Infectious triggers for vasculitis

Mirjan M. van Timmeren, Peter Heeringa, and Cees G.M. Kallenberg

Purpose of review
Infections have been suggested to contribute to disease induction and reactivation in many of the idiopathic vasculitides. This review describes and evaluates the evidence that microbes are involved in the etiopathogenesis of these diseases.

Recent findings
Large-vessel vasculitis has recently been associated with two specific bacteria. *Mycobacterium tuberculosis* is thought to have an inducing role in Takayasu arteritis and a *Burkholderia* bacterium might be involved in giant cell arteritis. Hepatitis B and C viruses have been linked to polyarteritis nodosa. In antineutrophil cytoplasmic autoantibody-associated vasculitis, and more specifically granulomatosis with polyangiitis (GPA), *Staphylococcus aureus* has been the focus of many studies. Chronic nasal carriage of *S. aureus* is related to endonasal activity and disease relapses in GPA patients. Moreover, antibacterial treatment is known to reduce the risk for disease relapses. If and how pathogens trigger vasculitis is still unclear, but several potential mechanisms have been suggested and are briefly reviewed here.

Summary
Although many observations suggest a link between infections and the development of vasculitis, no direct proof exists. Transcriptomic and proteomic studies of the pathogens involved could aid in identifying specific or common traits of pathogens that are relevant for the development and reactivation of vasculitis.

Keywords
granulomatosis with polyangiitis, hepatitis B and C virus, infection, *Staphylococcus aureus*, systemic vasculitis

INTRODUCTION
Vasculitides are systemic diseases characterized by inflammation of blood vessels. Any type and size of vessel can be affected. The most common forms of vasculitis were categorized and defined in the International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides held in 1994 [1]. Since then, there have been substantial advances in our understanding of vasculitis and changes in medical terminology. Therefore, a second International Chapel Hill Consensus Conference was held in 2012 to revise the nomenclature [2**]. Apart from adjusting names and definitions, other categories of vasculitis, one of them being ‘vasculitis-associated with probable cause’ comprising some of the, traditionally called, secondary vasculitides, have been added. The latter category includes, for example, hepatitis B virus (HBV)-related polyarteritis nodosa (PAN), hepatitis C virus (HCV)-related cryoglobulinemic vasculitis, and syphilis-associated vasculitis, emphasizing the role of infectious agents in vasculitis development. The cause of most vasculitides has not been fully elucidated, but infections have been suggested to contribute to the induction and reactivation of some forms. In this review, the possible role of infectious agents in the cause of the primary vasculitides (listed in Table 1) will be discussed.

LARGE-VEssel VASCULITIS
Takayasu arteritis is an often granulomatous arteritis predominantly affecting the aorta and its major branches with an onset usually before the age of 50 years. Already for several decades, a possible association of Takayasu arteritis with tuberculosis has been suggested, mainly because Takayasu...

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arteritis is more common in individuals originating from Asia, Africa, and South America, where the incidence of tuberculosis is high, and because granulomatous lesions are observed in both diseases [3,4]. The finding that humoral and cell-mediated immune responses directed toward mycobacterial heat-shock proteins have been reported in these patients supports this idea, though these responses were, to a lesser degree, also present in healthy controls [5]. Although previously the presence of Mycobacterium tuberculosis in the arterial lesions of these patients could not be shown [6], Soto et al. [7] recently identified IS6110 and HupB gene sequences of Mycobacterium tuberculosis in 23 of 33 (70%) aortic tissues from patients with Takayasu arteritis. Though not directly proving, it suggests that a previous infection with M. tuberculosis might play an inducing role in Takayasu arteritis, perhaps via cross-reactivity against vascular peptides that mimic the antigens of M. tuberculosis [8].

