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# The Crux

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ISO 9001

## Editorial

**Vasculitis** (plural: *vasculitides*) is a group of disorders that destroy blood vessels by inflammation. Both arteries and veins are affected. Lymphangitis is sometimes considered a type of vasculitis. Vasculitis is primarily caused by leukocyte migration and resultant damage. Although both occur in vasculitis, inflammation of veins (phlebitis) or arteries (arteritis) on their own are separate entities.

Vasculitis can be classified by the cause, the location, the type of vessel or the size of vessel.

- *Underlying cause*. For example, the cause of syphilitic aortitis is infectious (aortitis simply refers to inflammation of the aorta, which is an artery.) However, the causes of many forms of vasculitis are poorly understood. There is usually an immune component, but the trigger is often not identified. In these cases, the antibody found is sometimes used in classification, as in ANCA-associated vasculitides.
- *Location of the affected vessels*. For example, ICD-10 classifies "vasculitis limited to skin" with skin conditions (under "L"), and "necrotizing vasculopathies" (corresponding to systemic vasculitis) with musculoskeletal system and connective tissue conditions (under "M"). Arteritis/phlebitis on their own are classified with circulatory conditions (under "I").
- *Type or size of the blood vessels* that they predominantly affect. Apart from the arteritis/phlebitis distinction mentioned above, vasculitis is often classified by the caliber of the vessel affected. However, there can be some variation in the size of the vessels affected.

According to the size of the vessel affected, vasculitis can be classified into:
Large vessel: Polymyalgia rheumatica, Takayasu's arteritis, Temporal arteritis. Medium vessel: Buerger's disease, Cutaneous vasculitis, Kawasaki disease, Polyarteritis nodosa.Small vessel: Behçet's syndrome, Churg–Strauss syndrome, cutaneous vasculitis, Henoch–Schönlein purpura, Microscopic polyangiitis, Wegener's granulomatosis, Golfer's vasculitis, cryoglobulinemia.

GO ON! TURN OVER TO READ COMPLETE CLINICO-DIAGNOSTIC ASPECTS OF VASCULITIDES UNDER **"DISEASE DIAGNOSIS"**

**"INTERPRETATION"** segment outlines for you Sputum Culture. How to collect, how to interpret and all the rest.

**"TROUBLESHOOTING"** portion defines the style and science of Specimen Form Submission. Appears too unimportant but many a Labs have been declined ISO accreditation because of improper forms. Get wiser!

No, we have not overlooked **"BOUQUET"**

## DISEASE DIAGNOSIS

# VASCULITIDES

The vasculitides comprise a heterogeneous group of diseases with the common histopathologic feature of inflammation and necrosis of blood vessel walls. The etiologic factors associated with triggering of endothelial injury include: infections, drugs, autoantibodies, malignancies, abnormal circulating proteins, and underlying systemic disease. Half of all cases, however, do not present a clear etiology or association and are considered idiopathic. The varied causes coupled with the myriad of clinical presentations and an imperfect classification system can make the diagnosis of specific forms of vasculitis difficult. Physicians need to integrate clinical assessment with laboratory data in order to differentiate between the disorders where the vasculitic process represents a benign, self-limited disease from those that may be severe or even life threatening. Rapid and accurate diagnosis leads to optimal treatment options.

### Introduction

Vasculitis is defined as inflammation and fibrinoid necrosis of the blood vessel wall. It may present in a wide variety of clinical manifestations depending on the localization and size of the vessels involved, type of inflammatory infiltrate, and associated conditions. The variety of clinical presentations associated with the many etiologies of vasculitis may make the diagnosis of specific forms of vasculitis difficult. This is important, as some vasculitides with similar clinical presentation have very different prognoses and treatments. Palpable purpura, the most common clinical presentation of vasculitis, may represent a benign and self-limited disease, as is the case of some drug eruptions, or it may be a part of a life-threatening entity as in microscopic polyangiitis. Recent advances, however, have contributed significantly to our understanding of this heterogeneous group of diseases, allowing for more accurate diagnosis and optimal treatment regimens. This article will focus on syndromes and associated conditions of cutaneous necrotizing vasculitis, as well as vasculitis syndromes.

### Classification

Although various attempts have been made to create a universally accepted classification scheme, the classification of the vasculitides remains a matter of controversy. Some classification systems have focused on the size of the vessels, while several other classification schemes have been based on histologic findings. According to this latter classification scheme, the vasculitides are divided according to the type of dominant inflammatory cells, such as neutrophils, lymphocytes, and macrophages, affecting either small or large vessels. Both types of classification scheme are imperfect, as overlap of vessels of various sizes may occur, and the type of inflammatory infiltrate may change over time. For example, neutrophils may predominate early in the inflammatory infiltrate but may be replaced by a lymphocytic or granulomatous infiltrate later. The most recent classification schema proposed by the American College of Rheumatology (ACR) uses both vessel size and type of inflammatory infiltrate. It classifies vasculitis as follows: polyarteritis nodosa (PAN), Churg-Strauss syndrome, Wegener's granulomatosis, hypersensitivity vasculitis, Henoch-Schönlein purpura, giant cell arteritis, Takayasu's arteritis, granulomatous angiitis of the central nervous system, Berger's disease, and Kawasaki disease (Appendix A). In this schema, hypersensitivity vasculitis corresponds to cutaneous small vessel vasculitis. According to the classification proposed by the ACR, the criteria for the diagnosis of hypersensitivity vasculitis includes the presence of at least three of the following: disease onset greater than 16 years old; use of medication at disease onset; presence of palpable purpura; maculopapular rash; and biopsy showing neutrophils in a perivascular or extravascular location. The presence of three of the criteria must be present for diagnosis and is 83.9 percent specific and 71 percent sensitive. It should be remembered that these classifications were primarily designed to be used in clinical trials, not necessarily to be used for clinical practice or to differentiate between the vasculitides. In 1994, the Chapel Hill Consensus Conference (CHCC) created an alternative schema for classification of the major types of vasculitis. According to the CHCC, the vasculitides are divided into large, medium, and small-vessel vasculitis, In the small vessel group, cutaneous leukocytoclastic angiitis is defined as "isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis."

