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## Clinical and epidemiological Studies in ANCA-associated vasculitis

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# Clinical and Epidemiological Studies in ANCA-associated vasculitis

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# Clinical and Epidemiological Studies in ANCA-associated vasculitis

Jens Rathmann, MD



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DOCTORAL DISSERTATION

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*Faculty opponent*

Professor Dr. Alfred Mahr, Kantonsspital Sankt Gallen  
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<p><b>Abstract</b></p> <p><b>Objectives:</b> This thesis aims to provide an overview of the epidemiology of AAV in southern Sweden, to evaluate different classification criteria in AAV. In addition we study if infection is a risk factor for later development of AAV comparing patients with AAV with a matched population cohort and to examine the occurrence of severe infections as an outcome in AAV.</p> <p><b>Methods:</b> All adult patients diagnosed with AAV between 1997 and 2019 in the study area of 14 municipalities in Southern Sweden were identified and classified according to EMA algorithm and to the recently published ACR/EULAR classification criteria. Changes in the incidence and prevalence of AAV were studied over 23 years. Using a non-AAV age, sex and place of residence matched population the association of prior infections and later development of AAV was analysed with a logistic regression model. Events of severe infections after AAV diagnosis were identified and studied, incidence rate of severe infections was calculated.</p> <p><b>Results:</b> Stable incidence with 30 cases per million inhabitants and rising prevalence are observed under the study period. Incidences are rising with age. The prevalence of 469/million in 2015 is the highest ever reported. Classification with the new ACR/EULAR criteria shows good agreement with earlier criteria (96% EGPA, 85% GPA, 75% MPA) but even with a classification based on ANCA serology alone (PR3 99%, MPO 84%). Infection, especially in the respiratory tract, is associated with later development of AAV. A history of prior infections is more likely in MPO-positive cases. In patients with AAV, severe infection occurs in 40% of cases after the onset of AAV. The incidence rate of severe infection is 9.1 per 100 person-years of follow-up but significantly higher during the first year with 22.1 per 100 person-years. High age and high disease activity independently predict the occurrence of severe infection.</p> <p><b>Conclusion:</b> The incidence of AAV is stable in our area. The prevalence has increased substantially during the last decades, which can be attributed to better treatment and management and therefore increased survival. An ANCA based classification of AAV produces similar results as the new ACR/EULAR classification criteria. MPO-positive AAV is associated with prior infection. Severe infections are common problem in AAV especially in the first year, they are among the leading causes of death in vasculitis patients.</p>		
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# Clinical and Epidemiological Studies in ANCA-associated vasculitis

Jens Rathmann, MD



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**MADE IN SWEDEN** 

*Wer glaubt etwas zu sein, hat aufgehört etwas zu werden*

Sokrates

*To my parents*



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## List of publications

- I. **Rathmann J**, Segelmark M, Englund M, Mohammad AJ. Stable incidence but increase in prevalence of ANCA-associated vasculitis in southern Sweden – a 23-year study (submitted manuscript)
- II. **Rathmann J**, Segelmark M, Mohammad AJ. Evaluation of the 2022 ACR/EULAR Classification Criteria for ANCA-Associated Vasculitis in a population-based cohort from Sweden (manuscript).
- III. **Rathmann J**, Stamatis P, Jönsson G, Englund M, Segelmark M, Jayne D, Mohammad AJ. Infection is associated with increased risk of MPO- but not PR3-ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2022 Nov 28;61(12):4817-4826. doi: 10.1093/rheumatology/keac163. PMID: 35289842; PMCID: PMC9707308.
- IV. **Rathmann J**, Jayne D, Segelmark M, Jönsson G, Mohammad AJ. Incidence and predictors of severe infections in ANCA-associated vasculitis: a population-based cohort study. *Rheumatology (Oxford)*. 2021 Jun 18;60(6):2745-2754. doi: 10.1093/rheumatology/keaa699. PMID: 33253372.

## List of abbreviations

ACR	American College of Rheumatology
ANCA	Antineutrophil cytoplasmic antibody
AZA	Azathioprine
BVAS	Birmingham Vasculitis Activity Score
cANCA	cytoplasmic ANCA
CHCC	Chapel Hill Consensus Conference
CRF	Case report form
CI	Confidence interval
CYC	Cyclophosphamide
DCVAS	Diagnostic and Classification Criteria in Vasculitis
E.coli	Escherichia coli
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme-linked immune sorbent assay
EMA	European Medicines Agency
ENT	Ear nose and throat
EULAR	European Alliance of Associations for Rheumatology
EUVAS	European Vasculitis Society
GC	Glucocorticoids
GN	Glomerulonephritis
GPA	Granulomatosis with polyangiitis
HR	Hazard ratio
ICD	International classification of diseases (ICD10 (10 <sup>th</sup> edition))
IIF	Indirect immunofluorescence
ILD	Interstitial Lung Disease
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	Methotrexate
OR	Odds ratio
pANCA	perinuclear ANCA
PAN	Polyarteritis nodosa
PR3	Proteinase 3
PCP	Pneumocystis pneumonia
PSV	Primary systemic vasculitis
PY	Person years
RA	Rheumatoid arthritis
RTX	Rituximab
S.aureus	Staphylococcus aureus
SI	Severe infection
SHR	Skåne Healthcare Register
SLE	Systemic lupus erythematosus
VDI	Vasculitis damage index

# Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of rare inflammatory diseases primarily affecting small blood vessels throughout the body. Inflammation in blood vessels can lead to blood vessel damage, tissue damage, organ dysfunction and eventually organ damage. According to clinicopathological characteristics(1) three phenotypic variants are recognized, granulomatosis with polyangiitis (GPA, earlier Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, earlier Churg Strauss syndrome). In most cases of AAV ANCA can be detected. The discovery of an association of ANCA with vasculitis in 1985(2) was a milestone in the understanding of small vessel vasculitis and had considerable effects on the diagnostics, treatment and management of these diseases. Although the three phenotypes share certain features as necrotizing vasculitis and pauci-immunity, there are distinct differences between each disease subtype. GPA usually presents as a necrotizing, granulomatous inflammation with frequent involvement of the sinonasal area, the upper and lower respiratory tract and the kidneys. ANCA with PR3 specificity is often present. Microscopic polyangiitis almost always affects the kidneys and often the lungs, changes in the upper respiratory and sinonasal area as in GPA are rarely observed. ANCA positivity is frequent, predominantly with specificity for myeloperoxidase (MPO). EGPA is associated with asthma, tissue and blood eosinophilia, pulmonary infiltrates and ear-nose and throat involvement. ANCA is found less frequently compared to the other phenotypes, usually with MPO-specificity(3). AAV can occur localized or as severe multisystem disease. The aetiology of AAV is largely unclear but a complex interplay of genetics and environmental factors is discussed. AAV are rare diseases with a combined incidence of approximately 20 cases per million inhabitants.

Prior to the introduction of immunosuppressive treatment, patients with AAV faced poor prognosis with high mortality(4). Introduction of glucocorticoids and immunosuppressive agents has improved prognosis considerably, and new treatment regimens have been introduced throughout the years. Today AAV often has a chronic relapsing character, entailing to a certain degree a focus shift to the management of accumulated damage and disease or treatment induced comorbidities. A considerable part of this thesis concerns infections in AAV. Infections are frequently implicated in the development of autoimmune disease and although many studies have observed clues and associations in most cases a clear

causality is not established. The same applies to AAV, where some infectious agents have been implicated, for example *Staphylococcus aureus* has been shown to influence relapse rates, but a clear link is not established. Another dimension of infections in AAV is the development of infections after the diagnosis of AAV. The nature of the disease and/or its treatment makes patients with AAV prone to infections. Strategies to prevent and manage infections are therefore a common clinical challenge in vasculitis treatment today.

## Antineutrophil cytoplasmic antibodies (ANCA)

The first description of ANCA was made by Davies et al.(5) in 1982. Patients with segmental glomerulonephritis (GN) exhibited a factor in their sera that stained the cytoplasm of neutrophil granulocytes. In 1985, van der Woude et al.(2) described a cytoplasmic immunofluorescence pattern of autoantibodies directed against components in granulocytes in patients with active GPA, demonstrating for the first-time association between these antibodies and vasculitis. A perinuclear fluorescence pattern was discovered in the following years. Proteinase-3(6) and myeloperoxidase(7) were identified as target antigens, with PR3 exhibiting a cytoplasmic pattern (cANCA) and MPO a perinuclear pattern (pANCA) on indirect immunofluorescence. Both antigens are predominantly found in azurophilic granules mainly in neutrophil granulocytes but to minor extent in monocytes and macrophages(8). Myeloperoxidase is a lysosomal enzyme contributing to pathogen clearing in phagosomes(9), proteinase-3 plays a role in the degradations of proteins at site of inflammation(10). A cytoplasmic or perinuclear ANCA pattern however can be caused by reactivity with other proteins, a p-ANCA pattern has been observed for lactoferrin, elastase and BPI (bactericidal permeability-increasing protein), the latter, though, can produce both patterns, but predominantly c-ANCA(11). Today, ANCA belong to the routine workup if AAV is suspected. Earlier a two-step process for the analysis of ANCA was recommended, i.e., an initial screening test with IIF, with positive samples advancing to a second test with immunoassays(12). Due to the fast evolution and good performance of the immune assays and considerable variability of IIF, the latest consensus now recommends ELISA as first line test, in cases of uncertainty a second immune assay or IIF can be used(13). ANCA usually refers to the IgG isotype, other isotypes have been described but the clinical significance is unclear.

ANCA are not specific for AAV, especially when analysed by IIF. A similar cytoplasmic or perinuclear pattern can be observed in other diseases, inflammatory bowel disease(14), infections(15), especially endocarditis, which can even clinically present with vasculitis-like symptoms(16, 17), and certain malignancies(18).

ANCAs have been detected in samples from healthy individuals(19), these antibodies exhibited low titres and avidity and less capability to activate neutrophils in vitro(20). In addition, it has been shown that differences in MPO-ANCA epitopes specificities exist between ANCAs in healthy and diseased individuals(21). Interestingly the same study also identified ANCAs in patients that were earlier designated as ANCA negative, the authors report a ceruloplasmin fragment masking the specific epitope needed for detection in assays.

The distribution of ANCA serotype shows geographic variation, see below.

### **The role of ANCA in the pathogenesis of AAV**

Animal models of AAV have shown a pathogenic role of ANCAs. Mice injected with MPO-ANCA antibodies developed GN with a paucity of immune deposits(22), moreover a case of diaplacental transfer of MPO-ANCA with MPA in a new-born has been reported(23). To date, no similar animal model for PR3 exists, probably due to differences in human and murine PR3 expression(24). Falk et al.(25) demonstrated that cANCA- and MPO-ANCA in vitro activated neutrophils, with consecutive release of reactive oxygen species and degranulation with potential vascular inflammation. Other links between adaptive and innate immunity have been observed, ANCA can in vitro activate neutrophils to release proinflammatory cytokines as IL-1 $\beta$ (26) or CXCL8(27). Neutrophil extracellular traps (NETS) first described in 2004 are net like structures composed of DNA and various proteins (including MPO and PR3)(28) released by the neutrophil as a means to kill pathogens. ANCA have been shown to induce this process(29). ANCA activation of neutrophils has even been shown to cause the release of complement activating factors(30), a discovery paving the way for complement inhibiting treatment approaches.

### **Clinical importance of ANCA**

PR3-positive- and MPO-positive-AAV differ genetically(31, 32) and in terms of disease course and outcome(33). PR3-positive vasculitis is more likely to relapse(34, 35). A study evaluating data from the RAVE trial (a trial comparing Rituximab (RTX) to Cyclophosphamide (CYC) for remission induction in AAV) on treatment response according to either phenotypic or serotype- classification demonstrated that PR3 positive patients were twice as likely to achieve remission when treated with RTX compared to CYC(36). No association between treatment and remission were observed for MPO positive disease or GPA/MPA. Another interesting finding of the study was that choice of induction agent influenced the conversion to ANCA-negativity, PR3-positive patients became significantly more often ANCA-negative at 6 months than patients with MPO-positive AAV when treated with RTX as opposed to CYC. High ANCA-titres are frequently found in

patients with active systemic disease, and these titres often decrease during therapy(37). The use of serial ANCA testing to predict relapse is controversial and subject of ongoing discussion as studies on this question show conflicting results(38). A meta-analysis found a rise or persistence of ANCA during remission to be modestly predictive of future relapse(39). The authors see a potential in future prediction models with integration of clinical features and future biomarkers.

## Aetiology

The aetiology of ANCA-associated vasculitis is largely unknown. Findings from epidemiologic studies suggest a complex interplay of environmental and genetic factors.

### Genetics and epigenetics

The first question in terms of genetic associations is usually if familial aggregation of a disease occurs. There are several studies describing occurrence in relatives of diseased individuals(40, 41). These studies are usually small case series. A larger case control study from Sweden(42) examining the risk of GPA in relatives of patients with the disease found a low risk for GPA in close relatives. A relative risk of 1.56 was found, according to the researchers in the same range as that of rheumatoid arthritis (RA). Several studies have examined associations between single nucleotide polymorphism and the risk of developing disease. An example for such a polymorphic is the Pi system controlling the concentration of Alpha1 antitrypsin ( $\alpha$ -1 AT) in the plasma. Subnormal plasma levels are predominantly associated to the PiZ allele (proteinase inhibitor Z-allele) of this gene. The serin protease Proteinase 3, the target of PR3 antibodies is naturally inhibited by  $\alpha$ -1 AT and associations between its deficiency and pulmonary emphysema(43), autoimmunity(44) and vasculitis(45) have been observed. Elzouki et al.(46) demonstrated that carriers of the heterozygous PiZ allele were at higher risk of developing GPA than the general population. Interestingly a follow up study comparing PR3 positive patients with this allele to patients without it demonstrated poorer prognosis and more extensive organ involvement in the PiZ-positive group(47). Genome wide association studies (GWAS) have been conducted in AAV in the last years, Lyons et al.(32) found that GPA and MPA are genetically distinct, but the genetic association is stronger with ANCA specificity than with the phenotype, moreover they found that HLA-DP and the genes coding for  $\alpha$ <sub>1</sub>-antitrypsin (*SERPINA1*) and proteinase 3 (*PRTN3*) were strongly associated with PR3-ANCA whereas *HLA-DQ* was associated with MPO-ANCA. The GWAS(31) conducted in EGPA patients a few years later could demonstrate that similar genetic subsets exist when stratifying after MPO-ANCA. A large meta-analysis found 33



genetic variants associated with AAV(48). Most genetic variants are located inside the major histocompatibility region, (MHC), *HLA-DPA rs9277341* showed a strong protective effect whereas *HLA-DPBI\*0401* entailed the strongest risk for developing AAV. *HLA-DPBI\*0401* was also found to have association with GPA development by Watts et al.(49). Some epigenetic modifications, altering gene activity or expression have been identified in AAV, for example DNA- or histone-methylation(50, 51).

## **Environmental factors**

The incidence of AAV increases with age. This could imply accumulation of exposure time to environmental factors or unknown factors associated with ageing. Associations with drugs, air pollutants, solvents, farming, animal exposure and UV-light and infections have been observed.

## **Silica**

Silica also known as quartz or chemically Silicon dioxide  $\text{SiO}_2$  is one of the most abundant materials on earth. Besides its abundance in nature, it occurs ubiquitous in building materials. Crystalline silica dust is released in the context of mining, engineering, construction or demolition, thus also in disastrous events. After the 1995 Kobe earthquake as well as after the great eastern earthquake in Japan in 2011, people were exposed to large quantities of silica dust by building collapse or dust contained in sludge. A marked increase in new cases of AAV (MPO-ANCA positive disease) in both areas was observed in the years after the catastrophe(52, 53). In case of the 2011 earthquake doubled incidence rates were reported. However, this could not be replicated in a study from New Zealand examining incidences before and after the Christchurch earthquake from 2011(54). The prevalence of AAV was examined in the “quarry rich” region of Alsace in northern France, patients with AAV were identified by ICD-code (International classification of diseases) and a geospatial analysis was performed. The researchers found a higher risk for GPA and renal limited vasculitis (but not for MPA) in communes with quarries compared to those without, in addition the number of GPA cases increased with proximity to quarries(55). A possible mechanism how  $\text{SiO}_2$  might contribute to AAV development could be silica induced alveolar macrophage activation, chemotaxis of neutrophils to the site, phagocytosis by macrophages and presentation of neutrophil antigens, i.e., PR3 and MPO to other immune cells(52, 56). Silica has even been shown to induce apoptosis(57) and it has been implicated in the pathogenesis of other rheumatic disease for example systemic lupus erythematosus (SLE)(58). A meta-analysis on the association between silica exposure and AAV confirmed significant association, with comparable odds for GPA and MPA in studies only studying one phenotype(59). The study mentions three studies examining latency

periods, between initial exposure to silica and AAV diagnosis, with latencies ranging from 13 to 32 years.

## **Ultraviolet radiation**

An explanation for the “North-South gradient” (see chapter Incidence Geography) in AAV incidences could, besides genetics, be the exposure to UV radiation resulting in decreased Vitamin D synthesis in the skin. Increasing latitudes correspond to decreasing ambient UV B radiation especially in the winter(60) and decreased vitamin D production in the skin(61). An inverse association especially in winter for GPA and EGPA incidence (but not MPA) and extent of UV radiation has been observed(62). The authors propose a lack of vitamin D induced regulatory effect on T-cells as possible mechanism. Little et al.(63) further analysed a possible association in a large Irish-British registry-based study with over 2000 AAV cases even integrating Vitamin D status (via proxy cumulative weighted UV B). The study showed that low ambient UVB and vitamin D deficiency is associated with relapse in AAV, however, no significant association between AAV phenotype or ANCA serology subtype could be found for latitude, UVB radiation or UVB predicted Vitamin D status. A limitation of the study is the narrow latitudinal corridor, the cohort was recruited from, restricting genetic and latitudinal variability.

## **Farming/animal exposure and others**

A study from the UK(64) found a clear association between farming and GPA and MPA but a distinguishment between exposure to crops or animals was not possible. The same study even found an association between solvent exposure for GPA but not MPA. A case control study from Sweden on occupational risk factors could not find an association with farming(65) whereas a study from New Zealand could(66). A recent study reported a significant association between exposure to horses and GPA, furthermore an association to farming of crops and cattle(67).

## **Drugs**

Antithyroid drugs primarily propylthiouracil (PTU) are associated with MPO-ANCA and MPA like disease is sometimes observed(68). Most cases are seen in China where PTU is frequently used. Cross reactivity between thyroid peroxidase the enzyme inhibited by PTU and MPO has been described(69). Other drugs are hydralazine and minocycline, both drugs are not only associated with vasculitis but even with lupus like syndrome(3). Cocaine induced vasculitis has two components, a necrosis of the septal cartilage induced by cocaine itself that can mimic GPA and a levamisole(70% of cocaine worldwide is contaminated with this anthelmintic agent) induced, in most cases MPO- and many even PR3-positive systemic

vasculitis with arthralgias, skin and ENT involvement and neutropenia(70). Leukotriene antagonists for the treatment of asthma have been implicated in EGPA but causality is unclear and further data is needed(71). Drug induced vasculitis symptoms usually subside upon termination of the drug, but in some cases immunosuppressive treatment is warranted(72).

## **Infection**

Infections are often implicated in diseases with unknown or potentially multifactorial aetiology, especially autoimmune diseases. Autoimmunity implies the recognition and attack of host tissue by the immune system. Infections might introduce or enhance this recognition of host tissues as a target by different mechanisms. Ercolini et al.(73) describe four mechanisms by which pathogens may cause autoimmunity: molecular mimicry, epitope spreading, bystander activation, and cryptic antigens.

Observations of seasonal and cyclical increase of incidence may point to infection with more frequent onset of vasculitis following seasonal peaks of for example respiratory infections. However, these observations are inconsistent in different studies, describing incidence peaks in different seasons and making it difficult to draw conclusions. Another finding potentially pointing to infections is the simultaneous finding of infectious agents in cultures with either new onset or relapse of AAV. *Staphylococcus aureus* has been implicated in this context. A Dutch study observed a higher relapse rate in GPA patients that were chronic nasal carriers of *S. aureus*(74) and later demonstrated that treatment with Cotrimoxazole reduced relapse rates in GPA patients(75). Recently a French study(76) could neither demonstrate an association between nasal *S. aureus* carriage or Cotrimoxazole use and AAV disease progression or relapse rates, but higher rates of chronic *S. aureus* carriage in AAV patients were observed. For *S.aureus*, a possible molecular mimicry mechanism has been proposed(77). An immune response to peptides that are complementary to the AAV-autoantigen (complementary PR3 (cPR3) and PR3, respectively) could elicit autoantibodies against the autoantigen itself. In mice such a mechanism has been shown with the presence of cPR3 specific memory T-cells and the detection of anti-PR3 after immunization with cPR3(77, 78). Peptides that mimic cPR3 have been described for *S. aureus* and interestingly structural analogies to peptides found in Ross River virus and *Entamoeba histolytica*(77), two organisms associated with presence of ANCA in earlier studies(5, 79). Multiple observations on differences in titres or patterns of antibodies to different virus or bacteria have been made, but these are often observations that do not prove causality and that might be influenced by other factors, in some cases later studies could not verify such associations, as for example in Parvovirus B19(80). It can be hypothesized that the large number of associations described between microorganism and the observations of ANCA-positivity reinforces a multifactorial aetiology where

different initial triggers including infections are possible then merging in a certain disease pattern. Some studies not focusing on single organisms but rather on infections in general have shown associations between prior infections and subsequent development of autoimmune disease. In a large Danish study, cases with a history of hospitalization for an infection exhibited a dose dependant increased risk of developing autoimmune disease(81). Studies on specific diseases as Sjögren syndrome(82), inflammatory myopathies(83) and giant cell arteritis(84) have demonstrated similar associations.