Giant cell arteritis resembles Takayasu arteritis except that it has a predilection for the branches of the carotid and vertebral arteries, and an onset usually after the age of 50 years. A multitude of infectious microorganisms have been proposed to be involved in the disease pathogenesis. Despite reports on the presence of Chlamydia pneumonia, parvovirus B19, and human herpes viruses in lesional tissue from patients, no clear evidence exists that these viruses are associated with giant cell arteritis [9,10]. Mohammadi et al. [11] recently

**KEY POINTS**

- Takayasu arteritis has been linked to Mycobacterium tuberculosis infection, perhaps via cross-reactivity against vascular peptides that mimic the antigens of M. tuberculosis.
- *Burkholderia* bacteria were recently identified in patients with giant cell arteritis and caused inflammation of pulmonary blood vessels upon injection in mice, suggestive of a causal link in this disease.
- Hepatitis B virus (HBV)-associated and hepatitis C virus (HCV)-associated polyarteritis nodosa (PAN) have a clinical presentation different from nonviral PAN and require antiviral treatment.
- In HCV-associated mixed cryoglobulinemia, HCV has been suggested to drive B-cell proliferation via interaction of an HCV envelope protein, E2, with the signaling molecule CD81 on patients’ lymphocytes.
- In granulomatosis with polyangiitis (GPA), chronic nasal carriage of *Staphylococcus aureus* is related to endonasal activity and disease relapses which can be reduced with antibacterial treatment; current research aims to identify the staphylococcal traits that are implicated in disease onset and relapses.

**Table 1.** Primary vasculitides with (most important) microbial agents and infections presumed to be involved in the development of the disease

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<td>‘New’ to be identified virus; Bacteria such as <em>Staphylococcus aureus</em> and <em>Streptococcus pyogenes</em> that are capable of superantigen production</td>
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found human papillomavirus DNA in temporal artery biopsies from 16 of 22 patients with giant cell arteritis. Furthermore, Koening et al. [12] reported the presence of a *Burkholderia*-like strain in temporal arteries from 9 of 10 patients with giant cell arteritis using 16S rRNA analysis. When the cultured *Burkholderia*-like strain was injected into C3H/HeSnJ mice, these mice developed inflammation of pulmonary blood vessels, suggesting that this *Burkholderia*-like bacterium might contribute to the development of giant cell arteritis. Clearly, this finding needs to be confirmed.

**MEDIUM-VESEL VASCULITIS**

PAN, one of the medium-sized vessel vasculitides, has been associated with HBV, HCV, and HIV infection. In the revised 2012 Chapel Hill nomenclature, HBV-related PAN was even grouped into a specific subgroup of vasculitides, namely ‘vasculitis associated with probable cause’, emphasizing the role of infections. The prevalence of HBV-associated, HCV-associated, and HIV-associated PAN largely coincides with the prevalence of the underlying infections. In France, for example, the incidence of HBV-associated PAN has declined over the years in parallel with the introduction of HBV vaccination and improvements in blood transfusion safety [13]. In an excellent recent review by Patel et al. [14], the differences between HBV-associated, HCV-associated, and HIV-associated PAN have been highlighted. Apart from differences in the severity of the disease, with HBV-related PAN being the most severe and HIV-related PAN being the mildest form, and the occurrence of relapses, most frequent in HCV-related and least frequent in HIV-related PAN, another specific difference is the reported duration of the viral infection prior to PAN development. For HBV-related PAN, this is approximately 20 years [15], but for HBV-related PAN this is usually less than a year [13]. Testing for HBV, HCV, and HIV in patients suspected of PAN is important, as antiviral treatment can then be added to immunosuppressive treatment [16]. When the virus is eliminated, this generally results in complete remission of the disease without occurrence of relapses and in prevention of long-term hepatic complications.

Kawasaki disease affects the medium-sized vessels, in particular the coronary arteries, and usually occurs in early childhood. It has been suggested to result from an abnormal immunological response to one or more infectious triggers in genetically susceptible individuals [17]. Viruses, such as Epstein-Barr virus, adenovirus, HIV, and, more recently, human coronavirus NL63 and bovavirus, have been described to be involved [18–20]. However, subsequent studies on these viruses were unconvincing and, more specifically, Rowley et al. [21] were unable to identify any known virus by high-throughput sequencing of RNA derived from laser-captured bronchial epithelium of patients with acute Kawasaki disease, although aggregates of virus-like particles could be detected. The authors suggested that a so far, unknown virus might be associated with Kawasaki disease.

