Epidemiology and Etiology of Wegener Granulomatosis, Microscopic Polyangiitis, Churg-Strauss Syndrome and Goodpasture Syndrome: Vasculitides with Frequent Lung Involvement

Aude Gibelin, M.D.,[1] Carla Maldini, M.D.,[1] and Alfred Mahr, M.D., M.P.H., Ph.D.[1]

Downloaded by: World Health Organization (WHO). Copyrighted material.

ABSTRACT

This review focuses on the epidemiological characteristics and etiologies of four primary systemic vasculitides with frequent lung involvement, namely Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and Goodpasture syndrome (GPS). Elucidation of the mechanisms underlying these vasculitides with frequent lung involvement is complicated by their rarity, which hampers the undertaking of large-scale studies; difficulties in classification; and their multifaceted clinical presentations, which infer the existence of several etiologic pathways. Notwithstanding, epidemiological research showed some evidence for international, interethnic, and temporal variations of the frequencies of these four vasculitides; led to the identification of several genetic and environmental risk factors; and provided insight on the extent to which genes and environment might contribute to their development. Available data support the concept that WG, MPA, CSS, and GPS have unique and shared risk determinants. Although the precise causes of these vasculitides are not yet fully understood and the development of prevention strategies is out of our reach at present, current knowledge enables the formulation of etiologic hypotheses to provide caregivers and their patients with valuable information on the nature of these rare entities.

KEYWORDS: Epidemiology, etiology, lung vasculitis, ANCA-associated vasculitis, Goodpasture syndrome

This review addresses the current status of our knowledge on the epidemiology and etiology of four primary systemic vasculitides with frequent lung involvement: Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and Goodpasture syndrome (GPS).

[1]Department of Internal Medicine, Hospital Saint-Louis, University Paris 7–Paris Diderot, Paris, France.

Address for correspondence and reprint requests: Alfred Mahr, M.D., Department of Internal Medicine, Hospital Saint-Louis, University Paris 7–Paris Diderot, Assistance Publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75475 Paris Cedex 10, France (e-mail: alfred.mahr@sls.aphp.fr).

Lung Vasculitis and Alveolar Hemorrhage; Guest Editor, Loïc Guillevin, M.D.

Semin Respir Crit Care Med 2011;32:264–273. Copyright © 2011 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.
DOI: http://dx.doi.org/10.1055/s-0031-1279824.
ISSN 1069-3424.

THE CONCEPT OF ''LUNG VASCULITIS'': FOCUS ON WG, MPA, CSS, AND GPS

The lung is a possible target of primary systemic vasculitides and, for some of the defined entities, a commonly involved organ. Thus the term *lung vasculitis* does not pertain to a genuine disease but rather has to be understood as a clinical–pathological process involved in the genesis of pulmonary manifestations. Alveolar capillaritis is the most prominent form of lung vasculitis, presenting clinically as diffuse alveolar hemorrhage due to blood leaking into the alveoli. Herein, the term *lung vasculitis* is used in the broader sense of a systemic vasculitis known to affect the lungs.

Four systemic vasculitides are tightly associated with pulmonary involvement: WG, MPA, CSS, and GPS. All four entities are categorized among the primary systemic vasculitides predominantly affecting small-sized vessels and closely linked to particular autoantibodies, namely anti-neutrophil cytoplasmic antibodies (ANCA) or anti-glomerular basement membrane (anti-GBM) antibodies.[1,2] ANCAs can occur in WG, MPA, and CSS, and these three diseases are commonly referred to as the ANCA-associated vasculitides (AAVs). Anti-GBM antibodies are found in GPS, which is also known as anti-GBM disease.

Although diffuse alveolar hemorrhage may be observed in all four entities, several other pulmonary features are encountered. These include parenchymal nodules and masses (in WG), asthma and eosinophilic pneumonia (in CSS), or interstitial lung disease (in MPA). With the exception of asthma, which is a key feature of CSS, the frequency of lung involvement also varies, and all patients do not have pulmonary manifestations. Importantly, not all respiratory symptoms have vasculitis as the underlying pathophysiology, and some of them are likely attributable to granulomatous inflammation (in WG), eosinophilic infiltration (in CSS), or bronchial hyperreactivity or allergy (in CSS).

Pulmonary manifestations are sometimes diagnosed in other systemic vasculitides. However, they are either highly uncommon events (e.g., pulmonary artery aneurysms in Behçet syndrome) or leave unclear whether they truly reflect structural changes of the respiratory system (e.g., cough in giant cell arteritis). Similarly, lung symptoms observed in secondary, connective tissue disorder–associated vasculitis are not considered herein.

EPIDEMIOLOGICAL INVESTIGATION OF LUNG VASCULITIS

Three elements must be considered when analyzing what is currently known about the epidemiological characteristics of WG, MPA, CSS, and GPS. First, the different clinical, pulmonary and extrapulmonary, and histological attributes of these four entities make it unlikely that they have a unique common pathway. The sometimes adopted approach of investigating AAVs as a single group is therefore not straightforward. Further complexity arises from the possibility that each disease encompasses several etiologically distinct phenotypic variants (e.g., predominantly granulomatous and predominantly vasculitic WG or ANCA-positive and ANCA-negative CSS). Second, the available classification systems for these diseases remain imperfect and do not arrive at unequivocal categorizations. This situation hampers between-study comparability, and misclassification may obfuscate the identification of entity-specific etiologic factors. Third, despite the remarkably increased number of relevant publications, the amount of available data remains limited. Moreover, owing to the rarity of the conditions considered here, the frequently small patient-sample sizes negatively affect the statistical power of studies and carry a risk of false-positive findings due to sampling errors.

Population Burden

The intensity with which the frequency of WG, MPA, CSS, and GPS has been studied varies greatly among the four vasculitides and across continents. So far, relevant studies have been performed in Europe, the United States, Australia, and New Zealand.[3–23] For the time being, there are no data on the burden of any of these four diseases for the Asian and southern American continents or for GPS in any location.

