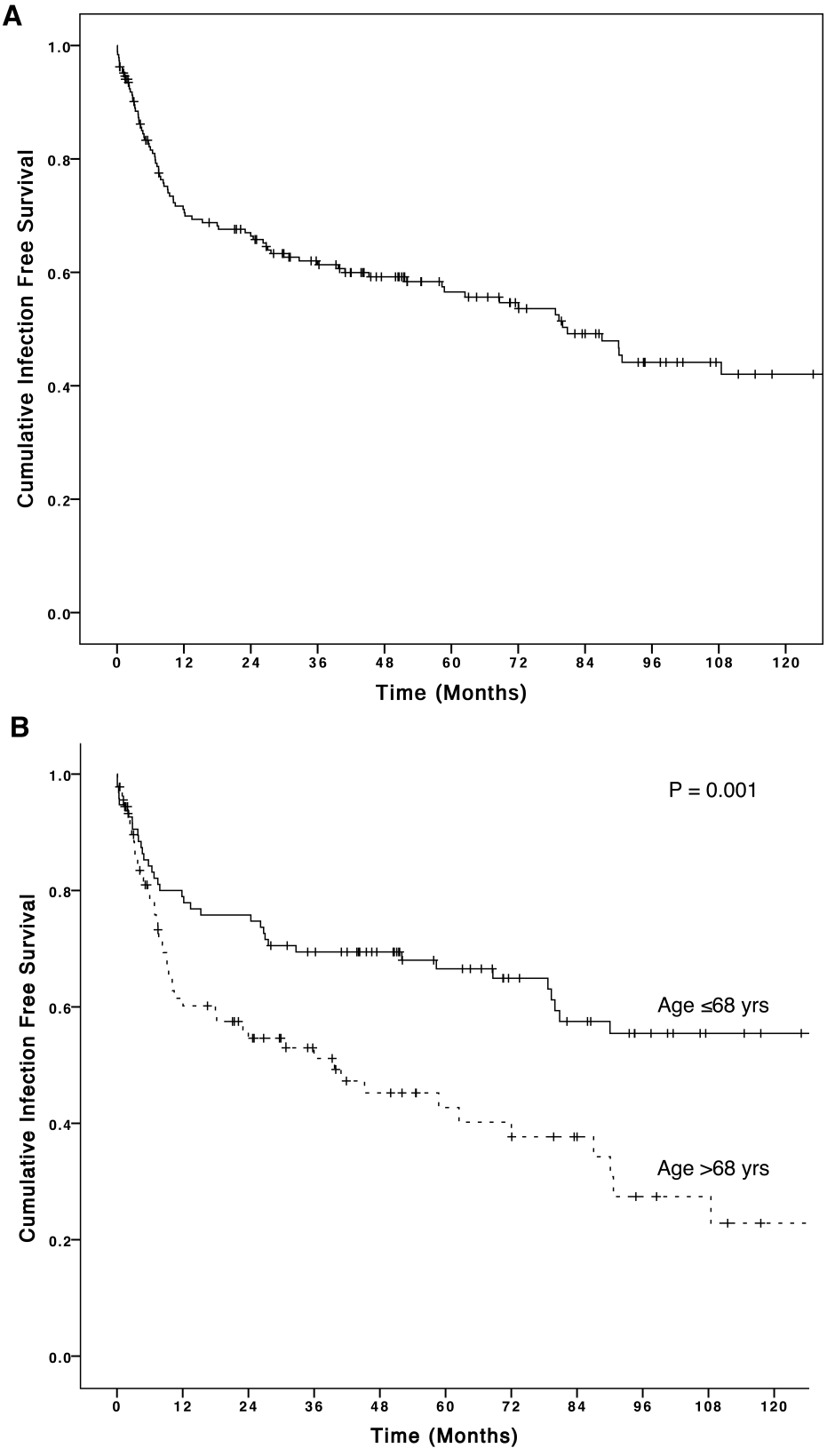


*Figure 1*. Kaplan–Meier infection-free survival curves for 186 patients with ANCA-associated vasculitis. (A) All patients. (B) All patients stratified by age at diagnosis (log-rank test). ANCA: antineutrophil cytoplasmic antibody.