### Epidemiology

Cutaneous and systemic vasculitis are uncommon, and reliable epidemiological data are limited. In addition, as disease definitions vary, data may vary based on the definitions used. Watts, et al., studied patients with biopsy-proven cutaneous vasculitis between January, 1990 and December, 1994. From this data, they estimated the annual incidence of cutaneous vasculitis to be 38.6 cases per million (95 percent CI 30.6-48.1). They found the incidence to be greater in women (50.4 cases per million) than in men (26.0 cases per million). Cutaneous leukocytoclastic vasculitis, as defined by the CHCC, was found to be 15.4 cases per million. A female predominance was observed with an estimated 24.2 cases per million cases compared to males (6.0 cases per million). Studies from England, Spain, and Scandinavia show that the overall annual incidence of primary systemic vasculitis is approximately 20 cases per million. Vasculitis appears more common with advanced age. Scott and Watts observed higher incidence in the age group between 65 and 74 years old, with 60 cases per million, whereas Tidman and colleagues noted a maximum incidence in men aged 55 to 64. An age-specific increase in incidence has long been observed in patients over 80 years for giant cell arteritis. In various populations, certain types of vasculitis appear more common. Given the estimated incidence of all types of vasculitis elsewhere, the incidence of PAN and microscopic polyangiitis among the ethnic Kuwaiti population in Kuwait was found to be high (16 per million and 24 per million) in one study. This suggests either genetic or environmental factors may be at work in certain populations. Studies of associations of human leukocyte antigens with systemic vasculitis have obtained varying results. Boki, et al., studied 66 patients with a diagnosis of cutaneous necrotizing vasculitis in Greece from 1982 to 1995. They failed to find a statistically significant difference in the frequency of HLA-class I and II alleles between patients with Wegener's granulomatosis, PAN, and Churg-Strauss syndrome when compared to controls. However, Genciki, et al., did observe a reduced frequency of HLA-DRw6 in patients with Wegener's granulomatosis in a cohort study involving 102 patients in Germany. The precise role of HLA-class antigens on the development of vasculitis, however, remains to be determined. A retrospective study of hospitalizations for vasculitis in a Norwegian community showed an overall prevalence of 43.9 per 100,000 persons. When evaluating for specific types of vasculitis, they found an incidence of 1.3 per 100,000 for Churg-Strauss syndrome, 2.7 for cutaneous necrotizing vasculitis, 3.3 for Henoch-Schönlein purpura, 3.3 for polyarteritis nodosa, 5.3 for

Wegener's granulomatosis, and 27.9 for temporal arteritis. Recently published studies suggest that the impact of vasculitis may be significant and greater than previously anticipated. An approximate estimate of costs for hospitalizations due to PAN, Wegener's granulomatosis, hypersensitivity vasculitis, giant cell arteritis, and Takayasu's arteritis in the US is $150 million per year. Likely costs are greater, once associated costs of outpatient care and loss of productivity are calculated.

## Clinical Presentation

Vasculitis, regardless of its cause, most commonly presents as palpable purpura (Figure 1). Palpable purpura is a raised, non-blanchable erythema and signifies extravasation of red cells outside of blood vessels. However, in addition to this pathognomonic sign, a myriad of lesions may occur including red macules, wheals, papules, nodules, ulcers (Figure 2), vesicles, and blisters (Figure 3). The clinical presentation may vary, depending on the size of the vessel involved. Cutaneous small- and medium-sized vessel disease may present with a reticulate pattern that outlines the cutaneous vasculature. Large vessels that supply a larger area of skin may present with widespread purpura and necrosis. The lesions are distributed often symmetrically, most commonly on the lower legs, but can occur anywhere in the body. Lesions typically occur in areas of dependency but may occur in areas of trauma or pressure. Mucosal involvement is rare, and if present, manifests itself in the form of petechiae, hemorrhagic blisters, and ulcers. Usually, cutaneous lesions heal within one to four weeks if a single initiating factor is the cause, for example, drug exposure. However, if cutaneous ulcers occur, healing may be prolonged. There may also be residual scarring and hyperpigmentation. Vasculitis may, however, be recurrent and/or intermittent with new crops of lesions appearing for months or years. In some cases, the episode of cutaneous vasculitic lesions may be associated with fever, malaise, arthralgia, and myalgia. The skin is often the only organ involved, but in some cases, may be part of a systemic vasculitis correlated to an underlying disease. Although the classic clinical lesions of vasculitis, palpable purpura, are typical, other conditions may appear clinically similar. Emboli leading to palpable lesions can occur in patients with endocarditis, left atrial myxoma, or due to cholesterol emboli. Thrombocytopenia and disseminated intravascular coagulopathy present as widespread purpura; however, the purpura is usually non-palpable in these cases. The differential diagnosis for the other clinical presentations of vasculitis including ulceration are myriad; therefore, histologic confirmation is essential.

