Therapy for Vasculitic Neuropathies

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Opinion statement

The term vasculitis refers to a pathologic condition defined by inflammatory cell infiltration and destruction of blood vessels. Systemic vasculitis is classified as primary (eg, polyarteritis nodosa, Churg-Strauss syndrome) or secondary, the latter associated with connective tissue disorders, infections, medications, and rarely, as a paraneoplastic phenomenon. Neuropathy is a common complication of systemic vasculitis and is related to ischemic nerve fiber damage with axon loss. Peripheral neuropathy may be the sole manifestation of vasculitis, a condition termed nonsystemic vasculitic neuropathy (NSVN). Treatment of vasculitic neuropathy requires long-term immunosuppressive therapies with potential side effects. The diagnosis of vasculitis should be established by tissue (preferably nerve) biopsy. High-dose prednisone is the standard platform therapy for patients with systemic and NSVN; for those with systemic vasculitis, at least 3 to 12 months of treatment with cyclophosphamide (monthly intravenous pulse or daily oral therapy) is also necessary to sustain remission and allow successful prednisone tapering. The use of cyclophosphamide in patients with NSVN is controversial, but recent retrospective data suggest that those treated with prednisone and cyclophosphamide from the outset fare better than those initially treated only with prednisone. If prednisone is administered as monotherapy, cyclophosphamide should be added after several months if there is no improvement or relapse occurs with tapering of prednisone. Intravenous pulse and daily oral cyclophosphamide probably offer similar efficacy, although the risk of complications is greater with oral therapy. Azathioprine can be safely substituted for cyclophosphamide after 3 months without an increased relapse rate. Azathioprine, methotrexate, intravenous immune globulin, mycophenolate mofetil, plasma exchange, and rituximab can be offered to patients who are intolerant or have a contraindication to cyclophosphamide. However, efficacy is unproven for any of these therapies. Interferon-α, sometimes combined with plasma exchange, is used to treat vasculitis associated with hepatitis B infection. Some patients also may improve with corticosteroids. The classification of diabetic lumbosacral radiculoplexus neuropathy as a vasculitic disorder remains controversial. However, there is compelling pathological evidence that this condition represents a T-cell–mediated microvasculitis. Some patients treated with intravenous corticosteroids may have greater recovery and improved pain control.

Introduction

The term vasculitis refers to the pathological process of blood vessel wall inflammation and destruction causing ischemic or hemorrhagic damage of tissues supplied by the affected vessels [1]. Vasculitis may be classified based on the size of the affected vessel (large, medium, or small artery), or whether the condition is a primary systemic disease (eg, polyarteritis nodosa), secondary to an associated connective tissue disorder (eg, rheumatoid

arthritis), hypersensitivity response to an infection (eg, HIV or hepatitis C virus), drug exposure, malignancy, or in some cases, idiopathic (eg, cases of pathologically verified vasculitis associated with lumbosacral plexus neuropathy) [2, Class III; 3; 4, Class III].

CLINICAL FEATURES OF SYSTEMIC VASCULITIC NEUROPATHY

Peripheral neuropathy is a recognized complication of vasculitis, but its frequency is unknown, in part because vasculitic conditions are uncommon and observations have been derived from neuromuscular centers with an interest in these diseases. For the practicing clinician, certain clinical and laboratory features should raise suspicion for a vasculitic neuropathy. Classically, patients have painful sensory loss and weakness in the distribution of multiple peripheral nerves, so-called "mononeuritis multiplex." However, perhaps more commonly there is a confluence of multiple mononeuropathies that evolves in a summated fashion to produce a generalized, asymmetric, polyneuropathy or a lumbosacral plexus neuropathy. In some cases, the clinical pattern resembles a nondescript distal, symmetric, pure sensory or sensorimotor polyneuropathy [5, Class III; 6,7; 8, Class III]. The course may be explosive at onset, but more often the neuropathy develops in a stuttering or stepwise pattern over weeks to months. Occasional patients have a very chronic, insidious course with symptoms that have been present for years at the time of diagnosis [9]. The course may be indolent and static in some patients with nonsystemic vasculitic neuropathy (NSVN).