The reported incidence and prevalence estimates are summarized in Tables 1 and 2, respectively. Hence, the respective annual incidence rates of WG, MPA, and CSS range between 2.1 and 15, 2.1 and 17.5, and 0.5 and 3.1 per million. GPS incidence is not known but is thought to be less than 1[24] or even lower than 0.1 per million.[25] Assuming a life expectancy of 75 years and an incidence of 20 per million person-years for the four vasculitides combined, the lifetime risk[26] of developing WG, MPA, CSS, or GPS is 1 per 670 subjects. Prevalence data provide a very similar picture regarding the comparative frequencies of WG, MPA, and CSS (Table 2). All four vasculitides satisfy the definitions for rare ("orphan") diseases used in Europe (ie, prevalence below 500 per million) and the United States (prevalence below 1 in 1500 people).

An important epidemiological characteristic of WG is its sharp rise in incidence over the last few decades (Fig. 1). Results of Swedish and Norwegian investigations suggested a gradual two to fourfold incidence rise of WG over the periods 1975 to 2001[12] and 1984 to 1998,[13] respectively. WG prevalence in Norwich County in the United Kingdom doubled over the period 1990 to 2005,[22] albeit changes in prevalence rates may also be affected by variations of survival rates. It is not known if analogous incidence changes over time exist for MPA, CSS, or GPS. Whether the increasing WG

Downloaded by: World Health Organization (WHO). Copyrighted material.

Table 1 Annual Incidence Rates (Per Million) for Wegener Granulomatosis (WG), Microscopic Polyangiitis (MPA), and Churg-Strauss Syndrome (CSS)

Country of Study	Study Period	Study Population	Criteria	WG	MPA	CSS	First Author (Reference)
Spain	1988–1997	Age > 20 years	ACR	4.77		1.06	Gonzáles-Gay[7]
Spain	1998–2001	Age > 15 years	CHCC	2.95	7.91	1.31	Gonzales-Gay[9]
Germany	1998–1999	All ages	CHCC	5–8	1–3	0–2	Reinhold-Keller[19]
Germany	1998–2002	All ages	CHCC	6–12	2–3	0–2	Reinhold-Keller[18]
United Kingdom	1988–1993	Adults	ACR	8.5			Carruthers[3]
United Kingdom	1988–1994	Adults	ACR	8.5	2.4	2.4	Watts[4]
United Kingdom	1988–1997	Age > 15 years	ACR/CHCC	8.7–10.3	6.8–8.9	1.5–3.7	Watts[23]
United Kingdom	1990–2005	All ages	Clinical diagnoses	8.4			Watts[22]
Sweden	1975–2001	All ages	Discharge diagnoses	3.3–11.9			Knight[12]
Sweden	1997–2006	All ages	ECCA	9.8	10.1	0.9	Mohammad[16]
Norway	1984–1998	Age ≥ 15 years	ACR	6.0–14.4			Koldingsnes[13]
Norway	1988–1998	Age > 15 years	ACR/CHCC	10.5	2.7	0.5	Watts[31]
Norway	1992–1996	All ages	ACR	6.6		2.7	Haugeberg[10]
Lithuania	1990–1999	Age > 16 years	ACR	2.1		1.3	Dadoniene[6]
Finland	1996–2000	All ages	Discharge diagnoses	9.3			Takala[21]
New Zealand	1999–2003	All ages	Discharge diagnoses	5.8–15		0.8–2.8*	O'Donnell[29]
Australia	1995–2004	Age ≥ 15 years	ACR/CHCC	8.4–8.8	2.3–5.0	2.2–2.3	Ormerod[17]
Australia	2001–2005	All ages	Discharge diagnoses	11.2*			Hissaria[11]

*Values derived from 5-year incidence rates.
CHCC, Chapel Hill consensus classification[83]; ECCA, European medicines agency (EMA) consensus classification algorithm[84]; ACR, American College of Rheumatology.[85]

incidence reflects new environmental influences, changing classification, or heightened awareness is a matter of uncertainty. Keeping the caveat in mind that the time elapsed since the introduction of routine ANCA testing is still short, there are some indications that the rising WG incidence has not leveled off in the post-ANCA era.[12,13,21]

Demographic Characteristics

WG, MPA, CSS, and GPS occur primarily during adulthood, but their age-specific incidence rates are not uniformly distributed across age groups. Population-based data indicate that the WG or MPA incidence peaks for the age groups of 55 to 64 or 65 to 74 years.[9,13,27] In contrast, the CSS incidence peak occurs slightly earlier in life, at 30 to 40[17] or 55 to 64 years.[23] For GPS, a bimodal distribution was advanced with incidence peaks at 20 to 30 years and 60 to 70 years.[28] Despite these observations, the wide age ranges during which each of the four entities first manifests may imply that stochastic (chance) events are at work in their pathogeneses.

Sex-specific incidence rates do not provide a clear indication for uneven gender distributions for any of the four diseases. This lack of a gender effect infers that

Table 2 Prevalence Rates (Per Million) for Wegener Granulomatosis (WG), Microscopic Polyangiitis (MPA), and Churg-Strauss Syndrome (CSS)

Country of Study	Study Period	Study Population	Criteria	WG	MPA	CSS	First Author (Reference)
Germany	1994	All ages	CHCC	42–58	0–9	2–7	Reinhold-Keller[20]
France	2000	Age ≥ 15 years	ACR/CHCC	23.7	25.1	10.7	Mahr[15]
United Kingdom	1997	Age > 15 years	ACR	62.9			Watts[23]
United Kingdom	1990–2005	All ages	Clinical diagnoses	28.8–64.8			Watts[22]
Sweden	2003	All ages	ECCA	160	94	14	Mohammad[14]
Norway	1996	All ages	ACR	53		13	Haugeberg[10]
Norway	1998	Age ≥ 15 years	ACR	95.1			Koldingsnes[13]
United States	1986–90	All ages	Discharge diagnoses	26–32			Cotch[5]
New Zealand	2003	All ages	ACR/CHCC	93.5/112	NR/37		Gibson[8]
Australia	1995–2004	Age ≥ 15 years	ACR/CHCC	64.3–95.0	17.5–39.1	11.7–22.3	Ormerod[17]

CHCC, Chapel Hill consensus classification[83]; ECCA, European medicines agency (EMA) consensus classification algorithm[84]; ACR, American College of Rheumatology[85]; NR, not relevant.