With respect to bacteria, the most frequently implicated types in Kawasaki disease are *Staphylococcus aureus*, *Streptococcus pyogenes*, and also some less common pathogens, such as *Yersinia pseudotuberculosis* and *Mycoplasma pneumonia*. These are all capable of producing superantigens, which are considered to have an important role in the induction of aberrant immune responses (reviewed in [22]). Superantigens bind to MHC class II molecules on antigen-presenting cells and interact simultaneously with specific Vβ segments of the T-cell receptor, and as such stimulate, in an antigen-independent way, all T cells that utilize a particular group of Vβ segments. Superantigen-secreting *S. aureus* and *S. pyogenes*, in particular the toxic shock syndrome toxin-1 (TSST-1) superantigen, have been isolated periodically from bacteriological surveys of patients affected with Kawasaki disease [23–25]. More recently, Suenaga et al. [26] reported a higher detection rate of superantigen genes in the stool from patients with Kawasaki disease than in healthy controls. Moreover, selective expansions of particular Vβ-carrying circulating T cells compatible with superantigen-driven T-cell expansion has been reported in the sera of patients with Kawasaki disease [24,27]. However, so far these data have not been confirmed and no clear association between specific infectious agents and the development of Kawasaki disease has been identified.

**SMALL-VESEL VASCULITIS**

Small-vessel vasculitis (SVV) is subdivided into two categories, that is, immune complex SVV, which is characterized by moderate to marked vessel wall deposits of immunoglobulins and complement, and antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, characterized by a paucity of vessel wall immune components.

**Immune complex vasculitis**

The immune complex vasculitides comprise anti-glomerular basement membrane (anti-GBM) vasculitis, cryoglobulinemic vasculitis, IgA vasculitis, and hypocomplementemic urticarial vasculitis (HUV).

Anti-GBM disease was recently included as a form of vasculitis in the revised Chapel Hill nomenclature of vasculitides.
Nomenclature, but is not a novel disease [28]. It is characterized by circulating autoantibodies directed against the alpha-3 chain of type IV collagen. This antigen, present in the GBM and alveolar basement membrane, is under normal conditions hidden from autoantibodies. The cause of this disease is not fully elucidated. In addition to genetically determined susceptibility, environmental factors, such as infectious organisms, are thought to trigger the disease. But apart from some older studies showing an increased incidence of the disease during influenza epidemics, no definite proof has been found [29].

Cryoglobulinemic vasculitis is characterized by circulating cryoglobulins, that is, cold-precipitable immunoglobulins, and cryoglobulin-containing immune complexes frequently deposited in small vessels in the skin, glomeruli, and peripheral nerves. In type I cryoglobulinemia, the cryoglobulins consist of single monoclonal immunoglobulins; in type II and III, they consist of, respectively, monoclonal and polyclonal immunoglobulins, mixed with rheumatoid factor, hence also called mixed cryoglobulinemia. HCV infection, having a global prevalence of around 2% but with a substantial geographic variation, is associated with mixed cryoglobulinemia in around 50% of infected patients and with cryoglobulinemic vasculitis in 5–10% of patients [30,31]. In southern Europe, particularly in Italy, HCV-associated cryoglobulinemic vasculitis is more common than in northern Europe, which might be related to the incidence of HCV infection [31]. Though these associations suggest a role for HCV infections in the induction of disease, the exact pathogenic mechanisms have not been elucidated. It has been suggested that HCV drives the proliferation of B cells. An HCV envelope protein, E2, has been shown to interact with CD81, a signaling molecule expressed by hepatocytes, and B and T lymphocytes [32]. This interaction is believed to trigger chronic B-cell stimulation [33]. In line with this, Charles et al. [34] have demonstrated clonal expansion of hypermutated, rheumatoid factor-bearing marginal zone-like IgM’CD27+ B cells in patients with HCV-associated mixed cryoglobulinemia. In subsequent studies, they showed that these cells have a global transcriptional profile not suggestive of proto-oncogenesis, but rather suggestive of anergy and apoptosis [35]. Clearly, more research is needed to clarify the exact role of HCV in disease pathogenesis, though it is evident that antiviral therapy aiming at eradication of HCV has improved patient survival rates [16,36].