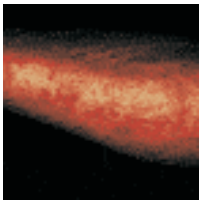


**Figure 1.**
Patient with systemic lupus and vasculitis with clinical lesions of palpable purpura.

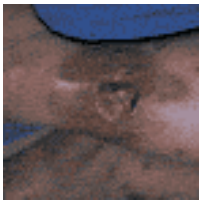


**Figure 2.**
Patient with rheumatoid arthritis and cutaneous ulcer due to vasculitis.

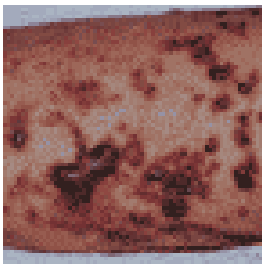


**Figure 3.**
Vasculitis presenting as hemorrhagic bullae.

## Histopathology

Skin involvement in vasculitis may either occur as a sole entity or as part of vasculitis involving other organ systems. In either case, the histology may be similar. Cutaneous vasculitis is usually characterized by involvement of the post capillary venules with endothelial cell swelling, neutrophilic invasion of blood vessel walls, presence of disrupted neutrophils (leukocytoclasia), extravasation of red blood cells, and fibrinoid necrosis of the blood vessels walls. These features generated the term cutaneous necrotizing vasculitis (CNV), which refers to leukocytoclastic vasculitis affecting the small and medium vessels that supply nutrients to the skin. In later stages, thrombosis of affected small vessels is frequently observed, as well as hyalinization and fibrosis of vessel walls. As the histologic picture may be identical, whether the vasculitis occurs only in the skin or as a component of systemic small-vessel vasculitis, it is imperative the physician exclude systemic involvement or an underlying cause, see Table 2. Based on histopathologic findings, CNV can be divided in two major groups: leukocytoclastic form, due to deposition of immune complexes on blood vessel wall (type III hypersensitivity reaction), and a lymphomonocytic form, caused by immune-mediated vessel injury. Some authors consider these two forms as different stages of the same process. That is, over time a predominantly neutrophilic infiltrate will be replaced by lymphocytes or monocytes. Several specific syndromes where vasculitis may be present, such as granuloma faciale, erythema elevatum diutinum, and Behcet's syndrome, show no clear evolution into a mononuclear inflammatory infiltrate for a long period of time, unless they are treated or begin to regress. Along with the immune complex and cell-mediated mechanisms of endothelial injury, fibrinolytic activity is decreased in the late phase of cutaneous vasculitis, which may lead to thrombosis and consequently hypoxia and necrosis of the vessel. Langerhans cells, neuropeptides, vascular tone, and gamma/delta T lymphocytes also appear to be involved in self perpetrating the initial immune-complex mechanism of leukocytoclastic vasculitis.

## Etiology and Associations

The etiology of a vasculitic syndrome is probably multifactorial with influences on disease expression caused by ethnicity, genes (HLA and others), gender, and environment (ultraviolet exposure, infections, drugs, smoking, and surgery). Frequent associations include infectious agents, medications, connective tissue diseases, and malignancies among others (Table 2). One half of all patients with cutaneous vasculitis, however, have no definite etiologic agent or associated disease. Among the idiopathic vasculitides are Henoch-Schönlein purpura, urticarial vasculitis, erythema elevatum diutinum, nodular vasculitis, and cutaneous polyarteritis nodosa (Appendix A and B).

## Pathogenesis

### Infectious Causes

Infection may be the most common trigger leading to vasculitis. As a model, vasculitis due to infection is mediated through a type III or immune-complex reaction where the antigens are the infectious agents or antigenic portions of them. After the zone of equivalence is reached, the immune complexes precipitate and become trapped within vessel walls, stimulating an immune response that ultimately leads to vascular injury. Candida polysaccharides and fragments of gram-positive and gram-negative organisms can activate the alternate pathway and also lead to the inflammatory reaction characteristic of vasculitis. Alternatively, direct endothelial cell invasion can be the main pathogenic process in infections caused by cytomegalovirus, herpes simplex, rickettsiae, fungi, and bacteria. Recent concepts suggest other mechanisms may be at work as well in the development of vasculitis within the context of infection. Cytokines, such as tumor necrosis factor and various interleukins, are produced directly by the stimulation from the infectious agents. Subsequently, recruitment of neutrophils to the small vessels occurs and leads to the development of vasculitis. Vasculitis related to infection due to streptococcus and staphylococcus has been associated with this mechanism of vascular injury. The association between hepatitis B and polyarteritis nodosa (PAN) has been well documented. One report found 54 percent of patients with PAN having hepatitis B virus (HBV) infection. Hepatitis C (HCV) infection has also been associated with vasculitis mediated through the production of cryoglobulins. A genetic susceptibility was proposed by Lenzi, et al., in 1998, who reported the association between HCV-related cryoglobulinemia and HLA-B8 and DR3 markers. Mycoplasma, HIV, and cryptococcal infections have also been reported to cause vasculitis.

### Drugs

Drugs have often been implicated as the etiologic agents of vasculitis and are reported to cause approximately 10 percent of the cases of vasculitis. Among the drugs most frequently implicated have been sulfonamides, penicillin, allopurinol, thiazides, hydantoins, aspirin, and propylthiouracil. Cases of minocycline-related vasculitis have also been recently reported. Penicillin causes vasculitis by conjugating to serum proteins and mediating immune-complex vasculitis as in type III hypersensitivity reactions. Drugs such as propylthiouracil and hydralazine appear to induce antibody production, specifically antineutrophil cytoplasmic antibodies (ANCA), although a clear cut causal relationship has not yet been proved.

### Malignancy

The association of vasculitis and malignancy is less common. When the two occur together, it is most commonly seen with malignancies of the lymphoproliferative system. Solid tumors, such as lung, colon, and gastrointestinal carcinomas, have been reported less frequently. The mechanisms of endothelial injury associated with malignancies include abnormal production of proteins, leading to formation of immune complexes, which bind antigens on vessel walls. Additionally, cell surface antigens may be similar in both neoplastic and endothelial cells, and molecular mimicry may lead to the development of vasculitis. Another potential pathogenic mechanism of defective apoptosis has also been proposed.

