Epidemiology of the Vasculitides

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KEYWORDS

• Epidemiology primary • Secondary • Vasculitis • Autoimmune • Nervous system

KEY POINTS

- The epidemiology of vasculitis has witnessed extraordinary advances in the past decade.
- These advances have been influenced by the worldwide increased recognition and accurate classification and diagnosis of the vasculitides, and insights brought by genome-wide association studies and online genetic biological repositories that allow researchers to freely access a wide array of genetic and clinical resources.
- The result is improved understanding of the heritable factors of the systemic vasculitides.
- This article reviews the current knowledge of the epidemiology of vasculitides in different global regions.

INTRODUCTION

The publication of recent genome-wide association studies (GWAS) has brought awareness to the understanding of susceptibility factors designated genetic risk loci for many of the vasculitides, supporting the interplay of immunologic, environmental, and shared genetic susceptibility in the etiopathogenesis of vasculitic disorders, With an incidence and prevalence of primary systemic vasculitis that is steadily increasing and an impact that is being reported worldwide in developed countries, government and nongovernmental organizations, and other key stakeholders have not developed sufficient programs for the prevention and surveillance of these disorders. This article focuses on the epidemiology of the major large-vessel, medium-vessel, and small-vessel vasculitides shown in **Box 1**. A review of the epidemiology and classification of primary systemic vasculitides was published earlier.[1]

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Box 1
Classification of primary systemic vasculitides

Large-Vessel Vasculitis

Giant cell arteritis (formerly temporal arteritis) (GCA)

Takayasu arteritis (TAK)

Medium-Vessel Vasculitis

Kawasaki disease (KD)

Polyarteritis nodosa (PAN)

Small-Vessel Vasculitis

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Granulomatosis with polyangiitis (formerly Wegener granulomatosis) (GPA)

Microscopic polyangiitis (formerly microscopic polyarteritis) (MPA)

Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) (EGPA)

LARGE-SIZE VESSEL VASCULITIS

Giant Cell Arteritis

Background

Giant cell arteritis (GCA) is a chronic granulomatous vasculitis of large and medium-sized vessels that frequently affected the thoracic aorta and its branches, with a mean age of diagnosis of age 76 years and a male-to-female ratio of 1.5:1.[2] Both GCA and polymyalgia rheumatica (PMR), a related disorder, are probably polygenic diseases in which multiple environmental and genetic factors influence susceptibility and severity.[3] For both the purpose of epidemiologic studies and in clinical practice, GCA has been classified according to the 1990 American College of Rheumatology (ACR) criteria[4] and designed to discriminate between different types of vasculitides. The 5 discriminatory features include age older than 50 years at onset, new onset of localized headache, temporal artery tenderness or decreased temporal artery pulse, erythrocyte sedimentation rate greater than 50 mm/h, and biopsy of an artery showing necrotizing arteritis characterized by a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells. Unrecognized and untreated or inadequately treated, there is a high likelihood of large-artery complications including increased morbidity and mortality,[5] especially as a result of aortic aneurysm and dissection and large-artery stenosis.

Epidemiology

The epidemiology of GCA was reviewed by Gonzalez-Gay and colleagues.[6] Since 2000, relatively large cohort studies exemplifying the epidemiologic aspects of GCA in different regions of the world have been reported from Australia,[7,8] Germany,[9] Israel,[10] Japan,[11] New Zealand,[12] Norway,[13,14] Spain,[15,16] Sweden,[17] the United Kingdom (UK),[18] and the United States (USA).[19] Smaller nonepidemiologic case series of patients with GCA have been reported from Brazil,[20] Saudi Arabia,[21] Mexico,[22] and Japan[11] where the incidence is very low, especially in Japan where a nationwide survey of GCA demonstrated a correspondingly low prevalence of 1.47 cases per 100,000 population. The global incidence and prevalence of GCA is summarized in **Table 1**.

Table 1
Global incidence and prevalence of GCA

Authors,[Ref.] Year	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Kobayashi et al,[11] 2003	Japan	1997	1.47	—
Herlyn et al,[9] 2004	Germany	2006	2.71	171
Dunstan et al.[7] 2014	Australia	1992–2011	3.20	—
Bas-Lando et al,[10] 2007	Israel	1980–2004	9.50	—
Gonzalez-Gay et al,[15] 2005; Gonzalez-Gay et al,[16] 2007	Spain	1981–2005	10.13	—
Mohammad et al,[17] 2014	Sweden	1997–2010	13.3	—
Salvarani et al,[19] 2004	USA	1950–1999	18.8	—
Smeeth et al,[18] 2006	UK	1990–2001	22.0	—
Haugeberg et al,[13] 2003; Haugeberg et al,[14] 2000	Norway Norway Norway	1992–1996 1992–1996 1992–1996	27.50 36.70 32.8	— — —

The highest known incidence of GCA was reported by Haugeberg and colleagues,[13,14] without major differences between northern and western Norway compared with southern Norway. By comparison, very low incidence rates of GCA were found in Saudi Arabian,[21] Mexican,[22] and Japanese populations.[11] Dustan and colleagues[7] found evidence of seasonal variation in the incidence of GCA in Australian Bureau of Statistics population data for South Australia, noting higher rates in the summer months ($P<.015$). Abdul-Rahman and coworkers[12] noted a cyclic annual incidence with peaks in 5 years between 1996 and 2005, and a statistically insignificant ($P<.9$) but suggestive seasonal variation nonetheless, with more cases diagnosed in the spring than in summer, fall, and winter. Bas-Lando and coworkers[10] noted more common onset of GCA in the late spring and early summer, with fluctuation in the annual incidence that included 3 distinctive peaks during the 25-year period of observation among 170 patients in Jerusalem between 1980 and 2014. Ninan and coworkers[8] noted that the relative survival for different follow-up periods in South Australian patients with GCA linked to birth, death, and marriage registry records showed mortality similar to that of the general population of age-matched and sex-matched controls. According to Herlyn and colleagues,[9] who studied inhabitants of the city of Luebeck and the rural region of Segeberg in northern Germany, GCA was the most prevalent systemic vasculitis in 2006, with 171 per million inhabitants, followed by granulomatosis with polyangiitis (GPA) with a prevalence rate of 98 per million inhabitants. The prevalence rate of GCA doubled in northern Germany for those aged 50 years or older from 240 to 440 per million inhabitants between 1994 and 2006, and from 87 to 171 per million population overall. There was a difference in both period prevalence and incidence rates between the urban and rural areas, with an incidence of GCA of 27.1 per million inhabitants per year in urban Luebeck compared with 14.7 per million inhabitants per year in rural Segeberg ($P = .2$), while respective prevalence rates were 237 and 116 per million population overall and 586 and 311 per million inhabitants of age 50 years or older.