Virtually all patients with neuropathy caused by systemic vasculitis also have constitutional symptoms, including fever, weight loss, and organ-specific involvement, such as rash, renal, bowel, or pulmonary involvement. Serologic abnormalities frequently indicate a systemic inflammatory process (Table 1). Others have an established diagnosis of a connective tissue or other inflammatory disorder, followed by the development of a neuropathy that suggests a vasculitic pattern [10•]. Examples of such disorders include rheumatoid arthritis, cryoglobulinemia, sarcoidosis, systemic lupus erythematosus, and Sjögren syndrome [11; 12, Class III; 13–15]. Tests that identify organ involvement in patients with systemic vasculitic neuropathy or a connective tissue disorder with secondary vasculitis and neuropathy are listed in Table 1.

Vasculitic neuropathy has been linked to viral infections, including hepatitis B (usually associated with polyarteritis nodosa), hepatitis C with or without cryoglobulinemia, and HIV infection [12,16, Class III; 17–20; 21,22, Class III]. Accordingly, serologic studies for these conditions are also recommended.

Paraneoplastic vasculitic neuropathy is a rare complication of malignancy and is usually associated with small cell carcinoma or lymphoma [23, Class III].

Table 1. Laboratory studies in the evaluation of patients with suspected vasculitic neuropathy

Complete blood count with eosinophil count
Renal function studies
Serum glucose and glycosylated hemaglobin (lumbosacral plexus neuropathy)
Liver function studies
Urinalysis
Erythrocyte sedimentation rate
C-reactive protein
Anti-nuclear antibody
Rheumatoid factor
Complement levels (C3, C4, CH50)
Antineutrophil cytoplasmic antibody level
Cryoglobulins
Anti-dsDNA and Sm antibodies
Anti-SSA and SSB antibodies
Anti-Scl 70 and centromere antibody
Lyme titer
Hepatitis B virus titer
Hepatitis C virus titer
HIV titer
Cytomegalovirus titer
Epstein-Barr virus titer
Serum and urine immunofixation electrophoresis
Angiotensin-converting enzyme

Neuropathic features may precede the diagnosis of malignancy and manifest as a progressive asymmetric or symmetric sensorimotor axonal polyneuropathy or mononeuritis multiplex. Constitutional symptoms may be absent. Vasculitic neuropathy has been described anecdotally as a complication of prescription medications (eg, interferon-α) or as a consequence of illicit drug use, such as cocaine [24].

Electrodiagnostic studies are especially helpful by demonstrating widespread, subclinical involvement in patients previously considered to have an "idiopathic" axonal polyneuropathy. For example, although the "classic" EMG pattern of multifocal axon loss is not always readily observed, finding prominent asymmetries of the compound muscle action potential or sensory nerve action potential amplitude between nerves in one limb, or homologous nerves in opposite limbs, or greatly reduced amplitudes in nerves of the arm with normal potentials in the leg, indicates an asymmetric, non–length dependent, axon loss pattern [25,26]. Conduction block occasionally may be detected if the EMG is performed within a few days of ischemic nerve infarction; the conduction block disappears a few days later after Wallerian degeneration of the distal nerve segment. This phenomenon has been termed "pseudo-conduction block" [27]. The most commonly affected motor nerves are peroneal (90%), tibial (38%), ulnar (35%), and median (26%) [28, Class III].

Cutaneous nerve biopsy establishes the diagnosis of vasculitic neuropathy in most cases. A nerve biopsy is mandatory to confirm the diagnosis in patients with suspected NSVN. A combined muscle and nerve biopsy may increase the diagnostic yield and is recommended [29]. Characteristic pathological findings include: 1) T cells and macrophages invading small epineurial arteries (often < 100 μm in size); and 2) destruction or structural damage of the vessel wall with fibrinoid necrosis [29; 30, Class III]. Other supportive features of vasculitis are vessel wall narrowing or lumen occlusion, hemosiderin deposits or hemorrhage in the vessel wall, neovascularization, epineurial, perivascular inflammation, immune complex deposition, and a characteristic "ischemic" pattern of multifocal nerve fiber loss with variable degrees of axon degeneration among different nerve fascicles [3]. The sensitivity of nerve or nerve/muscle biopsy is approximately 60% if vessel wall destruction is required [29; 30, Class III].