### Connective Tissue Diseases

Vasculitis also may be associated with a variety of connective tissue diseases, such as systemic lupus erythematosus (SLE), scleroderma, dermatomyositis, rheumatoid arthritis, and Sjögren's disease. As in other types of vasculitis, the severity of the clinical presentation may vary from mild (limited to the skin) to severe, widespread, and/or sometimes life threatening. Virtually any organ may be affected, and no sized vessel is immune. For example, in SLE the deposition of immune complexes containing [ds] DNA antibodies within the blood vessel wall leads to activation of the complement cascade and induction of inflammatory changes. This may lead to skin or larger vessel involvement especially in the kidneys and central nervous system. Vasculitis in rheumatoid arthritis more often develops in HLA-DR4 patients and is usually severe with involvement of skin (presenting with deep cutaneous ulcers and gangrene) and peripheral nerves. Sjögren's syndrome can be associated to cutaneous vasculitis in up to 30 percent of cases. It is characterized by the triad of keratoconjunctivitis, xerostomia, and rheumatoid arthritis. Cutaneous lesions may vary from palpable purpura to widespread ecchymoses. The existence of circulating antineutrophilic cytoplasmic antibodies was first reported by Davis, et al., in 1982. ANCA-associated small vessel vasculitis includes three major diseases: Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis. In microscopic polyangiitis, ANCA is present by immunofluorescence studies in 50 percent of the patients often as a perinuclear pattern (p-ANCA). These autoantibodies are directed against myeloperoxidase when identified by enzyme-linked immunosorbent assay (ELISA). Half of the patients with Churg-Strauss syndrome have ANCA antibodies directed against proteinase 3 presenting as a cytoplasmic staining pattern (c-ANCA) with immunofluorescence. Wegener's granulomatosis, however, is most strongly associated with ANCA autoantibodies. Over 75 percent of patients with Wegener's granulomatosis have c-ANCA detected by immunofluorescence. In patients with systemic involvement, the percentage is even higher with approximately 90 percent of patients demonstrating c-ANCA positivity. The pathogenic mechanism is not clearly known, and other factors may play a role in the development of these diseases.

### Cryoproteins

Cryoglobulinemia occurs as a consequence of deposition of cryoglobulins leading to thrombi formation in medium and small vessel walls. Three types of cryoglobulins have been identified. Type I or monoclonal cryoglobulinemia is seen in patients with malignant diseases, such as myeloma or benign lymphoproliferative conditions, such as Waldenström's macroglobulinemia. This classically does not lead to vasculitis but rather thrombotic phenomena that can chronically resemble vasculitis; type II or mixed cryoglobulinemia combines a polyclonal and a monoclonal immunoglobulin. This type of cryoglobulinemia is less often associated with malignancies and is more often associated with infectious or inflammatory diseases. Type III is comprised of only polyclonal immunoglobulin. Type II is most commonly associated with hepatitis C infection, and the monoclonal component is IgM kappa. Both type II and type III cryoglobulinemia can lead to vasculitis. The clinical features in those patients are purpura, arthritis, peripheral neuropathy, and glomerulonephritis.

### Other Vasculitides

Of the idiopathic vasculitis, Henoch-Schönlein purpura is the most common in children. It is mediated by IgA and the dominant IgA subclass is the IgA1. The pathogenesis of this IgA deposition within vessel walls, however, remains unknown. Although urticaria due to bradykinin release may be seen in various types of vasculitis, a specific clinical syndrome of urticarial vasculitis is associated with low levels of CH50, C1q, C4, or C2, blood eosinophilia, and leukocytosis. Some patients with urticarial vasculitis have antinuclear antibodies, the presence of rheumatoid factor, or cryoglobulinemia, while other patients have an associated serum sickness, systemic lupus erythematosus, and Sjögren's

syndrome. Recently, urticarial vasculitis has also been reported in association with monoclonal IgM gammopathy, the so-called Schniltzer's syndrome. The clinical picture is characterized by the persistent urticarial wheals in typically middle-aged women. In these patients, urticarial lesions last longer than 24 hours (differentiating it from urticaria) and may be associated with itching, pain, or burning sensations. The lesions may occur anywhere, especially in sites of pressure. Erythema elevatum diutinum is a vasculitis of unknown cause with raised edematous purpuric plaques typically over the joints, especially of the hands. It is considered by some to be an allergic reaction to streptococcal superantigens. Histologically, the pattern is that of a leukocytoclastic vasculitis.

## Nomenclature

Vasculitis nomenclature is often quite confusing. For example, livedoid vasculitis is clinically characterized by painful purpuric lesions of the lower extremities that frequently ulcerate, leaving white, stellate atrophic scars (atrophie blanche) with dyspigmentation and teleangiectasia. Although clinically resembling a vasculitis, it is in fact a vasculopathy, not a vasculitis -- that is, a thrombotic phenomenon without inflammation. Associations with cutaneous cholesterol embolism, systemic lupus erythematosus, cryoproteins, and cerebrovascular disease (Sneddon's syndrome) have been described. Highlighting the difference between vasculitis and livedoid vasculitis, Papi and colleagues reported that different pathogenic mechanisms are operative in livedoid vasculitis and cutaneous small vessel vasculitis, confirming the former is not a vasculitic process but an occlusive vasculopathy.

## Diagnosis

Although often clinically apparent, excluding other conditions that may present similarly is the initial step in evaluating a patient with an eruption suggestive of vasculitis. Additionally, accurate diagnosis of the different forms of vasculitis will depend on the integration of a complete medical history, thorough physical exam, and laboratory data. The aim of the investigations should be directed toward determining a potential cause or associated disorder, as well as determining the presence or absence of organ system involvement.