Differences in incidence between regional populations of the world may be explained in part by immunogenetic and environmental factors that account for differences in susceptibility and may contribute to severity and outcome.[23] In 1980, Kemp

and coworkers[24] performed human leukocyte antigen (HLA) tissue-type antigen determinations for the A, B, and C antigens in the sera of 88 mixed cases of clinical GCA and PMR with an overwhelming representation of women and only sporadic familial occurrence, demonstrating no significant deviation from a sample compared with 3164 blood donor controls. In 1983, Armstrong and colleagues[25] studied 55 patients with GCA and PMR, typed for HLA A, B, C, and DR loci, noting a significantly increased frequency of DR4, Cw3, and Cw6, with the increase in Cw3 possibly attributed to linkage disequilibrium to DR4. Among 128 DNA samples for 128 patients and 145 ethnically matched controls in a case-control association study to determine whether patients with GCA and PMR from a sample in Lugo, northwestern Spain, showed identical HLA class II associations, Dababneh and colleagues[26] found that the association of HLA-DRB 1*0401 and GCA reached statistical significance in the total GCA group of patients, but less so for DRG1*0101 and *0102. An association was also observed between the RA DRB1 shared epitope (SE) and GCA that was primarily accounted for by the presence of a single copy of the SE; moreover, an SE-bearing allele of DRB1 was observed in patients with jaw claudication and visual manifestations. The genetic susceptibility to GCA was supported by reports of the contribution of shared HLA class II gene polymorphisms in mannose-binding lectin variant alleles by Jacobsen and coworkers[27]; in DR4 by Jacobson,[27–29] Richardson,[30] and Barrier and colleagues[31]; in DR3 by Lowenstein and colleagues[32]; in DRB1 by Martinez-Taboda,[33] Weyand,[34,35] and Gonzalez-Gay and colleagues,[36] in Cw3 by Hansen and colleagues[37]; and in major histocompatibility complex (MHC) class I MICA and HLA-B gene polymorphisms by Gonzalez-Gay and coworkers.[38]

Takayasu Disease

Background

In contrast to GCA, Takayasu arteritis (TAK) occurs in individuals younger than age 40 years and presents with large vessel-sized vasculitis of the aorta and its branches. For the purpose of epidemiologic studies, the case definition has generally followed the ACR 1990 criteria for the classification of TAK.[39] The evolution and characterization of pediatric-specific vasculitis classification criteria and the associated clinical syndromes have been reviewed.[40,41] An understanding of the inflammatory lesions in TAK, like that of GCA, has been advanced by immunologic studies, revealing a clearer understanding of the pathophysiology, which may be affected by the genetic background of different global regions. The inflammatory cell infiltrate in aortic tissue specimens of affected patients is composed of neutrophils, macrophages, $CD4^+$ and $CD8^+$ T-cells, natural killer (NK) cells, and macrophages. Infiltrating $\alpha\delta$T cells and NK cells seems to facilitate endothelial cell apoptosis through production of perforin and killer cell lectin-like receptor subfamily K (NKG2D). The latter activating C-type lectin family receptor triggers NK cells and costimulates $CD8^+$ α/β T-cell receptor$^+$ T-cells, while $CD4^+$ T helper 1 (Th1) cells that secrete interferon-γ promote giant cell and granulomatous lesion formation.[42–45] Peripheral T-cells, notably Th1 and Th17, contribute to the pathophysiology of GCA and TAK[46,47] as do MHC I and II molecules and endothelial intracellular adhesion molecules, expressed in tissue lesions of the aorta with TAK.[42,48]

Epidemiology

Two GWAS conducted in TAK, respectively identifying 379 UK cases and 1985 controls[49] and 451 USA/Turkish cases and 1115 controls,[50] noted strong associations with *IL12B* located at the 5q33.3 chromosome locus (rs6871626), and susceptibility to the Max-like protein X (*MAX*) gene transcription factor-like 4 positioned at the

17q21.2 chromosome locus (rs665268),[49] whereas those in the UK alone[49] exhibited independent associations at the 6p21.32 chromosome locus in *HLA-DQB1/HLA-DRB1* (rs113452171; rs189754752). *HLA-DQB1* specifies the autoimmune response against insulin-producing islet cells that leads to insulin-dependent diabetes mellitus, while the function of *HLA-DRB1* is to present processed foreign antigens to T cells. The USA/Turkish group reported another susceptibility locus at the Fc fragment of immunoglobulin G (IgG) low-affinity IIa and IIIa receptors (*FCGR2A/3A*) at the 1q23.3 chromosome locus (rs10919543), leading to increased mRNA expression of *FCGR2A* and proteasome-assembling chaperone 1 (*PSMG1*). With receptors present on monocytes, macrophages, neutrophils, NK cells, and T and B lymphocytes, *FCGR2A/3A* play an essential role in the protection of the organism against foreign antigens by removing antigen-antibody complexes from the circulation, and participate in diverse functions such as phagocytosis of immune complexes and modulation of antibody production by B cells. Located at the 21q22.2 chromosome locus, *PSMG1* is involved in the maturation of the mammalian 20S proteasomes with a yet clear implication for TAK.

The global incidence and prevalence of TAK is summarized in **Table 2**. Watts and colleagues[51] using the primary care UK General Practice Research Database and the secondary care-based Norfolk Vasculitis Register from 2000 to 2005, applied the ACR 1990 criteria for incident cases[39], covering a population of 445,000. The authors identified 16 cases with a first diagnosis of TAK and an annual incidence of 0.8 per million, and calculated as the number of incident cases divided by the total person-years, which remained stable throughout the study period. The annual prevalence of TAK was 4.7 per million, with an increase during the course of the study period from 3.6 to 6.3 per million. Mohammad and Mandl[52] studied 3 health care districts of southern Sweden with a total population of 983,419 as of 2011 to identify incident cases of TAK among 5 hospitals in the study area and in all private rheumatology clinics between 1997 and 2011, noting 13 cases that fulfilled the ACR 1990 criteria for TAK.[39] Among them, 8 were of Swedish ancestry, 1 of Asian, 2 of Arab, 1 of African, and 1 of northern European descent. The annual incidence rate was estimated at 0.8 per million for the whole population. The point prevalence of TAK as of June 2012 was estimated at 13.2 per million for the whole population. The incidence findings were comparable with the reported incidence of 0.8, 0.5, and 0.4 per million, respectively, in previous studies from Sweden,[53] Germany,[54] and eastern Denmark,[55] although the prevalence of TAK was somewhat higher than the prevalence of 6.4 per million previously reported in Sweden.[53]