Downloaded by: World Health Organization (WHO). Copyrighted material.

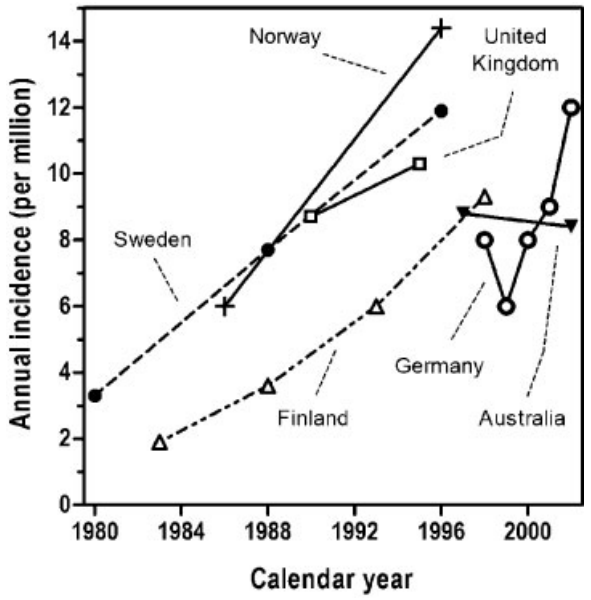

Figure 1 Temporal changes of annual incidence rates for Wegener granulomatosis reported from several population-based studies: • Knight (Sweden)[12]; + Koldingsnes (Norway)[13]; □ Watts (United Kingdom)[23]; ▼ Ormerod (Australia)[17]; △ Takala (Finland)[21]; ○ Reinhold-Keller (Germany).[18]

factors closely related to sex-specific physiology are not important etiologic determinants.

Geographic and Interethnic Variations

Results from population-based surveys support the existence of differential international variations in the occurrence of WG, MPA, CSS, and GPS. It has become a well-accepted notion that the geographic distribution of WG decreases with decreasing latitude, both north and south of the equator. In Nordic countries, the incidence or prevalence of WG is roughly two- to sevenfold higher than that in southern Europe. A similar discovery was made in the southern hemisphere, with a threefold higher incidence, controlled for age, sex, and ethnicity, of WG in the southernmost compared with the northernmost part of New Zealand.[29] Formal quantification of this gradient indicated a significant 3% increase of WG incidence with each degree of latitude.[30] A similar, albeit not statistically significant, observation was made for CSS. In contrast, no clear latitude-frequency correlation was identified for MPA,[30] thereby challenging the hypothesis that MPA might follow an inverse, increasing north-to-south pattern for the Northern Hemisphere.[31] The increased frequencies of WG and CSS in higher latitudes could point to a protective role of sunlight exposure, possibly via beneficial effects on vitamin D production, although they could also be explained by genetic or other environmental factors.[30]

Ethnic origin is also thought to play a part in the development of WG, MPA, CSS, and GPS. In a multiethnic population from France, WG, MPA, and CSS (and polyarteritis nodosa) were twice as prevalent among inhabitants of European versus non-European descent; in particular, non-European cases of WG were rare.[15] In New Zealand, WG and CSS are two to four times more common in people of European ancestry than in Maoris, Asians, or Pacific Islanders.[29] The predilection of WG and CSS for individuals of Caucasian ethnicity is furthermore underscored by the paucity of case series reported from countries outside Europe, North America, or Oceania,[32–36] and a population-based study on renal vasculitis in Japan that found no case of WG or CSS.[37] Observations from case series support that Caucasian ethnicity is also the predominant ethnic background of GPS.[28,38] Conversely, evidence is mounting that MPA might be more common in Asians than populations of European descent. According to a study on ANCA-associated renal vasculitis in the Miyazaki Prefecture in Japan, the MPA incidence was three times higher than that in Norwich County in the United Kingdom.[37,39]

More data are needed to obtain a more definitive assessment of the magnitude of geographic and interethnic differences in the frequencies of these diseases. Should the ethnic differences in disease risk be confirmed, clues on the etiologies of WG, MPA, CSS, or GPS could be provided by new studies focusing on the development of these vasculitides among people migrating from high-to-low-risk geographic areas or vice versa.

Genetic Factors

Particularly over the last decade, genetic susceptibility to WG, MPA, CSS, or GPS has been increasingly investigated. So far, all genetic studies relied on hypothesis-driven, candidate-gene approaches exploring functionally relevant gene variants inside or outside the major histocompatibility complex. While that research identified several statistically significant associations with investigated gene loci, interpretation of those findings frequently remains hampered by the lack of replication efforts or small effect sizes that could reflect linkage disequilibrium rather than an association with the true causal gene. Hypothesis-free genome-wide association studies (GWASs) are in progress for WG and MPA and may lead to the identification of yet unknown common susceptibility variants. Given that GWASs require sample sizes of 1000 case subjects or more, it is questionable whether this approach will be suitable for diseases as rare as CSS or GPS.

Another constraint to the study of genetic susceptibility to WG, MPA, CSS, or GPS comes from the difficulty of conducting studies designed to assess the degree of disease clustering among families, twins, or adopted siblings of probands with the disease. The low frequency of AAVs or GPS in the general population

Downloaded by: World Health Organization (WHO). Copyrighted material.

hinders the application of such methodological designs because they require analyzing very high numbers of family pedigrees to be informative. Bearing this caveat in mind, published reports on familial WG, MPA, CSS, or GPS are uncommon. Two partly overlapping registry-linkage studies from Sweden estimated the familial recurrence risk of WG among first-degree relatives to be 1.6 to 3.0-fold higher than that among control relatives.[40,41] Collectively, these observations suggest that the genetic burdens of WG, MPA, CSS, and GPS might be modest.