## Laboratory Evaluation

The laboratory evaluation in these situations may include an assessment for ANCA, antinuclear antibodies, complement levels, cryoglobulins, antistreptolysin O antibodies, Hemoccult testing, antibodies for viral hepatitis, as well as determining the presence of a rheumatoid factor. Urinalysis may detect glomerular involvement. Radiographs, and if indicated, computerized topography and magnetic resonance imaging may be useful in diagnosing occult respiratory tract or neurologic disease.

## Tissue Samples

Histological evaluation of the skin lesions is paramount. A biopsy of the lesion may yield the typical features of cutaneous vasculitis (see above). Additional findings on histopathology may aid in suggesting an underlying systemic disease. For example, in patients with cryoglobulinemia, eosinophilic material can be found in the vessel wall lumen; or for example, in patients with lupus erythematosus, there is frequently mucin deposition in the dermis, as well as an interface inflammatory infiltrate that may be seen along with the changes of vasculitis. Thrombosis of the small blood vessels can be a result of septic vasculitis. Tissue biopsies sent for culture may detect an infectious cause. Immunofluorescence testing of skin to detect bound antibodies will be helpful in certain diseases. Characteristic deposits of IgA within the vessel wall is observed in immunofluorescence studies of Henoch-Schönlein purpura.

## Treatment

Identification and removal of the possible causal agent -- for example, stopping a suspected medication -- should be undertaken, if possible. Patients with disease restricted to the skin will often require only symptomatic treatment. Additionally, for localized or limited disease, antihistamines, colchicine, or dapsone along with supportive care as well may be useful. For lower extremity lesions, leg elevation and compression of leg lesions may also be helpful. In certain situations, specific treatments have been found to be helpful. For example, potassium iodide is useful in treating nodular vasculitis. Systemic corticosteroids in doses of 60-80mg per day may be utilized if lesions are widespread. When present systemic disease suggests the need for immediate and sometimes aggressive therapy, depending on the extent of disease and/or organ involvement. An infectious etiology should be ruled out whenever possible before the introduction of immunosuppressive therapy. Often a combination of corticosteroids and immunosuppressants is needed. One combination suggested for severe cases with multiple organ involvement includes treatment with glucocorticoids plus cyclophosphamide. In a study published by Hoffman in 1992, among 158 patients, 133 were treated with daily cyclophosphamide and corticosteroids. This combined therapy resulted in a mortality rate of 13 percent with a follow-up period of eight years. Without treatment, the mean survival for systemic vasculitis is often much worse, about five months. Due to the toxicity of cyclophosphamide (hemorrhagic cystitis and bladder carcinoma) Nowack, et al., treated 11 patients with pulse cyclophosphamide. They found, after a mean follow-up period of 4.5 years and a total of 501 pulses, the majority was in complete remission without evidence of either hemorrhagic cystitis or malignancy. In a series reported by Stone, et al., patients with non-life-threatening Wegener's granulomatosis were treated with methotrexate and daily prednisone. The combination was found to be safe and effective. Seventy-four percent of the patients achieved a remission, but the majority required continued treatment. A new agent, mycophenolate mofetil (MMF), has been recently studied as maintenance therapy for Wegener's granulomatosis and microscopic polyangiitis. Maintenance of remission for 15 months was achieved with a combination of MMF and low-dose corticosteroids. One patient relapsed and overall the medication was well tolerated. In addition to chemotherapy, others have tried physical modalities with varied success. One such treatment -- plasmapheresis, for acute management of severe vasculitis -- remains controversial. It appears to be useful, especially for life-threatening cryoglobulinemia, but the disease may rebound once therapy is discontinued. As cryoglobulinemia is frequently associated with hepatitis C infection, interferon alpha has shown to be of benefit in several controlled studies. Due to the variety of clinical presentations of vasculitis, the variety of patients with vasculitis, and the number of different immunosuppressant combinations available, controlled trials are limited; therefore, larger, controlled studies are necessary to confirm these findings.

## Appendix A

### Clinical Syndromes of the Systemic Vasculitis

**Polyarteritis Nodosa.** Polyarteritis nodosa is characterized by inflammation and fibrinoid necrosis of small- and medium-sized arteries.

It manifests in middle-aged men as nodular lesions along the course of an artery, frequently on the lower extremities. The lesions are often in different stages of development and may occur at the bifurcation of the vessels. The major features of this disease are intestinal organ infarction and hemorrhage (bowel, pancreas, gallbladder), neuropathy, and myalgia. Severe renal involvement is found in 25 percent of cases.

**Churg-Strauss Syndrome.** Churg-Strauss syndrome is defined by the presence of asthma, allergic rhinitis, pulmonary and systemic small-vessel vasculitis, extravascular granulomas, and blood eosinophilia. Allergic rhinitis and asthma are usually the first symptoms, followed by the onset of blood and tissue eosinophilia and later by infiltration of the lung and/or gastrointestinal tract. The vasculitic lesion typically occurs three years after the onset of the allergic manifestations. The vascular inflammation in Churg-Strauss syndrome is more likely to affect small arteries, but veins may also be involved. Heart, gastrointestinal tract, renal, and neurologic involvements are the main causes of death in these patients. As in polyarteritis nodosa, middle-aged adults are mainly affected. The presence of autoantibodies directed against myeloperoxidase in neutrophils (p-ANCA) has been implicated in the pathogenesis of this disease

**Wegener's Granulomatosis.** Wegener's granulomatosis shares clinical similarities with Churg-Strauss syndrome and polyarteritis nodosa. However, renal involvement is more prominent and is characterized histologically by focal necrotizing glomerulonephritis. Additionally, granulomatous inflammation of the upper and lower respiratory tract and necrotizing vasculitis of small- and medium-sized vessels characterize this systemic disorder. Middle-aged men are more frequently affected. The presence of ANCA antibodies against proteinase 3 is a highly sensitive marker of this disease.