MEDIUM-SIZE VESSEL VASCULITIS

Polyarteritis Nodosa

The ACR 1990[56] and the Chapel Hill Consensus Conference (CHCC)[57] criteria for polyarteritis nodosa (PAN) have been used for the case definitions of most epidemiologic

Table 2
Global incidence and prevalence of TAK

Authors,[Ref.] Year	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Watts et al,[51] 2009	UK	2000–2005	0.8	4.7
Mohammad and Mandl,[52] 2013	Sweden	1997–2011	0.8	—
Waern et al,[53] 1983	Sweden	1969–1976	0.8	6.4
Reinhold-Keller et al,[54] 2005	Germany	1998–2000	0.5	—
Dreyer et al,[55] 2011	Demark	1990–2009	0.4	—

studies, as well as the criteria of other investigators[58,59] for adult cases, and the criteria of the Turkish Pediatric Vasculitis Study Group[60,61] for pediatric cases, stratified into cutaneous and classic PAN. This author was unable to find any GWAS for PAN.

The global incidence and prevalence of PAN is shown in **Table 3**. Mahr and colleagues[59] defined PAN as a predominantly medium-size-vessel disease that occurs alone or in association with hepatitis B virus (HBV) infection. These investigators angiographically documented aneurysms or histologic proof of vessel inflammation, without glomerulonephritis, lung hemorrhage, or Antineutrophil cytoplasmic antibody (ANCA) positivity, in a capture-recapture study in the calendar year 2000 in Seine-St Denis, a northeastern suburb of Paris with a population of 1,093,515 adults, 28% of whom were of non-European ancestry, from among general practitioners, departments of all of the public hospitals, 2 large private clinics, and the National Health Insurance System. The prevalence of PAN was estimated at 30.7 per million adults. However, previous studies based on the most restrictive and biopsy-dependent CHCC[57] criteria estimated PAN to be 9 per million adults, in comparison with 33 per million based on the less specific ACR criteria[56] that fail to discriminate between microscopic polyangiitis (MPA) and PAN. The total prevalence estimate for all disorders was 90.3 per million which, substratified for geographic origin, showed a 2-fold higher incidence rate for subjects of European than non-European ancestry, respectively, 104.7 compared with 52.5 per million. Not more than 30% of the PAN cases seemed to be HBV related, with most diagnosed during the 1980s, suggesting that the reported incidence of HBV-associated PAN of 77 per million noted in a small population of Alaskan Eskimos with high rates of HBV infection[62] was currently decreasing as a consequence of vaccination campaigns and the improved safety of blood products. Mohammad and colleagues[63] studied incident cases of PAN, GPA, MPA, and eosinophilic granulomatosis with polyangiitis (EGPA) in 2 health care districts of South Sweden (central and southwest Skâne) containing 14 municipalities with a population of 641,763 for the period 1997 to 2006 from hospital databases, identifying 144 cases of primary systemic vasculitis, of which 6 were PAN. The annual incidence rate was 21.8 per million for all patients and 0.9 per million for PAN. Watts and colleagues[64] studied incident cases of PAN, GPA, MPA, and EGPA in 2 regions of Europe, among general medical practices of the Norwich Health Authority (NHA) in Norfolk, UK covering 413,500 patients, and in the referral center of Lugo, Spain at the Hospital Xeral-Calde with a population of 250,000 people between 1988 and 1998. The study used the 2012 revised CHCC[57] and ACR criteria,[56] noting an overall incidence

Table 3
Global incidence and prevalence of PAN

Authors,[Ref.] Year	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Jennette et al,[57] 2013	USA	2012	—	30.7
Lightfoot et al,[56] 1990	USA	1990	—	9.0
Mohammad et al,[63] 2009	Sweden	1997–2006	0.9	—
Watts et al,[64] 2001	UK[a]	1988–1998	9.7	—
	Spain[b]	1988–1998	6.2	—
Omerod and Cook,[65] 2008	UK[a] + Spain[b]	1995–1999	2.3	—
	UK[a] + Spain[b]	2000–2004	1.1	—

[a] Norwich.
[b] Lugo.

of primary systemic vasculitis of 18.9 in Norwich compared with 18.3 per million in Spain, with a higher incidence of PAN in Norwich than in Spain, 9.7 versus 6.2 per million, respectively. Omerod and Cook[65] studied the prevalence and incidence of primary systemic vasculitides for the two 5-year periods of 1995 to 1999 and 2000 to 2004 in the Australian Capital Territory and the surrounding rural regions. Altogether, 41 cases of primary systemic vasculitides including PAN, GPA, MPA, and EGPA were identified between 1995 and 1999, and 67 between 2000 and 2004. This yielded a prevalence of 95 and 148 per million, with a similar annual incidence of 17 per million for Norwich, UK and Lugo, Spain; and a disease-specific incidence for PAN of 2.2 and 1.1 for the 2 successive periods.

Kawasaki Disease

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, is an acute, self-limited systemic vasculitis of medium- and small-size vessels occurring predominantly in children aged 6 months to 5 years.[66] It is the second commonest childhood vasculitis and the leading cause of acquired childhood heart disease in developed countries.[67,68] The distribution is worldwide, with an incidence in Japanese populations 10-fold to 15-fold greater than in Caucasians.[69] Before revision of the criteria for KD, the classification was based on either Japanese[70] or the American Heart Association (AHA) classification.[71] The former criteria, applied in Japanese epidemiologic studies of KD, required the presence of 5 of the following 6 criteria: characteristic fever, bilateral conjunctivitis, changes in lips and oral cavity, polymorphous exanthema, changes of peripheral extremities, and cervical lymphadenopathy, whereas those of the latter, used in American and Caucasian studies, generally required fever plus 4 of the remaining 5 criteria. Two recent modifications to the criteria for KD made by the European League Against Rheumatism/Pediatric Rheumatology European Society consensus criteria conference,[61] which may alter the carriage of epidemiologic studies in the future, included the addition of perineal desquamation describing changes in the extremities; moreover, fewer than 4 of the remaining 5 criteria were deemed necessary in the presence of fever and coronary arterial involvement demonstrated by echocardiography. To emphasize pediatric vasculitis disease even before retrospective and prospective epidemiologic studies, a half-century of 1,335,045 postmortem examinations from the Annual of Pathologic Autopsy Cases in Japan from 1958 to 2008 identified 380 cases of vasculitis in children, more than one-half of which were KD and other disease entities including unclassified vasculitis, PAN, purpuric vasculitis, TAK, and others. Moreover, the postmortem findings for 24 of 125 childhood vasculitides performed before 1976 and diagnosed as non-KD were later consistent with KD.