NONSYSTEMIC VASCULITIC NEUROPATHY

The features of NSVN are similar to those of systemic vasculitis; most patients have pain, weakness, and sensory loss in peripheral nerve territories, with slow progression over months to years that conforms to: 1) classic mononeuritis multiplex (13% to 45%); 2) confluent multiple mononeuropathies leading to an asymmetric, sensorimotor, axonal polyneuropathy, plexopathy, or polyradiculoneuropathy involving the arms and legs or legs alone (30% to 85%); or 3) distal symmetric polyneuropathy (2% to 25%). The variable frequency of these patterns is related to heterogeneous selection criteria among research centers [31, Class III; 32; 33••, Class III]. Virtually all patients with NSVN report neuropathic pain and sensory symptoms; therefore, alternative conditions should be considered in those with a painless or pure motor neuropathy [33••, Class III]. A few patients have a pure sensory polyneuropathy [7; 33••, Class III]. In contrast with systemic vasculitic neuropathy, there are no other organs involved, although some patients have nonspecific symptoms such as weight loss and fatigue. Anemia and an increased erythrocyte sedimentation rate are present in one third of patients, but other laboratory test results are normal. The EMG shows a multifocal or generalized, asymmetric axonal neuropathy affecting motor and sensory fibers, with the peroneal, tibial, and ulnar nerves most commonly affected [31,33••, Class III]. The course of NSVN is more indolent compared with systemic vasculitic neuropathy, and symptoms may be present for several years before the diagnosis is established [9; 31, Class III]. Probably less than 10% of patients with NSVN develop systemic features with long-term follow-up [31, Class III].

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

The nosology of lumbosacral radiculoplexus neuropathy in patients with diabetes mellitus remains controversial. Ninety-five percent of patients have type II diabetes mellitus [3,34••,35–37]. Weight loss is common, but other systemic features are absent. Patients develop the abrupt onset of severe unilateral pain typically localized to the thigh or hip regions. The pain persists for days to weeks, followed by weakness in muscles innervated by the upper lumbar motor roots or plexus, leading to atrophy and substantial weakness of the hip flexors, knee extensors, and thigh adductors. Weakness may spread to distal leg muscles, and conversely, the condition may begin with weakness of L5 and S1-2 muscles. Virtually all develop weakness in the contralateral limb as the condition advances. The course is monophasic, and most patients reach a plateau after several months. Although the natural history suggests spontaneous recovery and a favorable outcome in most patients, many are left with permanent and disabling leg weakness [3,34••]. There are persuasive pathological data indicating that the primary pathology of diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) is a T-cell mediated microvasculitis involving small epineurial and perineurial vessels. Associated findings include perivascular inflammation (without vessel wall destruction) composed of CD4+ and CD8+ lymphocytes, focal or multifocal axon loss, expression of inflammatory cytokines and membrane attack complex deposition in vessel walls, and deposition of hemosiderin in or adjacent to blood vessels [34••].

Treatment

Systemic vasculitic neuropathy

- There have been no controlled trials of therapy for patients with SVN. The best available evidence has been gleaned from retrospective analysis of patients with vasculitic neuropathy and from treatment trials for primary systemic vasculitis (Table 2). The traditional approach has been corticosteroids (oral prednisone, 1 mg/kg per day, sometimes preceded by 3–5 days of high-dose intravenous solumedrol) combined with cyclophosphamide (orally, 1–2 mg/kg per day or intravenous pulse cyclophosphamide, 1 g/m^2) [38,39, Class I]. Prednisone is tapered over 6 to 12 months, and

azathioprine or methotrexate may be substituted for cyclophosphamide after 3 to 6 months in patients with stable disease [40, Class I]. Intravenous immune globulin (IVIG) [41,42, Class III], rituximab [43, Class III], mycophenolate mofetil (MMF) [44, Class III], and infliximab [45,46, Class III] may be helpful in some cases. Interferon-α 2a may be beneficial in patients with Churg-Strauss syndrome who have been refractory to traditional combination therapy [47, Class III].

- In those with hepatitis B–associated polyarteritis nodosa and hepatitis C with cryoglobulinemia, plasma exchange (PE) may be effective by removing the inciting antigen [5,16, Class III]. Pegylated interferon and ribavirin are recommended treatments for patients with hepatitis C infection and cryoglobulinemia, although reports have suggested that interferon may worsen vasculitic neuropathy in some cases [48, Class I; 49,50,51, Class III]. Prednisone and other immunosuppressive agents also are required in some cases (Table 2) [5,41,51, Class III]. Aggressive antiviral therapy is indicated in patients with HIV or cytomegalovirus-associated vasculitic neuropathy, and prednisone has been anecdotally reported to be effective in some patients [2,21,22,52, Class III]. Toxin- or medication-induced vasculitic neuropathy can be managed successfully by removal of the offending agent, and prednisone also may be necessary. Treatment of paraneoplastic vasculitic neuropathy is directed at the primary malignancy. In patients for whom cancer therapy has failed, trials of prednisone and cyclophosphamide should be offered [23, Class III].