**Henoch-Schönlein Purpura.** Henoch-Schönlein purpura is the most common vasculitis in children. It is characterized by immune-complex deposition of IgA within vessel walls of venules, capillaries, and arterioles. Typical clinical features include arthralgia, abdominal cramps, and renal involvement often preceded by a streptococcal infection in children.

**Giant Cell Arteritis.** Giant cell arteritis, or temporal arteritis, is primarily a disease of the elderly patient. It involves the small- and medium-sized extracranial arteries. The most common symptom is headache followed by visual symptoms ranging from blurred vision to sudden blindness. Cutaneous necrosis in the temporal area may be seen. Marked elevated erythrocyte sedimentation rate is the rule.

**Takayasu's Arteritis.** Takayasu's arteritis is an inflammatory fibrosing arteritis affecting predominantly the aorta and its major branches. It is common in Japan. It affects especially young women; the initial symptoms may be fever, nightsweats, weakness, and joint pain followed by cardiovascular manifestations such as heart failure, palpitations, bruits, and syncope. The absence of pulses due to large vessel disease has led to the name "pulseless disease."

**Granulomatous Angiitis of the Central Nervous System.** Granulomatous angiitis of the central nervous system is probably an immunological vasculitis with very poor prognosis; most patients die within one year of disease onset. Some cases may be associated with cerebral amyloid angiopathy, while infection is seen to be the triggering factor in others. The clinical manifestations include headache, focal symptoms, and rarely transient ischemic attack and stroke.

**Kawasaki Disease.** Kawasaki disease is a rare vasculitic syndrome involving medium-sized vessels afflicting especially children. It presents as fever, conjunctivitis, pharyngitis, strawberry tongue, erythema of palms and soles or edema of the extremities, polymorphous non-vesicular rash, and cervical adenopathy. The complication of most concern is the involvement of the coronary arteries. Treatment includes aspirin and intravenous immunoglobulin.

**Thromboangiitis Obliterans or Buerger's Disease.** Thromboangiitis obliterans or Buerger's disease is characteristically an inflammatory occlusive disease affecting medium and small arteries and veins. Its prevalence is higher in Europe and Asia, and males between 20 and 40 years old are most commonly affected. Almost all of the patients with this syndrome are smokers, which indicates a possible etiology for this disease. The pathogenic mechanisms, however, remain unclear. Common complaints are claudication of the foot or lower extremity, gangrene, or cyanosis of the fingers and ulcers.

## Appendix B

### Idiopathic Vasculitis

**Erythema Elevatum Diutinum.** Erythema elevatum diutinum (EED) is a rare skin disorder with unknown etiology. Clinically, it manifests as persistent brown to red papules, nodules, and plaques prominently over extensor surfaces of the extremities. Individuals from 40 to 60 years old are most frequently affected. The histology is that of a leukocytoclastic vasculitis with deposits of C3 at the basal lamina of small vessels. EED has been reported to occur in association with hematological malignancies, infections, and autoimmune disorders. The course of the disease is usually protracted with frequent relapses and spontaneous resolution after five to 10 years. Treatment with dapsone elicits dramatic improvement of the cutaneous lesions.

**Cutaneous Polyarteritis Nodosa.** Cutaneous polyarteritis nodosa (CPN) is a skin-limited vasculitis affecting medium vessels of the dermis. The relationship to hepatitis B infection is not clearly determined as in the cases of systemic polyarteritis nodosa, and the etiology remains unknown. Painful nodules, ulcerations, or livedo reticularis are the most common clinical presentations of CPN. Frequently, the lower extremities are involved, but lesions may also occur on the trunk and upper extremities. Middle-aged males are most frequently afflicted. Histologically, one can observe a predominantly neutrophilic infiltrate surrounding the walls of medium-sized arteries. Treatment options include steroids or steroids with cyclophosphamide.

**Nodular Vasculitis.** Nodular vasculitis (NV) is a lobular vasculitis associated with vasculitis of the septal blood vessels. Characteristically, it presents as chronic nodules on the posterior and lateral surfaces of the legs. These nodules are erythematous, painful lesions that often ulcerate and leave atrophic scars after healing. Infections are one of the most important causes of NV, and this disease has been frequently associated with tuberculosis. The pathogenic mechanisms, however, remain unknown. Treatment includes anti-inflammatory drugs, steroids, anti-tuberculosis therapy, dapsone, and gold.

**Urticarial Vasculitis.** Urticarial vasculitis is a disorder characterized by the presence of urticarial wheals lasting more than 24 hours. Histologically, there is leukocytoclastic vasculitis affecting the post-capillary venules. On direct immunofluorescence deposits of immunoglobulins, C3 or fibrinogen can be observed in 70 percent of cases. Systemic involvement can be manifested most commonly by arthralgia and abdominal pain, and patients of any age can be affected. There is no universally effective therapy. Anti-inflammatory agents, colchicine, and antihistamine therapy can be useful in milder forms of the disease. Systemic steroids show some benefit, but the long-term side effects limit its use.