*Table 2*. Rates of first severe infection among 186 patients with ANCA-associated vasculitis and reference population of 744 persons.

| Infections | AAV, n | AAV, Person-yrs | Rate | Ref., n | Ref., Person-yrs | Rate | Rate Ratio | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|
| All severe infections | 86 | 740 | 116.2 | 118 | 4602 | 25.6 | 4.53 | 3.39–6.00 | < 0.001 |
| All septicemias | 19 | 1039 | 18.2 | 29 | 4906 | 5.91 | 3.09 | 1.64–5.66 | 0.004 |
| Nonspecific septicemia | 9 | 1088 | 8.27 | 9 | 4953 | 1.82 | 4.55 | 1.60–13.8 | 0.02 |
| Gram-negative septicemia | 9 | 1064 | 8.46 | 12 | 4958 | 2.42 | 3.49 | 1.30–9.29 | 0.03 |
| *Staphylococcus aureus* septicemia | 3 | 1095 | 2.74 | 4 | 4959 | 0.81 | 3.40 | 0.50–51.2 | 0.2 |
| Acute URTI | 15 | 1043 | 14.3 | 8 | 4942 | 1.62 | 8.88 | 3.54–25.9 | 0.001 |
| Influenza and pneumonia | 46 | 918 | 50.1 | 73 | 4763 | 15.3 | 3.27 | 2.21–4.76 | < 0.001 |
| *Clostridium difficile* | 7 | 1080 | 6.48 | 6 | 4957 | 1.21 | 5.35 | 1.54–23.8 | 0.03 |
| Nonspecific infection | 12 | 1031 | 11.6 | 22 | 4880 | 4.51 | 2.58 | 1.16–5.43 | 0.04 |
| Skin infections | 8 | 1060 | 7.55 | 7 | 4961 | 1.41 | 5.35 | 1.69–19.8 | 0.02 |

ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; Ref.: reference; URTI: upper respiratory tract infection.

*Table 3*. Rate and rate ratios of severe infections and septicemia in 186 patients with ANCA-associated vasculitis during 2 time periods: the early cohort (1998–2003) versus the recent cohort (2004–2009).

| Infections | AAV, n | AAV, Person-yrs | Rate | Ref., n | Ref., Person-yrs | Rate | Rate Ratio | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|
| Early cohort | | | | | | | | | |
| All infections | 23 | 175 | 131 | 26 | 974 | 26.7 | 4.91 | 2.68–8.86 | < 0.001 |
| All septicemias | 6 | 230 | 26.1 | 3 | 1018 | 2.95 | 8.86 | 1.89–553 | 0.03 |
| Recent cohort | | | | | | | | | |
| All infections | 29 | 168 | 172 | 28 | 918 | 31 | 5.65 | 3.24–9.74 | < 0.001 |
| All septicemias | 5 | 218 | 22.9 | 4 | 953 | 4.2 | 5.46 | 1.18–61.1 | 0.7 |

Severe infections occurred during the first 12 months after AAV diagnosis. ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis.

compared to patients with GFR > 50 (23/65, 35.4%; p = 0.03). After excluding all patients with ESRD who developed severe infection, the rate of severe infections was still higher among those with a GFR < 50 (ml/min/1.73 $m^2$) at diagnosis [40.5% vs 34.4% (age-adjusted HR 1.32); 95% CI 0.76–2.31; p = 0.3].

During followup, 32 patients (17.2%) developed ESRD. The median time from diagnosis of AAV to ESRD was 4.6 months [IQR 0.06–44.1; mean 21.7 (± 30.2)]. Of the 32 patients with ESRD, 22 (68.8%) had severe infection compared to 64 of the 154 patients without ESRD (41.6%, p = 0.005). ESRD occurred before severe infections in 15 out of 22 patients (68%). The median time from the date of ESRD to first severe infection (based on 15 cases) was 7.1 months (IQR 2.7–11.9); mean 13.9 months (± 19.8).

In univariable analyses, severe infections were associated with older age and higher s-creatinine at diagnosis while the presence of ENT involvement and high hemoglobin were associated with lower risk of severe infections (Table 4). The HR for every 10-year increase in age was 1.50 (95% CI 1.27–1.78; p < 0.001) and for every 100 µmol/l increase in s-creatinine at diagnosis was 1.12 (95% CI 1.04–1.20; p = 0.001). When a multivariable analysis was applied, only age at diagnosis was associated with severe infection (Table 4).

*Associations of severe infections*. Death (due to any cause) occurred during the followup period in 46.5% of those with severe infection compared to 26% among those without severe infection (p = 0.004). Seven patients developed ESRD after having experienced an episode of severe infection. The median time from infection to start of renal replacement therapy was 6.73 months (IQR 2.2–73.0). The cumulative survival rate for patients with infections was lower compared to those with no infection. The 1-, 5-, and 10-year survival rate for those with infection was 86.0%, 64.8%, and 38.6%, respectively, compared to those with no infection: 87.0%, 80.3%, and 73.5%, respectively (p = 0.04).