The global incidence and prevalence of KD is shown in **Table 4**. Saundankar and colleagues[72] identified hospitalized patients in Western Australia with the diagnosis of KD, noting a steady increase in the mean annual incidence from 7.96 between 1990 and 1999 to 9.34 per 100,000 children younger than 5 years between 2000 and 2009, with the peak incidence of 15.7 per 100,000 in 2005. Lin and colleagues[73] identified hospitalized discharges with the diagnosis of KD in Ontario, noting a mean annual incidence of 26.2 per 100,000 for children younger than 5 years, 6.7 per 100,000 for 5- to 9-year old children, and 0.9 per 100,000 for those 10 to 14 years old, which steadily increased from 14.39 to 26.24 per 100,000 from 1995 to 2006. Ma and colleagues[74] studied all children sent to 1 of 50 hospitals in Shanghai, noting a mean annual incidence of 46.32 per 100,000 children younger than 5 years that steadily increased from 36.78 to 53.28 between 2003 and 2007. Li and coworkers[75] identified cases of KD in children younger than 5 years in 212 hospitals in Sichuan

Table 4
Global incidence and prevalence of KD

Authors,[Ref.] Year	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Saundankar et al,[72] 2014	Australia	1990–1999	7.96	—
	Australia	2000–2009	9.34	—
	Australia	2005	15.7	—
Lin et al,[73] 2010	Canada[a]	1995–2006	26.2[b]	—
	Canada[a]	1995–2006	6.8[c]	—
	Canada[a]	1995	14.39[d]	—
	Canada[a]	2006	26.24[d]	—
Ma et al,[74] 2010	China[e]	2003–2007	46.32[b]	—
	China[e]	2003	36.78[b]	—
	China[e]	2007	53.28[b]	—
Li et al,[75] 2008	China[f]	1997–2001	7.06[b]	—
	China[f]	1997	8.57[b]	—
	China[f]	2001	9.81[b]	—
Du et al,[76] 2007	China[g]	2000–2004	49.4[b]	—
	China[g]	2000	40.9[b]	—
	China[g]	2004	55.1[b]	—
Fischer et al,[77] 2007	Denmark	1981–2004	4.5–5.0	—
Holman et al,[78] 2010	Hawaii, USA	1996–2006	50.4	—
Ng et al,[79] 2011	Hong Kong	1994–1997	26.0	—
	Hong Kong	1994–1997	39.0	—
Singh et al,[80] 2011	North India	1994	0.51	—
	North India	2007	4.5	—
Nakamura et al,[81] 2012	Japan	2009	206.2	—
	Japan	2010	239.6	—
Park et al,[82] 2011	Korea	2006–2008	113.1	—
	Korea	2006	108.7	—
	Korea	2008	113.1	—
Schiller et al,[83] 1995	Sweden	1990–1992	2.9	—
	Sweden	1990–1992	6.2[b]	—
Lue et al,[84] 2013	Taiwan	2006	66.24[b]	—
Huang et al,[85] 2009	Taiwan	2003–2006	153.0	—
	Taiwan	2003–2006	69.0[b]	—
Harnden et al,[86] 2002	UK	1991	4.8	—
	UK	2000	9.2	—
Holman et al,[87] 2010	USA	2006	20.8	—

[a] Ontario.
[b] Age less than 5 years.
[c] Age 5 to 9 years.
[d] Age 10 to 14 years.
[e] Shanghai.
[f] Sichuan Provence.
[g] Beijing.

Province, noting a steady increase in the incidence from 8.57 to 9.81 per 100,000, with an average incidence throughout the latest 5 years of 7.06 per 100,000. Du and coworkers[76] conducted a hospital-based survey of KD in 45 Beijing hospitals, identifying 1107 KD patients with a mean annual incidence of 49.4 per 100,000 in children younger than 5 years, and a steady increase from 2000 to 2004 that ranged from

40.9 to 55.1 per 100,000. Fischer and colleagues[77] performed a population-based hospital study of KD children in Denmark from 1981 to 2004, identifying 360 cases of KD in children younger than 15 years and noting a mean annual incidence of 4.5 to 5 per 100,000 person-years, with a gradual increase over the study period. Holman and colleagues[78] conducted a retrospective analysis of children aged less than 18 years and focusing on those younger than 5 years hospitalized in Hawaiian hospitals from 1996 to 2006, noting a mean annual incidence of 50.4 per 100,000 children younger than 5 years, ranging from 45.5 to 56.5. Japanese children who had the highest mean annual incidence of 210.5 per 100,000 exceeded the mean Asian and Pacific pediatric annual incidence of 62.9 per 100,000 children, followed by native Hawaiian children with an incidence of 86.9, other Asian children with an incidence of 84.9, and Chinese children with an incidence of 83.2 per 100,000, exceeding that of whites with an KD incidence of 13.7 per 100,000 children. Ng and colleagues[79] conducted retrospective and prospective studies of KD in Hong Kong from 1994 to 1997 and then from 1997 to 2000, identifying 696 children younger than 15 years and noting a higher incidence of KD in the prospective period (39 versus 26 per 100,000 children). Singh and colleagues[80] analyzed the records of children younger than 15 years with KD in Chandigarh, North India, identifying 196 cases. There was an increasing incidence of disease from 0.51 to 4.5 cases during the period from 1994 to 2007. Nakamura and coworkers[81] conducted the 21st nationwide survey of 23,730 KD children treated between 2009 and 2010, noting an annual incidence rate of 206.2 and 239.6 per 100,000, establishing the highest rate ever for Japan in 2010. Park and coworkers[82] surveyed Korean hospitals for the period of 2006 to 2008, identifying 9039 KD children and noting an outbreak rate of 108.7 100,000 in 2006 that increased to 113.1 per 100,000 in 2008, with a mean annual incidence of 113.1 per 100,000 children. Schiller and colleagues[83] examined a national prospective study of KD children over a 2-year period from 1990 to 1992, recording an annual incidence rate of 2.9 per 100,000 children younger than 16 years, and a rate of 6.2 per 100,000 children younger than 5 years. Lue and colleagues[84] conducted nationwide hospital surveys of KD in Taiwan in 2006, noting an incidence of 66.24 per 100,000 children younger than 5 years, representing the highest of any preceding survey. Huang and colleagues[85] investigated the epidemiology of KD by using national insurance claims made between 2003 and 2006, noting an annual incidence of KD of 153 per 100,000 in children younger than 1 year with an overall incidence of 69 per 100,000 children younger than 5 years. Harnden and colleagues[86] analyzed hospital admission data for childhood KD in England for the period 1991 to 2000, identifying 2215 emergency admissions representing an incidence that increased from 4.8 to 9.2 per 100,000 in this time period. Holman and coworkers[87] performed a retrospective analysis of emergency childhood admission for KD in the USA using the Kids' Inpatient Database and a Nationwide Inpatient Sample for 2006, noting an incidence of 20.8 per 100,000 children.

