A. Chapel Hill Definition of Systemic Vasculitis

The pathological definition of vasculitis is based on the inflammatory infiltration and necrosis of the walls of blood vessels. The clinical symptoms vary greatly in accordance with the extent and location of the affected vessel segments. As a result, diagnosis of vasculitis is very complex. A number of classifications exist, but the classification based on the size of the affected vessel has proved to be useful in clinical applications. This classification is called the Chapel Hill definition after the place where the consensus conference was held (see Table 6 of the Appendix).

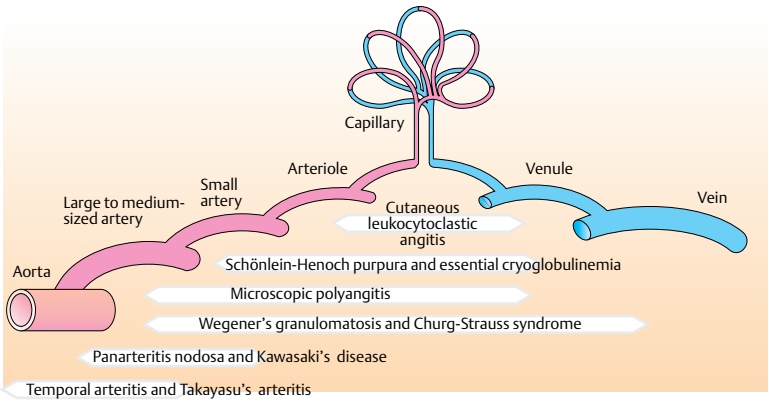
B. Classification of Vasculitis According to Mechanism of Development

An alternative system classifies the vasculitides according to their mechanism of development, thereby focusing on vessel lesions directly attributable to autoantibodies (ANCA- and AECA-associated vasculitis; see p. 197). The formation of circulating immune complexes plays a key role in the pathogenesis of many vasculitides. Depending on their composition, that is, the type and size of the foreign antigen or autoantigen and of involved antibodies, these immune complexes mediate the activation of inflammatory effector mechanisms (e.g., activation of complement, monocytes, lymphocytes, and thrombocytes; production of cytokines; chemotaxis of granulocytes) on the endothelium. This results in histologically demonstrable intravascular and perivascular infiltration and fibrinoid necrosis of the vessel wall.

The symptoms of vasculitis can occur in basically any infection and are common in infections by the following pathogens: *Streptococcus*, *Salmonella*, *Mycobacterium*, *Spirochaetales*, hepatitis B virus, HIV, Epstein–Barr virus, *Aspergillus*, *Leishmania*, and *Filaria*. In malignant diseases (e.g., Hodgkin's disease and hairy cell leukemia), the primary pathogens are those that affect the lymphoreticular system. A history of the use of medications, such as antibiotics, isoniazid, gold, D-penicillamine, potassium iodide, and busulfan must be considered as a potential cause.

Chapel Hill Definition of Systemic Vasculitis

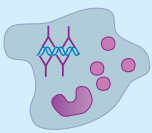
Vasculitis involving large vessels
• Giant cell (temporal) arteritis
• Takayasu's arteritis
Vasculitis involving medium-sized vessels
• Polyarteritis nodosa
• Kawasaki's disease
Vasculitis involving small vessels
• Wegener's granulomatosis
• Churg–Strauss syndrome
• Microscopic polyangiitis
• Schönlein–Henoch purpura
• Essential cryoglobulinemic vasculitis
• Cutaneous leukocytoclastic angiitis



A. Chapel Hill definition of systemic vasculitis

Immune vasculitis:
pauci-immune vasculitis,
autoantibody- associated

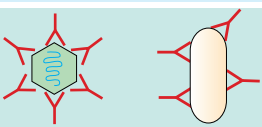
ANCA: Wegener's granulomatosis,
microscopic polyangitis
AECA: Kawasaki's disease



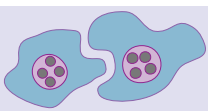
Immune complex vasculitis:
autoantigen induced: SLE