The COVID19 pandemic has been a major global problem for roughly three years. Considerable scientific efforts on its pathogenesis and treatment as well as vaccination have been made. There are reports of development of AAV in relation to COVID19 infection(85) as well as vaccination(86). A study from Greece describes a patient with MPO positive pulmonary renal syndrome shortly after vaccination, achievement of remission under CYC induction treatment but vasculitis relapse together with COVID19 infection after a few months(87). It remains unclear if these are true associations or coincidences. COVID has been associated with several other autoimmune diseases(88-90). Molecular mimicry(88), cytokine storm(91) and excessive NET formation(88) have been proposed as explanations. NETs might be a link between COVID and AAV, as NETs are induced in both. In AAV NETs induce complement and complement inhibition with C5aR1 is an established treatment that also shows promising results in COVID-19(92).

## Pathogenesis

The pathogenesis of AAV is complex, involving innate and adaptive immunity. Genetics, environment, age as well as inflammation, or infections might trigger loss of tolerance to PR3 and MPO, resulting in autoreactive T- and B-cells and consecutive autoantibody, i.e. ANCA production(3). ANCA can themselves activate neutrophils(26, 27). However, this process can be facilitated through priming of neutrophils by for example TNF- $\alpha$ (93), LPS(94), or C5a(95). Priming leads to the presentation and release of MPO and PR3 on the surface of neutrophils(96). Infection might constitute such a priming event. Neutrophil granulocytes play a key role in the pathogenesis of AAV, as these cells are the target of autoantibodies and effectors at the same time. Neutrophils activated by ANCA adhere and penetrate vessel walls, release toxic oxygen species as well as proinflammatory cytokines recruiting and activating more cells to the area as well as activating complement via the alternate pathway. In addition, NETS are released. The result is a necrotizing inflammation in the respective tissue with injury to vessel walls resulting in the release of plasma proteins including coagulation factors that upon activation degrade to fibrin leading to fibrinoid necrosis(96). Alba et al.(97)

describe this mechanism for kidney, skin, and other organ systems. In alveolar tissue this process could result in loss of capillary integrity with transition of erythrocytes into the alveolar space, i.e., alveolar haemorrhage. The severity of the initial injury determines the extent of fibroblast activation and collagen deposition, i.e., fibrosis and sclerosis and therefore permanent organ damage(97).

## Epidemiology

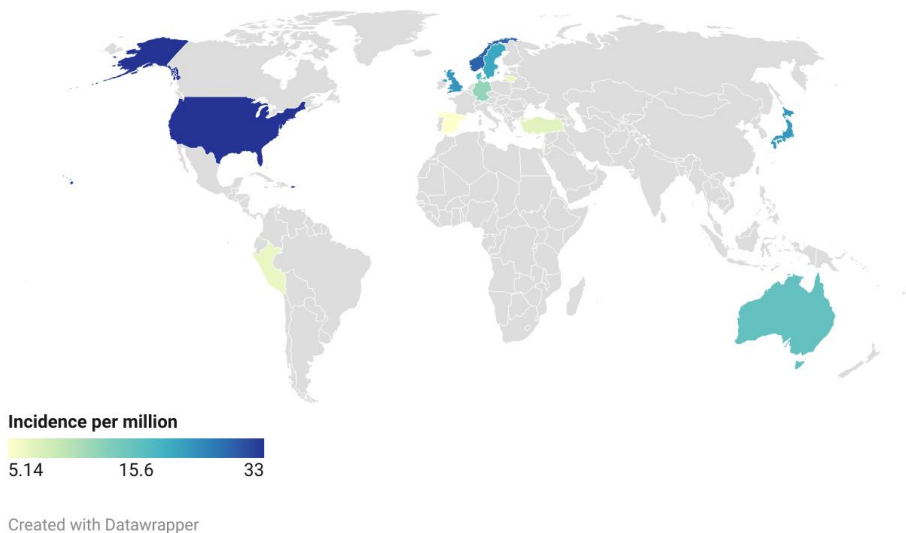
Epidemiology aims to identify frequency, patterns of occurrence, possible causes and risk factors of a given condition in a population to identify aetiological mechanisms and plan allocation of healthcare resources. It further aims to contribute to the development of prevention-strategies. In order to include cases in epidemiologic studies and to make these studies comparable in a larger scale a common agreement on case definition is essential. The introduction of disease definitions and classification criteria in the last decades has facilitated this process. This also reflects in the growing number of epidemiologic studies in the field. Several epidemiologic studies on AAV have been conducted during the last decades (Figure 1, Table 1). However, available studies are predominantly from certain regions of the world as Europe, North America, and Australia. There is little data from Japan, China, and South America and none from India or Africa. As geographic differences in disease phenotype and ANCA serology distribution have been observed more data from other areas of the world is needed. Changes in disease definitions during the last decades limit the comparability of studies from different time periods. MPA for example, was earlier included in the PAN group, and PAN was a frequent disease among the PSV. In 1994 the CHCC defined MPA as a disease entity different from PAN, which has since become a rare disease whereas MPA is more common.

## Incidence

AAVs are rare diseases with a combined incidence of 13-20 million in the early 2000s(98). Recent studies from Norway and the USA reported incidence of 24.7/million(99) and 33/million(100), respectively. Compared to the earliest studies from the 1980s an increase in incidence could be observed. Andrews et al.(101) reported a combined incidence for GPA and MPA of 1.5/million in the UK in the beginning of the eighties and 6.1/million in the second half of the same decade. Similar increases for GPA could be observed in studies from Finland(102) (1.9/million between 1981-1985, 3.6/million between 1986 and 1990, 6/million between 1991 and 1995 and 9.3/million between the years 1996 and 2000) and Sweden(103)(3/million, 1975-1985, 8/million 1986-1990 and 12/million between 1991 and 2000). Several factors may explain this increase in incidence of AAV.

First, a true increase in incidence of AAV, second, the introduction of ANCA-testing in the mid-eighties, which since then has evolved to a standard routine in ANCA diagnosis. A third possible explanation is the introduction and continuous development of disease definitions and classification criteria, which also partly links to the fourth factor of increased disease awareness of AAV among physicians. Differences in study methodology (i.e., recruitment, cohort design, underlying population) as well as differences secondary to geography, genetics, environment, and access to and quality of healthcare may explain differences in incidence between different regions. Most epidemiologic studies in AAV were conducted in Europe followed by other western countries as Australia, New Zealand, and the USA. There is comparably little data from the Middle East, South America, and Asia. In Europe, the incidence of AAV is comparable, however some studies indicated geographic differences in the incidence of GPA and MPA, the so called “North South gradient”, indicating higher GPA incidence in northern latitudes and same for MPA in southern latitudes. This discussion is ongoing, MPA incidence, however, did not differ from southern Europe in an earlier study from Southern Sweden(104). Though few studies have been conducted, data from Asia shows considerably different phenotype distribution with few cases of GPA (2.7/million) and higher incidence of MPA (18.2/million)(105) in Japan. A recent study from South Korea(106) states that MPA was the most common AAV in the studied cohort, but exact numbers for all phenotypes are not provided. There is a predominance of MPO-positivity in Asian cohorts compared to the rest of the world.

## ANCA-associated vasculitis



**Figure 1.** Incidence of ANCA associated worldwide, selected studies since 2003 that reported all phenotypes (see Table 1 for references)

**Table 1.** Incidence per million in selected studies

Incidence/ million	AAV	GPA	MPA	EGPA	Classification
<b>Australia 2008,</b> <b>Ormerod (86)</b>	15.6	8.4	5.0	2.2	ACR/CHCC(MPA)
<b>Germany, Schleswig Holstein</b> <b>2005, Reinhold-Keller(107)</b>	12.4	8.6	2.7	1.1	CHCC
<b>Japan 2011,</b> <b>Fujimoto(105)</b>	22.7	2.1	18.2	2.4	EMA
<b>Lithuania, Vilnius 2005,</b> <b>Dadoniene(108)</b>	6.4	2.1	3	1.3	ACR/CHCC(MPA)
<b>Norway, Tromsø, 2020,</b> <b>Nilsen(99)</b>	28.7	15.6	10.4	2.7	EMA
<b>Peru 2006 Lima, Sánchez(109)</b>	6.64	0.5	4	0.14	CHCC
<b>Spain2003, Malaga</b> <b>Gonzalez-Gay(110)</b>	5.14	2.1	3.4	0.64	CHCC
<b>Sweden, Lund, 2009,</b> <b>Mohammad(104)</b>	20.8	9.8	10.1	0.9	EMA
<b>Turkey, Edirne,2013,</b> <b>Pamuk(111)</b>	7.3	4.8	2.3	1.2	ACR/CHCC(MPA)
<b>United Kingdom, Nottingham</b> <b>2016</b> <b>Pearce(112)</b>	23.1	8.2	13.4	1.5	EMA
<b>USA, Olmsted,</b> <b>2017, Berti(100)</b>	33	13	16	4	ACR/CHCC/EMA
<b>Denmark, 2020,</b> <b>Nelveg-Kristensen(113)</b>	18.5				ICD-10 national registry
<b>Israel, Jerusalem, 2016,</b> <b>Nesher(114)</b>	6.6	4.1	2.3	1.2	ACR, CHCC (MPA)
<b>Peru, Lima, 2006</b> <b>Sánchez(109)</b>	4.6	0.5	4	0.14	CHCC
<b>Italy, Reggio Emilia, 2014,</b> <b>Catanoso(115)</b>		3.4			EMA
<b>Argentina, 2019, Pierini(116)</b>		9	14		CHCC
<b>Poland, 2014, Kanecki(117, 118)</b>		7.7		1.5	ICD-10
<b>Canada, Saskatschewan, 2013,</b> <b>Anderson(119)</b>		4.6	7.1		ACR,CHCC (MPA)
<b>France, nationwide, 2022,</b> <b>Bataille(120)</b> (Data from 2017)		2.8	2.7		ICD-10

Selected studies since 2003 that reported incidences of AAV, last available data from all countries

### *Seasonality*

Seasonal onset of vasculitis could support the theory of aetiology due to environmental factors as allergy(121), infection(122), or sun exposure(62). Occurrence of certain pathogens peaks in certain seasons, as for example influenza virus and pneumococci in the winter and poliovirus in the summer(123). The same applies for environmental factors as sunlight or pollen. The results of studies in this field are contradictory. Some authors report highest incidence in winter(122, 124) and presume a link between more frequent infections during this period. In a study from France, the onset of GPA was higher during summer(121), which might point

to allergic mechanisms secondary to pollen. Most patients in the study recalled ENT symptoms as being the first sign of disease onset. In addition GPA has been associated with a history of allergy(64). Other studies report no seasonality at all(125, 126). To study these relationships is challenging as numerous factors might have an influence. In case of infection, factors as pathogen survival outside a host, host behaviour and immune function, and abundance of vectors(127) all might play a role.

### *Geography*

There are geographic differences in the distribution of AAV-phenotypes, the incidences of GPA and MPA are reciprocal when comparing an Asian cohort to a European one, with MPA being much more common in Japan and GPA more common in the UK(105). The distribution of ANCA-serotype shows a similar pattern with most Japanese patients being MPO positive and most patients in the UK PR3 positive. A “North-South gradient” concerning PR3-positivity(128) and the distribution of GPA and MPA has been proposed(129), with PR3 positivity and GPA incidence increasing from equator to pole and MPA increasing from pole to equator. The finding of such a gradient for GPA inside the country of New Zealand(130) reinforced this theory. However, more recent findings do not support the notion of such gradient with comparable incidence rates in studies from the USA(100) and Norway(99)(Table 1).

### **Prevalence**

The prevalence is a measure of disease burden and outcome, and a product of incidence and mortality. Studies have shown considerable increase in the prevalence of AAV (Table 2). In a cohort from Northern Germany, prevalence of GPA doubled and that of MPA and EGPA tripled between 1994 and 2006 with identical case definition(131). In Northern Norway, the prevalence of all disease phenotypes in AAV almost doubled from 180/million in 2003 to 352 in 2013, the highest increase was described for MPA from 8/million to 58/million. Prevalence for GPA (261/million) and EGPA (33/million) were the highest ever reported(99). A study from Minnesota reported comparable prevalence of all AAV (421/million) with almost equal distribution of GPA (210/million) and MPA ((184/million) which was the highest ever reported prevalence in MPA). Increasing prevalence can to a certain extent be attributed to rising incidence, but also to improved survival due to better management, treatment, and increased physician awareness.



**Table 2.** Selected studies from different geographical areas in the world reporting prevalence

Prevalence/million	Time period	AAV	GPA	MPA	EGPA	Classification
Australia, Canberra, Ormerod(132)	2000-2004	156.4	95	39.1	22.3	ACR/CHCC MPA
France, Paris, Mahr(133)	2000	59.4	23.7	25.1	10.7	ACR/CHCC MPA
Germany, Luebeck/Bad Segeberg(131)	1994 2006	74 150	58 98	9 28	7 24	ACR/CHCC EMA
Norway, Tromsø(99)	2003 2008 2013	181 274 352	154 226 261	8 29.2 58.2	18.9 18.6 32.9	EMA EMA EMA
Spain, Malaga, Romero(134)	2010	44.9	15.8	23.8	5.3	ACR/CHCC MPA
Sweden, Skåne, Mohammad(135)	2003	268	160	94	14	EMA
Turkey, Thrace, Pamuk (111)	2013	69.3	41.9	19.3	8.1	ACR/CHCC MPA
USA, Olmsted, MN, Berti(100)	2015	420	218	184	18	EMA

All numbers prevalence per million, selection of studies that reported all three phenotypes

## Classification of ANCA-associated vasculitis

The aim of classification criteria is to ensure selection of homogenous populations for the inclusion in epidemiological studies or clinical trials. Thus, classification criteria are not intended to capture the whole spectrum and heterogeneity of a disease rather key features shared by most patients. In contrast, diagnostic criteria are generally more heterogenous in order to identify as many patients as possible with a given condition and to distinguish vasculitis from non-vasculitis. Until now, there are no designed or validated diagnosis criteria for AAV or any other vasculitic condition apart from Behçet disease(136). However, a recently completed large multinational project; the DCVAS, was aiming to establish both diagnostic criteria and classification criteria. The DCVAS resulted in recently published classification criteria (see below) for AAV. At this time, it is unlikely the project will also yield diagnostic criteria(137). Currently, the diagnosis of AAV is made on the basis of clinical, histopathological, and serological characteristics of these diseases integrating available classification criteria and definitions, though not designed for this purpose.

## **Historical background of classification in vasculitis**

In Hippocrates original description(138) of oral and genital ulcers as well as ocular inflammation, which is arguably one of the first descriptions of vasculitic symptoms (though the term was not established), several characteristics are present that today constitute diagnostic criteria for Behçet disease. In modern times, Kussmaul and Meiers(139) description of a patient with systemic symptoms such as fever, weakness, pain, and weight loss, where autopsy later showed nodular thickening of medium sized arteries is regarded as the first description of vasculitis. In 1866, they established the term periarteritis nodosa, a condition today called polyarteritis nodosa, that for many years was synonymous for all vasculitis. Kussmaul and Maier even described lesions and necrotizing inflammation in the kidney, what would be termed microscopic PAN by Davson et al later(140, 141).

In the mid-20<sup>th</sup> century, several forms of vasculitis were described for example Wegener's granulomatosis(142) and Churg-Strauss syndrome(143). Zeek's classification from 1952 differentiates between 5 forms of necrotizing vasculitis(144), it was the first systematic effort to classify these disease entities. During the following decades several authors proposed classification criteria, often only with minor modifications from Zeek's original proposal, as changing order or adding new subgroups. Examples for such criteria are those by deShazo(145) or Gilliam and Smiley(146). The latter, however, introduced for the first time the concept of vessel size, i.e., differentiating according to vessel size primarily involved. Further developments are described below in detail, in short the American College of Rheumatology introduced classification criteria for seven different forms of vasculitis in 1990(147), the Chapel Hill consensus conference defined different forms of vasculitis in 1994(148) and revised in 2012(1). Watts et al.(149) designed in 2007 a classification algorithm to combine ACR1990 criteria and CHCC 1994. The latest developments in the field are the recently published new classifications for AAV(150-152) that emerged out of the DCVAS project and are endorsed by ACR and EULAR.

## **ACR1990 classification criteria**

In 1990, the American College of Rheumatology (ACR) proposed criteria(147) for the following seven forms of vasculitis: polyarteritis nodosa (PAN), Churg-Strauss syndrome (CSS, currently EGPA)(Table 4), Wegener's granulomatosis (WG, currently GPA)(Table 3), Hypersensitivity vasculitis, Henoch-Schönlein purpura (IgA vasculitis), Giant cell (temporal) arteritis, and Takayasu arteritis. Data was prospectively collected between 1982 and 1987 from 48 centres in North America and Mexico with the goal to define criteria distinguishing different types of vasculitis from each other. The final criteria incorporated clinical, histopathological as well as laboratory items. Antineutrophil cytoplasmic antibodies were described in 1985(2). In the following years their clinical importance became more and more

apparent(153), however, as the test did not exist during data collection for the ACR-criteria(154), ANCA were not included. It is important to point out that the criteria were intended as classification and not diagnostic criteria, although they are used as such in clinical practice. In an evaluation by Rao et al.(155) the criteria performed poorly in diagnosing vasculitis in a cohort of patients referred to rheumatology for evaluation of possible vasculitis. Though improving patient selection for clinical trials and epidemiological studies and thereby contributing to rising research effort in the field, the absence of ANCA and the omission of the disease entity later termed microscopic polyangiitis (MPA) were shortcomings of the criteria.

**Table 3.** ACR 1990 criteria for Wegener’s granulomatosis (currently GPA)

Criterion	Definition
<b>Nasal or oral inflammation</b>	Painful or painless oral ulcers or purulent or bloody nasal discharge
<b>Abnormal chest radiograph</b>	Chest radiograph showing nodules, fixed infiltrates, or cavities
<b>Urinary sediment</b>	Microhematuria (>5 red blood cells per high power field) or red cell casts
<b>Granulomatous inflammation on biopsy</b>	Granulomatous inflammation within arterial wall or in the peri- or extravascular area (artery or arteriole)

Modified from Leavitt et al.(154). A patient is said to have WG if 2/4 criteria are present.

**Table 4.** ACR criteria for CSS (currently EGPA)

Criterion	Definition
<b>Asthma</b>	History of wheezing or diffuse high pitched rales on expiration
<b>Eosinophilia</b>	Eosinophilia >10% on white blood cell differential count
<b>Mono- or polyneuropathy</b>	Development of mononeuropathy, multiple mononeuropathies or polyneuropathy, or polyneuropathy attributable to systemic vasculitis
<b>Pulmonary infiltrates, non fixed</b>	Migratory or transitory pulmonary infiltrates on radiographs attributable to systemic vasculitis
<b>Paranasal sinus abnormalities</b>	History of acute or chronic paranasal sinus pain, tenderness or radiographic opacification of the paranasal sinuses
<b>Extravascular eosinophils</b>	Biopsy including artery, arteriole or venule showing accumulation of eosinophils in extravascular areas

Adapted from Masi et al.(156). At least 4 of 6 criteria need to be present in order to classify a patient as having EGPA

## Chapel Hill consensus conference (CHCC)

The participants of the CHCC were vasculitis experts from different medical and scientific specialties. They agreed on a nomenclature system for vasculitis, primarily defining different diseases according to size of vessels involved, histopathological findings, and the presence of clinical findings, for example the presence of eosinophilia and asthma in EGPA. The revision of the CHCC in 2012 introduced Behçet disease, Cogan’s syndrome as well as vasculitis associated with systemic disease (SLE, RA) and vasculitis associated with probable specific etiology (for example hydralazine associated vasculitis or cancer associated vasculitis). The term EGPA was introduced replacing the earlier eponym Churg-

Strauss (a similar name change from Wegener to GPA had been implemented shortly before(157)) In addition it was proposed to divide the small vessel vasculitides in the subgroups ANCA-associated vasculitis and immune complex small-vessel vasculitis, accounting for the paucity of immune deposits in vessel walls in the former and the opposite in the latter. CHCC were neither classification nor diagnostic criteria nevertheless the definitions were used for case inclusion in several studies.