Eight GWAS and linkage analysis studies of KD[88–92] have led to susceptibility genetic loci for KD. Onouchi and colleagues[88] performed a nonparametric GWAS of sib pairs on 75 full sib pairs, 3 sib trios, and 1 half-sib, applying Japanese criteria,[70] and identified a candidate gene locus at 12q24 (maximum logarithm-of-odds [LOD] score = 2.69), with possible linkage to 4q35, 5q35, 5q34, 6q27, 7p15, 8q24, 18q23, 19q13, Xp22, and Xq27. Moreover, 90 genes were believed to be expressed in organs related to immune function among the 128 genes that mapped within 1 LOD confidence interval of the linkage position on chromosome 12. Burgner and coworkers,[89] on behalf of the International Kawasaki Disease Genetics Consortium, investigated genetic determinants of KD susceptibility in a GWAS of 119 Caucasian KD patients and 135 matched controls using the AHA criteria.[71] The investigators[89] noted

associations with 40 single-nucleotide polymorphisms (SNPs) and 6 haplotypes, most significantly at *NAALADL2* (rs17531088) and *ZRHX3* (rs7199343). The latter, also known as ATBF1, which encodes a large enhancer-binding transcription factor known to be polymorphic and interactive with several proteins including protein inhibitor of activated signal transducer and activator of transcription 3 (STAT3), is activated by interleukin (IL)-6 that is involved in innate immune reactivity. The function of the N-acetylated α-linked acidic dipeptidase-like 2 (NAALADl2) gene, which showed the greatest change in transcript levels between acute and convalescent KD, contributes to Cornelia de Lange syndrome, a multisystem malformation syndrome. Tsai and coworkers[90] conducted a GWAS in a Han Chinese population in 250 KD patients and 446 controls residing in Taiwan, using the AHA criteria.[71] The most strongly associated SNPs were detected in 3 novel loci close to the coatomer protein complex β-2 subunit (*COPB2*) gene (rs1873668, rs4243399, rs16849083), as well as in the intronic region of the endoplasmic reticulum aminopeptidase 1 (*ERAP1*) gene (rs14981). COPB2 coats non–clathrin-coated vesicles and is essential for Golgi budding and vesicular trafficking, whereas ERAP1 plays a role in trimming peptides to the optimal length for HLA)class I presentation, cleaving cell surface receptors for proinflammatory cytokines. Kim and coworkers, on behalf of the Korean Kawasaki Disease Genetics Consortium,[91] conducted a GWAS among 186 Korean KD patients and 600 controls, applying the disease definition according to the AHA,[71] and noted susceptibility loci for KD at the 1p31 region and 2p13.3 chromosomal loci. A putative KD susceptibility locus (rs5277409) mapped to chromosome 1p31, and the coronary artery lesion (CAL) locus (rs7604693) mapped to the Pellino 1 protein (*PELI1*) (rs7604693) gene in the 2p13.3 region encoding PEL1, an intermediate component in the signaling cascade initiated by toll-like receptors and the IL-1 receptor (*IL1R*) gene, which are associated with innate and adaptive immune responses. Khor and colleagues[92] performed a GWAS in 2173 KD patients of European and Asian descent, noting 2 significant loci in the Fc fragment of IgG, low-affinity 2A receptor (*FCGR2A*) (rs1801274), and for the rs2233152 SNP near the melanoma inhibitory activity (*MIA*), inositol 1,4,5-trisphosphate 3-kinase C (*ITPKC*) gene. Whereas the FCGR2A, present on monocytes, macrophages, neutrophils, NK cells, T-cells, and B-cells, participates in the phagocytosis of immune complexes and modulation of antibody production by B cells, ITPKC acts as a negative regulator of T-cell activation through the Ca^{2+}/NFAT signaling pathway; contributing to immune hyperactivity. Lee and coworkers[93] performed a GWAS in 622 KD patients and 1107 controls in a Han Chinese population residing in Taiwan, using the AHA criteria,[71] and noted 2 loci significantly associated with KD, including one at the B-lymphoid tyrosine kinase (*BLK*) gene and the other at *CD40*. Whereas the *BLK* gene seems to play an important role in the expression of B cell signaling, activation, and antibody secretion, *CD40* is instead a member of the tumor necrosis factor receptor superfamily, and its interaction with the CD40 ligand (CD40L) leads to cross-talk, integrating strong antigenic signals and microbial stimuli to induce IL-17-producing $CD4^+$ T-cells that contribute to inflammation and the development of autoimmune disease. Onouchi and coworkers[94,95] performed a GWAS in 428 Japanese KD patients and 3379 controls, noting significant associations in the *FAM167A-BLK* region at 8p22 to 23 (rs2254546) in the *HLA* region at 6p21.3 (rs2857151), and in the *CD40* region at 20q13 (rs48130030), also replicating the association of a functional SNP of *FCGR2A* (rs1801274). Although ubiquitously expressed, the function of *FAM167A* has not been well characterized. Yan and coworkers[95] analyzed variants of 6 SNPs in 358 Japanese KD patients and 815 controls, identifying 3, rs1801274, rs2857151, and rs22554546 respectively corresponding to *FCGR2A*, *HLA*, and *BLK* genes, noting a significant effect and stronger association on KD than single-locus, 2-loci, and 3-loci

combinations; moreover, a significant association with CALs was noted in KD, with high-risk genotypes at both rs1801274 and rs2857151.

SMALL-SIZE VESSEL VASCULITIS

Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

The classification of the ANCA-associated vasculitides (AAV) has been controversial[96] with existing systems developed by the ACR,[97,98] the CHCC,[57] and the European Medicines Agency algorithm[99] to provide a standardized method for their application in epidemiologic studies, each with separate deficiencies, especially when applied to unselected patients. These systems were developed as classification criteria and not as diagnostic criteria. As there were no validated diagnostic criteria for AAV, the Diagnostic and Classification Criteria for Vasculitis Study, developed by Watts and colleagues,[99] led to the consensus development and validation of diagnostic criteria by an algorithm to avoid inclusion of patients with other conditions. So defined, the investigators noted an annual incidence of 11.3 for GPA and 5.9 per million for MPA, with respective prevalence at the end of calendar year 2008 of 145.9 per million for GPA and 63.1 per million for MPA. Lyons and colleagues[100] conducted a GWAS in a cohort of 1233 UK subjects with AAV and 5884 controls, noting both MHC and non-MHC associations with AAV, with the strongest genetic association with the antigenic specificity of ANCA and not with the clinical syndrome. Those with anti-proteinase 3 (PR3) ANCA were associated with *HLA-DP* (rs3117242) at the 6p21.32 chromosome locus, as well as those encoding α1-antitrypsin (*SERPINA1* to *SERPINA11*) (rs7151526) at the 14q32 chromosome locus and proteinase 3 (*PRTN3*) (rs62132295) at the 19p13.3 chromosome locus, while anti-myeloperoxidase ANCA (MPO) was associated with *HLA-DQ* (rs5000634) at the 6p21.32 chromosome locus. These studies confirmed that the pathogenesis of AAV had a genetic component and that the genetic distinction between GPA and MPA was associated with ANCA specificity. Moreover, the response against the PR3 autoantigen was a central pathogenic feature of PR3-AAV, distinct from MPO-AAV.