Infection related:
hepatitis B (classic PAN)
hepatits C

Granulomatous vasculitis:
giant cell arteritis
– Takayasu's arteritis
– temporal arteritis



Infection-related vasculitis:
– virus-associated: CMV
– rickettsia
– spirochaeta



Tumor-associated vasculitis:
cryoglobulinemia
lymphomatoid granulomatosis
hairy cell leukemia

B. Subtypes of vasculitis according to mechanism of development

A. Theory of the Development of Vasculitis Based on Wegener's Granulomatosis

Proteinase 3 (PR3), the target antigen of antineutrophil cytoplasmic antibodies (c-ANCA), is a central mediator in the pathogenesis of this vasculitic disease. PR3 is not accessible to the antibodies in the presence of resting polymorphonuclear neutrophil granulocytes (PMN) in the azurophilic granules (**1**). Prior activation by proinflammatory cytokines leads to the development of adhesion molecules on PMN and endothelial cells (EC) and to the translocation of intracytoplasmic PR3 on the cell membrane (**2**). The PMN then adhere to the endothelial cells (**3**). The PMN are then activated and start to degranulate due to the binding of ANCA to membrane-bound PR3. In the vicinity of endothelial cells, the PMN release toxic mediators and lysosomal proteins that are not accessible to the α-proteinase inhibitor. This results in lysis of the endothelial cells and necrotizing vasculitis (**4**).

B. Wegener's Granulomatosis

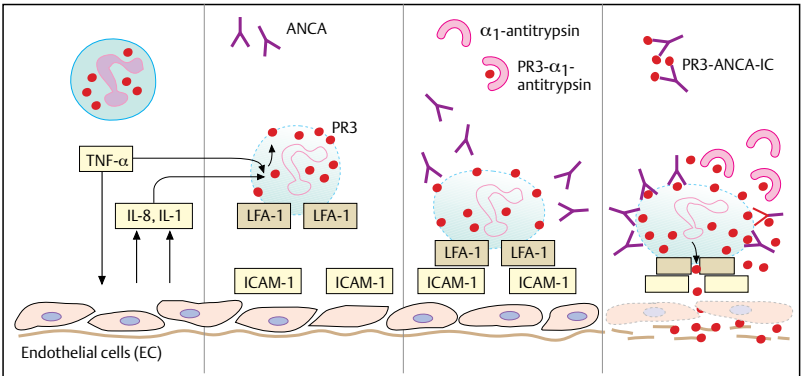
Wegener's granulomatosis usually involves the upper and lower respiratory tract and the kidneys, but additional symptoms of vasculitis may also occur in other organ systems. In most cases, the disease initially manifests as a chronic inflammation of the upper respiratory tract in conjunction with mucosal ulceration, purulent rhinitis, sinusitis or inflammation of the middle ear, and progressive destruction and deformity of the cartilaginous part of the nasal skeleton. Pulmonary manifestations include tracheobronchial erosions, pneumonia, and granulomas that may undergo cavernous degeneration. The main clinical features are coughing and hemoptysis, and the systemic features include fever and weight loss. Renal involvement (proteinuria, hematuria, progressive renal failure), arthralgia, purpura, skin ulcerations, and episcleritis are common manifestations in the generalization stage. Involvement of the heart, peripheral nerves, or gastrointestinal tract is less common. The detection of serum antibodies against PR3 (c-ANCA) is a relatively specific finding.

C. Churg–Strauss Syndrome

Churg–Strauss syndrome is a vasculitic disease closely associated with allergic diathesis (history of allergic rhinitis, bronchial asthma, chronic sinusitis, or drug allergies). Transient eosinophilic pulmonary infiltrates are often detected at the onset of the disease. As the disease progresses, organ manifestations similar to those observed in polyarteritis nodosa (PAN) develop with symptoms of arthralgia, palpable purpura, gastrointestinal pain, and hypertension. Renal involvement is uncommon. The main cause of death in these patients is cardiac failure due to cardiomyopathy. Blood tests reveal nonspecific signs of inflammation and massive eosinophilia with counts of over 1500/mm^3 (up to 80% in the differential count), high levels of total IgE, and sometimes rheumatoid factors.

D. Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a necrotizing vasculitic disease of the medium-sized (primarily visceral) arteries. The clinical picture is usually characterized by extensive yet nonspecific symptoms including general malaise, fever, weight loss, and arthralgia. Peripheral nerve involvement may manifest by way of mononeuritis multiplex (pain, parasthesia or paresis in the innervated area of the affected nerves) in the early stages due to vasculitis of the vasa nervorum. Central nervous manifestations, such as apoplectic infarctions, convulsions, or psychoses, are less common. Kidney involvement is very common, especially glomerulonephritis associated with proteinuria and hematuria. The condition can rapidly progress to renal failure. HBs antigen can be detected in up to 50% of cases.



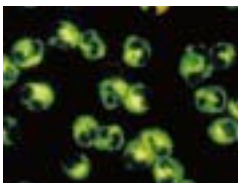
1. Resting PMN and EC

2. PMN and EC preactivated

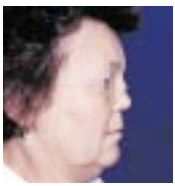
3. PMN adherent to EC

4. PMN activated by ANCA

A. Vasculitis development theory e.g., in Wegener's granulomatosis

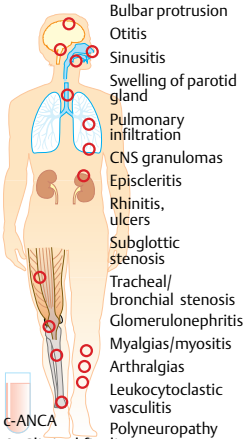


2. C-ANCA



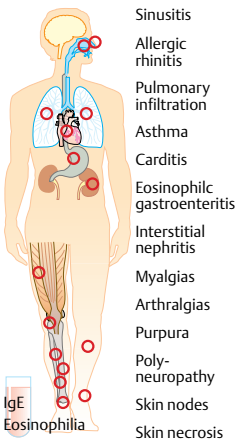
3. Saddle nose

4. Vasculitis of the toes

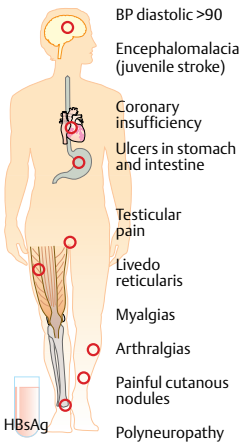


1. Clinical findings

B. Wegener's granulomatosis



C. Churg-Strauss syndrome



D. Polyarteritis nodosa

There are two types of giant cell arteritis (GCA): *Takayasu's arteritis*, which affects the aorta and its branches, and *temporal arteritis*, which involves the large cranial arteries. The histological features of both types are massive thickening of the arterial wall or frank arterial stenosis (**A.6**) and the presence of polynuclear giant cells (**A.4**). The pathogenesis of these diseases is still unclear. Genetic predisposition (HLA-DR4) and T-helper cell-mediated immune mechanisms leading to granuloma formation, possibly due to still unidentified infections, are the main hypotheses on the pathogenesis of GCA.

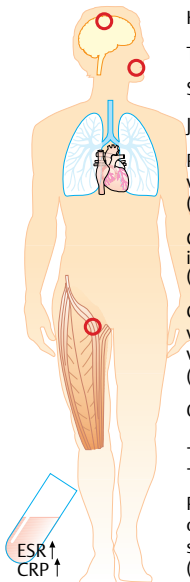
A. Giant Cell Arteritis: Temporal Arteritis and Takayasu's Arteritis

Temporal arteritis (called also *cranial arteritis* and *Horton's arteritis*) is a relatively common disease in patients over 50 years of age; see (**3**) for diagnostic criteria. Ratio in women to men is 2:1. There is primary involvement occurs in arteries of the head region (e.g., the temporal artery, retinal artery, and cerebral arteries) but other vessel regions may also be affected. Apart from general symptoms like fever, lassitude, and weight loss, other common symptoms include headache, hyperesthesia in the head region, and palpable induration of the temporal artery (**7**). The most feared complication is sudden blindness due to retinal artery occlusion. Symptoms such as visual impairment, eye aches, or light sensitivity require intensive investigation and rapid therapeutic intervention. Fundoscopy reveals occlusion of retinal artery branches or papillary edema. Scalp ulceration due to a lack of circulation is a rare complication (**8**).