**Table 5.** Selected key-features of AAV and subtypes established by CHCC 1994(148) and 2012(1)

<b>ANCA-associated vasculitis</b>	<b>Pauci immunity Predominantly affecting small vessels Associated with PR3 or MPO antibodies</b>
<b>GPA/Wegener's</b>	Necrotizing inflammation involving the upper and lower respiratory tract Presence of granulomatous or nongranulomatous inflammation Necrotizing glomerulonephritis is common Limited disease
<b>MPA</b>	Microscopic polyangiitis was proposed as term for a reno-pulmonary vasculitis syndrome without granulomatous inflammation No granulomatous inflammation Necrotizing glomerulonephritis is very common Capillaritis in the lung is common
<b>EGPA/Churg-Strauss</b>	EGPA replaces Churg-Strauss syndrome Eosinophil rich necrotizing inflammation of the respiratory tract Associated with asthma and eosinophilia Presence of granulomatous or non-granulomatous inflammation Limited disease

## European medicines agency (EMA) algorithm

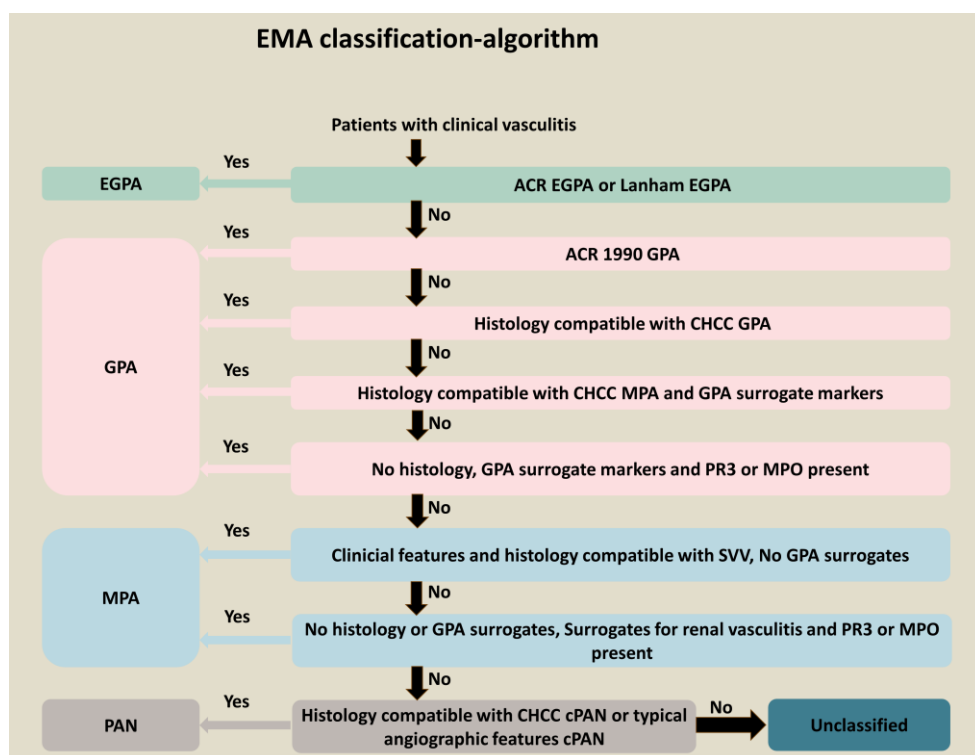
The EMA algorithm (Figure 2) was introduced 2007 by Watts et al.(149). The ACR1990 criteria and CHCC-definitions from 1994 overlapped with each other and there was a need for consensus on how to apply these two systems together(158). The intention of the authors was not to develop new criteria, rather to give a manual on how to use ACR1990 criteria and CHCC nomenclature together. In addition, guidance concerning the use of surrogate markers and ANCA were incorporated. Though the CHCC introduced the concept of surrogate markers no set of markers was provided. A prerequisite for application of the algorithm is a clinical diagnosis of vasculitis (AAV and PAN) in a patient aged 16 or above with a minimum of 3 months follow up time. In addition, criteria shown in table 6 are required, surrogate markers for vasculitis are shown in table 7.

**Table 6.** Entry criteria for the EMA algorithm

<b>A</b>	<b>Symptoms or signs compatible with or characteristic for vasculitis</b>
<b>B</b>	Minimum one of the following <ul style="list-style-type: none"> <li>• Histopathological proof of vasculitis</li> <li>• Positive ANCA serology</li> <li>• Other diagnostic measures indicating vasculitis (angiography, neurography)</li> <li>• Eosinophilia (10% or <math>1.5 \times 10^9/l</math>)</li> </ul>
<b>C</b>	No other plausible diagnosis (cancer, infection, secondary vasculitis, and pseudovasculitis)
A+B+C should be present, if B1 is negative symptoms in A should be "characteristic"	

Modified from Watts et al.(149)

The algorithm was validated(149) in a cohort from the UK as well as in cases from the participating authors, demonstrating very good agreement with the prior standard ( $\kappa$  statistic 0.89).The algorithm was even validated in a cohort from China(159) and has been used for the classification in various epidemiological studies(99, 112), even in earlier studies of the cohort which is subject of this thesis(104).Watts et al. reported no difference in classification performance despite revision of the CHCC in 2012(160).



**Figure 2.** EMA algorithm modified from Watts et al.(149), patients enter the algorithm at the top and are either classified to the left upon fulfilling respective criteria or advance downward.cPan: classic polyarteritis nodosa, SVV: small vessel vasculitis. Lanham criteria for EGPA(161)

**Table 7.** Surrogate markers for vasculitis, adapted from Watts 2007(149)

Surrogate markers for GPA (1 marker necessary to support GPA diagnosis)	Surrogate markers for renal vasculitis
<ul style="list-style-type: none"> <li>• X-ray evidence of fixed pulmonary infiltrates, nodules or cavitations present &gt;1 month</li> </ul>	<ul style="list-style-type: none"> <li>• Hematuria associated with red cell casts or &gt;10% dysmorphic erythrocytes <b>or</b></li> </ul>
<ul style="list-style-type: none"> <li>• Bronchial stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• 2+ hematuria and</li> <li>• 2+ proteinuria</li> </ul>
<ul style="list-style-type: none"> <li>• Bloody nasal discharge and crusting &gt;1 month</li> <li>• Chronic sinusitis, otitis media or mastoiditis for &gt;3 months</li> <li>• Retroorbital mass or inflammation (Pseudotumor)</li> <li>• Subglottic stenosis</li> <li>• Saddle nose/destructive sinunasal disease</li> </ul>	

## The 2022 ACR/EULAR criteria for the classification of AAV

The ACR/EULAR criteria for the classification of AAV(150-152)(Figure 3) published in March 2022, emerged out of the DCVAS(162), a joint international venture by the ACR, EULAR and the vasculitis foundation to develop diagnostic and classification criteria in the primary systemic vasculitides (GPA, MPA, EGPA, Takayasu arteritis Giant cell arteritis and Polyarteritis nodosa). The underlying observational study included almost 7000 patients with any vasculitis or vasculitis mimickers in 32 countries, the majority from Europe and the United States.

The criteria for AAV were developed in five stages. A large set of candidate items was generated through expert opinion including items from ACR1990, CHCC and items from disease activity and damage indices (BVAS and VDI). After consensus a set of items was integrated in the case report form (CRF) of the second stage, the DCVAS observational study. Included in this study were cases with the vasculitides as stated above but even cases with other vasculitides (Behçet’s disease, primary central nervous system vasculitis, IgA vasculitis, isolated aortitis) and vasculitis mimickers (infection, cancer, other inflammatory conditions). The list of candidate items was further refined towards AAV and thereby reduced by consensus in the steering committee. Clinical cases with data generated through evaluation of the DCVAS CRF was used to produce clinical scenarios. Those were in step four sent to international vasculitis experts, whose diagnostic assessment would then be used as diagnostic gold standard. Thus, a final set of 91 items and 2072 cases was generated and via advanced statistical analysis a final set of weighted criteria was developed for the three AAV-phenotypes. The criteria were then validated in other cases from the DCVAS cohort. The authors report sensitivities for GPA, MPA, and EGPA of 92.5%, 90.8% and 84.9% and specificities of 93.8%, 94.2% and 99.1%, respectively, in the validation set. The criteria are the first classification criteria to incorporate ANCA, modern imaging and pulmonary fibrosis. As ANCA today is a cornerstone in clinical management of AAV, an incorporation in classification

criteria has long been requested. The developers account for this granting ANCA-specificity a considerable weight in the new criteria.

ACR/EULAR 2022 AAV classification criteria for AAV		
Prerequisites: Diagnosis of small-medium vessel vasculitis established and vasculitis mimicks excluded		
GPA	MPA	EGPA
<ul style="list-style-type: none"> <li>Nasal (crusts, discharge, ulcers, congestion, perforation) +3</li> <li>Cartilage (ear, nose, stridor, endobronchial, saddle nose) +2</li> <li>Hearing loss +1</li> </ul>	<ul style="list-style-type: none"> <li>Nasal (crusts, discharge, ulcers, congestion, perforation) -3</li> </ul>	<ul style="list-style-type: none"> <li>Asthma +3</li> <li>Nasal polyps +3</li> <li>Mononeuritis multiplex +1</li> </ul>
<ul style="list-style-type: none"> <li>Positive cANCA or PR3 +5</li> <li>Chest imaging (nodules, mass, cavitation) +2</li> <li>Granuloma on biopsy +2</li> <li>Sinus imaging (effusion, consolidation) +1</li> <li>Pauci-immune GN on biopsy +1</li> <li>Positive pANCA or MPO -1</li> <li>Blood eosinophils <math>\geq 1 \times 10^9/l</math> -4</li> </ul>	<ul style="list-style-type: none"> <li>Positive pANCA or MPO +6</li> <li>Chest imaging (Fibrosis/ILD) +3</li> <li>Pauci-immune GN on biopsy +3</li> <li>Positive cANCA or PR3 -1</li> <li>Blood eosinophils <math>\geq 1 \times 10^9/l</math> -4</li> </ul>	<ul style="list-style-type: none"> <li>Blood eosinophils <math>\geq 1 \times 10^9/l</math> +5</li> <li>Extravascular eosinophil rich inflammation on biopsy +2</li> <li>Positive cANCA or PR3 -3</li> <li>Hematuria -1</li> </ul>
Sum score 10 items <b><math>\geq 5</math> =GPA</b>	Sum score 6 items <b><math>\geq 5</math> =MPA</b>	Sum score 7 items <b><math>\geq 6</math> =EGPA</b>

Figure 3. ACR/EULAR classification criteria for AAV ( Modified from references (150-152))

## ANCA-associated vasculitis – the disease

AAV is subdivided into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The three subtypes share common laboratory, histopathological and clinical features as well as the predilection for vasculitis in small vessels, and the presence of ANCA in variable frequency.

### Granulomatosis with polyangiitis (GPA)

GPA is characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract and necrotizing vasculitis in small to medium vessels(1). It often (70-100%(163)) presents with ear nose and throat (ENT) symptoms (bloody

nasal discharge, crusting, chronic-otitis-media, sinusitis, inflammation, and destruction of the nasal cartilage). Furthermore, lung involvement in 50-90% of cases(163), with inflammation in the lower respiratory tract with findings of nodules and cavitation on pulmonary imaging or in severe cases alveolar haemorrhage. Kidney involvement with necrotizing glomerulonephritis is frequently (50-80%) reported(164). GPA can be systemic or localized, the latter often with sinonasal symptoms only. GPA can include a variety of other organ systems for example eyes, skin, or the peripheral nerves though in lower frequencies than above mentioned symptoms. Most patients (up to 75% with systemic disease, fewer in localized disease) with GPA exhibit a cytoplasmic ANCA pattern with antibodies directed against proteinase-3 (PR3). GPA with MPO-positivity occurs in up to 30% of cases while ANCA is negative in 5%(3). Among the three phenotypes, GPA is most likely to relapse (up to 40% within 2 years)(165).

### **Microscopic polyangiitis (MPA)**

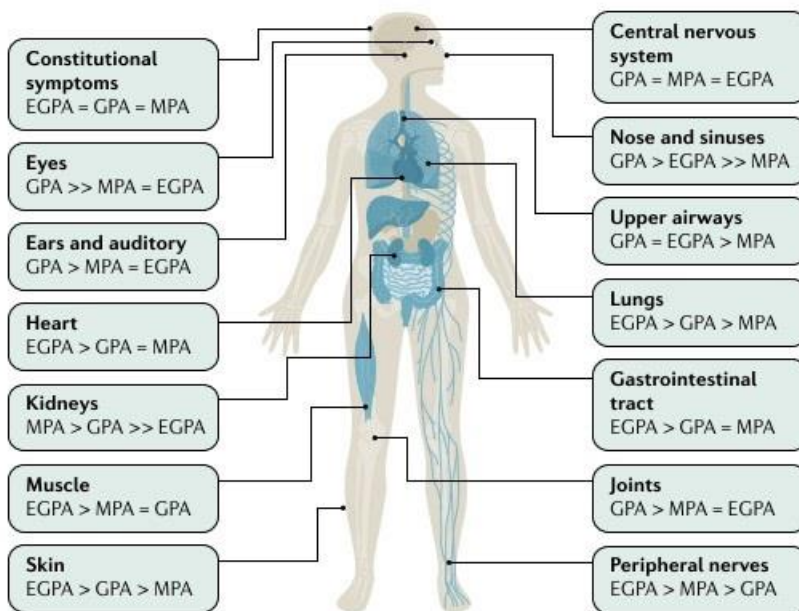
Microscopic polyangiitis is a necrotizing vasculitis predominantly affecting small vessels(1). Granulomatous inflammation does not occur. It usually presents with decreasing renal function, microhaematuria with cellular casts and mild proteinuria(166).The kidneys are involved in 90-100%(164), and the disease can be restricted to the kidney only, referred to by some authors as renal limited vasculitis (RLV)(167). The lung is involved in 25-55%of cases(168) with symptoms as cough, dyspnea, or alveolar haemorrhage, the latter with variable severity. The pulmo-renal syndrome, is a combination of diffuse alveolar haemorrhage and glomerulonephritis, an often life-threatening disease affecting MPO more than the other phenotypes(168). Pulmonary involvement in AAV and especially in MPA can also present as interstitial lung disease (ILD)(169, 170). In MPA patients it usually presents with a histopathological and/or radiologic pattern of usual interstitial pneumonia (UIP) and it was exclusively found in MPO-positive patients(171). In a French study on pulmonary fibrosis (a condition included in ILD) in AAV, fibrosis diagnosis preceded vasculitis onset in 45% of patients(172). A latency from a few months to 12 years has been described by other authors(173). Other affected organs in MPA are the skin (35-62%), peripheral nervous system (14-58%) and the gastrointestinal tract (30-56%)(168). Constitutional symptoms as fever, weight loss and myalgia are common at presentation(166, 168). Mukthiar et al. describe lower relapse rates than in GPA but worse survival(165). ANCA is positive in up to 90% of cases, predominantly with MPO-specificity (up to 65%)(3).

### **Eosinophilic granulomatosis with polyangiitis (EGPA)**

EGPA is an eosinophil-rich granulomatous inflammation often affecting the respiratory tract in addition necrotizing vasculitis of small and medium vessels



occurs(1). Besides vasculitic features as the other AAVs, EGPA also encompasses signs and symptoms related to hypereosinophilia. EGPA is almost always associated with asthma and eosinophilia(174). Patients can exhibit nodular lung disease as in GPA, in addition sinonasal symptoms, usually more allergic and not destructive. EGPA can involve the gastrointestinal tract, the peripheral nervous system and the heart. ANCAs can be found in up to 40% of EGPA cases, predominantly with MPO-specificity(3). The disease shows different appearances with respect to ANCA-status, on the one hand a vasculitic type with skin disease, neuropathy and rapid progressive GN in MPO positive patients and on the other hand a type with cardiomyopathy, lung infiltrates and gastrointestinal involvement driven by eosinophils(174).



**Figure 4.** Organinvolvement and approximate frequencies in the AAV phenotypes. Reprinted by permission from Springer Nature, Nature Reviews Disease Primers, ANCA-associated vasculitis, Kitching, R (2020)

## Disease assessment and outcome measures in AAV

Two components can be described in chronic relapsing diseases as AAV: Disease activity as a reversible component and damage as irreversible. Distinguishing damage from disease activity is essential for clinical decision making as irreversible damage should not warrant increase of immunosuppression. Vasculitis symptoms can be heterogenous, as different organ systems can be involved. Evaluating and monitoring disease activity therefore cannot be accomplished with a single

biomarker or biopsy, assessment instead needs to include a survey of symptoms in different organ systems. Outcomes as remission and relapse are defined by presence, absence or return of disease activity(175) and assessment warrants accurate and reproducible assessment of disease activity.

#### *Assessment of disease activity*

Birmingham Vasculitis Activity Score (BVAS) (Figure 5) is a tool for the evaluation of disease activity, primarily in clinical trials. It was introduced in 1994(176) and its latest revision (Version 3) was published in 2008(177). BVAS is a score based on a list of clinical and laboratory manifestations in different organ systems. In the latest revision the score encompasses 56 items in 9 organ systems. Items are weighted and generate higher scores according to their clinical importance. In addition, there is a maximum score in every category(176). Items should only be scored if presence is attributable to active vasculitis. The total score is 63. The BVAS is the standard tool for the assessment of disease activity(175).

#### *Assessment of organ damage*

Damage is an outcome that cannot be reversed with therapy(178). It can be induced by disease or treatment. Due to better management and treatment, mortality in AAV has significantly decreased in the last decades but the chronic relapsing character of the disease exposes the patient to new phases of increased disease activity and intensified treatment with the potential for subsequent damage. The vasculitis damage index (VDI)(Figure 6) was introduced in 1998 by Exley et al.(179) to aid in separating damage from disease activity. The index consists out of 64 items in 11 categories (10 organ specific and 1 relating to side effects of treatment), each items generates 1 point. Items are permanent, thus the VDI score can only increase or remain the same over time. An item can be scored if it has been present for 3 months and occurred after the onset of vasculitis. Items in the VDI are scored regardless of whether damage is attributable to vasculitis, drug induced or due to another comorbidity. Damage can severely impair quality of life; its prevention is therefore an important goal of vasculitis therapy. High damage has been shown to predict mortality(180, 181), VDI is recommended as standard outcome measure(175). As all items have similar weight, the score does not reflect that some forms of damage exert greater impact on patient health than others, but there is an ongoing discussion to account for this in the future(182).

#### *Five-Factor Score*

The Five-Factor Score (FFS) was introduced in 1996 by the French vasculitis study group (FVSG) with the primary objective to predict survival of patients with PAN, MPA and EGPA(183). Five items were included in the original version, with each item generating 1 point. 5-year mortality rates for 0,1 and 2 points were 12%, 26% and 46%, respectively.

- Proteinuria >1g/day
- Renal insufficiency: creatinine  $\geq 140$   $\mu\text{mol/L}$ ,
- Gastrointestinal involvement (bleeding, perforation, infarction, or pancreatitis)
- Central nervous system involvement
- Cardiomyopathy

The FFS was revised in 2009 to even include GPA(184). In cases with GPA and EGPA, the presence of ENT manifestations was observed to be associated with better survival, the final score also incorporates 5 factors each generating 1 point: Age >65 years, cardiac insufficiency, renal insufficiency, gastrointestinal involvement, and the absence of ENT manifestations. Reported 5-year mortality rates for 0,1 and 2 points were 9%, 21% and 40%, respectively. The FFS can be used for assessment of prognosis and assist in deciding on treatment in certain cases of AAV. A study on long term outcomes of patients with EGPA by the FVSG(185) showed that patients treated according to initial disease severity, assessed by the FFS, with patients with FFS=0 only receiving GCs and patients with FFS  $\geq 1$  receiving GCs plus CYC exhibited comparable survival and relapse rates.

#### *Disease extent index*

The disease extent index (DEI) was introduced in 1994 and is intended for use in GPA(186, 187). Points are scored in case of active vasculitis in different organ systems. The score captures different domains of disease than the BVAS and should therefore be used as a supplement(187, 188).



## VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*

Patients often have co-morbidity before they develop vasculitis, **which must not be scored**

Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)

A new patient should **usually have a VDI score of zero**, unless:

- (a) they have had vasculitis for more than three months of onset of disease, and  
 (b) the damage has developed or become worse since the onset of vasculitis

	No	Yes	Name		
<b>1. Musculoskeletal</b>			<b>Trial Number</b>		
None	<input type="checkbox"/>		<b>Date</b>		
Significant muscle atrophy or weakness		<input type="radio"/>	<b>Centre</b>		
Deforming/erosive arthritis		<input type="radio"/>			
Osteoporosis/vertebral collapse		<input type="radio"/>	<b>7. Peripheral vascular disease</b>	<b>No</b>	<b>Yes</b>
Avascular necrosis		<input type="radio"/>	None	<input type="checkbox"/>	
Osteomyelitis		<input type="radio"/>	Absent pulses in one limb		<input type="radio"/>
<b>2. Skin/Mucous membranes</b>			2 <sup>nd</sup> episode of absent pulses in one limb		<input type="radio"/>
None	<input type="checkbox"/>		Major vessel stenosis		<input type="radio"/>
Alopecia		<input type="radio"/>	Claudication >3 mths		<input type="radio"/>
Cutaneous ulcers		<input type="radio"/>	Minor tissue loss		<input type="radio"/>
Mouth ulcers		<input type="radio"/>	Major tissue loss		<input type="radio"/>
<b>3. Ocular</b>			Subsequent major tissue loss		<input type="radio"/>
None	<input type="checkbox"/>		Complicated venous thrombosis		<input type="radio"/>
Cataract		<input type="radio"/>	<b>8. Gastrointestinal</b>		
Retinal change		<input type="radio"/>	None	<input type="checkbox"/>	
Optic atrophy		<input type="radio"/>	Gut infarction/resection		<input type="radio"/>
Visual impairment/diplopia		<input type="radio"/>	Mesenteric insufficiency/pancreatitis		<input type="radio"/>
Blindness in one eye		<input type="radio"/>	Chronic peritonitis		<input type="radio"/>
Blindness in second eye		<input type="radio"/>	Oesophageal stricture/surgery		<input type="radio"/>
Orbital wall destruction		<input type="radio"/>	<b>9. Renal</b>		
<b>4. ENT</b>			None	<input type="checkbox"/>	
None	<input type="checkbox"/>		Estimated/measured GFR ≤ 50%		<input type="radio"/>
Hearing loss		<input type="radio"/>	Proteinuria ≥ 0.5g/24hr		<input type="radio"/>
Nasal blockage/chronic discharge/crusting		<input type="radio"/>	End stage renal disease		<input type="radio"/>
Nasal bridge collapse/septal perforation		<input type="radio"/>	<b>10. Neuropsychiatric</b>		
Chronic sinusitis/radiological damage		<input type="radio"/>	None	<input type="checkbox"/>	
Subglottic stenosis (no surgery)		<input type="radio"/>	Cognitive impairment		<input type="radio"/>
Subglottic stenosis (with surgery)		<input type="radio"/>	Major psychosis		<input type="radio"/>
<b>5. Pulmonary</b>			Seizures		<input type="radio"/>
None	<input type="checkbox"/>		Cerebrovascular accident		<input type="radio"/>
Pulmonary hypertension		<input type="radio"/>	2 <sup>nd</sup> cerebrovascular accident		<input type="radio"/>
Pulmonary fibrosis		<input type="radio"/>	Cranial nerve lesion		<input type="radio"/>
Pulmonary infarction		<input type="radio"/>	Peripheral neuropathy		<input type="radio"/>
Pleural fibrosis		<input type="radio"/>	Transverse myelitis		<input type="radio"/>
Chronic asthma		<input type="radio"/>	<b>11. Other</b>		
Chronic breathlessness		<input type="radio"/>	None	<input type="checkbox"/>	
Impaired lung function		<input type="radio"/>	Gonadal failure		<input type="radio"/>
<b>6. Cardiovascular</b>			Marrow failure		<input type="radio"/>
None	<input type="checkbox"/>		Diabetes		<input type="radio"/>
Angina angioplasty		<input type="radio"/>	Chemical cystitis		<input type="radio"/>
Myocardial infarction		<input type="radio"/>	Malignancy		<input type="radio"/>
Subsequent myocardial infarction		<input type="radio"/>	Other		<input type="radio"/>
Cardiomyopathy		<input type="radio"/>	Total VDI Score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. <input style="width: 50px; height: 20px;" type="text"/>		
Valvular disease		<input type="radio"/>			
Pericarditis ≥ 3 mths or pericardectomy		<input type="radio"/>			
Diastolic BP ≥ 95 or requiring antihypertensives		<input type="radio"/>			

VDI. Modified from Exley AR, Bacon PA, Luqmani et al (1997) Development and initial validation of the VDI ... Arthritis Rheum 40: 371-380

Figure 6. Vasculitis damage index

Reprinted from Exley et al(179) with permission from John Wiley and Sons

# Treatment

The current treatment of ANCA associated vasculitis consists of two cornerstones: Induction of remission and maintenance of remission.

## **The evolution of treatment of AAV**

Prior to the introduction of immunosuppressive treatments and glucocorticoids (GC) the prognosis of AAV was very poor. In a retrospective study Walton reported a GPA mortality of 80% within a year(4). GC was introduced in the beginning of the 50's and synthetic derivatives a few years later(189). GC treatment improved survival(190) and case studies with immunosuppressives(191) showed favourable results. The study by Fauci et al(192) established the usefulness cyclophosphamide (CYC) in the treatment of vasculitis, with over 80% of patients achieving remission. In the following years the same research group presented larger studies introducing combination treatment with glucocorticoids (192). Remission was achieved in over 90% of cases. Daily GC and oral CYC thus became standard treatment. However, the treatment regimen with peroral CYC entailed considerably high cumulative doses and side effects attributable to its short- and long-term toxicity. Side effects as haemorrhagic cystitis, infertility, bladder cancer and lymphoproliferative malignancies(193) became obvious. Thus, treatment regimens decreasing cumulative CYC dose were warranted. In the CYCAZAREM trial by Jayne et.al(194) from 2003 the researchers could show that the rate of relapses did not increase if CYC was substituted by Azathioprine (AZA) after remission. This meant a decrease in exposure time and dose of CYC and established the concept of remission maintenance treatment. The CYCLOPS trial(195) from 2009 demonstrated no differences in remission rates when comparing pulsed intravenous CYC (IV CYC) against a daily peroral regimen, with the benefit of reduced cumulative CYC doses in the IV CYC regimen. Long term follow-up of this trial(196) showed higher relapse rates with the IV CYC regimen, however without impacting long term morbidity or survival. Treatment with biologic agents has emerged in several inflammatory diseases since the late 90's. The RAVE(197) and RITUXVAS(198) trial established the use of the anti-CD20 monoclonal antibody Rituximab for remission induction in vasculitis, both trials reported comparable remission rates with RTX compared to CYC but even comparable rates of infection. The effectiveness and superiority of RTX in remission maintenance, compared to established treatment with AZA was shown in MAINRITSAN trial(199). CD-20 is present on most B-cells except plasma cells (200) and RTX causes B-cell depletion through different mechanisms(201), after interaction with this antigen. Though treatment of AAV has changed considerably through the years the use of glucocorticoids has been a constant since the 1950's. The short- and long-term side effects of glucocorticoids from infection susceptibility, hypertension, osteoporosis,

cataract and peptic ulcers to name a few were observed in EUVAS trials(202) as well as higher frequencies of permanent organ damage in individuals with prolonged steroid treatment(203). These findings highlight the need for reduction of steroid exposure or for steroid free alternatives. Recently the PEXIVAS(204) trial demonstrated non inferiority of a reduced GC dose regimen regarding death and end stage renal disease, in addition a lower risk of serious infection was observed in the first year. Different GC regimens during inductions were also studied in the LOVAS trial(205). It demonstrated non inferiority of a RTX/low dose GCs regimen compared to RTX/high dose GC regimen regarding induction of remission at 6 months, with less infections in the low dose group. The ADVOCATE trial(206) studied the C5a receptor inhibitor Avacopan as an alternative to glucocorticoids, the new drug was noninferior to a prednisone taper regarding remission at week 26 and superior at 1 year with respect to sustained remission. Plasma exchange was previously a treatment option in patients with severe renal disease as it has been shown to improve renal recovery rates in the MEPEX trial(207). Plasma exchange is even recommended for another severe vasculitis manifestation, diffuse alveolar haemorrhage, The PEXIVAS(204) trial could not show a treatment effect in these patients and states no difference in mortality or rate of end-stage renal disease (ESRD). However, as certain subgroups of patients might benefit from plasma exchange(208), the discussion continued, a recent meta-analysis(209) states no difference in mortality, a reduced risk of ESRD at 1 year but an increased risk of serious infection.

There is fewer data on treatment strategies in EGPA due to the rarity of this condition. Non severe EGPA (FFS=0) can be treated with GC alone with a high rate of remission (93%) but relapses in about 40% of cases(210). Adding AZA as induction agent did not change the rate of remission or relapses(211). Severe EGPA is treated as the other AAV with GC and CYC for induction followed by maintenance agents. There are no clinical trials examining the role of RTX in EGPA, a retrospective multicentre study reported 50% remission at 1 year and higher remission rates in ANCA-positive individuals(212). Early results from the French REOVAS trial comparing RTX to conventional induction in EGPA does not show superiority of RTX in achieving remission and reports comparable relapse rates as well as GC doses for the compared groups(213). A clinical trial in patients with relapsing or refractory EGPA published in 2017(214) demonstrated that the interleukin 5 antagonist Mepolizumab is an effective treatment for EGPA.

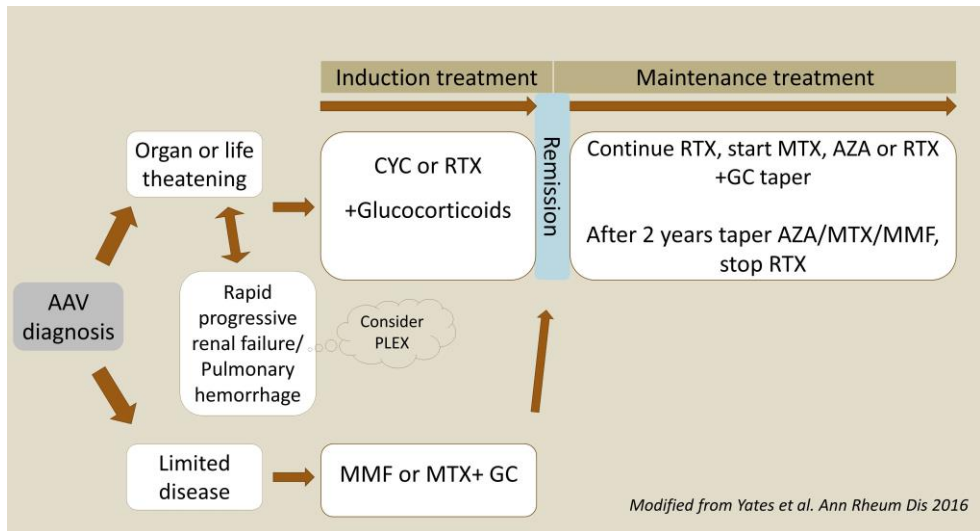
## **Current treatment of AAV**

In the induction phase, treatment with either CYC (by daily oral or pulsed intravenous dose) or rituximab combined with high dose glucocorticoids (usually 50-75mg initially) is recommended. In certain cases, adjunctive therapy with plasma exchange(207) and intravenous immunoglobulins(215) can be considered. Glucocorticoids are tapered within a few months, today a regimen introduced by the PEXIVAS trial(204) with a dose of 20mg/day by 7 weeks and 5mg/d after 19 weeks is standard of care. Glucocorticoids are usually continued in low doses throughout the maintenance phase or even longer. In the maintenance phase patients induced with cyclophosphamide should receive either azathioprine, methotrexate, mycophenolate-mofetil or rituximab. Patients induced with RTX continue with RTX every 6 months, above named agents can be alternatives in special cases. In patients with limited/non organ threatening disease treatment with methotrexate or mycophenolate-mofetil are equally effective as CYC in achieving remission at 6 months, in case of MTX at the price of higher relapse rates with potential later need for CYC.

Additional treatment is recommended in national(216) and regional guidelines(217):

- Osteoporosis prophylaxis with calcium and d-vitamin and antiresorptive agents
- PJP-prophylaxis with cotrimoxazole (atovaquone or inhaled pentamidine can be alternatives)
- Vaccination against pneumococci, influenza, and hepatitis B
- Antifungal prophylaxis
- Gastric ulcer prophylaxis with H2 blocking agent or proton pump inhibitor.





**Figure 7.** EULAR Treatment algorithm for AAV, 2016. Modified from Yates(38)  
 PLEX: Plasma exchange, MMF: Mycophenolat mofetil, MTX: Methotrexate, AZA: Azathioprine, RTX: Rituximab, CYC: Cyclophosphamide, GC: Glucocorticoids

## Outcome in ANCA-associated vasculitis

### Relapses in AAV

Relapse is very common in AAV and will occur in most patients that initially achieved remission(218). Relapse rates in different trials show a large variation, with a 69% of cases relapsing within 5 years in the NORAM trial(219, 220) comparing MTX to CYC with cessation of treatment after 12 months and 21% within 5 years with the use daily oral CYC in the CYKLOPS trial(195, 196). Relapse rates in these trials were influenced by choice of immunosuppression, mode of delivery and length of treatment. Risk factors for relapse in AAV are PR3-positivity(221), GPA(222), cardiovascular involvement(35). Decreased renal functions was observed to be associated with lower relapse risk(35).

### End stage renal disease (ESRD)

Between 14-40% of AAV patients advance to ESRD during follow up in different studies(223-225). Differences in frequencies vary according to age, renal involvement, and function at diagnosis and ANCA specificity. MPO positive patients exhibit renal involvement in most cases and are more likely to develop ESRD(33). Creatinine level and the need for haemodialysis at diagnosis predict later

ESRD(226). Patients with initial haemodialysis remained dialysis dependant in 80% of cases in a study by Lionaki et al.(227) Patients with ESRD exhibited lower relapse rates, but increased rates of infection and higher mortality compared to patients with preserved kidney function.

## **Comorbidities**

### *Infection*

Infections are a common problem in vasculitis. Reported frequencies vary considerably across different trials and studies. In observational studies frequencies between 20-60% have been reported(228), but often the severity of infection remains unclear. In clinical trials adverse events as infections are often graded, in the RAVE trial(197), a study comparing induction with CYC to RTX, 7% of patients in each group suffered a severe infection, whereas such was observed in approximately 30% of patients in the MEPEX trial(207). The latter was a trial studying patients with severe renal disease with a creatinine level of 500 µmol or more. This exemplifies difficulties in comparing infection rates in different studies. Risk factors for infections identified in earlier studies are older age(229), leukopenia(230), lymphopenia(231), high cumulative CYC and GC doses(232) as well as dialysis dependency(227) and higher serum creatinine(233, 234) at baseline. A Chinese study reported pulmonary involvement of AAV as a predictor of later infections (235). The respiratory tract is most common site of infection in several studies(230, 232, 236, 237). Other common infections are septicaemia(230), urinary tract infections(231, 238) and opportunistic infections(229, 232, 239). With the introduction of new treatment strategies as RTX there was a hope for fewer infectious side effects but results in clinical trials show comparable rates of infections(197, 240). In long term follow up of RTX treated patients 29% suffered severe infection and hypogammaglobulinemia occurred in several patients(241). The latter may predispose to recurrent infections and warrant substitution(242). Even for RTX treated patients the respiratory tract is the most common site of infection(243).

The prophylactic use of cotrimoxazole decreases incidence of *Pneumocystis jirovecii* pneumonia significantly(244) and the it has even been shown to reduce the risk of severe infections(238).

The incidence of severe infections in other rheumatic diseases has been reported to range between 2.9-3.9 per 100 person-year in RA(245, 246) and 2.9 per 100 person-year in SLE(247). Patients with dialysis dependency have a high risk of infections(227, 248). In a study comparing the risk of severe infection of AAV patients to a matched background population a risk ratio of 4.5 was reported(234).

Infections are among the leading cause of death in vasculitis patients today, a pooled analysis of early trials conducted by the European Vasculitis Society (249) found infections to be the leading cause of death (48%) before vasculitis itself in the first year and later among the most frequently observed besides vasculitis, and cardiovascular disease.

#### *Venous thromboembolism*

Patients with autoimmune disorders have higher risk of venous thromboembolic events(VTE)(250), this has also been established for AAV in several studies(251, 252). In a study from southern Sweden, 18% of patients with AAV were affected by VTE(252), with higher incidences early in the disease course and high disease activity and old age predicting VTE. In the same study, compared to the general population a 30-fold risk increase for DVT and a 10-fold increase for PE is reported. Various mechanisms explaining the hypercoagulability in conjunction with inflammation are discussed(253) and prophylactic treatment will likely be addressed in upcoming trials.

#### *Cardiovascular disease*

An increased risk of cardiovascular disease has been observed in patients with AAV(254). In a meta-analysis a cardiovascular risk increase of approx. 65% was reported. Cardiovascular events were more likely to occur in the first years after diagnosis(255). Accelerated arteriosclerosis secondary to inflammation or other factors has been discussed as a possible explanation(256). However, as this mechanism is not completely understood it cannot be addressed therapeutically reinforcing the importance of good management of traditional risk factors for cardiovascular disease even in AAV patients(256). A cross sectional study from the Netherlands and Canada found that management of traditional risk factors was treated suboptimal in the studied cohort. With respect to risk increasing factors as chronic inflammatory state or the presence of chronic kidney disease in AAV-patients the authors propose a risk multiplier on prediction models as for example in rheumatoid arthritis(257).

#### *Malignancy*

An increased risk for malignancies has been demonstrated for several autoimmune diseases as RA(258), SLE(259), myositis(260) or Sjögren's syndrome(261). An increased risk for cancer in AAV, especially GPA has been observed in several studies(262). A meta-analysis comparing standardized incidence ratio (SIR) of cancer from 6 studies report an overall SIR of 1.74, with non-melanoma skin cancer, bladder cancer and leukaemia being most frequently observed(263). However, these cancer types have also been shown to be associated with CYC treatment and a considerable proportion of the patients included in the studies were diagnosed with AAV between 1970 and 1990. In addition, the proportion of GPA patients was much

higher, the relapsing character of GPA might have warranted higher doses or longer exposure to immunosuppressive, potentially oncogenic treatment. Due to decreased doses and exposure time to CYC, rates of these cancers are falling(3). Patients treated with RTX did not show higher cancer rates than the general population in a study from 2016(264). However not all cancer can be attributed to treatment toxicity alone, therefore cancer surveillance is warranted in AAV as in other autoimmune disease.

#### *Mortality and causes of death*

Before the introduction of modern immunosuppressive treatment mortality rates in AAV were extremely high, up to 80% within a few months(4). AAV are chronic relapsing diseases with accumulation of damage over time. In a study from southern Sweden with 140 patients, higher mortality was observed in the vasculitis cohort compared to the background population with a standardized mortality ratio of 2.77(104). A pooled analysis(249) of four clinical trials conducted by the EUVAS with a total of 535 patients reported a 1-, 2- and 5-year survival of 88%, 85% and 78%, respectively, and a mortality ratio of 2.6 compared to the general population. Older age decreased renal function and high disease activity predicted mortality. The main causes of death were infection, vasculitis, cardiovascular disease, and malignancy, with infections being the main cause of death within the first year and cardiovascular death becoming most common during the remaining follow up time.

# Aims of this thesis

The overall aim of this thesis is to improve our knowledge on the epidemiology of AAV, to study the role of infection in the aetiology of AAV and to characterize the occurrence of severe infections in patients with established AAV.

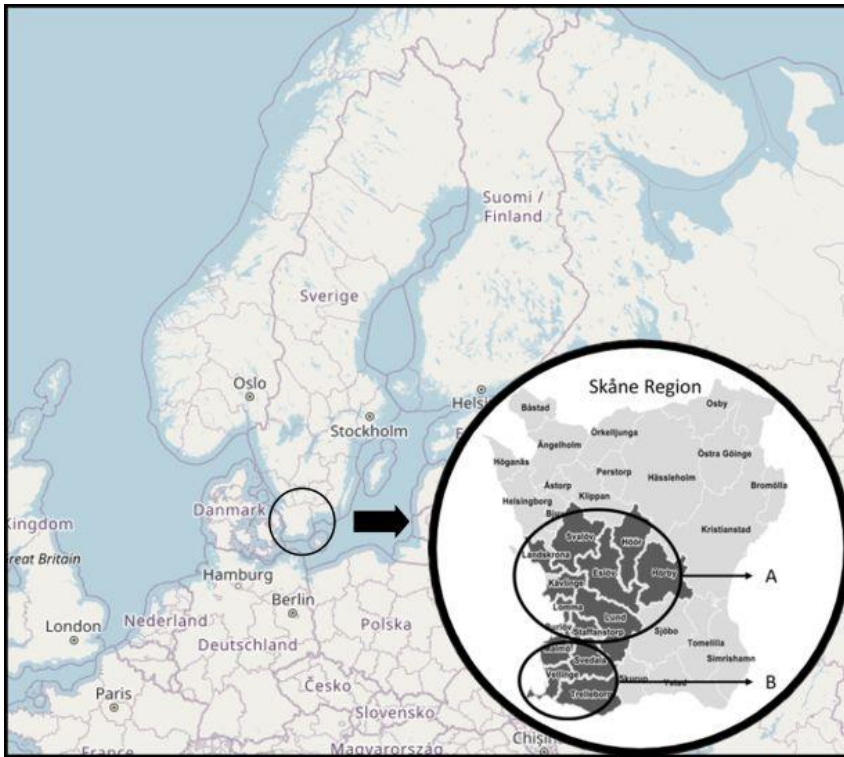
Specific aims were:

- To study incidence and its variation as well as prevalence during a 23-year period in a population-based cohort from southern Sweden (Study I)
- To evaluate the new ACR/EULAR classification criteria for AAV and to compare with earlier established classification systems and disease definitions (Study II)
- To study if a history of infection predisposes to the development of AAV and to determine if AAV patients with prior infections differ from those without in terms of clinical presentation (Study III)
- To study and describe severe infections in patients with AAV and to determine the incidence (Study IV).

# Methods

## The study area and population

The study area comprised 14 municipalities in the region of Skåne, the southernmost region of Sweden with a total population of 1.35 million. Together with Copenhagen and surrounding area it belongs to the Öresundregion, a European metropolitan region with almost 4 million inhabitants. Most people in Skåne are employed in the service industry (79%) followed by manufacturing (17.5%) and agriculture (2%), the unemployment rate was 4.8 in 2021(265). The study area includes rural and urban areas including the cities of Lund and Malmö. The mean population density in the study area is 333/km<sup>2</sup> compared to 25km<sup>2</sup> nationally. The total population in the study area was approximately 790 000 in December 2018. The total adult population was 623 872. The study area is served by four hospitals, Skåne university hospital with campuses in Lund and Malmö, a tertiary and referral centre for nearly 1.7 million people. Furthermore, there are hospitals in the cities of Landskrona and Trelleborg with internal medicine inpatient services. Study areas designated A and B were used for the estimates of incidence and comorbidities, and area A was used for prevalence estimates (Figure 8).