Nonsystemic vasculitic neuropathy

- Treatment of NSVN remains controversial. Because the prognosis is generally more favorable than that of SVN, many experts think prednisone is sufficient, and cyclophosphamide should be added in patients who fail to respond to corticosteroids [53,54, Class III]. A retrospective analysis has suggested that patients treated with combined therapy had greater recovery and fewer relapses at 6 months, compared with those who were treated only with prednisone [31,33••, Class III]. The latter approach is favored in most cases, combining oral daily prednisone with intravenous pulse cyclophosphamide for 6 months. This regimen has been well-tolerated in my patients. Prednisone monotherapy is a reasonable alternative in those with contraindications to cyclophosphamide or modest neurologic deficits and an indolent course.

Diabetic lumbosacral radiculoplexus neuropathy

- Retrospective series have suggested that PE, corticosteroids, and IVIG may be beneficial for patients with DLSRPN [4,55–57, Class III]. A randomized controlled trial indicated that when intravenous methylprednisolone (1 g) was administered several times per week for 12 weeks, numerous neurologic symptoms, including pain, improved compared with placebo [58, Class I]. However, there was no significant difference in the primary endpoint, the time to improve 4 points in the lower limb impairment score [58, Class I]. Until further randomized studies are completed, it seems reasonable to offer patients with DLSRPN an empiric trial of intravenous methylprednisolone, especially for those with severe pain or substantial functional disability.

Table 2. Vasculitic neuropathies: recommended treatments

Syndrome	Case series	Reported response rate	Case reports
Primary systemic vasculitis			
Polyarteritis nodosa, microscopic polyangiitis, Churg-Strauss syndrome, Wegener's granulomatosis	Prednisone 1 mg/kg/day and oral cyclophosphamide 2 mg/kg/day, or pulse intravenous cyclophosphamide 1 g/m^2; taper prednisone over 6–12 months; taper cyclophosphamide over 6–12 months, or convert to azathioprine 1–2 mg/kg/day after 3–6 months if clinically stable	40% to 100%	IVIG, plasma exchange, rituximab, infliximab, mycophenolate mofetil
	Or convert to methotrexate 15–25 mg orally or intravenously every week for 12–24 months		Interferon-α 3 million IU three times/week for treatment-refractory cases
Temporal arteritis			Prednisone 1 mg/kg/day, tapered over 3–12 months
Rheumatoid vasculitis	Prednisone and cyclophosphamide; methotrexate	Approximately 50%	Six to 12 plasma exchanges, IVIG, penicillamine, azathioprine
Lupus vasculitis			Prednisone, cyclophosphamide, rituximab; azathioprine, methotrexate, IVIG
Sjögren syndrome	Prednisone, cyclophosphamide	Approximately 10% to 20%	IVIG, plasma exchange, penicillamine, hydroxychloroquine
Systemic sclerosis			Prednisone, cyclophosphamide
Sarcoidosis	Prednisone	50% to 100%	IVIG, cyclosporine, cyclophosphamide, methotrexate; azathioprine
Drug-induced vasculitis			Stop offending agent; prednisone
Paraneoplastic			Treat malignancy; cyclophosphamide
HBV-polyarteritis nodosa vasculitis	Prednisone, plasma exchange, interferon-α 2b	Approximately 80%	
HCV-associated cryoglobulinemic vasculitis	Plasma exchange, prednisone +/- cyclophosphamide, interferon-α	40% to 70%	IVIG, rituximab, cyclosporine, cyclophosphamide
HIV-associated vasculitis without cytomegalovirus infection			Prednisone, zidovudine and plasma exchange; prednisone monotherapy
HIV- and cytomegalovirus-associated vasculitis	Ganciclovir and foscarnet		
Nonsystemic vasculitic neuropathy	Prednisone, +/- oral or intravenous pulse cyclophosphamide; add cyclophosphamide for treatment-refractory cases	60% to 95%	
Lumbosacral plexus neuropathy	Intravenous methylprednisolone, prednisone	60% to 100%	

HBV—hepatitis B virus; HCV—hepatitis C virus; IVIG—intravenous immunoglobulin.