Nevertheless, genetic case-control studies led to the discovery of several susceptibility loci for WG, MPA, CSS, or GPS (Table 3). Particularly, histocompatibility leukocyte antigen (HLA) class II molecules that are involved in the orchestration of the secondary immune response appear to exert a genetic effect. The strongest and most consistently identified HLA association refers to *HLA-DRB1*1501*, which, according to a meta-analysis of four genetic association studies, conferred a striking ninefold risk of GPS.[42] Because this allele was carried by up to 90% of GPS cases, it was estimated that 50 to 90% of the population risk is attributable to this factor.[42] For WG and CSS, respective associations with *HLA-DPB1*0401* (odds ratio: 3.0 to 3.9)[43,44] and *HLA-DRB4* (odds ratio: 1.9 to 2.5)[45,46] were computed. In Japan, an MPA association with *HLA-DRB1*0901* (odds ratio: 2.2) was reported[47] but awaits replication.

Apart from the HLA loci, the probably best-described genetic finding is the link between WG and α_1-antitrypsin (α_1AT) deficiency. An association of WG with the α_1AT-deficiency *Z* allele, and possibly the *S* allele, was repeatedly found.[48,49] Further evidence for a causal relationship between α_1AT deficiency and WG comes from the observation that homozygous (*ZZ*, *SS*) or composite heterozygous (*SZ*) deficiency-allele carriers were at substantially increased risk for WG compared with subjects carrying the deficiency alleles in a heterozygous state (odds ratio: 15 vs 1.5).[50] Because α_1AT-deficiency alleles were found only in a minority of patients, their effect might at best explain 8% of WG cases.[50] The pathway by which deficiency in the anti-protease α_1-AT predisposes to WG remains enigmatic, and it is unknown whether α_1AT also confers risk for MPA, CSS, or GPS. There is evidence that WG with positive perinuclear–anti-myeloperoxidase-ANCA serology, which is the predominant ANCA pattern in MPA and CSS, is not linked to α_1AT deficiency.[50]

While the former findings suggest that WG, MPA, CSS, and GPS harbor distinct susceptibility loci, they also appear to share some genetic determinants. The

Table 3 Selected Genetic Factors Associated with Wegener Granulomatosis (WG), Microscopic Polyangiitis (MPA), Churg-Strauss Syndrome (CSS), or Goodpasture Syndrome (GPS)

Gene/Polymorphism	Disease	Allele (A) or Gene (G) Frequencies for Cases	Odds Ratio*	First Author (Reference)
*HLA-DR2/HLA-DRB1*1501*	GPS	64–79% (G)	8.5	Phelps[42]
HLA-DR4	GPS	Not reported	1.4	Phelps[42]
*HLA-DPB1*0401*	WG	70–77% (A)	3.01–3.91	Heckmann,[43] Jagiello[44]
*HLA-DRB1*04*	CSS	20–39% (A)	1.86–2.49	Vaglio,[45] Wieczorek[46]
*HLA-DRB1*07*	CSS	16–27% (A)	1.57–2.42	Vaglio,[45] Wieczorek[46]
HLA-DRB3	CSS	35–41% (A)	0.54–0.61	Vaglio,[45] Wieczorek[46]
*HLA-DRB1*0901*	MPA	50% (G)	2.2	Tsuchiya[47]
Alpha$_1$-antitrypsin deficiency (*Z/S* alleles)	WG	2.3% (G)	14.58	Mahr[50]
*PTPN22*620W*	WG	16% (A)	1.75–2.01	Carr,[51] Jagiello[52]
*PTPN22*620W*	MPA	Not reported	2.55	Carr[51]
CD226 Gly307Ser	WG	50% (A)	1.23	Wieczorek[54]
CTLA-4 rs3087243 G>A	AAV	41% (A)	0.84	Carr[51]
CTLA-4 –318T	WG	31% (G)	0.36	Giscombe[55]
CTLA-4 + 49G	AAV	70% (G)	1.92	Slot[56]
CTLA-4 AT repeat	WG	47% (G)	0.38	Zhou[58]
CTLA-4 AT repeat	WG	22% (G)	0.4	Spriewald[57]
IL-10.G allele 134	WG	21% (A)	3.11	Zhou[86]
IL-10 –1082AA	WG	25% (G)	2.82	Bártfai[87]
IL-10 –1082AA	MPA	39% (G)	5.43	Bártfai[87]
IL-10 –3575/–1082/–592 TAC haplotype	CSS	39% (G)	1.73	Wieczorek[88]

*Values refer either to allelic or genotypic odds ratios.
The Table includes only findings that were either replicated or with other evidence for a causal role.
AAV, ANCA-associated vasculitides.

Downloaded by: World Health Organization (WHO). Copyrighted material.

620W polymorphism of the protein tyrosine phosphatase nonreceptor (*PTPN22*) gene, which encodes a lymphoid tyrosine phosphatase that acts as a negative regulator of signaling through the T cell receptor, was found to be associated with WG and MPA.[51,52] This finding is pertinent because *PTPN22*620W* has emerged as an important risk locus for human autoimmunity. A meta-analysis combining two studies gave a pooled odds ratio of 1.40 for the risk of developing WG or MPA associated with this genetic polymorphism.[51] In contrast, *PTPN22*620W* may not be associated with CSS.[53] Genetic studies also uncovered associations with other autoimmune disease–associated gene variants, such as the *CD226* Gly307Ser gene polymorphism[54] or various distinct polymorphisms in the cytotoxic T-lymphocyte antigen-4 (*CTLA-4*) gene exerting either deleterious or protective effects.[51,55–58] In line with those findings, familial clustering of WG with rheumatoid arthritis[59] or autoimmune diseases at large[41] has been shown, although with only a relatively modest risk increase of ~1.3.

Additional genetic associations with one of the considered vasculitis entities are summarized in Table 3.

Environmental Factors

Despite offering the theoretical possibility of disease prevention, the study of environmental risk factors has so far been accorded inadequate attention in the context of WG, MPA, CSS, and GPS. A possible explanation for the scarcity of that research is that environmental etiologies are even less tractable than genetic influences. Compared with genetic research, the study of environmental determinants is methodologically complicated by the vagaries of recall bias, the need for establishing the temporal sequence between exposure and event, and the more complex assessment of dose–effect relationships.