**Figure 8.** The Study; two healthcare districts in the south-west part of Skåne, the southernmost region in Sweden. Area A & B: incidence ; Area A: Prevalence estimation.

## Data Sources

Every person living in Sweden receives a personal identity number (PIN), the number is unique for each individual and is used as an identifier for all communication with government, authorities, healthcare, and private companies. The number enables cross linking between different databases.

### The Skåne healthcare register (SHR)

The SHR(266) is an administrative database established in 1998. Data on all consultations with health care providers including date and diagnosis according to ICD-10 are registered. The proportion of physician consultations that have an assigned ICD code has been near 100% for inpatient consultations since introduction. The SHR was used to identify all AAV patients (see below), to identify prior infections and to identify comorbidities.

## **Pathology databases**

The histopathology reports from Department of Pathology in Lund and Malmö were free text searched after the word “vasculitis”. Individuals with occurrence of the search word were recorded with their personal identity number. The Renal biopsy register, a register where all patients that have undergone renal biopsy in 8 reporting hospitals in Southern Sweden, was searched for terms “Wegener’s granulomatosis”, “microscopic polyangiitis” as well as “crescentic and necrotizing” glomerulonephritis. Individuals with these search terms were recorded with their PIN.

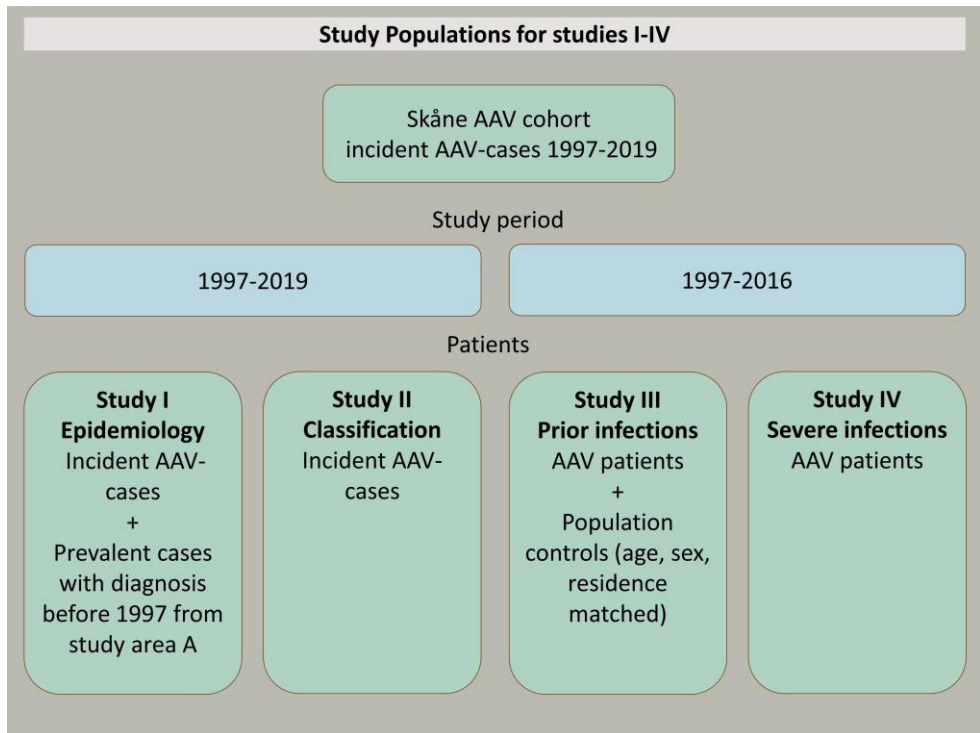
## **ANCA databases**

All analyses of ANCA antibodies in the Skåne area are conducted by either the Department of Clinical immunology in Lund or by the private lab Svar Life Science (previously known Wieslab AB). Records of all positive ANCA samples analysed by these two laboratories during the study periods were obtained. All case records of individuals with positive ANCA samples were reviewed to ascertain diagnosis of small vessel vasculitis.

## **The patients**

All patients in this study had a diagnosis of small vessel vasculitis based on symptoms compatible with, or typical of vasculitis and supported by histopathological or serological (ANCA-positivity) findings. If biopsy was not conclusive surrogate markers for small vessel vasculitis or granulomatous disease were used as described above for inclusion in EMA algorithm(149). The latter was also used to classify all patients. All patients were from a defined geographic area in southern Sweden. The cohort with incident AAV cases is used in all 4 studies included in this thesis. Due to different study periods different numbers of cases were included in the four studies in this thesis, see specific study methods





**Figure 9.** Study Populations included in this thesis

### *Study I and II*

For incidence estimates in study I and all analyses in study II all adult patients diagnosed with AAV between 1997 and 2019 and living in the study area were included (Figure 9).

For prevalence estimates all patients from incidence estimates at point prevalence (pp) dates and all patients diagnosed with AAV before 1997, alive at pp and living in study area A (Figure 8) were included.

### *Study III and IV*

All adult incident AAV cases between 1997 and 2016 inside the study area were included in these studies (Figure 9).

## Study Design

Study I, II and IV comprise epidemiological cohort studies with the aim to estimate incidence and prevalence, evaluate classification and study occurrence and incidence of severe infections and comorbidities.

Study II: To evaluate the newly introduced ACR/EULAR 2022 classification criteria and compare these to earlier established criteria

Study III: A combination of a case control and cohort study where AAV patients are compared to matched population controls in order to estimate the risk of developing AAV with respect to prior infection. The second part of the study is a cohort study comparing AAV patients with or without prior infection.

Study IV: To study the incidence rate of severe infections diagnosed after the onset of AAV and to study predictors for severe infection. For certain analyses the cohort was stratified into two age groups, age  $\geq 65$  years and age  $< 65$  years, in addition, as predominant treatment regime with CYC changed from oral CYC to IV CYC around 2004 (due to data from the CYCLOPS-trial) the cohort was divided in an early (1997-2004) and recent cohort (2005-2016).

## Case retrieval and ascertainment

The Skåne Healthcare register was searched for ICD-codes M300-M319 every two years to identify patients that were assigned diagnoses in the AAV group (applies to all studies included in this thesis). In addition, all positive ANCA analyses conducted during the study period by the two laboratories analysing ANCA in the area (the Svar laboratory and the laboratories of department of Clinical Immunology in Lund) were reviewed and persons with positive test results were identified. In addition, during the first 6 years, the histopathological databases from the department of Pathology in Lund, were searched using free text of “vasculitis” or name of diseases. A case completeness rate of 93% could be achieved by combining only the ICD based SHR and the ANCA databases(135) during 1997 through 2002. From 2003 and onward, only these two retrieval sources were used for the rest of the study period. All search results were crossmatched for doublets and all potential cases were crosschecked in the population registry for living inside the study area by the PIN (personal identity number) as matching criteria. If this was the case all available case records were searched and reviewed to confirm a diagnosis of vasculitis. Patients fulfilling these criteria (see Patients) were then classified as GPA, MPA or EGPA using EMA algorithm.

## Classification

All patients with a clinical diagnosis of small vessel vasculitis were classified into GPA, MPA or EGPA according to the EMA algorithm, this applies to all studies included in this thesis. For study 4 all patients earlier classified by EMA, were also reclassified by applying ACR/EULAR 2022 criteria.

## Definitions

### *Severe infection*

Infection occurring 1 or more month after AAV diagnosis requiring hospitalization and intravenous antimicrobial treatment for 3 days.

### *End-stage renal disease*

Defined as ongoing dialysis or successful renal transplant.

### *Date of diagnosis*

The date of diagnosis was defined as the date on final (diagnostic) biopsy report or if this was not available, the date when immunosuppression was initiated. In cases where the exact day could not be established the 15<sup>th</sup> of respective month was recorded as date of diagnosis.

### *Glomerular filtration rate (GFR)*

Glomerular filtration rate was estimated through calculations with Modification of Diet in Renal Disease formula (MDRD)(267) generating an estimated GFR (eGFR).

### *Comorbidities*

In order to be assigned to the comorbidities analysed, a case needed to have a corresponding ICD code assigned by a physician in the SHR.

## Data collection

Demographic, laboratory, serological, histopathological, imaging data as well as clinical data were collected for all patients at diagnosis and during the follow up by case record review. Data concerning type of infection and infectious agents were collected for every event of serious infection identified for study 4. Patients were followed from time of diagnosis until respective end of study or death.

# Specific study methodology

## *Study I*

Incidence estimation: incidence was estimated for each year for all cases, disease specific, age-specific incidence was estimated for different age groups, and sex specific. Prevalence was estimated for all cases alive at dates of point prevalence (pp), disease and sex specific. The SHR was searched for ICD codes of comorbidities in the AAV patients. Prevalence of comorbidities (Diabetes, hypertension, stroke, myocardial infarction, and cancer) and outcomes end stage renal disease and mortality was assessed. Seasonal incidence: variation in occurrence of disease according to seasons, which were defined as follows: winter: December-February, spring: March-May, summer: June-August and autumn: September-November. To study incidence in different age-groups the following age-groups were defined (age in years): 18–39, 40–54, 55–69, 70–84, and  $\geq 85$  years

## *Study II*

All cases were reclassified using the ACR/EULAR2022 criteria for ANCA-associated vasculitis. In a further step classification by ANCA-serotype was done, i.e., PR3 positive patients were assigned GPA and MPO positive patients MPA. In a first analysis this was done even for patients earlier assigned EGPA by EMA, in a second analysis these patients were excluded from the ANCA-serotype classification.

## *Study III*

This study was done in two steps.

### 1. Case-control (Figure 10):

The SHR was used to randomly select 10 controls from the general population (matched by age, sex and place of residence), furthermore it was searched for all Infection ICD-codes assigned to patients and controls prior to date of AAV diagnosis/index date for controls. All events of infection were identified. The SHR was established in 1998, to allow for a 2-year exposure period data on previous infection were collected from 1 January 2000 until 31 December 2016. The date of AAV-diagnosis in cases was defined index date in respective controls. Infections preceding AAV diagnosis/index date in controls less than three 3 months were excluded (A further analysis with 6 months latency period was also conducted).

The matched controls were sampled from the general population. All persons that had consulted a physician during the study period and were living in the defined study area and had not been assigned an ICD diagnosis M300-M319 were identified and were eligible as matched controls. For each AAV case potential non AAV

controls with the same sex, age  $\pm 1$  year and living in the same area (township or postal code of residence) were identified. Of those fulfilling matching criteria 10 controls were randomly chosen. The date of AAV diagnosis in cases was defined index date in respective controls

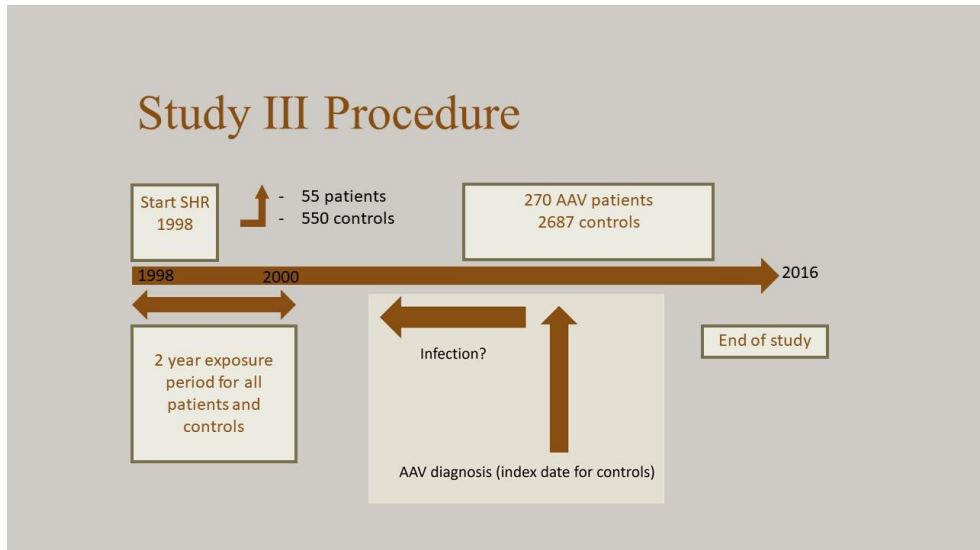


Figure 10. Procedure used in study III

## 2. Cohort-study

The SHR was searched for ICD codes of comorbidities. AAV patients with and without prior infections were compared with respect to the following data after the onset of AAV: organ involvement, laboratory and serological parameters, outcome and occurrence of comorbidities.

### *Study IV*

All events of severe infections were identified by detailed review of all available case records. In addition, a search strategy including all assigned infection related ICD-codes on discharge summaries and all periods where antimicrobial treatment was identified via ATC code on patients' medication lists in case records. Immunosuppressive treatment as well as laboratory, microbiology and imaging data were reviewed at every infection event. Only infections events fulfilling study definition of "severe infection" were included.

# Statistical analyses

## *General*

The Statistical Package for Social Science Software (SPSS) for Windows by IBM was used for all statistical calculations in this thesis. Continuous, normally distributed data are presented as mean with standard deviation (SD), continuous non normally distributed data as median with interquartile range (IQR). For comparisons between groups student's t-test was used for normally distributed data and Mann-Whitney test for non-normally distributed data. Categorical variables were compared with Chi-square test.

## **Specific statistical analyses**

### *Study I*

Incidence estimates were conducted using total adult population of the respective year as the denominator and number of patients newly diagnosed that year as the numerator. For prevalence estimates the total number of patients with AAV alive and living in the study area A at point prevalence date was used divided by the total adult population in the study area A. For the study of seasonal variation, a Poisson regression was conducted to estimate seasonal incidence ratios, winter was the reference in this model.

### *Study II*

Kappa ( $\kappa$ ) statistic was used to explore agreement between the different classification systems, observed agreement is expressed as percentages.

### *Study III*

Infections were aggregated in different groups for example upper respiratory or ear nose and throats infections etc. To estimate the association between infection and later development of AAV a conditional logistic regression model was employed, with AAV/no AAV as binary outcome and prior infection as exposure. The latter was defined as any episode of infection diagnosed by a physician in hospital or outpatient setting. In stage one all AAV cases were compared to their respective matched controls, in the next stage the AAV cohort was stratified according to ANCA serotype, both serotype-groups were then compared to their respective matched controls again. To quantify a potential dose response relationship between prior infection and AAV occurrence odds ratios for AAV development with respect to the frequency of prior infection was analysed in a logistic regression model.

For the cohort study part of this study, i.e., comparing AAV patients with and without prior infection students t-test or Mann Whitney test were employed where appropriate.

#### *Study IV*

Estimation of incidence rate for severe infection was conducted by dividing the number of infection events by the sum of person-year of follow-up. Person-year time accordingly was the sum of follow-up time of all patients from date of AAV diagnosis to death/end of study. The procedure was analogous for the estimation of severe infections in patients with ESRD, only infections after the onset of ESRD were included and the person years of follow up was calculated from date of ESRD until death/end of study. Predictors of severe infections were studied by time to event analysis with a Cox regression model yielding hazard ratios, with time from AAV diagnosis until any of the following occurred: severe infection event, death, or end of study (31 December 2017). Variables for the regression model were selected based on clinical relevance and p-value <0.05 in first analysis. For the analysis of survival and infection free survival the Kaplan Meier method was used.

#### **Ethical considerations**

The study protocols of the included studies were approved by the Regional Ethical Review Board in Lund, Sweden (Dnr 2010-517) Informed consent was not obtained or required. Sensitive personal data, mainly the PIN was limited to the verification of AAV-cases and cross linking the cohort to medical registers. Pseudo-anonymized data was used for data management and statistical analyses.

# Results

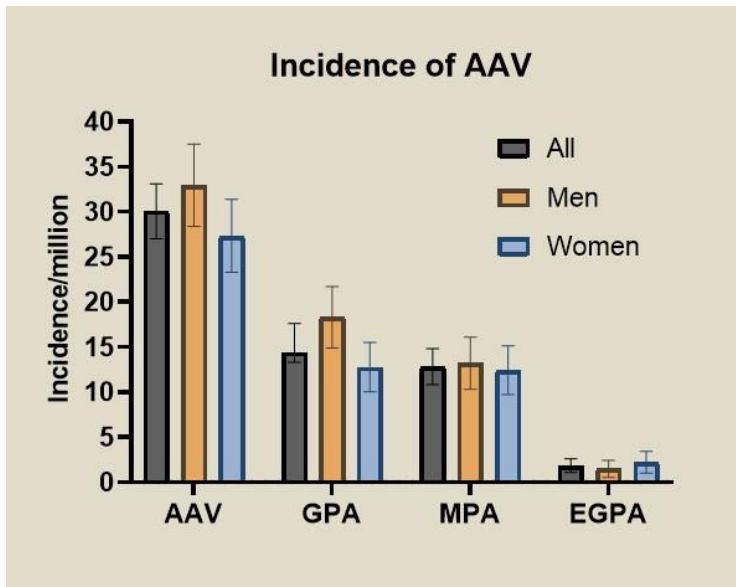
## Study I

All incidence and prevalence estimates are presented per million adults.

A total of 374 patients with a median age of 67.5 years (47% female) were diagnosed with AAV under the study period. 188 patients were PR3 positive, 161 MPO positive and 25 ANCA negative.

### *Incidence*

The mean annual incidence was for all AAV 30.1/million (95%CI 27.0–33.1) adults, 15.4/million (95%CI 13.3–17.6) for GPA, 12.8 (95%CI 10.8–14.8) for MPA, and 1.8 (95%CI 1.1–2.6) for EGPA (Figure 11).



**Figure 11.** Mean annual incidence of AAV and phenotypes (95% CI)



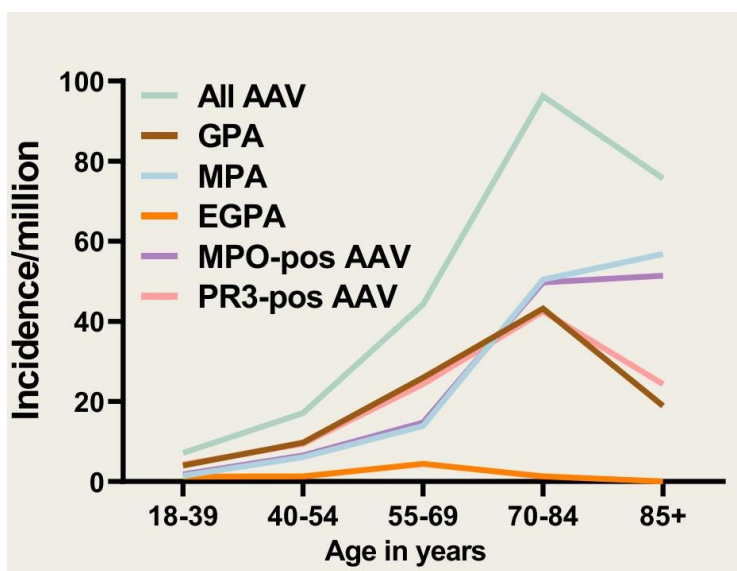
The incidence was higher in males than in females; 32.9 (95% CI 28.4–37.5) vs 27.3 (95% CI 23.3–31.4). The incidence was stable under the study period (Table 8).

**Table 8** Mean incidence per million of AAV during different time periods

Time period	Incidence/million (95% CI)
1997-2003	30.3 (24.4–36.1)
2004-2011	30.4 (25.2–35.7)
2012-2019	29.5 (24.6–34.4)

### Age-specific incidence

Highest incidences for all AAV, GPA and PR3-positive disease were observed in the age group 70 to 84 years, 96.2 (95% CI 80.6–111.7), 44.5 (95% CI 33.9–55.1) and 43.8 (95% CI 32.2–52.9), respectively. Peak incidence for EGPA was in the age group 55 to 69, almost no cases were diagnosed with EGPA above this age. MPA and MPO-positive disease however showed age peaks in the oldest age group (85+ years) 56.8 (95% CI 32.5–81.1) and 51.4 (95% CI 28.3–74.5), respectively (Figure 12).



