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PREVENTION OF VASCULITIS MEASURES TO TREAT IT

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ABOUT ARTICLE

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Abstract: Vasculitis is inflammation of blood vessels, often with ischemia, necrosis, and organ inflammation. Vasculitis can affect any blood vessel—arteries, arterioles, veins, venules, or capillaries. Clinical manifestations of specific vasculitic disorders are diverse and depend on the size and location of the involved vessels, the extent of the organ involvement, and the degree and pattern of extravascular inflammation.

INTRODUCTION

Vasculitis may be

- Primary
- Secondary

Primary vasculitis has no known cause.

Secondary vasculitis may be triggered by an infection, a drug, or a toxin or may occur as part of another inflammatory disorder or cancer.

Histologic description of an affected vessel should include the following:

- A description of vessel wall damage (eg, type and location of inflammatory infiltrate, extent and type of damage, presence or absence of fibrinoid necrosis)
- A description of healing responses (eg, intimal hypertrophy, fibrosis)

Certain features (eg, predominant inflammatory cell type, location of inflammation) suggest particular vasculitic processes and may aid in the diagnosis. For example, in many acute lesions, the predominant inflammatory cells are polymorphonuclear leukocytes; in chronic lesions, lymphocytes predominate.

Inflammation may be segmental or involve the entire vessel. At sites of inflammation, varying degrees of cellular inflammation and necrosis or scarring occur in one or more layers of the vessel wall. Inflammation in the media of a muscular artery tends to destroy the internal elastic lamina. Some forms of vasculitis are characterized by giant cells in the vessel wall. In some vasculitic disorders, such as granulomatosis with polyangiitis or Kawasaki disease, the vessel inflammation (true vasculitis) is only part of the pathophysiology and there is predominant parenchymal inflammation in a characteristic pattern that involves specific organs.

Leukocytoclastic vasculitis is a histopathologic term used to describe findings in small-vessel vasculitis. It refers to breakdown of inflammatory cells that leaves small nuclear fragments (nuclear debris) in and around the vessels. Inflammation is transmural and nongranulomatous. Polymorphonuclear leukocytes predominate early; later, lymphocytes predominate. Resolution of the inflammation tends to result in fibrosis and intimal hypertrophy. Intimal hypertrophy or secondary clot formation can narrow the vessel lumen and cause tissue ischemia or necrosis.

Vasculitic disorders can be classified according to the size of the predominant vessel affected. However, there is often substantial overlap.

Findings	Possible Diagnoses
Predominantly nonnecrotizing granulomatous inflammatory infiltrate with lymphocytes, macrophages, and multinucleated giant cells	Giant cell arteritis Primary angiitis of the central nervous system (certain types) Takayasu arteritis
Fibrinoid vascular necrosis of the vessel wall with a mixed infiltrate consisting of various combinations of leukocytes and lymphocytes	Eosinophilic granulomatosis with polyangiitis (EGPA) Granulomatosis with polyangiitis (GPA) Immune complex–associated vasculitis Microscopic polyangiitis (MPA) Polyarteritis nodosa (PAN) Rheumatoid arthritis (RA)
IgA deposits*	Immunoglobulin A–associated vasculitis (formerly Henoch-Schönlein purpura)
Scant or complete absence of immunoglobulins and complement deposition in the vessel walls*†	EGPA GPA MPA
* These observations are noted using immunofluorescence staining.	
† Disorders thus characterized are called pauci-immune vasculitic disorders.	

Size of the affected vessels helps determine clinical presentation.

Regardless of the size of the vessels involved, patients can present with symptoms and signs of systemic inflammation (eg, fever, night sweats, fatigue, anorexia, weight loss, arthralgias, arthritis). Some manifestations are life-threatening or organ-threatening and require immediate treatment:

- Alveolar hemorrhage
- Rapidly progressive glomerulonephritis
- Mesenteric ischemia
- Vision loss in patients with giant cell arteritis

Small- and medium-sized vasculitides often manifest with skin lesions such as palpable purpura, urticaria, ulcers, livedo reticularis, and nodules.