## DISCUSSION

Our study presents data on the risk of severe infections among patients with AAV. We found a high rate of severe infection in AAV. Almost half of the patients experienced at least 1 severe infection during followup and the rate was almost 5× higher compared to the reference population.

Induction therapy with CYC and high doses of glucocorticoids is well known to predispose patients for infections[11]. However, in our study only 38% of infections occurred during the first 6 months after diagnosis, which is the period when higher-dose glucocorticoids are given. The majority of severe infections were diagnosed in the maintenance phase when azathioprine, low doses of glucocorticoids, or no immunosuppression are normally given. There are several reasons why patients with AAV may continue to have a high rate of severe infections after stopping induction therapy. First, there may be a carryover effect on the immune system

*Table 4*. Predictors of severe infection in 186 patients with ANCA-associated vasculitis, as determined by Cox-regression analysis.

| Predictors | Univariable Analyses | | | Multivariable Analyses | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p |
| Age at diagnosis, yrs | 1.50 | 1.27–1.78 | < 0.001 | 1.46 | 1.20–1.77 | < 0.001 |
| ESRD* | 1.59 | 0.91–2.78 | 0.1 | 0.99 | 0.46–2.13 | 0.9 |
| Sex, men | 1.40 | 0.91–2.13 | 0.1 | 1.30 | 0.81–2.08 | 0.2 |
| S-creatinine, $\mu$mol/l | 1.12 | 1.04–1.20 | 0.001 | 1.07 | 0.96–1.19 | 0.1 |
| Hemoglobin | 0.84 | 0.74–0.95 | 0.005 | 0.90 | 0.77–1.05 | 0.1 |
| ENT involvement | 0.60 | 0.39–0.94 | 0.02 | 0.95 | 0.54–1.66 | 0.9 |
| Anti-PR3 positivity | 0.91 | 0.58–1.42 | 0.6 | 1.14 | 0.66–1.98 | 0.6 |
| Early cohort | 0.88 | 0.56–1.36 | 0.5 | 0.79 | 0.47–1.33 | 0.7 |

* In this Cox-regression analysis, only patients in whom ESRD occurred before the infection event were included.
ANCA: antineutrophil cytoplasmic antibody; ESRD: endstage renal disease; PR3: proteinase 3.

from CYC, including sustained depletion of B-lymphocytes. Second, AAV can also inflict permanent damage that may predispose to infections. In our study, renal impairment was a major risk factor for subsequent severe infections. This was especially true for those who developed dialysis dependency, which regardless of cause is associated with an increased risk of hematogenous spread of bacteria. A third possibility for the high risk of infections in patients with AAV is that the immunological dysfunction that causes the autoimmune disease is also associated with a diminished capacity to combat microorganisms.

Patients with severe infection exhibited a worse prognosis for AAV[12]. Previous studies demonstrated that older age at diagnosis and worse renal function reduced patient survival[13,20]. As in previous studies[21], older age at diagnosis was associated with a higher risk of infection. Accordingly, there might be a synergistic effect of the triad of older age, higher s-creatinine at diagnosis, and the occurrence of infection that increases the mortality rate.

Low eGFR and ESRD were associated with a higher rate of infection. Owing to severe disease, patients with renal involvement may receive more glucocorticoids. Additionally, renal failure by itself impairs immune function, leading to increased risk of infection[22]. Our findings of high prevalence of infections among patients with ESRD are similar to previous reports[23,24]. In a large inception cohort of patients with AAV, Lionaki, *et al* found that infections were the cause of death in 43% of mortality cases in patients developing ESRD compared to 14% among the non-ESRD group[24]. McDonald, *et al* found that severe acute community-acquired infections requiring hospitalization were associated with chronic (predialysis) kidney disease[25].

The CYCLOPS and the RAVE studies showed that oral CYC was associated with leukopenia[17,26], and other studies have clearly linked leukopenia to infections and severe outcome[12]. When dividing our patients into an early and a more recent cohort, we found no differences in the rate of severe infection. During the study period, the local therapeutic practices for CYC changed from daily oral to IV pulse administration in response to results from the CYCLOPS study[17]. However, this did not affect the infection rate, as was anticipated. Similarly, in clinical trials comparing RTX to CYC, no differences in rates of infection were found between these 2 therapies in patients with severe AAV[26,27], emphasizing the unmet need for a treatment regimen for patients with AAV with low risk of infection.