**Figure 12.** Age specific incidence for different phenotypes and ANCA specificity

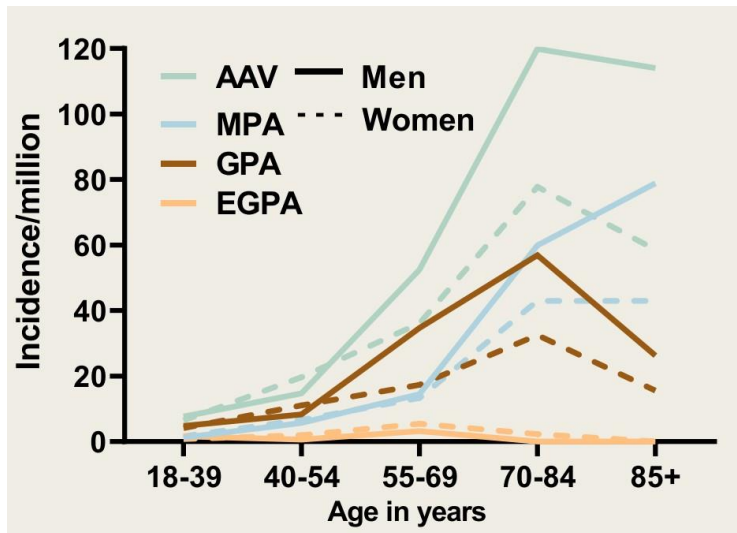


Figure 13. Age specific incidence for different phenotypes in men and women

### Seasonality

Incidence of AAV was highest in spring, (n=110, 29%), followed by summer (n=94, 25%) and autumn (n=90, 24%) and finally winter (n=80, 21%). Incidence rate ratios (IRR) for spring with winter as a reference were as follows: IIR (95% CI): AAV: 1.39 (1.04–1.86), GPA 1.43 (0.90–2.14), MPA 1.45 (0.90–2.26), PR3-positive: 1.27 (0.80–1.91), MPO-positive: 1.59 (1.02–2.48).

### Prevalence

The population in the prevalence study area has increased from 223419 in 2003 to 273135 in 2020. Prevalence per million adults for all AAV was 354 in 2003, 435 in 2010, 469 in 2015 and 428 in 2020 (Figure 14).

**Table 9** Demographics and clinical characteristics in 374 incident AAV cases between 1997 and 2019

Characteristics	All n=374	GPA n=192	MPA n=159	EGPA n=23	PR3- ANCA n=188	MPO- ANCA n=161
Age at diagnosis, years, median (IQR)	67.5 (55–77)	64 (52–73)	72 (60–81)	60 (37–63)	64 (53–74)	71 (60–80.5)
Sex, female (%)	174 (47)	81 (42)	79 (50)	14 (61)	73 (39)	87 (54)
Anti-PR3 (%)	188 (50)	150 (78)	37 (23)	1 (4)		
Anti-MPO (%)	161 (43)	36 (19)	117 (74)	8 (35)		
ANCA neg (%)	25 (7)	7 (3)	4 (3)	14 (61)		
CRP, median (IQR), mg/dl	74.5 (20.0–133.0)	92.0 (36.0–162.0)	68 (17.7–126.3)	10.0 (2.0–55.0)	107.0 (46.0–168.0)	48.5 (10.0–114.5)
Hb, mean (SD), mg/dl	109.8 (19.8)	113.4 (19.3)	102.2 (16.2)	133.6 (18.4)	112.2 (19.5)	104.8 (18.4)
Platelets count, 109/l, mean (SD)	374.7 (148.4)	406.6 (164.2)	340.4 (123.0)	351.2 (115.0)	414.8 (162.1)	337.7 (125.2)
Creatinine, at diagnosis (IQR), µmol/l	132.0 (73.0–299.0)	90.0 (67.0–203.5)	240 (122.0–382.0)	61.0 (51.0–74.0)	96.5 (68.2–252.0)	200 (103.0–359.5)
eGFR (MDRD), median (IQR), ml/min/1.73 m <sup>2</sup>	47.2 (16.8–87.9)	71.5 (25.8–100.6)	22.1 (11.5–47.5)	97.9 (83.5–125.2)	68.7 (20.2–99.8)	26.4 (12.8–61.1)
BVAS at diagnosis median (IQR)	15 (12–19)	16 (10.0–20.0)	15 (12.0–18.0)	12.5 (9.5–16.0)	17 (12–21)	15 (12–18)
<b>Organ involvement, n (%)</b>						
General n, (%)	282 (76)	156 (81)	113 (71)	13 (57)	163 (87)	105 (65)
Cutaneous n, (%)	39 (10)	18 (9)	17 (11)	4 (17)	19 (10)	13 (8)
Mucous membranes/Eyes n, (%)	30 (8)	24 (13)	5 (3)	1 (4)	24 (13)	5 (3)
Ear-nose and throat n, (%)	155 (41)	135 (70)	4 (3)	16 (70)	113 (60)	26 (16)
Chest n, (%)	197 (53)	123 (64)	56 (35)	18 (78)	114 (61)	61 (38)
Cardiovascular n, (%)	20 (5)	10 (5)	7 (4)	3 (13)	7 (4)	10 (6)
Abdominal n, (%)	9 (2)	4 (2)	4 (3)	1 (4)	6 (3)	1 (0.6)
Renal n, (%)	258 (69)	101 (53)	153 (96)	4 (17)	115 (62)	137 (85)
Nervous n, (%)	51 (14)	29 (15)	15 (9)	7 (30)	27 (14)	20 (12)
<b>Outcome</b>						
VDI 12m, (IQR)	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–2)	1 (0–2)	2 (1–3)
ESRD (%)	54 (14)	15 (8)	39 (25)	0 (0)	16 (9)	37 (23)
Mortality (%)	152 (41)	60 (31)	90 (57)	2 (9)	66 (35.3)	79 (49.1))

SD: standard deviation; IQR: interquartile range, GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; BVAS: Birmingham vasculitis activity score (range 0–63); VDI: vasculitis damage index (range 0–64); ESRD: end stage renal disease

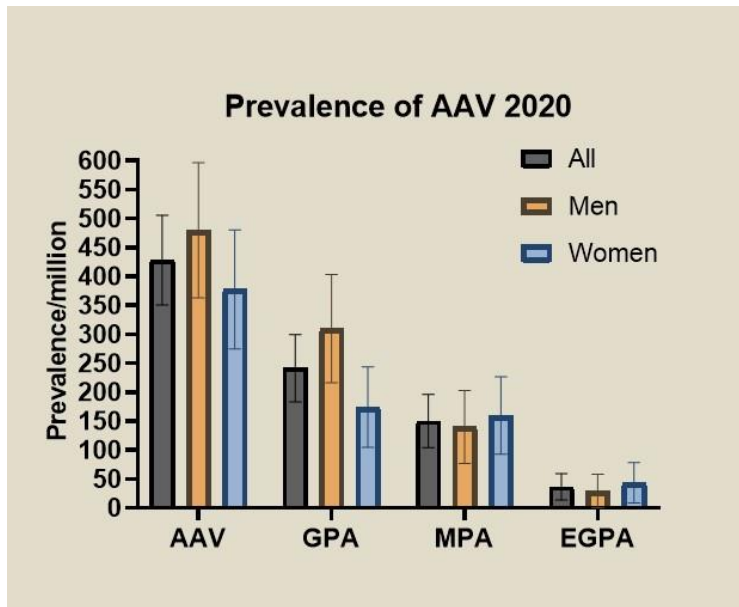
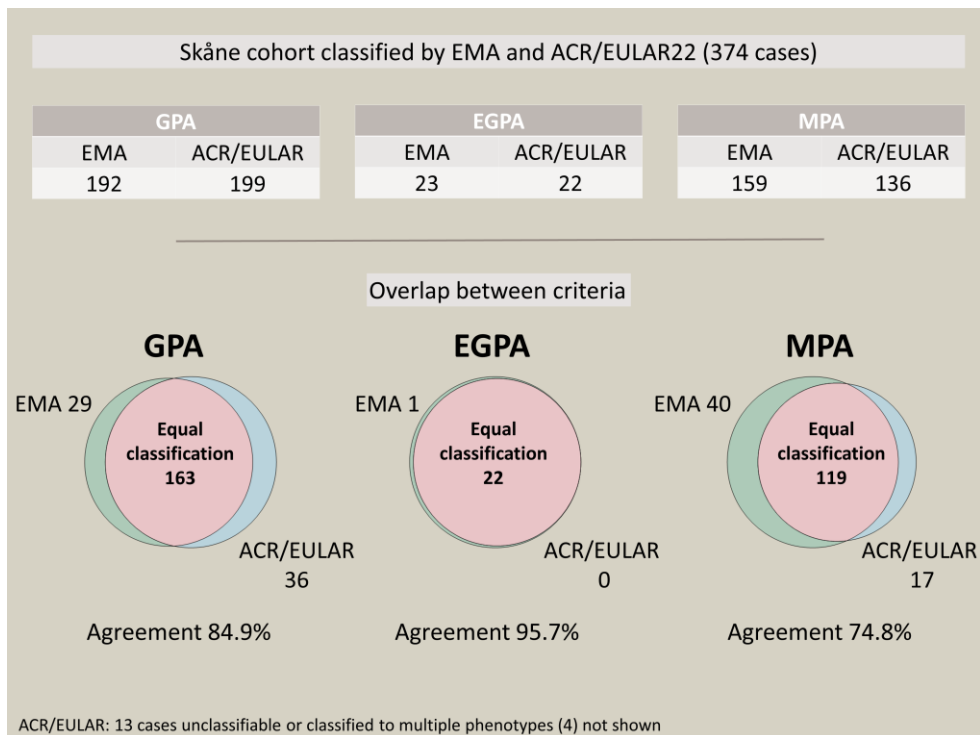


Figure 14. Point prevalence of AAV and phenotypes, January 1<sup>st</sup> 2020

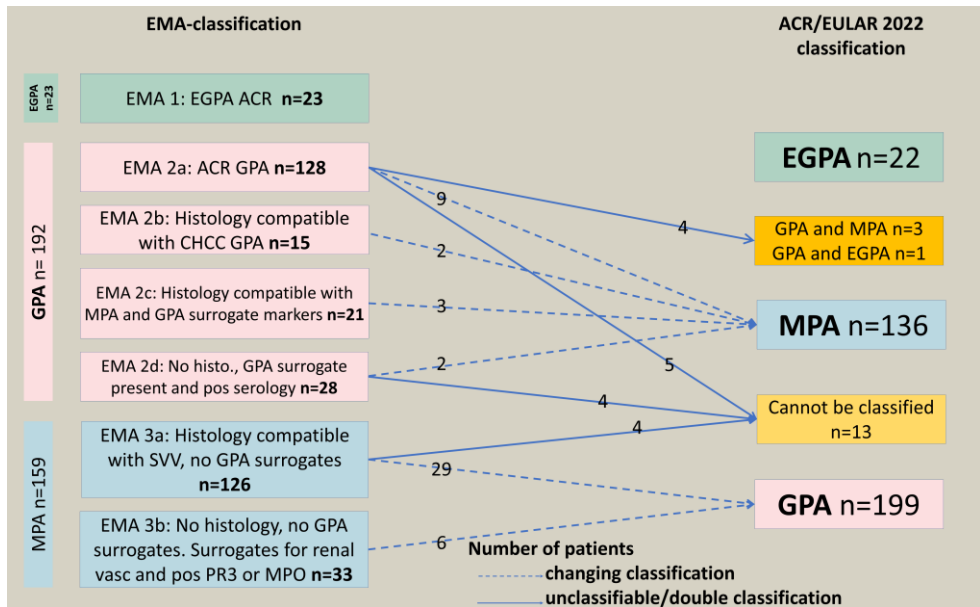
## Study II

Three hundred-seventy-four patients (47% female) with a median age of 67.5 years (IQR 55—77) were included in this study. 188 patients tested positive for PR3-ANCA, 161 for MPO-ANCA and 25 patients were ANCA negative. Results of classification by EMA and ACR/EULAR is shown in Figure 15.



**Figure 15.** Classification by EMA and ACR/EULAR2022 and overlap between criteria

When applying EMA algorithm (Figure 2) 192 patients were classified to GPA, 159 to MPA and 23 to EGPA, no cases were unclassifiable. When applying the new ACR/EULAR classification criteria (Figure 3) 199 cases are classified as GPA, 136 as MPA and 22 as EGPA, 13 cases cannot be classified, and 4 cases are classified into two phenotypes. The observed agreement between EMA and ACR/EULAR criteria is 84.9% for GPA, 95.7% for EGPA and 74.8% for MPA, the unweighted kappa ( $\kappa$ ) statistics was 0.66 (95% CI 0.60–0.74). 13.6% of cases change disease classification, 3.5% cannot be classified and 1.1% are assigned two phenotypes by ACR/EULAR. Shift of classification category from EMA to ACR/EULAR is observed in 51 cases (35 from MPA to GPA and 16 from GPA to MPA) (Figure 16) predominantly due to ANCA-specificity.



**Figure 16.** Cases classified differently by EMA and ACR/EULAR

We observed cases with granulomatous inflammation on histopathology earlier defined as characteristic to GPA, now being classified as MPA.

When assigning cases according to ANCA-specificity, high agreement with classification outcome of ACR/EULAR2022 is observed, 98.9% for GPA and 83.9% for MPA. (Table 10).

**Table 10.** Agreement between ACR/EULAR and ANCA based classification (PR3=GPA, MPO=MPA)

Classification	GPA	MPA	Agreement
<b>ANCA positives (n=349)</b>			
ACR/EULAR	186	135	GPA=98.9%
ANCA-serology	188	161	MPA=83.9%
ACR/EULAR EGPA excluded	186	135	GPA=99.5%
ANCA-serology EGPA excluded	187	153	MPA=88.2%

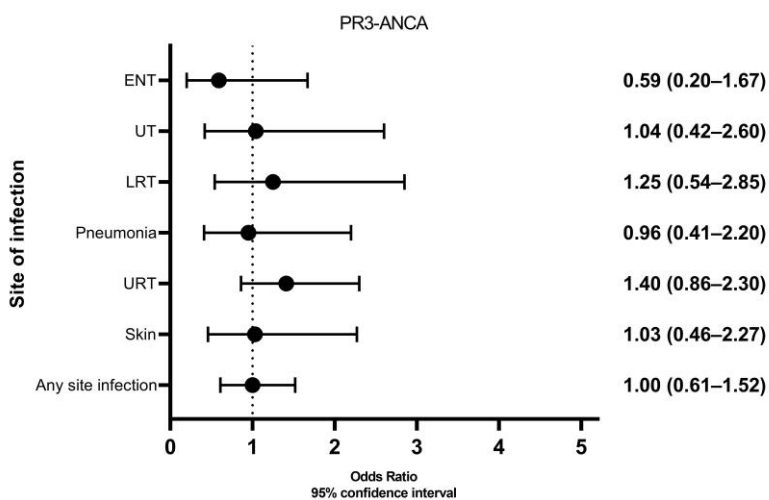
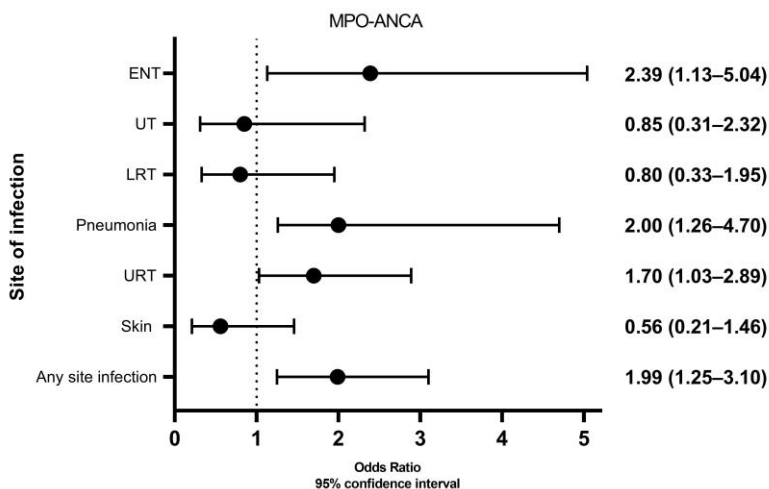
## Study III

### *Association of prior infection with AAV development*

A history of infection was observed in 146 (54%) patients and 1282 (48%) controls ( $p=0.04$ ). The time from infection to AAV-diagnosis/index date was shorter in AAV patients, but not statistically significant. Development of AAV was associated with prior infection at any site with an OR of 1.43 (95%CI 1.06–1.92), for pneumonia the OR was 1.68 (95%CI 1.02–2.77) and for upper respiratory infections OR was 1.57 (1.18–2.19).

### *Stratification according to ANCA-serology*

ANCA-serology was available for 251 patients, with 134 testing PR3-positive, 117 MPO-positive and 19 ANCA negative. When stratifying according to ANCA-serology, patients with MPO-positive AAV were more likely to have experienced prior infections than patients with PR3-positive vasculitis (OR for any site infection 1.99 (95%CI 1.25–3.1) for MPO vs 1.0 (95%CI 0.61–1.52) for PR3) (Figure 17). A similar association was observed when applying a 6-month latency period between infections and AAV-diagnosis date/index date.



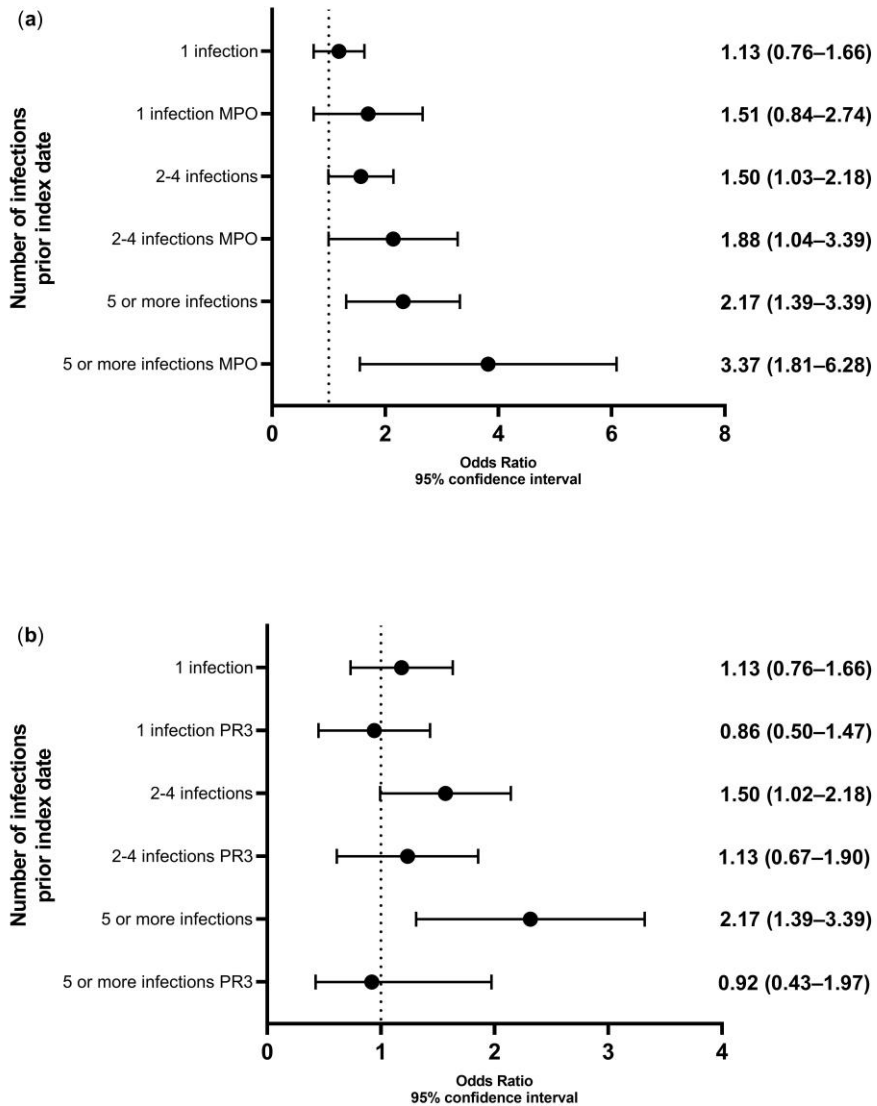
**Figure 17.** Odds ratios for AAV development after prior infection for MPO-(top) and PR3-serotype (bottom) Patients with MPO or PR3 positivity are compared to their respective matched controls, ENT: Ear nose and throat, UT: Urinary tract, LRT: Lower respiratory tract, URT: Upper respiratory

### *Dose response*

A dose response relationship between the number of prior infections and subsequent AAV development was observed with the odds ratio increasing from 1.13 (95% CI 0.76, 1.66) with one prior infection to 1.5 (95% CI 1.03–2.18) and 3.37 (95% CI



1.81–6.28) with 2-4 or 5 or more prior infections events. This association was only observed for the MPO-phenotype (Figure 18).



**Figure 18.** Odds ratios for developing AAV after one or multiple prior infections, stratified by ANCA serotype, a: MPO-ANCA, b: PR3-ANCA

### *Comparison of AAV patients with and without prior infections*

Patients with prior infections exhibited higher disease activity at diagnosis compared to those without (BVAS 15 vs 14) attributable to higher renal BVAS score. No difference in organ involvement of AAV, damage, rate of ESRD, mortality or frequency of comorbidities were observed between the groups.