The global incidence and prevalence of AAV is summarized in **Table 5**. Watts,[64,101] Ormerod,[65] Mohammad,[63] and Mahr and colleagues[59] evaluated the epidemiologic aspects of AAV globally in adults. In 2 regions of Europe, Norwich (UK) and Lugo (Spain), the incidence rate of GPA in Norwich was 10.6 per million compared with 4.9 per million in Lugo for 2008, with virtually equal age distribution of 34.1 per million between age 45 and 74 years, suggesting that environmental factors might be important in the their etiopathogenesis.[64] In a 10-year study of primary systemic vasculitis in the UK[101] in the NHA from 1988 to 1997, the annual incidence of GPA was 9.7, EGPA 2.7, and MPA 8.0 per million during the entire study period; however, a comparison of the periods 1988 to 1992 and 1993 to 1997 showed respective annual incidences toward an increase in all conditions (8.7 per million for GPA, 1.5 for EGPA, and 6.8 for MPA, compared with 10.3 for GPA, 3.7 for EGPA, and 8.9 for MPA). In a comparison of primary systemic vasculitis in the Australian Capital Territory and southeastern New South Wales between 1995 and 1999, and between 2000 and 2004, Ormerod and Cook[65] noted similar disease-specific incidences for each of the 2 periods, with 8.8 and 8.4 per million for GPA, 2.3 and 5.0 per million for MPA, and 2.3 and 2.2 per million for EGPA in the Australian Capital Territory in comparison with southeastern New South Wales, with a trend for higher values in MPA and GPA in rural areas. A similar relation was found in disease-specific prevalence for each of the 2 periods, with 64.3 and 95.0 per million for GPA, 17.5 and 39.1 per million for MPA, and 11.7 and 22.3 per million for EGPA in the Australian Capital Territory compared to southeastern

Table 5
Global incidence and prevalence of AAV

Authors,[Ref.] Year	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Watts et al,[101] 2000	UK	1988–1992	8.7[a]	—
	UK	1988–1992	6.8[b]	—
	UK	1988–1992	1.5[c]	—
	UK	1993–1997	10.3[a]	—
	UK	1993–1997	8.9[b]	—
	UK	1993–1997	3.7[c]	—
Ormerod and Cook,[65] 2008	Australia + UK	1995–1999	8.8[a]	64.3[a]
		2000–2004	8.4[a]	95.0[a]
		1995–1999	2.3[b]	17.5[b]
		2000–2004	5.0[b]	39.1[b]
		1995–1999	2.3[c]	11.7[c]
		2000–2004	2.2[c]	22.3[c]
Mahr et al,[59] 2004	France[d]	2000	—	23.7[a]
	France[d]	2000	—	25.1[b]
	France[d]	2000	—	10.7[c]
Mohammad et al,[63] 2009	Sweden	1997–2006	9.8[a]	—
	Sweden	1997–2006	10.1[b]	—
	Sweden	1997–2006	0.9[c]	—

[a] GPA.
[b] MPA.
[c] EGPA.
[d] Seine-St Denis County, Paris.

New South Wales. In incident cases of primary systemic vasculitis identified in the Seine-St Denis County of, Mahr and colleagues[59] estimated the prevalence of GPA as 23.7, MPA 25.1, and EGPA 10.7 per million adults in a population of 1,093,515, 28% of whom were of non-European ancestry, with an overall prevalence that was 2-fold higher for those of European (104.7 5 per million) compared with non-European ancestry (52.5 per million). Mohammad and colleagues[63] estimated incident cases of GPA, MPA, and EGPA in southern Sweden as 9.8, 10.1, and 0.9 per million, respectively, in a total population of 641,000 between 1997 and 2006, with a progressive increase in age-specific incidence rates over the study period.

REFERENCES

1. Scott DG, Watts RA. Epidemiology and clinical features of systemic vasculitis. Clin Exp Nephrol 2013;17:607–10.
2. Kermani TA, Warrington KJ, Crowson CS, et al. Large-vessel involvement in giant cell arteritis: a population based cohort study of the incidence-trends and prognosis. Ann Rheum Dis 2012;72:1989–94.
3. Salvarani C, Cantini F, Boiardi L, et al. Polymyalgia rheumatic and giant cell arteritis. N Engl J Med 2002;347:261–71.
4. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
5. Nuenninghoff DM, Hunder GG, Christianson TJH, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or