- Clinical evaluation
- Basic laboratory tests to detect inflammation or organ dysfunction (eg, complete blood count [CBC], erythrocyte sedimentation rate [ESR] or C-reactive protein, serum albumin and total protein, aspartate aminotransferase [AST] and alanine aminotransferase [ALT], blood urea nitrogen [BUN] and creatinine, urinalysis) and to stage disease process
- Laboratory tests to help determine the type of vasculitis (eg, antineutrophil cytoplasmic antibodies [ANCA]) if suggested by clinical assessment
- Laboratory and imaging studies that may help determine the cause of vasculitis (eg, cryoglobulins, hepatitis B surface antigen test, hepatitis B core and hepatitis B surface antibody tests and hepatitis C virus antibody test, , blood cultures) and extent of organ involvement
- Biopsy

Systemic vasculitis is suspected in patients with the following:

- Symptoms or signs suggestive of vasculitis (eg, temporal headache and jaw claudication suggesting giant cell arteritis)
- Ischemic manifestations (eg, ischemic stroke, limb claudication, mesenteric ischemia) out of proportion to a patient's risk factors for atherosclerosis
- Unexplained combinations of symptoms in more than one organ system that are compatible with vasculitis (eg, hypertension, myalgias, hemoptysis), particularly when symptoms of a systemic illness are present

Primary vasculitic disorders are diagnosed based on the presence of characteristic symptoms, physical findings, compatible laboratory test results, and exclusion of other causes (ie, secondary vasculitis).

Histologic examination is done whenever possible and may support the diagnosis of a particular vasculitic disorder (see table Histologic Clues to Diagnosis of Vasculitic Disorders). Clinical findings determine the differential diagnosis and thus direct laboratory testing.

Most routine laboratory tests yield results that are nonspecific and must be interpreted in the context of the entire clinical presentation. However, results can often help support the diagnosis, determine the location and degree of organ involvement, or suggest alternative diagnoses. Tests usually include CBC, ESR or C-reactive protein, serum albumin and total protein, AST, and ALT. Often, patients present with elevated ESR or C-reactive protein, anemia due to chronic inflammation, elevated platelets, and low serum albumin. Freshly voided urine must be tested for red blood cells, red blood cell casts, and protein to identify renal involvement. Serum creatinine levels should be checked and monitored. Leukopenia and thrombocytopenia are not typical of primary vasculitis and suggest an alternate diagnosis.

Detection of antineutrophil cytoplasmic antibodies (ANCA) may support the diagnosis of granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), or microscopic polyangiitis (collectively called ANCA-associated vasculitides). Standardized tests for ANCA include immunofluorescence staining and enzyme-linked immunosorbent assay (ELISA). Immunofluorescence staining of ethanol-fixed neutrophils can detect the cytoplasmic pattern of c-ANCA or the perinuclear pattern of p-ANCA. Then ELISA is used to check for antibodies specific for the major autoantigens: proteinase-3 (PR3), which produces the c-ANCA staining pattern, or myeloperoxidase (MPO), which produces the p-ANCA staining pattern seen on ethanol-fixed neutrophils. Because ANCA-associated vasculitides are rare, and the ANCA test is not completely specific, ANCA testing should be done only when the pretest probability for ANCA-associated vasculitis is moderately high. A positive ANCA test can occur in infections that can cause a secondary vasculitis, including endocarditis.

Other useful laboratory tests include hepatitis B and C serologic testing, serum and urine protein electrophoresis, antinuclear antibody and anti-extractable nuclear antigens panel, testing for the presence of cryoglobulins, and complement levels. Complement levels may be low in viral vasculitis, cryoglobulinemic vasculitis, lymphoproliferative disorders, or vasculitis secondary to other autoimmune diseases.

Further testing is determined by clinical findings. If indicated based on clinical findings, a chest x-ray should be done to check for infiltrates, but high-resolution noncontrast CT of the chest may be needed to check for subtle findings, such as small nodules or cavities. Bilateral diffuse infiltrates suggest

possible alveolar hemorrhage, which requires immediate diagnosis and treatment. Other imaging tests may be required. For example, magnetic resonance angiography of large blood vessels and the aorta is useful for diagnosis and monitoring when such vessels appear affected. If symptoms and examination suggest a neuropathy, electromyography may be helpful.

Because vasculitic disorders are rare and treatment may have severe adverse effects, tissue biopsy is done to confirm the diagnosis whenever possible. Clinical findings suggest the best site for biopsy. Biopsy results are most likely to be positive if taken from affected lung, skin, and kidney tissue. Blind biopsies of organs without clinical manifestations or laboratory suggestion of involvement have a low likelihood of providing positive results.

Treatment of Vasculitis

- Induction of remission for life-threatening or organ-threatening vasculitis with corticosteroids, often with cyclophosphamide or rituximab
- Induction of remission for less severe vasculitis with corticosteroids plus a less potent immunosuppressant (eg, methotrexate, azathioprine, mycophenolate mofetil) or rituximab
- Maintenance of remission with methotrexate, azathioprine, or rituximab, plus tapering of corticosteroids

Treatment of vasculitis depends on the etiology, the type of vasculitis, and extent and severity of disease. For secondary vasculitic disorders, removing the cause (eg, infection, drug, cancer) usually helps.