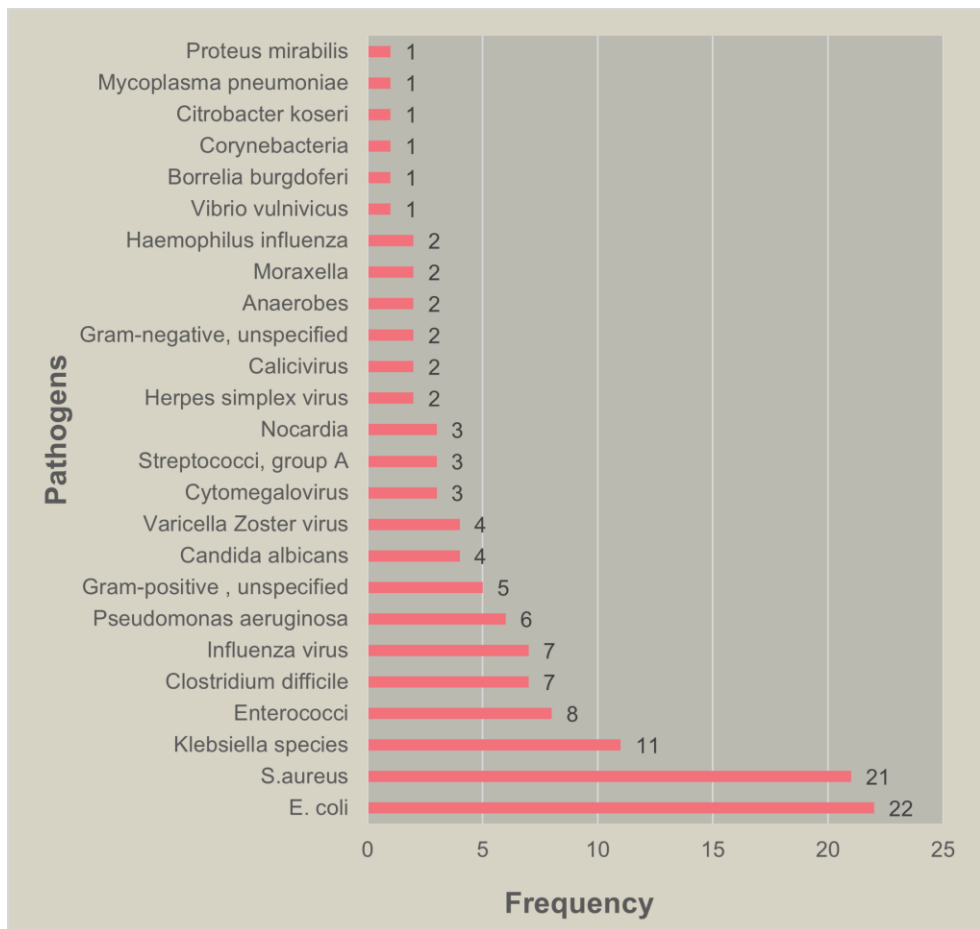
## Study IV

During 2307 person years of follow-up 210 severe infections (SI) were identified. 129 (40%) patients suffered at least one SI during follow up time and 81 (25%) had multiple infections. Eighteen percent of SI occurred within 6 months and 31% within the first year from diagnosis. Patients aged  $\geq 65$  years exhibited significant higher incidence rates than younger patients. Table 11 shows number of infection events and incidence rates at 1 year and for the total follow-up time.

**Table 11.** Incidence rates of severe infections in AAV stratified by age at diagnosis and early vs. recent cohort

<b>Patients</b>	<b>Infection 1 year n (PY)</b>	<b>1 year incidence (95%CI)</b>	<b>Infection total n (PY)</b>	<b>Total incidence (95% CI)</b>
<b>All (n=325)</b>	66 (299)	22.1 (16.7–27.4)	210 (2307)	9.1 (7.9–10.3)
<b>Age <math>\geq 65</math> yrs. (n=185)</b>	47 (160)	29.4 (21.0–37.8)	139 (1005)	13.8 (11.5–16.1)
<b>Age <math>&lt; 65</math> yrs (n=140)</b>	19 (139)	13.7 (7.5–19.8)	71 (1302)	5.5 (4.2–6.7)
<b>Early cohort (n=122)</b>	18 (112)	16.1 (8.6–23.5)	93 (1276)	7.3 (5.8–8.8)
<b>Recent cohort (n=203)</b>	48 (188)	25.5 (18.3–32.8)	117 (1031)	11.3 (9.3–13.4)

E.coli, S.aureus and Klebsiella were the most common bacterial organisms identified in cultures (Figure 19).



**Figure 19.** Infectious agents found in 122 cultures

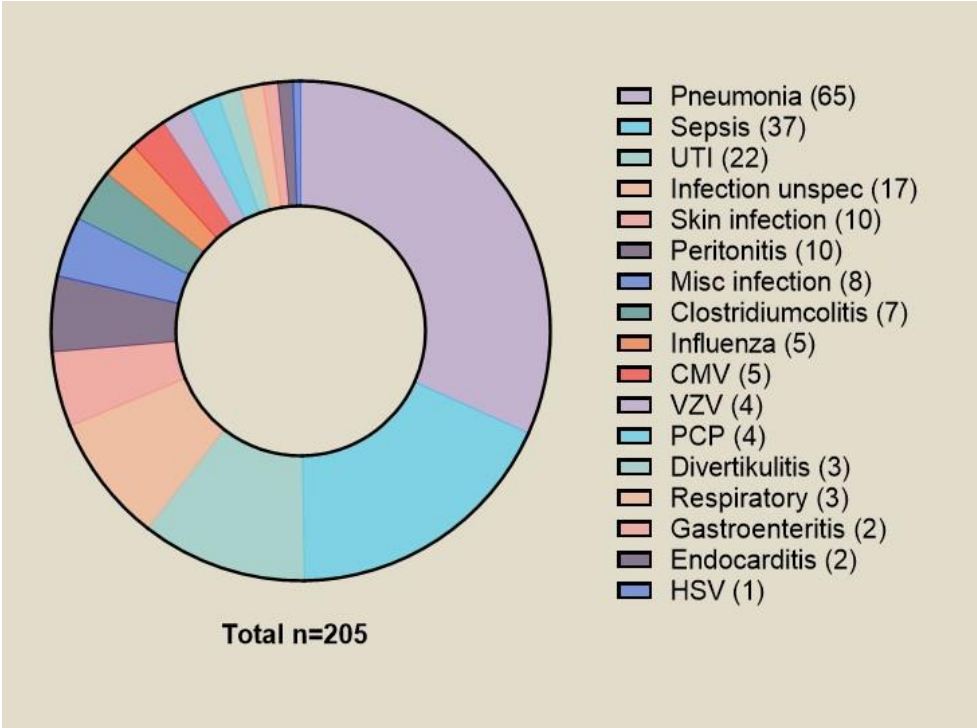
The most common SI were pneumonia (32%), followed by sepsis (18%) and urinary tract infections (10%). Opportunistic infections were seen in 6% of cases.

### *Predictors of severe infection*

Factors associated with SI in univariable analysis were higher disease activity at diagnosis measured by BVAS, older age, higher serum-creatinine, MPO-positivity and the absence of ENT involvement. In multivariable analysis only BVAS and age remained significantly associated with severe infections.

### *Patient outcome*

Patients with SI exhibited higher organ damage at 1 year, were more likely to contract ESRD and had higher mortality rate. Infection was the most common cause of death (22%) followed by cardiovascular disease (17.5%) and cancer (12.6%).



**Figure 20.** Types of severe infections under 5 years follow up, (frequency)  
 UTI: Urinary tract infection, Infection unspec: unspecified infection, CMV: Cytomegalovirus, VZV: Varicella zoster virus, PCP: Pneumocystis (jiroveci) pneumonia, HSV: Herpes simplex virus, Misc infection: miscellaneous infection (intraocular moraxella infection, prosthesis infection, neuroborreliosis, legionellosis, central line infection, catheter infection).

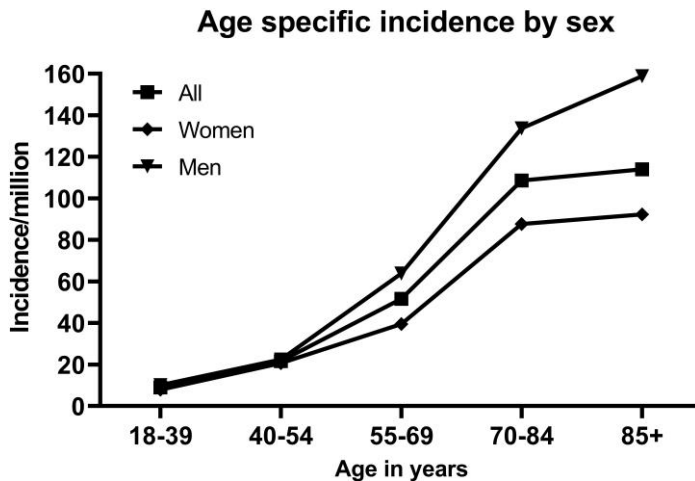
# Discussion

## *Epidemiology*

ANCA-associated vasculitides are rare diseases and are difficult to study in terms of epidemiology as either large populations or a long study time are required in order to generate enough cases to study. The cohort studied in this thesis constitutes, to the best of my knowledge, the largest population-based cohort of AAV patients to date. The population-based setting depicts real-life conditions with the whole spectrum of vasculitis from localized or mild to generalized or severe multisystemic disease. The case retrieval method employed has been shown to identify over 90% of cases with AAV in the study area(135). We used similar retrieval sources, case identifications and classification throughout the study period and observe a stable incidence for AAV and its phenotypes. Incidences of AAV and its phenotypes are in line with recent findings from Norway(99), UK(112) and the USA(100). A rise in incidence of AAV as it has been described in several earlier studies(102, 103, 268) could not be observed. Possible explanations for earlier observed rising incidences are primarily changes in disease definitions and classifications, increased physician awareness as well as the introduction of ANCA testing since the early 1990s. In our epidemiology study, the case retrieval was slightly modified under the study period, i.e., switch from three to two retrieval sources without significant compromise to retrieval rate. The previous report of incidences of AAV in our area was around 22 cases per million and was reported using the total population in the area, hence a lower incidence than the 30 per million adults is clearly explained by choice of adult population in the recent calculation of the incidence. Upon recalculation of the earlier analysis using adult population, the results are identical. Our data do not support the “north-south” gradient hypothesis of earlier studies, the incidences of GPA and MPA are comparable throughout the study period and the mean annual incidence is about equal to recent data from Tromsø, Norway and Olmsted, County, USA. EGPA is a very rare disease with 1.8 new cases per million adults per year in our analysis, which is comparable to earlier incidences reported from the UK (2.7/million)(268) and Australia (2.2/million)(132).

During the last decades the peak age at diagnosis has shifted to older ages. A study from Spain published in 2003 reported peak incidences of the primary systemic vasculitis (including PAN) to be in the age-group 55-64 years(110). Studies from the UK(268), Finland(102) and Norway(269) reported incidence peaks in the age group 65-74 years for GPA. However, a recent study from Nottingham in the UK,

analysing all AAV, reports peak incidence rates in the age group +85 years(112). We also observe an increase of incidence with age, highest incidences for all AAV and GPA are observed in the age-group 70-84 years and in the age group 85+ for MPA. In respect to the observations from Nottingham, we analysed our cohort including only cases diagnosed between 2007 and 2019 (to increase comparability by only including cases diagnosed after 2007) and make the same observation as Pearce et al. in the Nottingham study, i.e., we found that highest age-specific incidence is in the age group 85 years and older (Figure 21). A possible explanation for the increasing age at diagnosis is that AAV is today more often diagnosed in older patients due to improved awareness, easy access and availability of ANCA-testing and commencement of diagnostic workup regardless age or comorbidity burden. Improved awareness can be attributed to evolution of definitions, classification criteria and better education of the medical community on these diseases. A study examining outcome and treatment of AAV in elderly patients ( $\geq 75$  years) demonstrated significant better survival in patients treated with CYC or RTX compared to GC alone showing that even frail, elderly patients benefit from immunosuppression(270).



**Figure 21:** Age-specific incidence in patients with diagnosed between 2007 and 2019

A seasonal variation of the onset of AAV was observed in this cohort, with highest incidence in spring, primarily driven by MPO-positive cases. Together with our finding of the association of prior infection, again mainly driven by MPO-ANCA disease (Study III), our hypothesis is that infections, especially in the respiratory tract, during winter might trigger the development of MPO-positive AAV a few months later. Data from the literature on seasonality of AAV are contradictory, with

studies showing peaks in incidence during different seasons or no seasonal associations at all. Comparability is limited as different vasculitis phenotypes are studied, and in some studies the date of onset of symptoms instead of diagnosis was used and assessed with different methodology. Our study analysed all phenotypes of AAV and used the date of diagnosis according to our study definition.

The prevalence of AAV presented in this thesis is the highest ever reported in AAV with 469 cases per million adults in 2015 and a slightly lower value in 2020, 428 per million adults. The prevalence of AAV is increasing in our area as we previously reported a point prevalence of 340 cases per million adults for 2003 (re-calculated as previous p.p. presented per million inhabitants)(135) Our prevalence rates are comparable to a population-based cohort from the USA, where 421/million was reported(100), a Norwegian study also reports comparable rates and increase during a study period between 2003 and 2013(99). Prevalence is a product of incidence and survival. As we have demonstrated stable incidence during the study period, we believe that one important factor behind increasing prevalence in our area is improved patient survival. During the last few years, several regional, national, and international treatment guidelines for AAV have been issued(38, 216, 217, 271, 272), contributing to improvement of treatment and follow-up of AAV throughout the world. We presume good adherence to these guidelines in our area. The treatment of AAV is often multidisciplinary, in addition several research projects on different aspects of AAV and other vasculitis are ongoing in our area contributing to increased awareness and improved education on these diseases. Altogether we assume this results in a good quality of care and management in our area.

The prevalence reflects the burden of disease on health care and social services in each population. Beyond monetary costs this burden even encompasses life expectancy, morbidity, or quality of life. Knowledge of this burden facilitates defining priorities in healthcare, prevention, and policy(273, 274). Organ damage and comorbidities are common in AAV. From our area, a study on the extent of damage demonstrated that only 9% of prevalent AAV patients had no permanent organ damage according to the VDI(275).Furthermore, we tried to shed light on real life comorbidities using data extracted from the SHR. We found that our prevalent cases with AAV suffer increased rates of hypertension, cancer, diabetes, and cardiovascular disease. Rising prevalence of a complex disease as AAV poses challenges to a healthcare system. A case-control study on healthcare resource utilization (HRU) of patients with GCA in our area demonstrated higher HRU on all levels of healthcare (276). Even if GCA is a different disease with different epidemiology, we suppose a similar pattern in AAV. The high rate of organ damage and comorbidities in patients living in our area with AAV should be taken into consideration in planning necessary healthcare resources and facilities to cope with this type of high disease burden.

## Classification

Validated and easy to apply classification criteria are needed to facilitate epidemiologic studies and clinical trials. Good criteria are those with high sensitivity (only include those with a given vasculitis) and high specificity (exclude patients with other vasculitis). New well-designed criteria are timely needed. The currently widely used EMA algorithm(149) is based on ACR 1990 criteria and CHCC 1994 definitions. With the EMA algorithm as reference, we applied the new ACR/EULAR 2022 criteria for classification of AAV to our cohort and studied the latter's performance(150-152). Generally, we found good agreement between the two classification sets with a *kappa* of 0.66 with highest agreement for EGPA and lowest for MPA. The incorporation of ANCA and the considerable weight ANCA serology now has on outcome of classification arguably constitute the most extensive change the new criteria entail. There has been an ongoing discussion in the vasculitis literature if patients should be classified according to ANCA serology or phenotype or a combination of both(218, 277, 278). The results of the recent GWAS studies showing clear genetic distinction between PR3- and MPO-positive disease(32, 279), differences in treatment response to standard induction agents (RTX more effective in PR3-positive patients)(36) or higher probability of relapse in PR3-positive disease(221) favour serologic classification. We found that ANCA serology-based classification performs as good as the new criteria. We can therefore strongly argue for using ANCA based distinction between patients as a good, practical, and robust way to classify patients with AAV into PR3- and MPO-associated vasculitis. On the other hand, how should patients with ANCA-negativity be classified? Despite classic clinical symptoms this subgroup could potentially be excluded from future trials. So far, the new ACR/EULAR criteria have only been evaluated in AAV cohorts in South Korea (280-282) which also showed high agreement with the new criteria. The highest agreement in the Korean cohort was almost 97% for MPA(282), which shows lowest agreement in our cohort, 75%. Differences in MPO-positivity cannot explain this difference as MPO positivity in the MPA phenotype is almost equal in the two cohorts (97.4% Korea vs 99.3% Sweden). The most obvious difference between the Swedish and Korean cohort that might explain the differences in agreement must therefore be ILD item, an item that generates +3 points for MPA classification. Indeed only 8% of Swedish cases showed ILD compared to 50% of cases in Korea, which most probably explains the high agreement for MPA. Lowest agreement is described for GPA with 74% from the Korean group in contrast to our findings of 85%. As expected from a cohort from Asia there are more cases with MPO-positivity, and the number of MPO-positive GPA is considerably higher than in our cohort, (43% vs 19%), a fourth of the former GPA patients are assigned MPA due to antibody specificity with the new criteria, compared to 14% in our results. This exemplifies another finding when applying the new criteria: a considerable number of cases are classified to another phenotype, primarily due to ANCA specificity. This violates in certain cases earlier agreed criteria as for example the presence of granuloma in GPA as established by



the CHCC. A further limitation when applying the new ACR/EULAR criteria is unclassifiable cases, though only 3.5% of the cohort, we did not encounter this problem when employing EMA classification. 40% of the unclassifiable cases are ANCA negative.

Our comparison of the ACR/EULAR 2022 criteria with a strictly ANCA-based classification where PR3-positivity becomes GPA and MPO-positivity MPA demonstrates very high agreement between the two systems, 99% for GPA and 84% for MPA (with even higher values if EGPA is excluded). This means the new criteria are very near an ANCA-based classification and it remains to be seen in future studies if the new criteria live up to the considerable effort invested in their development.

### *Exposure to infection*

Infections are often implicated in the development of autoimmune disease as the same system installed and intended for host defence suddenly targets own tissue and causes disease. The exact mechanism for the loss of tolerance is unclear. ANCA antibodies can be found in healthy individuals(283) and can be present in AAV patients years before the disease onset(284). The fact that ANCA themselves are pathogenic(285) does not seem to be sufficient to initiate vasculitis but another factor, potentially infection might be needed to trigger vasculitis development. Several infectious agents have been associated with development of autoimmune disease in general(286), for vasculitis the association of hepatitis B (287) and C viruses(288) with PAN and cryoglobulinaemic vasculitis, respectively, demonstrates such association. We observe an association between exposure to infection especially of the respiratory tract and later development of AAV. An obvious question occurring is if early symptoms of vasculitis could have been misdiagnosed as infection. We employed a 3-months latency period from infection event to AAV diagnosis/index date to avoid misclassifying early vasculitis as infection. The choice of 3 months was arbitrarily and based on results of our earlier studies in this cohort showing a median diagnosis delay of 2 months(104). We also observed the same association between infections and AAV when employing a 6-month latency period. Other studies demonstrated a comparable association for autoimmune disorders as GCA(84) or inflammatory myopathies(83). The association in our study shows a dose (number of prior infections) dependency and is only evident in individuals developing MPO-positive vasculitis. As patients with immune system deficiencies and dysregulation might be prone to infections the observed association might however not be causal. Subclinical vasculitis processes in the airway or lungs could also predispose to infection. This might also explain our finding of the association only for later MPO positive vasculitis, interstitial lung disease (ILD) is primarily observed in MPO-positive individuals(172) and ILD can be present before obvious clinical vasculitis onset(289). Prior infectious events were only identified by ICD-codes and most infections were diagnosed in a primary care

setting; the accuracy of diagnosis could not be verified. However, patients and controls were matched and the diagnosis generating consultations took place months before the diagnosis of vasculitis. Diagnosis and treatment of cases later developing AAV should therefore not have differed from controls.

#### *Severe infection as an outcome*

Study IV studied incidence and types of severe infections (SI) in patients with AAV. Vasculitis itself but even its treatment compromises immune function, resulting in increased susceptibility to infection. Earlier studies demonstrated that infections are a common clinical problem in vasculitis occurring in 20-60% of patients and contributing considerably to morbidity and mortality (228). Infections are studied in several trials as adverse events and even in observational studies, but comparability is limited due to heterogeneity in patient populations and differences in definition and identification of infections events. Our study includes the whole spectrum of AAV in a population-based setting and our data should therefore be representative for severe infections in AAV in general. We observe that 40% of our patients suffers SI, which is comparable to other studies with similar or slightly modified definition of SI. A multicentre study from Greece (290) with a GPA/MPA cohort reported severe infection in 32%, a French study(232) of GPA patients reported SI in 31% of cases and 35% were observed in a MPO-positive dominated cohort from China(236). The main site of infection in our cohort is the respiratory system, followed by sepsis and urinary tract infection, which confirms earlier findings(223, 230, 233, 290). In our study, the rate of opportunistic infections is low (6%), good adherence to PCP prophylaxis recommendations might partly explain this. As patients might be admitted to hospitals in different cities and not all infections are primarily treated at a rheumatology or nephrology clinic one could raise the question if events of infection could have been missed, we consider this unlikely as digital patient records were searched for all specialties and hospitals in the area.