IgA vasculitis, frequently occurring in childhood, is characterized by the deposition of IgA within the vessel wall. Its cause is unknown, but infectious triggers, including Helicobacter pylori [37*], S. aureus [38*], and M. pneumoniae [39], have been considered to induce this disease (reviewed in [40**]). In addition to the aforementioned case reports, Xiong et al. [41*] reported that 49.3% (369 of 749) of Chinese children with IgA vasculitis had evidence of H. pylori infection compared with 23.4% (131 of 560) of healthy controls. Moreover, Alfredo et al. [42] described an infectious trigger in 29 out of 55 patients with IgA vasculitis. These observations clearly need confirmation in other cohorts.

HUV is an uncommon disease characterized by urticaria, hypocomplementemia, and anti-C1q antibodies. Hardly any associations of HUV with infections are described, except for a study [43] in Asian patients in which HUV was related to infection, mainly upper respiratory tract infection, in 8 out of 45 patients.

Antineutrophil cytoplasmic autoantibody-associated vasculitis

The ANCA-associated vasculitides comprise microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). They are strongly associated with ANCA, either directed to proteinase 3 (PR3) or to myeloperoxidase (MPO). PR3-ANCA is predominant in GPA and MPO-ANCA in MPA. The reported seasonal variation in these forms of vasculitis suggested the involvement of microbial agents [44], although others did not find seasonal influences [45]. In GPA, that is characterized by chronic necrotizing granulomatous inflammation with a predilection for the upper and lower respiratory tract, special attention has been given to S. aureus. It has been repeatedly shown that approximately 60–70% of GPA patients are chronic nasal carriers of S. aureus in contrast to only 20–30% of healthy people [46–49]. Moreover, S. aureus nasal carriage is associated with an increased risk of relapses in GPA patients and prophylactic antibacterial treatment with co-trimoxazole reduces the risk for relapses [46,50,51]. Recently, co-trimoxazole monotherapy in patients with GPA limited to the upper and lower airways was shown to induce remission in 35 of 49 (71%) patients [52*].

Apart from S. aureus, also other pathogens, such as Haemophilus influenzae, Streptococcus pneumoniae, and Klebsiella pneumoniae, are to a lesser extent found in the lower airways of GPA patients [53]. In line with the increased finding of pathogens in the airways of GPA patients are the findings of increased circulating antibody levels against several infectious agents, including HCV and H. pylori, in GPA patients compared with healthy controls [54].
Unfortunately, antibodies against *S. aureus* were not measured in that study. To check the capability of patients in raising an immune response against *S. aureus*, Hui *et al.* [55] measured the levels of the antimicrobial peptides LL-37 and hBD-3 in the nasal secretions of GPA patients and healthy controls. They found higher levels of LL-37 in both GPA patients and healthy controls that carry *S. aureus* than in noncarriers. Upon ex-vivo stimulation of nasal epithelial cells with *S. aureus*, increased levels of both antimicrobial peptides were measured, but the increase in hBD-3 in GPA patients was lower than the increase in healthy controls, suggestive of a dysregulated response to *S. aureus* in GPA patients. Overall, many observations suggest a link between GPA and infections, in particular *S. aureus*.