INFECTION

It is a long-held belief that the etiology of systemic vasculitides could be infectious. For vasculitides with frequent pulmonary involvement, this hypothesis is all the more relevant because lung disease could be explained by airborne infections. The most compelling observation to support an infectious cause comes from circumstantial evidence that the onset of these diseases is preceded by infectious events, and studies supporting that WG and MPA first become evident during the fall and winter months, a season with very frequent respiratory infection epidemics. However, controversy exists regarding this concept of seasonality in disease onset, with other studies suggesting either no WG seasonality[49] or its increased occurrence in summer.[60]

For the time being, direct support for an infectious cause of any of the four diseases under consideration is lacking. It was recently discovered that most patients with renal AAVs had antibodies directed against the lysosome-associated membrane protein 2 (LAMP2), and the molecular mimicry between LAMP2 and the adhesion protein FimH expressed by gram-negative bacteria.[61] Based on those observations, as yet unconfirmed, the implication of infection with gram-negative bacteria in the pathogenesis of WG and MPA was hypothesized. The link between nasal carriage of *Staphylococcus aureus* and WG generated a lot of interest in the past, even though the role of this pathogen, if any, can at best be regarded as relapse-initiating rather than as being a true causative agent. Attempts at identifying the responsible microorganisms might also be hindered by the possibility that numerous infectious agents might be able to precipitate WG, MPA, CSS, or GPS onset.

OCCUPATIONAL AND LIFESTYLE FACTORS

Exposure to crystalline silica stands out as the most convincing environmental risk factor, conferring a risk two to 14 times higher for WG, MPA, or CSS.[27,62–64] One study also detected a dose–effect relationship, with higher exposure conferring higher risk for ANCA-associated diseases.[65] Analogous observations were made for rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus,[66] and the hypothesis was put forth that exposure to silica or silica compounds acts as an adjuvant for autoantibody production. Various other positive relationships were suggested for WG, MPA, and CSS, including farming (particularly by contact with livestock),[27] organic solvents,[27] inhalation of particulate material and fumes,[67] and exposures to lead, cadmium,[62] or mercury.[68] Thus the role of occupational exposures as determinants of WG risk conflicts with a recent study that found no relationship between professional occupation and WG.[69]

The idea that the "hygiene hypothesis," which is based on the theory that the lack of early childhood infections augments the susceptibility to allergic and autoimmune diseases, may play a part in WG etiology could be supported by case–control studies, indicating a link with a prior history of allergy,[27,68,70] and the observation that WG predominates in people of higher socioeconomic status.[29] Studies assessing the risk between AAVs and smoking found that tobacco smoking decreased the risk,[71] whereas another study identified smoking as perhaps having a disease-modifying effect on WG.[72] Concerning GPS, there is an indication that smoking might enhance risk of developing GPS overall or for alveolar hemorrhage.[28]

DRUGS

The role of drugs or other therapies in inducing or causing WG, MPA, CSS, or GPS has given rise to numerous speculations. Most of the suggested links with drugs relied on case reports and provided only minimal

Downloaded by: World Health Organization (WHO). Copyrighted material.

scientific evidence. Two types of medications (ie, antithyroid drugs and anti-leukotriene–receptor antagonists) were more intensively studied as possible triggers for AAV, but their causative roles remain disputed. Both examples illustrate the complexity in disentangling association from causation in pharmacoepidemiological research.

The observation was recurrently made that ANCAs are detectable in subjects exposed to antithyroid agents, mainly propylthiouracil,[73–78] but also carbimazole and methimazole.[75,77] Results suggested that intake of an antithyroid agent conferred a significant 2.2- to 11-fold higher risk of testing ANCA-positive for various immunological specificities.[75,77] The fundamental question persists as to whether ANCA production coincides with vasculitis, and data from Asia suggest that as many as one out of four ANCA-positive propylthiouracil users develop a true vasculitis.[79] In contrast, data from the United States indicated that only 1.5% of 129 subjects with renal AAVs had a history of antithyroid treatment, whereas 20% of them had a prior history of thyroid disease (compared with 7% of control subjects, odds ratio: 3.7).[80] The latter study raised the question of whether the link between exposure to antithyroid drugs and AAVs might be confounded by the clustering of AAVs with autoimmune thyroiditis, and that, even if a true causal relationship exists, the use of antithyroid medications could only explain a minor fraction of AAV cases.[80] The mechanism by which antithyroid compounds might operate in ANCA synthesis remains elusive.

A similar question has been raised with respect to the leukotriene-receptor antagonists used to treat asthma. Numerous case reports have described asthmatics exposed to these medications who subsequently developed CSS. Findings from case–control studies confirmed an association between antileukotriene use and CSS development, but comparable relationships exist for other medications used to treat asthma (e.g., inhaled long-acting β-agonists or oral corticosteroids).[81,82] Those findings support that antileukotrienes are merely a marker of the severity and gradual worsening of the asthma preceding CSS onset, rather than a real culprit in CSS.

EPIDEMIOLOGY AND ETIOLOGY OF WG, MPA, CSS, AND GPS: CURRENT STATE AND FUTURE PERSPECTIVES

A significant body of data has accumulated from descriptive and etiologic epidemiological research on WG, MPA, CSS, and, to a lesser extent, GPS. A progressive shift has occurred from the paradigm of diseases of unknown etiology toward the concept that these four entities represent, like most chronic diseases, etiologically complex conditions caused by a combination of environmental and genetic factors. Results of this research suggest that these four vasculitides are the consequence of entity-specific etiologic factors (e.g., specific HLA associations) but also partly overlapping risk determinants, as illustrated by the link with the *PTPN22*620W* gene locus or silica exposure. Importantly, all of the identified etiologic factors common to WG, MPA, CSS, or GPS were also recognized as risk factors for other autoimmune diseases. Thus the etiologic link predisposing specifically to any combination of the four entities remains unclear.