# INTERPRETATION

## SPUTUM CULTURE

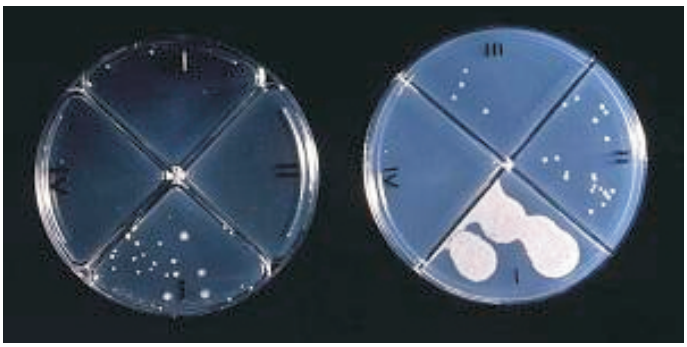
L.J. Medium

### Reference Range

The most common pathogens detected with a sputum culture are bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and *Klebsiella species*. Fungi are slow-growing eukaryotic organisms that can grow on living or nonliving organisms and are subdivided into molds and yeasts. Only a few of them grow in humans, and when they infect the respiratory system, they can cause serious infections. Overall, sputum specimens are observed for mucopurulent strands, leukocytes, and blood and culture results. The presence of normal upper respiratory tract flora should be expected in sputum culture. Normal respiratory flora include *Neisseria catarrhalis, Candida albicans,* diphtheroids, alpha-hemolytic streptococci, and some staphylococci.

### Interpretation

**Culture Plates**



A normal Gram stain of sputum contains polymorphonuclear leukocytes, alveolar macrophages, and a few squamous epithelial cells. The presence of normal flora does not rule out infection. Examination of a Gram-stained smear of the specimen frequently reveals whether the specimen is satisfactory or not. The quality of sputum samples is determined by the minimum number of squamous epithelial cells and polymorphonuclear leukocytes per low power field. An acceptable specimen has more than 25 leukocytes and fewer than 10 epithelial cells per low power field. An unacceptable sample can be misleading and should be rejected by the laboratory. Culture of the sputum on blood agar frequently reveals characteristic colonies, and identification is made by various serologic or biochemical tests. Cultures of *Mycoplasma* are infrequently done; diagnosis is usually confirmed by a rise in antibody titer. If Legionella pneumonia is suspected, the organism can be cultured on charcoal-yeast agar, which contains the high concentrations of iron and sulfur required for growth. If tuberculosis is suspected, an acid-fast stain should be performed immediately, and the sputum cultured on special media, which are incubated for at least 6 weeks. In diagnosing aspiration pneumonia and lung abscesses, anaerobic cultures are important.

### Collection and Panels

Equipment: Sterile, leak-proof container.

- Collecting the first sample before any antibiotic or antimicrobial therapy is initiated is necessary.
- Obtaining an early-morning expectorated specimen is most desirable. The first morning specimen is most concentrated and is less likely to be contaminated with saliva and nasopharyngeal secretions.
- Before beginning collection, ask the client to rinse the mouth with plain water. This removes secretions and oral plaque, which may contaminate the sample.
- Instruct the client to breathe deeply to stimulate coughing and expectoration. This loosens the secretions enough to expectorate.
- Collect the expectorated sputum in a leak-proof sterile container. Refrigerate the container until processing takes place. Sterility is important for culture results. Refrigeration slows other bacterial growth.
- Do not pool multiple samples in a 24-hr period. The client should be instructed to avoid adding saliva or nasopharyngeal secretions to the sputum sample. Avoids contamination of the sample.
- Ask respiratory therapy personnel to assist the patient in obtaining an "aerosol-induced" specimen if the cough is not productive. Patients breathe aerosolized droplets of a sodium chloride-glycerin solution until a strong cough reflex is initiated. The specimen often appears watery but is in fact material directly from alveolar spaces. It should be noted on the requisition as being aerosol induced.
- Cultures should be performed rapidly after collection, ideally within 2 hours; otherwise, the sample should be saved at 4°C.

### Background

#### Indications/applications

Sputum culture is used to diagnose pneumonia, bronchiectasis, bronchitis, or pulmonary abscess. It assists in the diagnosis of respiratory infections, as indicated by the presence or absence of organisms in culture. The 2007 Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) consensus guidelines recommend expectorated sputum specimens for hospitalized patients with signs and symptoms of pneumonia and any of the following conditions:

- Intensive care unit admission
- Failure of outpatient antibiotic therapy
- Cavitary lesions
- Active alcohol abuse
- Severe obstructive or structural lung disease
- Positive urine antigen test for pneumococcus
- Positive urine antigen test for Legionella (special culture media for Legionella needed)
- Pleural effusion

Sputum Gram stain and culture are indicated for all patients with hospital-acquired pneumonia.

### Considerations

- Contamination with oral flora may invalidate results.
- Specimen collection after antibiotic therapy has been initiated may result in inhibited or no growth of organisms.
- Note any current antibiotic therapy on the laboratory slip.

# BOUQUET

## In Lighter Vein

### The Blond Detective Exam.

A policeman detective was interrogating 3 blondes who were training to become detectives. To test their skills in recognizing a suspect, he shows the first blonde a picture for 5 second and then hides it.

"This is your suspect, how would you recognize him?"

The first blonde answers, "That's easy, we'll catch him fast because he only has one eye!"

The policeman says, "Well...uh...that's because the picture shows his PROFILE."

Slightly flustered by this ridiculous response, he flashes the picture for 5 seconds at the second blonde and asks her, "This is your suspect, how would you recognize him?"

The second blonde giggles, flips her hair and says, "Ha! He'd be too easy to catch because he only has one ear!"

The policeman angrily responds, "What's the matter with you two?? Of course only one eye and one ear are SHOWING because it's a picture of his profile!! Is that the best answer you can come up with?"

Extremely frustrated at this point, he shows the picture to the third blonde and in a very testy voice asks, "This is your suspect, how would you recognize him?"
He quickly adds "...think hard before giving me a stupid answer."

The blonde looks at the picture intently for a moment and says, "Hmmmm...the suspect wears contact lenses."

The policeman is surprised and speechless because he really doesn't know himself if the suspect wears contacts or not.

"Well, that's an interesting answer...wait here for a few minutes while I check his file and I'll get back to you on that."