For primary vasculitic disorders, treatment aims to induce and maintain remission. Remission is induced by using cytotoxic immunosuppressants and high-dose corticosteroids, usually for 3 to 6 months, until remission occurs or disease activity is acceptably reduced. The duration of remission is hard to predict and may depend on the type of vasculitis. For many patients, maintaining remission requires continuation of immunosuppressive therapy with or without a low dose of corticosteroids. During this period, the goal is to eliminate corticosteroids or reduce their dose and use alternative, less toxic immunosuppressants as long as needed.

All patients treated with immunosuppressants should be monitored for opportunistic and other infections. Testing for tuberculosis and hepatitis B, which can become reactivated by some immunosuppressive therapies, should be done. Prophylaxis against should be considered for patients receiving potent or prolonged immunosuppressive therapy.

Induction of remission

For less severe forms of vasculitis, low doses of corticosteroids and less potent immunosuppressants (eg, methotrexate, azathioprine, mycophenolate mofetil) may be used.

Severe, rapidly progressive and life- or organ-threatening vasculitis (eg, causing alveolar hemorrhage, rapidly progressive glomerulonephritis, or mesenteric ischemia) is a medical emergency requiring hospital admission and immediate treatment. Treatment typically consists of the following:

- Corticosteroids: High-dose corticosteroids (also called pulse corticosteroids) are often prescribed. Specific doses and drugs must be individualized. As one example, methylprednisolone 15 mg/kg or 1 g IV once a day for 3 days may be used, followed by 1 mg/kg prednisone or methylprednisolone orally (or, if hospitalized, sometimes IV) once a day for about 4 weeks. The dose is then tapered slowly, as tolerated, until the drug is stopped. Changes in tapering schedule may be necessary if the patient fails to improve or relapses.
- Cyclophosphamide: A dose of 2 mg/kg orally once a day is usually recommended for at least 3 months or until remission occurs. The white blood cell (WBC) count must be closely monitored, and the dose must be adjusted to avoid leukopenia. (WBC count should be maintained at > 3500/microL [> 3.5 x 109/L].) Alternatively, an IV cyclophosphamide regimen of 0.5 to 1 g/m2 at 2- to 4-week intervals is sometimes used. The dose should be reduced in patients with significant renal insufficiency, and WBC counts should be monitored frequently. Patients taking chronic high-dose corticosteroids, particularly with cyclophosphamide, should also be given prophylactic treatment against .
- Mesna:Mesna is mixed with IV cyclophosphamide to bind acrolein, a product of cyclophosphamide degradation that is toxic to the bladder epithelium and can lead to hemorrhagic cystitis and sometimes transitional cell carcinoma of the bladder. Long-term use of cyclophosphamide increases the risk of bladder cancer. One milligram of mesna is added for each milligram of cyclophosphamide. Recurrence of hematuria, especially without casts and dysmorphic red cells, should prompt a referral for urologic evaluation. Cystoscopy and renal imaging should be done to exclude cancer.
- Rituximab:Rituximab, a B cell-depleting anti-CD20 monoclonal antibody, has been shown to be noninferior to cyclophosphamide in inducing remission of severe ANCA-associated vasculitis. Rituximab is given as 375 mg/m2 IV once a week for 4 weeks. A widely used alternative regimen is two 1000-mg infusions given 2 weeks apart. Patients should also be given prophylactic treatment against .

B cell-depleting therapies will markedly blunt the response to vaccines for months after administration.

Remission maintenance

Corticosteroids are tapered to zero or to the lowest dose that can maintain remission. For some forms of vasculitis (most clearly demonstrated in ANCA-associated disease), weekly methotrexate (with folate) or daily azathioprine is prescribed to replace cyclophosphamide because these drugs have a better adverse effects profile. Periodic IV rituximab may also be used to maintain remission, but the optimal dosage and infusion interval have not been clearly established. The duration of this treatment varies, from one year to several years, depending on the patient, specific diagnosis, and propensity for relapse. Patients with frequent relapses may need to take immunosuppressants indefinitely.

Long-term use of corticosteroids can have significant adverse effects. Patients who are taking ≥ 7.5 mg of prednisone daily or equivalent doses of other corticosteroids should be given calcium and vitamin D supplements and bisphosphonates to help prevent or minimize osteoporosis; bone density monitoring should be considered. Additional corticosteroid supplementation may be needed in seriously ill patients or in those undergoing surgery who may have a suppressed hypothalamic-pituitary-adrenal axis, depending on the dose and duration of corticosteroid therapy and the duration and intensity of stress.

Recent studies have focused on developing treatments that limit corticosteroid exposure. Avacopan, a selective C5a receptor antagonist, is an available adjunctive therapy for severe active ANCA-associated vasculitis (1).

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