large artery stenosis) in patients with giant cell arteritis. Arthritis Rheum 2003;48:3522–31.
6. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454–61.
7. Dunstan E, Lester SL, Rischmueller M, et al. Epidemiology of biopsy-proven giant cell arteritis in South Australia. Intern Med J 2014;44:32–9.
8. Ninan J, Nguyen AM, Cole A, et al. Mortality in patients with biopsy-proven giant cell arteritis: a south Australian population-based study. J Rheumatol 2011;38:2215–7.
9. Herlyn K, Buckert F, Gross WL, et al. Doubled prevalence rates of ANCA-associated vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. Rheumatology (Oxford) 2014;53(5):882–9.
10. Bas-Lando M, Breuer GS, Berkun Y, et al. The incidence of giant cell arteritis in Jerusalem over a 25-year period: annual and seasonal fluctuations. Clin Exp Rheumatol 2007;25(Suppl 44):S15–7.
11. Kobayashi S, Yano T, Matsumoto Y, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. Arthritis Rheum 2003;49:594–8.
12. Abdul-Rahman AM, Molteno ACB, Bevin TH. The epidemiology of giant cell arteritis in Otago, New Zealand: a 9-year analysis. N Z Med J 2011;124:44–52.
13. Haugeberg G, Irgens KA, Thomsen RS. No major differences in incidence of temporal arteritis in northern and western Norway compared with reports from southern Norway. Scand J Rheumatol 2003;32:318–9.
14. Haugeberg G, Paulsen PQ, Bie RB. Temporal arteritis in Vest Agder County in southern Norway: incidence and clinical findings. J Rheumatol 2000;27:2624–7.
15. Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, et al. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. Medicine 2005;84:269–76.
16. Gonzalez-Gay MA, Miranda-Filloy JA, Lopez-Diaz MJ, et al. Giant cell arteritis in northwestern Spain. A 25-year epidemiological study. Medicine 2007;86:61–8.
17. Mohammad AJ, Nilsson JA, Jacobsson LT, et al. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. Ann Rheum Dis 2014;74(6):993–7.
18. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. Ann Rheum Dis 2006;65:1093–8.
19. Salvarani C, Crowson CS, O'Fallon M, et al. Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. Arthritis Rheum 2004;51:264–8.
20. De Souza AW, Okamoto KYK, Abrantes F, et al. Giant cell arteritis: a multicenter observational study in Brazil. Clinics (Sao Paulo) 2013;68:317–22.
21. Chaudhry IA, Shamsi FA, Elzaridi E, et al. Epidemiology of giant-cell arteritis in an Arab population: a 22-year study. Br J Ophthalmol 2007;91:715–8.
22. Alba MA, Mena-Madrazo JA, Reyes E, et al. Giant cell arteritis in Mexican patients. J Clin Rheumatol 2012;18:1–7.
23. Lane SE, Watts R, Scott DGI. Epidemiology of systemic vasculitis. Curr Rheumatol Rep 2005;7:270–5.
24. Kemp A, Marner K, Nissen SH, et al. HLA antigens in cases of giant cell arteritis. Acta Ophthalmol (Copenh) 1980;58:1000–4.

25. Armstrong RD, Behn A, Myles A, et al. Histocompatibility antigens in polymyalgia rheumatica and giant cell arteritis. J Rheumatol 1983;10:659–61.
26. Dababneh A, Gonzalez-Gay MA, Garcia-Porrua C, et al. Giant cell arteritis and polymyalgia rheumatica can be differentiated by distinct patterns of HLA class II association. J Rheumatol 1998;25:2140–5.
27. Jacobsen S, Baslund B, Madsen HO, et al. Mannose-binding lectin variant alleles and HLA-DR4 alleles are associated with giant cell arteritis. J Rheumatol 2002;29:2148–53.
28. Bignon JD, Ferec C, Barrier J, et al. HLA class II genes polymorphism in DR4 giant cell arteritis patients. Tissue Antigens 1988;32:254–8.
29. Bignon JD, Barrier J, Soulillou JP, et al. HLA DR4 and giant cell arteritis. Tissue Antigens 1984;24:60–2.
30. Richardson JE, Gladman DD, Fam A, et al. HLA-DR4 in giant cell arteritis: association with polymyalgia rheumatica syndrome. Arthritis Rheum 1987;30:1293–7.
31. Barrier J, Bignon JD, Soulillou JP, et al. Increased prevalence of HLA-DR4 in giant-cell arteritis. N Engl J Med 1981;305:104–5.
32. Lowenstein MB, Bridgeford PH, Vasey FB, et al. Increased frequency of HLA-DR3 and DR4 in polymyalgia rheumatica-giant cell arteritis. Arthritis Rheum 1983;26:925–7.
33. Martinez-Taboda VM, Bartolome MJ, Lopez-Hoyos M, et al. HLA-DRB1 allele distribution in polymyalgia rheumatica and giant cell arteritis: influence on clinical subgroups and prognosis. Semin Arthritis Rheum 2004;34:454–64.
34. Weyand CM, Hicok KC, Hunder GG, et al. The HLA-DRB1 locus as a genetic component in giant cell arteritis. Mapping of a disease-linked sequence motif to the antigen binding site of the HLA-DR molecule. J Clin Invest 1992;90:2355–61.
35. Weyand CM, Hunder NN, Hicok KC, et al. HLA-DRB1 alleles in polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. Arthritis Rheum 1994;37:514–20.
36. Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore) 2000;79:283–92.
37. Hansen JA, Healey LA, Wilske KR. Association between giant cell (temporal) arteritis and HLA-Cw3. Hum Immunol 1985;13:193–8.
38. Gonzalez-Gay MA, Rueda B, Vilchez JR, et al. Contribution of MHC class I region to genetic susceptibility for giant cell arteritis. Rheumatology (Oxford) 2007;46:431–4.
39. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129–34.
40. Ringold S, Wallace CA. Evolution of paediatric-specific vasculitis classification criteria. Ann Rheum Dis 2010;69:785–6.
41. Ruperto N, Ozen S, Pistorio A, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part 1: Overall methodology and clinical characterization. Ann Rheum Dis 2010;69:790–7.
42. Seko Y, Minota S, Kawasaki A, et al. Perforin-secreting killer cell infiltration and expression of a 65-kD heat-shock protein in aortic tissue of patients with Takayasu's arteritis. J Clin Invest 1994;93:750–8.

43. Wagner AD, Bjornsson J, Bartley GB, et al. Interferon-gamma-producing T cells in giant cell vasculitis represents a minority of tissue-infiltrating cells and are located distant from the site of pathology. Am J Pathol 1996;148:1923–33.
44. Sneller MC. Granuloma formation, implications for the pathogenesis of vasculitis. Cleve Clin J Med 2002;69(Suppl 2):SII40–3.
45. Weyand CM, Goronzy H. Medium- and large-vessel vasculitis. N Engl J Med 2002;349:160–9.
46. Deng J, Younge B, Olshen RA, et al. TH17 and Th1 T-cell responses in giant cell arteritis. Circulation 2010;121:906–15.
47. Terrier B, Geri G, Chaara W, et al. Interleukin-21 modulates Th1 and Th1 responses in giant cell arteritis. Arthritis Rheum 2012;64:2001–11.
48. Noguchi S, Numano F, Gravanis MB, et al. Increased levels of soluble forms of adhesion molecules in Takayasu arteritis. Int J Cardiol 1998;66(Suppl 1):S23–35.
49. Terao C, Yoshifuji H, Kimura A, et al. Two susceptibility loci to Takayasu arteritis reveal a synergistic role of the IL12B and HLA-B regions in a Japanese population. Am J Hum Genet 2013;93:289–97.
50. Saruhan-Direskeneli G, Hughes T, Aksu K, et al. Identification of multiple genetic susceptibility loci in Takayasu arteritis. Am J Hum Genet 2013;93:298–305.
51. Watts R, Al-Taiar A, Mooney J, et al. The epidemiology of Takayasu arteritis in the UK. Rheumatology 2009;48:1008–11.
52. Mohammad A, Mandl T. Takayasu's arteritis in southern Sweden. Presse Med 2013;42:719.
53. Waern AU, Andersson P, Hemmingsson A. Takayasu's arteritis: a hospital-region based study on occurrence, treatment and prognosis. Angiology 1983;34:311–20.
54. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, et al. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. Arthritis Rheum 2005;53:93–9.
55. Dreyer L, Faurschou M, Baslund B. A population-based study of Takayasu's arteritis in eastern Denmark. Clin Exp Rheumatol 2011;29(Suppl 64):S40–2.
56. Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 1990;33:1088–93.
57. Jennette JC, Falk RJ, Bacon PA, et al. International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.
58. Guillevin L, Lhote F. Polyarteritis nodosa and microscopic polyangiitis. Clin Exp Immunol 1995;101(Suppl 1):22–3.
59. Mahr A, Guillevin L, Poissonnet M, et al. 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;51:92–9.
60. Ozen S, Bakkaloglu A, Dusunsel R, et al. Childhood vasculitides in Turkey: a nationwide survey. Clin Rheumatol 2007;26:196–200.
61. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria* for the classification of childhood vasculitides. Ann Rheum Dis 2006;65:936–41.
62. McMahon BJ, Heyward WL, Templin DW, et al. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow-up. Hepatology 1989;9:97–101.
63. Mohammad AJ, Jacobsson LTH, Westman KWA, et al. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology 2009;48:1560–5.