While case–control studies support that both genes and the environment are implicated in the pathogenesis of WG, MPA, CSS, and GPS, the lingering question is to what extent do both factors weigh on disease occurrence. Data suggest that the degree of familial clustering is modest and, thus, imply a polygenic inheritance pattern and perhaps also low heritability. The possible incidence rise and substantial geographic variations of the frequencies of these vasculitides, which cannot be explained by genetic factors alone, also point toward a predominant role of the environment. However, the responsible environmental factors are not yet well known.

Much more research is needed to expand our understanding of the etiopathogenesis of WG, MPA, CSS, and GPS. The study of gene–gene and gene–environment interactions is a possible direction for future research. Each of the four conditions will have to be explored individually and also within specific subgroups; however, investigators' increasing attempts to analyze subgroups will be at the expense of generating spurious findings due to multiple statistical testing. Better international consensus on disease classification and collaborative networks will facilitate analyses of homogeneous patient groups with appropriate sample sizes to achieve sufficient statistical power. In addition to case–control association studies, the input of new population-based studies, ideally including as yet uninvestigated geographic areas, should not be dismissed. Such research will help further describe the racial, temporal, and latitudinal occurrence patterns of these vasculitides, and confirm or refute the current hypotheses.

Unraveling the causes of WG, MPA, CSS, and GPS may turn out to be a thorny undertaking fraught with various obstacles. The lack of clear gender predominance, the wide age ranges at disease onset, and the variability of clinical presentations suggest etiologic heterogeneity involving multiple causal models, and the interference of stochastic (chance) events. Even though these efforts might ultimately not be rewarded by discovering the exact etiologies, the ensuing insights could be useful for diagnostic, prognostic, or therapeutic purposes and enable caregivers and their patients to understand better the nature of these rare diseases.

Downloaded by: World Health Organization (WHO). Copyrighted material.

REFERENCES

1. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med 1997;337(21):1512–1523
2. Savage CO, Harper L, Adu D. Primary systemic vasculitis. Lancet 1997;349(9051):553–558
3. Carruthers DM, Watts RA, Symmons DP, Scott DG. Wegener's granulomatosis—increased incidence or increased recognition? Br J Rheumatol 1996;35(2):142–145
4. Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? Semin Arthritis Rheum 1995;25(1):28–34
5. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis: estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. Arthritis Rheum 1996;39(1):87–92
6. Dadoniene J, Kirdaite G, Mackiewicz Z, Rimkevicius A, Haugeberg G. Incidence of primary systemic vasculitides in Vilnius: a university hospital population based study. Ann Rheum Dis 2005;64(2):335–336
7. González-Gay MA, García-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997: clinical and epidemiologic aspects. Medicine (Baltimore) 1999;78(5): 292–308
8. Gibson A, Stamp LK, Chapman PT, O'Donnell JL. The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region. Rheumatology (Oxford) 2006;45(5):624–628
9. Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis Rheum 2003;49(3):388–393
10. Haugeberg G, Bie R, Bendvold A, Larsen AS, Johnsen V. Primary vasculitis in a Norwegian community hospital: a retrospective study. Clin Rheumatol 1998;17(5):364–368
11. Hissaria P, Cai FZ, Ahern M, Smith M, Gillis D, Roberts-Thomson P. Wegener's granulomatosis: epidemiological and clinical features in a South Australian study. Intern Med J 2008;38(10):776–780
12. Knight A, Ekbom A, Brandt L, Askling J. Increasing incidence of Wegener's granulomatosis in Sweden, 1975-2001. J Rheumatol 2006;33(10):2060–2063
13. Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. Arthritis Rheum 2000; 43(11):2481–2487
14. Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford) 2007;46(8):1329–1337
15. Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum 2004;51(1):92–99
16. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford) 2009; 48(12):1560–1565
17. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Intern Med J 2008;38(11):816–823
18. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gross WL. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. Arthritis Rheum 2005;53(1):93–99
19. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, et al. No difference in the incidences of vasculitides between north and south Germany: first results of the German vasculitis register. Rheumatology (Oxford) 2002;41(5):540–549
20. Reinhold-Keller E, Zeidler A, Gutfleisch J, Peter HH, Raspe HH, Gross WL. Giant cell arteritis is more prevalent in urban than in rural populations: results of an epidemiological study of primary systemic vasculitides in Germany. Rheumatology (Oxford) 2000;39(12):1396–1402
21. Takala JH, Kautiainen H, Malmberg H, Leirisalo-Repo M. Incidence of Wegener's granulomatosis in Finland 1981-2000. Clin Exp Rheumatol 2008;26(3, suppl 49):S81–S85
22. Watts RA, Al-Taiar A, Scott DG, Macgregor AJ. Prevalence and incidence of Wegener's granulomatosis in the UK general practice research database. Arthritis Rheum 2009;61(10): 1412–1416
23. Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum 2000;43(2):414–419
24. Salama AD, Levy JB, Lightstone L, Pusey CD. Goodpasture's disease. Lancet 2001;358(9285):917–920
25. Bolton WK. Goodpasture's syndrome. Kidney Int 1996;50(5): 1753–1766
26. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect 2001;127(2):305–314
27. Lane SE, Watts RA, Bentham G, Innes NJ, Scott DG. Are environmental factors important in primary systemic vasculitis? A case-control study Arthritis Rheum 2003;48(3):814–823
28. Shah MK, Hugghins SY. Characteristics and outcomes of patients with Goodpasture's syndrome. South Med J 2002; 95(12):1411–1418
29. O'Donnell JL, Stevanovic VR, Frampton C, Stamp LK, Chapman PT. Wegener's granulomatosis in New Zealand: evidence for a latitude-dependent incidence gradient. Intern Med J 2007;37(4):242–246
30. Gatenby PA, Lucas RM, Engelsen O, Ponsonby AL, Clements M. Antineutrophil cytoplasmic antibody-associated vasculitides: could geographic patterns be explained by ambient ultraviolet radiation? Arthritis Rheum 2009;61(10): 1417–1424
31. Watts RA, Lane SE, Scott DG, et al. Epidemiology of vasculitis in Europe. Ann Rheum Dis 2001;60(12):1156–1157
32. Kamali S, Erer B, Artim-Esen B, et al. Predictors of damage and survival in patients with Wegener's granulomatosis: analysis of 50 patients. J Rheumatol 2010;37(2):374–378
33. Cisternas M, Soto L, Jacobelli S, et al; Grupo de estudio de las vasculitis, Sociedad Chilena de Reumatología. Clinical features of Wegener granulomatosis and microscopic polyangiitis in Chilean patients [in Spanish]. Rev Med Chil 2005;133(3):273–278
34. Oh MJ, Lee JY, Kwon NH, Choi DC. Churg-Strauss syndrome: the clinical features and long-term follow-up of 17 patients. J Korean Med Sci 2006;21(2):265–271
35. de Souza FH, Radu Halpern AS, Valente Barbas CS, Shinjo SK. Wegener's granulomatosis: experience from a Brazilian tertiary center. Clin Rheumatol 2010;29(8):855–860