#### *Incidence rate of severe infection*

We observe an incidence rate of 9.1/100PY for the whole follow-up, with highest incidence rate in the first year (22.1/100PY). These observations are very similar to a recent Greek study(290) reporting 7.5 per 100PY for the whole follow up and 18.6 in the first year. Patients in the Greek study were younger and exhibit lower BVAS at diagnosis. A French meta-analysis examining SI in RTX treated patients (79% GPA) reports an incidence of 6.5 per 100PY, but the analysis has limitations, as RTX-treatment in some of the included studies was associated with treatment with other immunosuppressive drugs potentially influencing the results. Incidence rates of severe infections of 9.1 in our AAV cohort is considerably higher than reported figures in other rheumatic disease; between 2.5 and 3.9 per 100PY for rheumatoid arthritis(246, 291) and 2.9 per 100PY in systemic lupus erythematosus. A large American study from 2019 compared the incidence rate of SI in RA with non-

inflammatory rheumatic diseases (osteoarthritis, back pain syndromes, tendinitis, and other periarticular pain syndromes without any inflammatory rheumatic disease) and reported incidence rates of 1.96/100PY for RA and 1.34/100PY for noninflammatory conditions. We hypothesise that the group with non-inflammatory conditions could give an approximation of SI in the general population, the study otherwise used a similar SI definition and integrated virus, bacteria, and fungi. For comparison with incidence of severe infection in the background population: a large Norwegian study(292) reported incidence rates/per 100PY for pneumonia, urinary tract infection and sepsis/bacteremia of 0.64, 0.55 and 0.33, respectively, and 1.83 for all studied infections. Patients with ESRD have much higher risk of infection, with incidence rates between 20 and >30 per 100PY for SI(293, 294). The incidence rate of SI in ESRD patients in our cohort was even higher with 44.7 per 100PY. Lionaki et al.(227) found an incidence rate of all infections of 194/100PY in patients with ongoing immunosuppression and 104/100PY in patients without.

### *Predictors of severe infection*

In our cohort, age, BVAS, MPO-positivity, decreased renal function as well as the absence of ENT involvement predicted SI in a univariable model. In multivariable analysis age and BVAS at diagnosis remained independently associated with high risk of infection, findings that are confirmed by other studies(237, 290). We found a negative association between ENT involvement and SI. ENT involvement predicts better survival in AAV(181, 239), this is also accounted for in the revised FFS(184), where absence of ENT involvement constitutes one of the factors (applies to GPA and EGPA) for worse prognosis.

### *Glucocorticoids and immunosuppression*

Several studies have demonstrated that high cumulative doses of glucocorticoids and CYC increase the risk of infection(195, 232, 295, 296), even the treatment with RTX is associated with higher risks(198, 297). Others could not demonstrate such an association of severe infection and GC(230, 237). We did not observe a correlation between GC dose and infection. We recorded GC doses at different time points and due to the nature of a retrospective study with long follow-up time, cumulative doses could not be calculated. A difference in use of induction treatment and later development of infection could not be found, neither a difference in cumulative dose of CYC. Taking into consideration the shift of treatment modality from peroral to intravenous CYC around 2004 (Lund was a centre in the CYCLOPS study (195) and therefore adopted trial protocol) an early (1997-2004) and recent (2004-2016) cohort was analysed regarding given induction treatment and SI as an outcome. We observed higher incidence rates of severe infections in the recent cohort though for example the rate of ESRD was considerably higher in the early cohort. Several factors however can explain these findings. In the recent cohort, those who failed CYC may have received RTX later, potentially adding to the risk to contract infection. Furthermore, the recent cohort exhibited higher BVAS.

The PEXIVAS(204) trial has introduced a reduced dose GC regimen without compromise to the rate of remission but with the benefit of a lower frequency of infection. The trial though included patients with severe AAV making comparability to our cohort limited. A reduced-dose GC regimen was also examined in the LOVAS(205) trial, including patients without severe GN or pulmonary haemorrhage, all were treated with RTX and either high or low dose GC. Low dose GC was non inferior in terms of remission and adverse events (including severe infections) were less frequent.

### *Mortality*

Hundred-forty-three patients died during follow-up. Infection was the leading cause of death (32 cases (22.4%)), followed by cancer, cardiovascular disease, and vasculitis. Other studies report similar findings (230). Infection was also the main cause of death during the first year in a pooled analysis of EUVAS trials(249) and among the most common in the remaining follow up.

Finally, we conclude that infection is a common problem in AAV and measures to prevent and decrease frequency are needed. Less toxic treatments, new immunosuppressive agents, alternatives to GCs as well as preventive measures like vaccination and prophylaxis in certain cases will hopefully diminish this problem in the future. Research and continuous evolution of the prevention and management of infections need to continue, as recent global developments (COVID) remind us that infections surely will remain a challenge and the “other side” does not sleep.

# Strength and limitation

The studies included in this project use a large population-based cohort of AAV-patients with a long follow up time. The cohort comprises patients with the whole spectrum of ANCA-associated vasculitis from localized disease to mild or multi-system disease with severe organ dysfunction and damage. Many studies in AAV report data on patients included in clinical trials with considerable selection bias. Though our case retrieval has been slightly modified this did not compromise high retrieval rates, furthermore all cases were classified using the same classification system and by the same researchers. The retrospective nature of the studies is a limitation, clinical information on most cases could be retrieved using digital health care systems which are standard in Sweden, and which can considerably facilitate data collection, as they did in this study. Different digital systems were used in our area during initial study period, in addition paper documentation was also present during the first years making data collection more challenging and lack of complete data more likely.

# Conclusions

- The incidence of AAV in Southern Sweden is stable over a 23- year period and around 30 cases per million inhabitants
- The prevalence of AAV is the highest ever reported, 469 cases per million in 2015.
- There is substantial agreement between EMA and ACR/EULAR classification
- Outcome of strictly ANCA based classification is very similar to ACR/EULAR2022
- Infection especially in the respiratory tract, is associated with increased risk of later AAV development
- Patients with MPO-positive vasculitis are more likely to have had prior infection
- Severe infection is common in ANCA-associated vasculitis, occurring in 40% of patients
- Age and high disease activity at diagnosis predict severe infection

# Future research

The findings of this project will be followed up in future research projects, infections are a considerable problem in AAV-management and further investigations on the influence of glucocorticoids (cumulative doses, weight adapted doses, intravenous or peroral administration) or different inductions regimens are interesting.

Influence of reduced GC regimens as well as the complement inhibitor Avacopan on infection will be investigated.

Interstitial lung disease in AAV is an interesting question that will be investigated in this cohort.

Hypogammaglobulinemia occurs in RTX-treated patients and will be investigated in this cohort in the near future.

Findings on the association of infections with later development of AAV should be investigated further, with more refined analysis of the preceding infections.

# Deutsche Zusammenfassung

Vaskulitiden sind eine Gruppe von chronisch entzündlichen Erkrankungen, die mit Entzündungen der Blutgefäße einhergehen. Sie zählen zu den Autoimmunerkrankungen, d.h. Gewebe des Körpers werden vom eigenen Immunsystem als feindlich erkannt und attackiert. Zur Einteilung dieser Erkrankungen gibt es unterschiedliche Systeme, wobei eine Unterscheidung anhand der Größe der betroffenen Blutgefäße am häufigsten verwendet wird. Die vorliegende Arbeit beschäftigt sich mit der Gruppe der sogenannten Kleingefäßvaskulitiden, d.h. Entzündungen der kleinsten Blutgefäße wie Arteriolen, Venolen und Kapillaren. Solche Blutgefäße können überall im menschlichen Körper gefunden werden, was auch das Vorkommen dieser Erkrankungen in unterschiedlichsten Geweben und Organen erklärt. So ist ein Auftreten von Symptomen in nur einzelnen Organen wie Nase, Lunge, Haut, Herz oder Niere oder ein gleichzeitiges Auftreten in mehreren Organsystemen mit einer Reihe von verschiedenen Symptomen möglich. Die entstehenden Entzündungsherde können unter anderem zu Blutungen, Organfunktionsstörungen oder unter Umständen auch zu schweren Organschädigungen führen.

Eine Unterform der Kleingefäßvaskulitiden sind die sogenannten ANCA-assoziierten Vaskulitiden (AAV). ANCA steht für antineutrophile zytoplasmatische Antikörper. Hierbei handelt es sich um Antikörper, die gegen körpereigene weiße Blutkörperchen gerichtet sind. ANCA können bei den meisten Patienten mit einer ANCA-assoziierten Vaskulitis nachgewiesen werden. Das Vorkommen dieser Antikörper macht im Zusammenhang mit typischen Symptomen eine AAV wahrscheinlich, beweist sie jedoch nicht. Man unterscheidet zwei Typen von ANCA, die entweder gegen das Antigen Proteinase-3 (PR3) oder Myeloperoxidase (MPO) gerichtet sind. Die Diagnose wird durch eine Kombination aus Symptomen, Blutwerten (wie der ANCA-Test) und im besten Fall einer Gewebeprobe mit typischem Befund gestellt.

Die Kleingefäßvaskulitiden können wiederum in 3 Unterformen unterteilt werden: 1. die Granulomatose mit Polyangiitis (GPA, früher auch Wegener Granulomatose genannt) 2. die mikroskopische Polyangiitis (MPA) und 3. die eosinophile Granulomatose mit Polyangiitis (EGPA, früher auch Churg-Strauss Syndrom genannt). Die Symptome dieser drei Erkrankungen zeigen in vieler Hinsicht Überschneidungen, so können zum Beispiel alle Erkrankungen, jedoch in unterschiedlicher Häufigkeit, eine Entzündung der Nieren oder der Lungen mit sich



bringen. Für die GPA ist eine Entzündung des Hals Nasen Ohren Traktes mit Nasenbluten, Nasennebenhöhlenbeschwerden, Verkrustungen, Heiserkeit, sowie Beschwerden des Mittelohres typisch. Eine Beteiligung der oberen Atemwege und der Lungen, sowie der Nieren ist häufig. Die EGPA ist fast immer mit Asthma und Allergien assoziiert und die MPA tritt fast immer mit einer Entzündung der Nieren und der Lungen in Erscheinung.

Oft zeigen AAV schwere Krankheitsverläufe, die ohne schnelle und entschiedene Behandlung zu Organschwäche oder Tod führen können. Vor der Einführung von immunsuppressiven Therapien Anfang der achtziger Jahre wiesen die AAV eine hohe Sterblichkeit auf. Erste Behandlungserfolge konnten mit Kortison erzielt. Die Entzündungen konnten durch Kortisonbehandlung verringert werden, aber im Zuge einer Dosisreduzierung kam es oft zur Rückkehr der Erkrankungssymptome. Darüber hinaus treten bei längerer Kortisonbehandlung eine Reihe von Nebenwirkungen auf. In den letzten Jahrzehnten wurde das Behandlungsarsenal durch ein Reihe von Zytostatika und modernen Immuntherapien ergänzt, die die Aktivität der Erkrankung oft gut kontrollieren können. Das Ziel der Behandlung ist deshalb heute in erster Linie den Patienten in einen Zustand der Remission zu überführen und ihn bei Erreichen dieses Zustandes durch weitere Therapie dort zu stabilisieren. Die AAV können zum jetzigen Zeitpunkt nicht geheilt werden, sondern bedürfen einer kontinuierlichen Überwachung und angepassten Behandlung bei Auftreten neuer Symptome. Viele Patienten können bei erfolgreicher Behandlung relativ symptomfrei sein, andere erleiden Organschäden, die weiterer Behandlung bedürfen.

Die vorliegende Arbeit beschäftigt sich mit unterschiedlichen Aspekten der AAV. Eine Teilarbeit untersucht die Epidemiologie der AAV in einer populationsbasierten Kohorte im Süden Schwedens. Ziel ist es das Neuauftreten der AAV zu charakterisieren im Bezug auf Alter, Geschlechtsverteilung, Variation des Neuauftretens, sowie klinische Eigenschaften von betroffenen Patientengruppen zu charakterisieren. Unsere Studie demonstriert eine stabile Inzidenz der ANCA-Vaskulitis im Studiengebiet. Circa 30 Fälle/Millionen Einwohner erkranken pro Jahr an AAV, das Haupterkrankungsalter liegt bei circa 67 Jahren, Männer sind etwas häufiger betroffen. Die Inzidenz der Erkrankung ist stabil, was ähnliche Ergebnisse der letzten Jahre aus den USA und Norwegen bestätigt.

Eine weitere Teilarbeit beschäftigt sich mit der Einteilung dieser Erkrankungsgruppe für wissenschaftliche oder therapeutische Studien. Damit medizinische Studienergebnisse vergleichbar sind ist es essenziell, dass Forscher sich auf eine gemeinsame Definition und Klassifizierung von Krankheitszuständen geeinigt haben. Für die AAV existieren mehrere solcher Kriterien, die im Laufe der letzten Jahrzehnte angepasst und modernisiert wurden. Die aktuellsten Klassifizierungskriterien sind aus der größten, jemals im Vaskulitisbereich durchgeführten Studie hervorgegangen und wurden im Jahre 2022 veröffentlicht. Klassifizierungssysteme für Erkrankungen enthalten oft eine Reihe

unterschiedlicher Symptome, Blutwerte oder Befunde von Röntgen oder histologischen Untersuchungen. Damit ein Patient eine gewisse Diagnose erhalten kann muss eine bestimmte Kombination von Symptomen vorliegen. Die wesentliche Neuerung der letzten Kriterien ist die Aufnahme des ANCA-Blutwertes in diese Kriterien. Zusätzlich wird dem Vorhandensein dieses Wertes ein hoher Stellenwert eingeräumt. Die vorliegende Arbeit vergleicht das neue System mit dem vorher etablierten und kann im Wesentlichen feststellen, dass die Systeme ähnlich sind, allerdings führt der neuhinzugefügte ANCA-Test zu einigen Veränderungen bei der Klassifizierung der Erkrankungen. Wir stellen weiterhin fest, dass bei einer Klassifizierung nur anhand des ANCA-Tests (d.h. eine Klassifizierung in die Unterformen GPA oder MPA wird ausschließlich durch die Spezifität des ANCA Wertes (s.o., PR3 oder MPO) vorgenommen) ein fast identisches Klassifizierungsergebnis in unserer Studienpopulation auftritt, wie unter Benutzung der neuen Kriterien, was Fragen nach der Nützlichkeit der neuen Kriterien aufwirft.

Die Ursache für das Auftreten von Autoimmunerkrankungen ist nicht bekannt, eine multifaktorielle Ursache wird vermutet. Im Falle der AAV konnten Assoziationen mit Umweltfaktoren wie Infektionen, Silikat Exposition, Beschäftigung in der Landwirtschaft, Sonnenlichtexposition und Medikamenten gezeigt werden darüber hinaus existieren genetische Faktoren. Eine Teilstudie der vorliegenden Arbeit untersucht den Zusammenhang von Infektionen und der späteren Entwicklung einer AAV. Mit Hilfe eines regionalen Diagnoseregisters, welches Informationen über Diagnosen aller Arztbesuche im Studiengebiet speichert, wurden alle Infektionen von AAV-Patienten vor der Diagnose der AAV identifiziert und mit einer Kontrollpopulation ohne AAV verglichen. Die Analyse konnte zeigen, dass Infektionen häufiger bei Individuen auftreten, die im weiteren Verlauf eine AAV entwickeln. Dieser Zusammenhang wurde vor allem für Infektionen der Atemwege und der Lunge beobachtet. Hierdurch konnte also ein Zusammenhang zwischen dem Auftreten einer Infektion und der späteren Entwicklung einer AAV gezeigt werden.

Die Behandlung der AAV erfolgt mit Kortison und immunsuppressiven Medikamenten. Sowohl die Erkrankung selbst, als auch die Verwendung immunsuppressiver Medikamente führen zu einer Schwächung des Immunsystems mit dem Resultat eines erhöhten Infektionsrisikos. In der vierten Teilstudie der vorliegenden Arbeit wurde das Auftreten von schweren Infektionen untersucht. Diese wurden als Infektionen, welche einen mindestens 3-tägigen Krankenhausaufenthalt und die Zufuhr intravenöser antimikrobieller Medikamente erforderten, definiert. Die Analyse zeigte ein häufiges Vorkommen von schweren Infektionen bei AAV-Patienten. Eine solche Infektion konnte bei 40% der Patienten beobachtet werden. Schwere Infektionen treten vor allem während des ersten Jahres nach Beginn der AAV auf, sind wahrscheinlicher bei älteren Patienten sowie Patienten mit einer erhöhten Krankheitsaktivität der AAV zum Zeitpunkt der Diagnose. Darüber hinaus waren Infektionen vor Herz und Gefäß Erkrankungen, sowie Krebs die häufigste Todesursache in der Studienpopulation.

# Populärvetenskaplig sammanfattning

Denna avhandling studerar en grupp sällsynta sjukdomar som kallas för vaskulit. Begreppet betyder inflammation i blodkärl. Vaskuliter kan indelas i olika undergrupper, vanligast är en indelning enligt storleken av blodkärl som drabbas. Undergruppen som undersöks är så kallade ANCA-vaskuliter (AAV) som drabbar små blodkärl, alltså arterioler, kapillärer och venoler. ANCA betecknar en speciell antikropp som attackerar komponenter i vita blodkroppar och som förekommer hos de flesta patienter med dessa sjukdomar. Eftersom små blodkärl förekommer i alla vävnader kan symtom vid dessa sjukdomar uppträda i många organ. Oftast drabbas dock lungor, njurar, hud såväl som öron näsa hals området. AAV själva kan återigen uppdelas i tre olika typer som skiljer sig angående vilka organ som drabbas och vilka typiska symtom som uppträder. Man skiljer tre undertyper som kallas för granulomatos med polyangit (GPA), mikroskopisk polyangit (MPA) och eosinofil granulomatos med polyangit (EGPA). GPA angriper ofta näsa, öron och övre luftvägar, dessutom njurar och lungor, MPA uppträder nästan alltid i njurarna och ofta i lungorna, EGPA kännetecknas genom astma och allergi, näsbesvär och ibland symtom från lungor och njurar. Våra studier görs i en grupp av patienter som har drabbats av ANCA-vaskulit i ett definierat geografiskt område i Skåne mellan 1997–2019. Eftersom vi har identifierat och följer de allra flesta patienter i detta område kan dessa jämföras med den totala vuxna befolkningen i området. På så vis kan vi bedöma om nyinsjuknande (incidens) av sjukdomen har ändrats och om fler människor med dessa sjukdomar lever i området nu än för till exempel 15 år. AAV är allvarliga sjukdomar som leder till organsvikt och död utan behandling. Sedan införandet av immundämpande behandlingar med kortison och olika cellgifter har prognosen blivit betydligt bättre. Både sjukdomen i sig och behandlingen innebär dock nedsatt immunförsvar varför patienter har större risk för infektioner. I delarbete I undersöker vi nyinsjuknandet och antalet människor som lever med sjukdomen i vårt studieområde. Nyinsjuknandet under de sista 23 åren har varit stabilt med 30 nya fall per miljon vuxna invånare. Samtidigt har antalet människor som lever med sjukdomen ökat, 2003 var det cirka 330 per miljon och 2015 var det 469 per miljon. Vi misstänker att denna ökning beror på bättre prognos och därmed överlevnad för patienterna. Detta kan förklaras genom bättre behandlingar under de sista årtionden, vilket betyder inte bara nya mediciner utan också att man genom forskning, internationellt samarbete och utbildning har skapat mer kunskap och därmed bättre handläggande av dessa sjukdomar. I delarbete II av denna avhandling undersöks nya klassifikationer för ANCA-vaskulit. För att kunna studera olika

sjukdomar är det viktigt att forskare i hela världen är överens om diagnosernas definitioner, dvs vilka kliniska fynd, symtom och labprover som ska finnas och i vilken konstellation så att ett visst tillstånd kan kallas för GPA eller MPA till exempel. Dessa definitioner utvecklas hela tiden och nyligen har en internationell forskningsgrupp publicerat nya sådana kriterier för AAV. Vi har undersökt dessa kriterier och jämfört med de tidigare standardkriterierna. Vi kan konstatera att de nya fungerar bra, men att en indelning som bara klassificerar patienter enligt typ av ANCA-antikropp ger nästan samma resultat som de nya kriterierna. I delarbete III undersöktes om infektioner kan ha samband med utveckling av AAV. ANCA-vaskulit är en autoimmunsjukdom, där kroppen attackerar egna vävnader. Det spekuleras ofta i att sådana sjukdomar kan utlösas av infektion, eftersom systemet som bekämpar infektioner plötsligt riktar sig mot den egna kroppen. Med hjälp av ett diagnosregister, där alla diagnoser av sjukvårdskontakter i vårt område sparas har vi kunnat undersöka om patienter med ANCA vaskuliter har drabbats av infektioner innan de insjuknade i vaskulit. Med hjälp av registret kunde även några kontrollpersoner utan vaskulit väljas ut och sedan jämföras med vaskulitpatienter. Det visade sig att vaskulitpatienter i högre grad drabbades av infektioner innan deras insjuknande än kontrollpersoner och detta samband fanns endast för de patienter som uppvisade en viss typ av ANCA antikropp. Delarbete IV undersökte också infektioner, men här undersöktes allvarliga infektioner som lunginflammation eller blodförgiftning efter det att patienten har fått diagnosen ANCA-vaskulit och påbörjat behandling för sådan. Vi observerade att allvarliga infektioner är vanligt, de förekommer hos 40% av patienterna och uppträder framför allt hos äldre patienter och patienter som har en högaktiv ANCA-vaskulit initialt. Infektioner var utöver detta den vanligaste dödsorsaken i studien.

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