**FIGURE 1.** Possible mechanisms by which *Staphylococcus aureus* may induce or exacerbate granulomatosis with polyangiitis. (1) *S. aureus* present in the nasal cavity triggers bronchial epithelium and innate immune cells (such as monocytes, macrophages, and mast cells) in a Toll-like receptor (TLR) dependent manner to release proinflammatory cytokines. Possibly involved TLR ligands are the cell-wall components lipoteichoic acid (LTA) and peptidoglycan (Pgn), both TLR2 ligands, and CpG DNA (TLR9 ligand). (2) The produced proinflammatory cytokines, will on one hand, induce priming of neutrophils with translocation of the autoantigen proteinase-3 (PR3) to the neutrophil surface, and, on the other hand, promote the upregulation of adhesion molecules on vascular endothelial cells and primed neutrophils. Consequently, neutrophils adhere to the vascular endothelium and are recruited to the site of inflammation. (3) The proinflammatory environment may facilitate a break of self-tolerance to PR3, possibly via molecular mimicry of *S. aureus* (or other microbial) peptides that closely resemble the autoantigen PR3, leading to the production of anti-PR3 antibodies (PR3-ANCA). (4) PR3-ANCA fully activate primed neutrophils, resulting in degranulation, release of lytic enzymes, and production of reactive oxygen species that cause damage to the vascular endothelium. (5) Staphylococcal superantigens (SAgs) can stimulate in an antigen-independent way the B and T cells via simultaneous binding to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (which can be PR3-specific B cells) and the T-cell receptor variable region β (TCR-β). SAgs may also skew the T-cell differentiation into particular subsets. Apart from SAgs, other staphylococcal proteins, such as protein A from the bacterial cell wall, can activate B cells. ANCA, antineutrophil cytoplasmic autoantibody.
**STAPHYLOCOCCUS AUREUS AND GRANULOMATOSIS WITH POLYANGITIS: POTENTIALLY LINKING MECHANISMS**

If and how *S. aureus* contributes to GPA disease pathogenesis is not clear, but different theories exist (Fig. 1). In view of the persistent activation of circulating T cells in GPA patients, staphylococcal superantigens (SAgs) were proposed to be a chronic stimulus. Popa et al. [56] investigated this possible link, but could not detect a correlation between the presence of SAg genes and expansions of specific T-cell subsets in peripheral blood. In a later study [49], it was shown that GPA patients carrying *S. aureus* isolates positive for the superantigen toxic-shock-syndrome toxin 1 (TSST-1) have an increased risk for a disease relapse. Currently, we are investigating whether specific *S. aureus* types are colonizing GPA patients [57**]. A large number of nasal *S. aureus* isolates from GPA patients sampled over a 20-year period were subjected to genetic diversity analysis and revealed a limited degree of genomic diversity. Subsequent studies on proteomic and transcriptomic profiling of *S. aureus* might reveal whether particular staphylococcal traits can be implicated in GPA onset and relapses. Wohlers et al. [58**] recently showed that nasal epithelial cells of GPA patients have an altered cytokine expression pattern when compared with healthy controls as evidenced by reduced interleukin-8 and upregulated granulocyte colony-stimulating factor (G-CSF) levels and a reduced response to microbial stimulation. These observations support the hypothesis that GPA patients have a disturbed epithelial nasal barrier function that impacts the disease course. Other ways in which *S. aureus* could exert its effect include direct priming of neutrophils resulting in increased surface expression of the target antigen PR3, polyclonal B-cell activation by cell-wall components of the bacterium resulting in persistence of ANCA, and T-helper cell skewing to a particular subset. Additionally, microbial products may interact with Toll-like receptors (TLRs) present on and in immune cells and induce cell activation. Bacterial DNA, that contains immunostimulatory CpG dinucleotide motifs, is a ligand for TLR9, and CpG together with IL-2 has been shown to trigger the production of PR3-ANCA from autoreactive B cells *in vitro* [59]. Finally, molecular mimicry between microbial peptides and autoantigens has been described as a mechanism inducing autoimmunity. Antilysoosomal-associated membrane protein-2 (hLAMP-2) autoantibodies were shown to be present in patients with ANCA-associated vasculitis and were capable of neutrophil activation and endothelial damage *in vitro* [60]. Furthermore, LAMP-2 has homology with the bacterial adhesin FimH and immunization of rats with FimH resulted in antibodies reacting with LAMP-2 and pauci-immune focal necrotizing glomerulonephritis [60]. In three European cohorts, anti-hLAMP-2 autoantibodies were shown to be prevalent in more than 80% of patients with ANCA-associated vasculitis [61], but in another cohort from the United States the prevalence was four-fold lower and comparable to a control group with urinary tract infection [62]. Recently, Peschel et al. [63**] also found anti-hLAMP-2 autoantibodies in 8 of 11 patients with ANCA-negative pauci-immune focal necrotizing glomerulonephritis and showed that these antibodies had different LAMP-2 binding properties than the antibodies from ANCA-positive patients. The pathophysiological relevance of these autoantibodies is still unclear.