64. Watts RA, Gonzalez-Gay MA, Lane SE, et al. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. Ann Rheum Dis 2001;60:170–2.
65. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Intern Med J 2008;38:816–23.
66. Shulman ST, Rowley AH. Advances in Kawasaki disease. Eur J Pediatr 2004;63:285–91.
67. Dillon MJ, Eleftheriou D, Brogan PA. Medium-size-vessel vasculitis. Pediatr Nephrol 2010;25:1641–52.
68. De Rosa G, Pardeo M, Rigante D. Current recommendations for the pharmacologic therapy in Kawasaki syndrome and management of its cardiovascular complications. Eur Rev Med Pharmacol Sci 2007;11:301–8.
69. Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004;364:533–44.
70. Japan Kawasaki Disease Research Committee. Diagnostic guidelines for Kawasaki disease. 5th edition 2002. Tokyo. Available at: http://www.kawasaki-disease.org/diagnostic/index.html. Accessed November 1, 2018.
71. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. Pediatrics 2004;114:1708–33.
72. Saundankar J, Yim D, Itotoh B, et al. The epidemiology and clinical features of Kawasaki disease in Australia. Pediatrics 2014;133:e1009–14.
73. Lin YT, Manlhiot C, Ching JC, et al. Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. Pediatr Int 2010;52:699–706.
74. Ma XJ, Huang M, Chen SB, et al. Epidemiologic features of Kawasaki disease in Shanghai from 2003 through 2007. Chin Med J 2010;123:2629–34.
75. Li XH, Li HJ, Xu M, et al. Epidemiological survey of Kawasaki disease in Sichuan Province of China. J Trop Pediatr 2008;54:133–6.
76. Du A-D, Zhao D, Du J, et al. Epidemiologic study on Kawasaki disease in Beijing from 2000 through 2004. Pediatr Infect Dis J 2007;26:449–51.
77. Fischer TK, Holman RC, Yorita KL, et al. Kawasaki syndrome in Denmark. Pediatr Infect Dis J 2007;26:411–5.
78. Holman RC, Christensen KY, Belay ED, et al. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. Hawaii Med J 2010;69:194–7.
79. Ng YM, Sung RY, So LY, et al. Kawasaki disease in Hong Kong, 1994 to 2000. Hong Kong Med J 2005;11:331–5.
80. Singh S, Aulakh R, Bhalla AK, et al. Is Kawasaki disease incidence rising in Chandigarh, North India? Arch Dis Child 2011;96:137–40.
81. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009-2010 nationwide survey. J Epidemiol 2012;22:216–21.
82. Park YW, Han JW, Hong YM, et al. Epidemiologic features of Kawasaki disease in Korea, 2006-2008. Pediatr Int 2011;53:36–9.
83. Schiller B, Fasth A, Bjorkhem G, et al. Kawasaki disease in Sweden: incidence and clinical features. Acta Paediatr 1995;84:769–74.
84. Lue H-C, Chen L-R, Lin M-T, et al. Epidemiologic features of Kawasaki disease in Taiwan, 1976-2007: results of five nationwide questionnaire hospital surveys. Pediatr Neonatol 2013;55(2):92–6.

85. Huang WC, Huang LM, Chang IS, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003-2006. Pediatrics 2009;123:e401–5.
86. Harnden A, Alves B, Sheikh A. Rising incidence of Kawasaki disease in England: analysis of hospital admission data. BMJ 2002;324:1424–5.
87. Holman RC, Belay ED, Christensen KY, et al. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J 2010;29:483–8.
88. Onouchi Y, Tamari M, Takahashi A, et al. A genomewide linkage analysis of Kawasaki disease: evidence for linkage to chromosome 12. J Hum Genet 2007;52:179–90.
89. Burgner D, Davila S, Breunis WB, et al. A genome-wide association study identifies novel and functionally related susceptibility Loci for Kawasaki disease. PLoS Genet 2009;5:e1000319.
90. Tsai FJ, Lee YC, Chang JS, et al. Identification of novel susceptibility Loci for Kawasaki disease in a Han Chinese population by a genome-wide association study. PLoS One 2011;6:e16853.
91. Kim JJ, Hong YM, Sohn S, et al. A genome-wide association analysis reveals 1p31 and 2p13.3 as susceptibility loci for Kawasaki disease. Hum Genet 2011;129:487–95.
92. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. Nat Genet 2011;43:1241–6.
93. Lee YC, Kuo HC, Chang JS, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet 2012;44:522–5.
94. Onouchi Y, Ozaki K, Burns JC, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet 2012;44:517–21.
95. Yan Y, Ma Y, Liu Y, et al. Combined analysis of genome-wide-linked susceptibility loci to Kawasaki disease in Han Chinese. Hum Genet 2013;132:669–80.
96. Khan II, Watts RA. Classification of ANCA-associated vasculitis. Curr Rheumatol Rep 2013;15:383.
97. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101–7.
98. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094–100.
99. Watts RA, 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;66:222–7.
100. Lyons PA, Rayner TF, Watts RA, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214–23.
101. Watts RA, Lane SE, Bentham G, et al. Epidemiology of systemic vasculitis. Arthritis Rheum 2000;43:414–9.