Approximately 20–30% of patients with temporal arteritis have concomitant symptoms of polymyalgia rheumatica; see (**2**) for diagnostic criteria. The predominant features are pain in the proximal shoulder and thigh muscles. There are also general symptoms, such as lassitude, fatigue, depression, and low-grade fever, which are usually extensive.

A prominent laboratory feature of both diseases is a marked increase in the erythrocyte sedimentation rate (ESR) with values often in excess of 100 mm in 1 hour. Mild anemia and leukocytosis may also be detected. Bilateral biopsy of a longer segment of the temporal artery with serial-section histology is required to establish the diagnosis of temporal arteritis. In certain cases, the diagnosis can be established by demonstrating typical echographic changes by Doppler sonography. The prognosis is good, but steroid treatment must usually be administered for one to two years before a lasting remission is achieved.

Takayasu's arteritis (aortic arch syndrome) is a vasculitic disease that predominantly affects young women. The vasculitis involves the thoracic aorta and its branches. The predominant clinical features are therefore related to vessel stenosis, e.g., claudication, pulselessness, vascular murmurs, and/or hypertension. Fever, weight loss, myalgia, and arthralgia may also be observed in the initial inflammatory phase. Headache, dizziness, visual complaints, aortic insufficiency, and aneurysm are less common. The laboratory tests reveal extensive changes in nonspecific parameters of inflammation. Takayasu's arteritis responds well to steroids. However, the prognosis is much worse when extensive vessel lesions are present at the time of diagnosis (**5**).



Headache

Temporal arteritis

Scalp skin necrosis

Jaw claudication

Pulmonary vasculitis (rare)

Coronary insufficiency (rare)

Cerebral infarction via extracranial vessels (rare)

Ocular findings

– Loss of vision
– Eye muscle paresis

Polymyalgia of pelvis/ shoulder (bilateral)

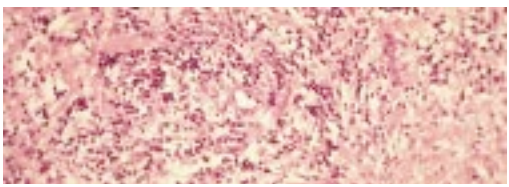
1. Clinical findings in temporal arteritis/ polymyalgia rheumatica

Aching shoulders and/ or bilateral stiffness
Disease onset within 2 weeks
Initial ESR increase of >40 mm in 1 hour
Morning stiffness >1 hour
Age over 65 years
Depression and/or weight loss
Bilateral tenderness on palpation of upper arm

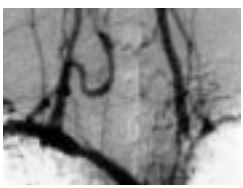
2. Diagnostic criteria of polymyalgia rheumatica

Patient over 50 years at first manifestation
Newly occurrent headache
Clinical findings in temporal arteries:
tenderness on palpation, pulselessness
highly increased ESR
positive arterial biopsy

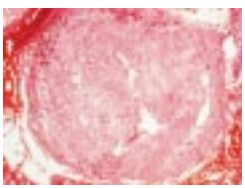
3. Diagnostic criteria of temporal arteritis



4. Histology of Takayasu's arteritis

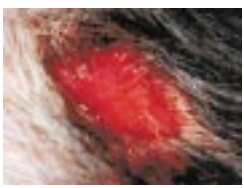


5. Branch stenosis in Takayasu's arteritis



6. Histology of occluded temporal artery

7. Temporal arteritis



8. Head skin ulcer

A. Clinical features of giant cell arteritis: Takayasu's and temporal arteritis