The data presented in our current study are representative for patients with AAV in general. Our study is based on a regional registry concentrating mainly on severe infections, which are diagnosed after hospitalization. The Swedish inpatient register has previously been validated for a number of medical conditions with high positive predictive value[28]. The register has also been validated for the accuracy of diagnosis of severe infections among patients admitted to the intensive care units in Sweden[29]. We cannot exclude bias in managing patients with severe systemic diseases such as AAV who presented with signs of infection. Possibly, physicians taking care of a patient with AAV would be more prone to admit these patients to hospital even if they are seeking healthcare for less severe symptoms compared to other patients. However, in a subanalysis from the same cohorts looking at rates of infection diagnosed after an outpatient consultation (data not shown), we found higher rates of infection among patients with AAV. Therefore, increased awareness of infections in AAV cannot explain the difference with the reference population.

Our study has several important strengths. We studied a large and well-characterized validated population-based cohort of patients with AAV with minimal selection or referral bias. Moreover, this study includes an inception cohort of subjects with AAV, therefore covering a wider spectrum of the natural history of AAV compared to cohorts of patients enrolled in clinical treatment trials.

Our study also has some limitations to consider. We did not discriminate between infection as the prime cause for hospitalization and infection as a secondary complication of admission for another reason. Because patients with vasculitis may have an increased risk for hospitalization for other comorbidities, this may have introduced bias, but this in itself does not detract from the message of an increased

overall severe infection risk. The lack of data on relapses makes it difficult to clearly discern the role of reintroduction of high doses of glucocorticoids, CYC, or other agents in the development of infections; thus, some of the infections late in the course could have occurred during treatment for relapses. Because we recorded only the first event of severe infection, we cannot depict the full effect of infections among patients with AAV. Only persons in the background population who were assigned an ICD code during the study period could be included as reference persons. This introduces the potential to underestimate the relative risk of infections in patients with AAV because the healthiest portion of the population was barred from the reference group. However, around 80% of the population of the county of Skåne had at least 1 healthcare visit generating an ICD code during the study period, which limits this potential bias. Further, patients with AAV are probably more prone to be hospitalized for an infection compared to individuals from the reference population even if the infection is of the same degree of severity; this factor would increase the estimate for infection among patients with AAV.

In our large population-based study, we report high rates of severe infection in patients with AAV compared with a reference population. Our data suggest that severe infections occurred both through the induction as well as the maintenance phase of treatment and that changing the route of administration of CYC will not fully ameliorate problems with infections in patients with AAV. Our data also stress that infection is part of a triad that includes older age and impaired renal function, which are associated with adverse outcomes in AAV.

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**APPENDIX 1.** ICD-10 codes used to classify diagnoses of infection.

| Diseases | ICD-10 Codes | Diseases (Septicemias) | ICD-10 Codes |
|---|---|---|---|
| Gastroenteritis | A09.9 | Septicemia, nonspecific, caused by: | A41.9 |
| Virus infections, nonspecific | B34.9 | Other gram-negative organism | A41.5 |
| Nonspecific infection | B99.9 | *Staphylococcus aureus* | A41.0 |
| Virus gastroenteritis | A08.4 | *Streptococcus pneumoniae* | A40.3 |
| *Clostridium difficile* infections | A04.7 | Other specific form of sepsis | A41.8 |
| Virus meningitis | A87.9 | Streptococcal sepsis, nonspecific | A40.9 |
| Bacterial infection, nonspecific | A49.9 | Other specific *Staphylococcus* | A41.1 |
| Infectious mononucleosis | B27.9 | Sepsis *Staphylococcus streptococci* group A | A40.0 |
| Herpes zoster | B02.9 | Other streptococcal sepsis | A40.8 |
| Gastroenteritis (rotavirus) | A08.0 | Anaerobic bacteria | A41.4 |
| Virus hepatitis | B15, B19 | *Streptococci* group D | A40.2 |
| Bacterial infections (causative agents) | B95, B97 | Salmonella sepsis | A02.1 |
| Infections in skin | L00-L08 | *Streptococci* group B | A40.1 |
| Acute upper respiratory tract infection | J00- J06 | Nonspecific *Staphylococcus*-species | A41.2 |
| Influenza and pneumonias | J09-J18 | *Candida* sepsis | B37.7 |
| Other acute lower respiratory tract infections | J20-J22 | *Haemophilus influenzae* | A41.3 |
| Pyogenic lower respiratory tract infections | J85-J86 | Acute meningococcal sepsis (bacteremia) | A39.2 |
| Infectious joint diseases | M00- M03 | Listeria | A32.7 |
| Acute lower urinary tract infection | N300, N308-N309 | Nonspecific meningococcal sepsis | A39.4 |

ICD-10: International Classification of Diseases, 10th version.