Downloaded by: World Health Organization (WHO). Copyrighted material.

36. Flores-Suárez LF, Villa AR. Spectrum of Wegener granulomatosis in a Mexican population. Ann N Y Acad Sci 2007; 1107:400–409
37. Fujimoto S, Uezono S, Hisanaga S, et al. Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. Clin J Am Soc Nephrol 2006;1(5):1016–1022
38. Teague CA, Doak PB, Simpson IJ, Rainer SP, Herdson PB. Goodpasture's syndrome: an analysis of 29 cases. Kidney Int 1978;13(6):492–504
39. Watts RA, Scott DG, Jayne DR, et al. Renal vasculitis in Japan and the UK—are there differences in epidemiology and clinical phenotype? Nephrol Dial Transplant 2008;23(12):3928–3931
40. Knight A, Sandin S, Askling J. Risks and relative risks of Wegener's granulomatosis among close relatives of patients with the disease. Arthritis Rheum 2008;58(1):302–307
41. Knight A, Sandin S, Askling J. Increased risk of autoimmune disease in families with Wegener's granulomatosis. J Rheumatol 2010;37(12):2553–2558
42. Phelps RG, Rees AJ. The HLA complex in Goodpasture's disease: a model for analyzing susceptibility to autoimmunity. Kidney Int 1999;56(5):1638–1653
43. Heckmann M, Holle JU, Arning L, et al. The Wegener's granulomatosis quantitative trait locus on chromosome 6p21.3 as characterised by tagSNP genotyping. Ann Rheum Dis 2008;67(7):972–979
44. Jagiello P, Gencik M, Arning L, et al. New genomic region for Wegener's granulomatosis as revealed by an extended association screen with 202 apoptosis-related genes. Hum Genet 2004;114(5):468–477
45. Vaglio A, Martorana D, Maggiore U, et al; Secondary and Primary Vasculitis Study Group. HLA-DRB4 as a genetic risk factor for Churg-Strauss syndrome. Arthritis Rheum 2007;56(9):3159–3166
46. Wieczorek S, Hellmich B, Gross WL, Epplen JT. Associations of Churg-Strauss syndrome with the HLA-DRB1 locus, and relationship to the genetics of antineutrophil cytoplasmic antibody-associated vasculitides: comment on the article by Vaglio et al. Arthritis Rheum 2008;58(1):329–330
47. Tsuchiya N, Kobayashi S, Hashimoto H, Ozaki S, Tokunaga K. Association of HLA-DRB1*0901-DQB1*0303 haplotype with microscopic polyangiitis in Japanese. Genes Immun 2006;7(1):81–84
48. Esnault VL, Testa A, Audrain M, et al. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. Kidney Int 1993;43(6):1329–1332
49. Mahr AD, Neogi T, Merkel PA. Epidemiology of Wegener's granulomatosis: Lessons from descriptive studies and analyses of genetic and environmental risk determinants. Clin Exp Rheumatol 2006;24(2, suppl 41):S82–S91
50. Mahr AD, Edberg JC, Stone JH, et al. $Alpha_1$-antitrypsin deficiency-related alleles Z and S and the risk of Wegener's granulomatosis. Arthritis Rheum 2010;62(12):3760–3767
51. Carr EJ, Niederer HA, Williams J, et al. Confirmation of the genetic association of CTLA4 and PTPN22 with ANCA-associated vasculitis. BMC Med Genet 2009;10:121
52. Jagiello P, Aries P, Arning L, et al. The PTPN22 620W allele is a risk factor for Wegener's granulomatosis. Arthritis Rheum 2005;52(12):4039–4043
53. Holle JU, Wieczorek S, Gross WL. Genetic association studies in ANCA-associated vasculitides: what we have learnt so far and what needs to be done in the future. Clin Exp Rheumatol 2010;28(1, suppl 57):5–7
54. Wieczorek S, Hoffjan S, Chan A, et al. Novel association of the CD226 (DNAM-1) Gly307Ser polymorphism in Wegener's granulomatosis and confirmation for multiple sclerosis in German patients. Genes Immun 2009;10(6):591–595
55. Giscombe R, Wang X, Huang D, Lefvert AK. Coding sequence 1 and promoter single nucleotide polymorphisms in the CTLA-4 gene in Wegener's granulomatosis. J Rheumatol 2002;29(5):950–953
56. Slot MC, Sokolowska MG, Savelkouls KG, Janssen RG, Damoiseaux JG, Tervaert JW. Immunoregulatory gene polymorphisms are associated with ANCA-related vasculitis. Clin Immunol 2008;128(1):39–45
57. Spriewald BM, Witzke O, Wassmuth R, et al. Distinct tumour necrosis factor alpha, interferon gamma, interleukin 10, and cytotoxic T cell antigen 4 gene polymorphisms in disease occurrence and end stage renal disease in Wegener's granulomatosis. Ann Rheum Dis 2005;64(3):457–461
58. Zhou Y, Huang D, Paris PL, Sauter CS, Prock KA, Hoffman GS. An analysis of CTLA-4 and proinflammatory cytokine genes in Wegener's granulomatosis. Arthritis Rheum 2004;50(8):2645–2650
59. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum 2009;60(3):661–668
60. Mahr A, Artigues N, Coste J, Aouba A, Pagnoux C, Guillevin L; French Vasculitis Study Group. Seasonal variations in onset of Wegener's granulomatosis: increased in summer? J Rheumatol 2006;33(8):1615–1622
61. Kain R, Exner M, Brandes R, et al. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nat Med 2008;14(10):1088–1096
62. Nuyts GD, Van Vlem E, De Vos A, et al. Wegener granulomatosis is associated to exposure to silicon compounds: a case-control study. Nephrol Dial Transplant 1995;10(7): 1162–1165
63. Hogan SL, Cooper GS, Savitz DA, et al. Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: a population-based, case-control study. Clin J Am Soc Nephrol 2007;2(2):290–299
64. Gregorini G, Ferioli A, Donato F, et al. Association between silica exposure and necrotizing crescentic glomerulonephritis with p-ANCA and anti-MPO antibodies: a hospital-based case-control study. Adv Exp Med Biol 1993; 336:435–440
65. Beaudreuil S, Lasfargues G, Lauériere L, et al. Occupational exposure in ANCA-positive patients: a case-control study. Kidney Int 2005;67(5):1961–1966
66. Parks CG, Conrad K, Cooper GS. Occupational exposure to crystalline silica and autoimmune disease. Environ Health Perspect 1999;107(suppl 5):793–802
67. Duna GF, Cotch MF, Galperin C, Hoffman DB, Hoffman GS. Wegener's granulomatosis: role of environmental exposures. Clin Exp Rheumatol 1998;16(6):669–674
68. Albert D, Clarkin C, Komoroski J, Brensinger CM, Berlin JA. Wegener's granulomatosis: possible role of environmental agents in its pathogenesis. Arthritis Rheum 2004;51(4):656–664
69. Knight A, Sandin S, Askling J. Occupational risk factors for Wegener's granulomatosis: a case-control study. Ann Rheum Dis 2010;69(4):737–740
70. Cuadrado MJ, D'Cruz D, Lloyd M, Mujic F, Khamashta MA, Hughes GR. Allergic disorders in systemic vasculitis: a case-controlled study. Br J Rheumatol 1994;33(8):749–753