**CONCLUSION**

Although many clinical and experimental observations suggest a link between infections and the development of vasculitis, no direct proof exists. Moreover, the exact mechanisms by which pathogens trigger vasculitis are unknown, although a number of potential mechanisms have been suggested as briefly reviewed here. In this respect, more detailed transcriptomic and proteomic studies of the pathogens involved could aid in identifying specific or common traits of pathogens relevant for the pathogenic mechanisms involved.

**Acknowledgements**

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**Conflicts of interest**

*There are no conflicts of interest.*

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- **•• of outstanding interest**

Infection and autoimmunity


These authors searched for the evidence of the presence of Mycobacterium tuberculosis in a large number of aortic tissues from patients with Takayasu arteritis, tuberculosis (as a positive control), and athero-sclerosis (as a disease control) in Mexico, a country that is known to have a high incidence of tuberculosis. They found IS6110 and HupB gene sequences of M. tuberculosis in the aortic tissues of 23 of 33 (70%) patients with Takayasu arteritis compared with only 17 of 53 (32%); P = 0.004 patients with atherosclerosis and 27 of 33 (82%) patients with tuberculosis. This study supports the hypothesis that Takayasu arteritis results from a (latent) tuberculosis infection.


The authors used 16S rRNA analyses to amplify a bacterial genomic sequence that was unique to the temporal arteries of patients with giant cell arteritis (GCA). With multilocus sequence typing (MLST), they identified this sequence as a Burkholderia-like strain from temporal arteries of subjects with giant cell arteritis. Arthritis Rheum 2012; 64:5379–5387.


The authors performed a meta-analysis of the previously published studies to evaluate the underlying association between Helicobacter pylori infection and IgA vasculitis (Henoch–Schönlein purpura). They included 10 eligible studies and found evidence of H. pylori infection in 369/749 (49.3%) patients with IgA vasculitis compared with 33.4% (131 of 560) of healthy controls. Furthermore, they found that H. pylori eradication therapy (4 studies with 266 patients) was capable of reducing the recurrence of IgA vasculitis (relative risk of 0.38).


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These authors used high-throughput sequencing of RNA derived from laser-captured bronchial epithelium of three patients with Kawasaki disease to search for any known virus. Somewhat unexpectedly they did not identify any known virus, but they observed virus-like particles in the epithelium with intracytoplasmic inclusion bodies with transmission electron microscopy, suggestive of the presence of a novel virus. Therefore, they found virus-like particles in the epithelium with intracytoplasmic inclusion bodies with transmission electron microscopy, suggestive of the presence of a novel virus.
The authors of this abstract analyzed the genetic diversity of a large number of nasal \textit{Staphylococcus aureus} isolates from granulomatosis with polyangiitis (GPA) patients that were sampled during a 20-year period. To assess the genetic diversity, they used two well-established methods: multilocus variable number tandem repeat fingerprinting (MLVF) and spa typing. This revealed a high genetic diversity with MLVF, but a more restricted genetic diversity with spa typing based on the presence of five predominant spa types in more than 50% of the isolates. These authors compared the baseline expression of 19 cytokines of primary nasal epithelial cells (NECs) from granulomatosis with polyangiitis (GPA) patients and healthy controls. They found reduced interleukin-8 and upregulated G-CSF levels in NEC from GPA patients. Furthermore, NEC from GPA patients showed a reduced response to stimulation with \textit{Staphylococcus aureus} supernatant. The authors hypothesize that GPA patients have a disturbed epithelial nasal barrier function.

The authors of this abstract evaluated the safety and efficacy of co-trimoxazole monotherapy in granulomatosis with polyangiitis (GPA) patients who had disease manifestations limited to the upper and lower airways. They retrospectively analyzed 49 patients who were treated between 1989 and 2012. With co-trimoxazole monotherapy, 35 of 49 (71%) patients attained remission with a median disease-free survival of 148 months, indicating that co-trimoxazole can be considered as a first-line therapy in patients with localized GPA. Clearly, conformation in a different cohort is needed.