He leaves the room and goes to his office, checks the suspect's file in his computer, and comes back with a beaming smile on his face.

"Wow! I can't believe it...it's TRUE! The suspect does in fact wear contact lenses. Good work! How were you able to make such an astute observation?"

"That's easy," the blonde replied. "He can't wear regular glasses because he only has one eye and one ear!"

## Wisdom Whispers

**Quotes:**

"The only man who never makes a mistake is the man who never does anything."

"Don't just look, OBSERVE..
Don't just swallow, TASTE..
Don't just sleep, DREAM..
Don't just think, FEEL..
Don't just exist, LIVE.."

"Falling down is not defeat, defeat is when you refuse to get up."

"Love makes the time pass. Time makes love pass."

"Forget about the people in your past.. They didn't make it to your future for a reason."

"Small children disturb your sleep, big children, your life."

"A true friend is someone who says nice things behind your back."

"Even if you are on the right track, you will get run over if you just sit there."

"There is no pillow so soft as a clear conscience."

"We never stand taller than when we stoop down to help someone who had fallen."

## Brain Teasers

1. **The deficiency of Lung surfactant, Dipalmitoyllecithin (DPL) causes, Respiratory Distress Syndrome. DPL is a –**
   A. Cerebroside
   B. Ganglioside
   C. Phospholipid
   D. Lipoprotein.

2. **Choose the correct statement**
   A. The melting point of a fatty acid increases with the increasing degree of unsaturation in the hydrophobic chain
   B. Most of the naturally fatty acids have trans double bonds
   C. Arachidonic acid is a relatively nonessential fatty acid
   D. The membrane lipids are rich in saturated fatty acids.

3. **Which out of the following fatty acids is a precursor of series -1 Eicosanoids?**
   A. Linoleic acid
   B. Arachidonic acid
   C. Eicosapentaenoic acid
   D. Linolenic acid.

4. **What is the cause of hyper acidity on long-term usage of Aspirin?**
   A. Inhibition of cyclo oxygenase
   B. Increased synthesis of PGs
   C. Inhibition of Phospholipase A2
   D. All of the above.

ANSWERS: 1-C, 2-C, 3-A, 4-A.

# TROUBLESHOOTING

## Specimen Form Submission

### Request Forms

Use individual requisition forms available from the laboratory. All test requests require a physician's written order to process a specimen. Follow the collection instructions for each type of specimen .

### Patient Identification

All patients from whom clinical specimens are obtained must be positively identified, utilizing at least two unique identifiers prior to specimen collection. Positive identification is the responsibility of the person collecting the sample .

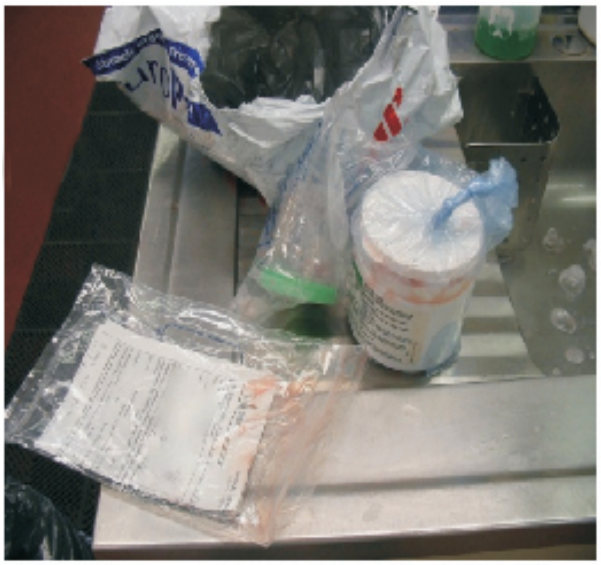
- Required Information
- All specimens must be labeled .

Specimen Labeling :The following information must be legibly recorded on a label affixed in an irreversible fashion to the specimen container :

- Patient's full name (not a nickname)
- Medical Record Number or other unique identifier (ID)
- Date and, if appropriate, time when specimen was obtained
- Specimen source
- Signature/ initials of collector
- The label should be affixed directly to the specimen container and not the bag.
- Bar coded pre printed labels with accession numbers generated by an information system may be used .
- Place the labeled specimen in the provided leak proof sealed plastic biohazard bag
- Place the matching requisition in the outside pouch of the bag

Transport specimens promptly : See specific test for temperature requirements. The date and signature/ initials of the collector must be recorded after the specimen has been collected and after verifying that the patient name and ID on the label agrees with that on the test requisition. This is the single most important factor in preventing errors in patient specimen identification .

Use of a request form wrapped around the container is not acceptable as a specimen label .Specimens will not be accepted if the information on the specimen label does not match the information on the accompanying requisition .



### Required Information on the Requisition Form

On all requests forms ,the following information is required

- Patient's name & address
- Patient's gender
- Date of birth
- The last six digits of the patient's social security number or other unique identifier (ID#) wherever mandatory legally and applicable.
- Date and if appropriate, time of collection
- Test/s requested
- Type or source of the specimen
- Requesting physician/ or Client Number
- Clinical information if requested
- All applicable medical necessity codes (ICD-9)
- Complete billing and insurance information wherever indicated

Providing additional relevant information may be important in alerting the laboratory of the need for special handling or specimen work-up. Tests sent to reference laboratories must have patient history information. The need for such information is indicated on the test request form.

### Reliability and Value of Test Results

The reliability and value of test results depends on numerous factors. Improper collection, transport, or processing of a specimen can decrease the quality of patient care or result in unnecessary additional testing or treatment. Laboratory personnel cannot label specimens nor complete requisition forms (source, time of collection, patient's name), which they have not collected. Mislabeled (specimen label does not match requisition) or unlabeled specimens should be rejected.

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