Downloaded by: World Health Organization (WHO). Copyrighted material.

71. Haubitz M, Woywodt A, de Groot K, Haller H, Goebel U. Smoking habits in patients diagnosed with ANCA associated small vessel vasculitis. Ann Rheum Dis 2005;64(10):1500–1502
72. Mohammad AJ, Segelmark M. Association of cigarette smoking with organ damage in primary systemic vasculitis. Scand J Rheumatol 2011;40(1):51–56
73. Gao Y, Zhao MH, Guo XH, Xin G, Gao Y, Wang HY. The prevalence and target antigens of antithyroid drugs induced antineutrophil cytoplasmic antibodies (ANCA) in Chinese patients with hyperthyroidism. Endocr Res 2004;30(2):205–213
74. Gunton JE, Stiel J, Clifton-Bligh P, Wilmshurst E, McElduff A. Prevalence of positive anti-neutrophil cytoplasmic antibody (ANCA) in patients receiving anti-thyroid medication. Eur J Endocrinol 2000;142(6):587
75. Harper L, Chin L, Daykin J, et al. Propylthiouracil and carbimazole associated-antineutrophil cytoplasmic antibodies (ANCA) in patients with Graves' disease. Clin Endocrinol (Oxf) 2004;60(6):671–675
76. Sera N, Ashizawa K, Ando T, et al. Treatment with propylthiouracil is associated with appearance of antineutrophil cytoplasmic antibodies in some patients with Graves' disease. Thyroid 2000;10(7):595–599
77. Slot MC, Links TP, Stegeman CA, Tervaert JW. Occurrence of antineutrophil cytoplasmic antibodies and associated vasculitis in patients with hyperthyroidism treated with antithyroid drugs: a long-term follow-up study. Arthritis Rheum 2005;53(1):108–113
78. Wada N, Mukai M, Kohno M, Notoya A, Ito T, Yoshioka N. Prevalence of serum anti-myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA) in patients with Graves' disease treated with propylthiouracil and thiamazole. Endocr J 2002;49(3):329–334
79. Zhao MH, Chen M, Gao Y, Wang HY. Propylthiouracil-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Kidney Int 2006;69(8):1477–1481
80. Lionaki S, Hogan SL, Falk RJ, et al. Association between thyroid disease and its treatment with ANCA small-vessel vasculitis: a case-control study. Nephrol Dial Transplant 2007;22(12):3508–3515
81. Hauser T, Mahr A, Metzler C, et al. The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study. Thorax 2008;63(8):677–682
82. Harrold LR, Patterson MK, Andrade SE, et al. Asthma drug use and the development of Churg-Strauss syndrome (CSS). Pharmacoepidemiol Drug Saf 2007;16(6):620–626
83. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994;37(2):187–192
84. Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007;66(2):222–227
85. Hunder GG, Arend WP, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis: introduction. Arthritis Rheum 1990;33(8):1065–1067
86. Zhou Y, Giscombe R, Huang D, Lefvert AK. Novel genetic association of Wegener's granulomatosis with the interleukin 10 gene. J Rheumatol 2002;29(2):317–320
87. Bártfai Z, Gaede KI, Russell KA, Muraközy G, Müller-Quernheim J, Specks U. Different gender-associated genotype risks of Wegener's granulomatosis and microscopic polyangiitis. Clin Immunol 2003;109(3):330–337
88. Wieczorek S, Hellmich B, Arning L, et al. Functionally relevant variations of the interleukin-10 gene associated with antineutrophil cytoplasmic antibody-negative Churg-Strauss syndrome, but not with Wegener's granulomatosis. Arthritis Rheum 2008;58(6):1839–1848

Downloaded by: World Health Organization (WHO). Copyrighted material.