St. Elizabeth's Medical Center experience

- Review of case files and nerve biopsy specimens from St. Elizabeth's Medical Center, Boston, MA, identified 29 patients with pathologically verified vasculitic neuropathy who were personally evaluated during a 12-year period; 21 had SVN and nine had NSVN. Treatment response and follow-up information were available in 14 patients with SVN and eight patients with NSVN.
- In the SVN group, three patients each had Churg-Strauss syndrome and Sjögren syndrome, two had B-cell lymphoma, and one each had polyarteritis nodosa, rheumatoid arthritis, temporal arteritis, cryoglobulinemia, dermatomyositis, and paraneoplastic vasculitic neuropathy (small cell lung carcinoma). Eight patients had mononeuritis multiplex, four had generalized asymmetric polyneuropathy (three with quadriparesis), and two had distal, symmetrical, sensorimotor polyneuropathy. All had neuropathic pain. Eight patients were treated with combined therapy with intravenous pulse or oral cyclophosphamide for 6 to 12 months and prednisone; seven (88%) had unequivocal improvement in strength, functional disability, and pain [33••, Class III]; one died without improvement (B-cell lymphoma). Two patients were treated with prednisone monotherapy, and one improved. One each received prednisone and PE, IVIG and oral cyclophosphamide, and PE alone—all improved. One patient declined therapy.
- In the NSVN group, six patients had mononeuritis multiplex and one each had generalized asymmetric polyneuropathy and distal symmetric polyneuropathy. Five patients received combined therapy with cyclophosphamide and prednisone, and three improved; two others had prednisone monotherapy and also responded, and one was treated with prednisone and azathioprine and improved. In summary, six of eight patients (75%) improved with immunosuppressive therapy.

Pharmacologic treatment

Prednisone

	Prednisone has been the accepted initial therapy for SVN and NSVN for decades but has never been subjected to a randomized controlled trial [5,8,28,30,31,33••, 53,54, Class III]. Most patients observe improved strength and less pain after several weeks to months. Maximal improvement may be delayed 6–12 months after initiation of prednisone because of the nature of axonal regeneration after nerve infarction.
Standard dosage	1–1.5 mg/kg per day. An alternate day regimen may be initiated after 2 or 3 months by tapering every few weeks by 5–10 mg on the alternate day, based on the clinical response. If there is a relapse, the dose should be increased to the minimum that induces improvement, and cyclophosphamide (intravenous pulse or daily oral therapy) should be added.
Contraindications	Systemic fungal infections, history of tuberculosis, osteoporosis, and active peptic ulcer disease.
Main drug interactions	Amphotericin B, phenytoin, and rifampin reduce the efficacy of prednisone. Concurrent use of aspirin or nonsteroidal anti-inflammatory agents increases the risk of gastrointestinal hemorrhage. Hypokalemia may be exacerbated when steroids are administered with diuretics (eg, furosemide).
Main side effects	Mood lability, insomnia, edema, osteoporosis, gastric irritation, myopathy, cataracts, hypertension, diabetes mellitus, aseptic necrosis of the femoral head, poor wound healing, and increased susceptibility to infections.
Special points	Long-term prednisone therapy may be poorly tolerated in those with certain medical conditions (eg, obesity, osteoporosis, diabetes). Careful monitoring of weight, blood pressure, blood glucose, and electrolytes is necessary. Bone density measurements and calcium, vitamin D, and bisphosphonate supplementation are warranted.

Cost/cost effectiveness Prednisone costs approximately $20/month and is probably cost effective in the treatment of vasculitic neuropathy. However, the cost of managing steroid-induced complications, such as hip fracture and gastrointestinal bleeding, may be expensive and add to potentially large "hidden" expenses associated with prednisone therapy.

Cyclophosphamide

Cyclophosphamide can be added to prednisone as combined therapy for patients with systemic and NSVN [5,28,31,33••, Class III; 38; 39, Class I]. The drug may be administered orally as a single daily dose or as pulse intravenous therapy on a monthly basis. I prefer to use intravenous pulse therapy at a dosage of 1 g/m^2, with subsequent dosage adjustments determined by the nadir of the leukocyte count, with a target of 2–3 K/μL. The maximal leukopenic effects of this regimen occur at 2 weeks and allow for safer administration and monitoring compared with oral therapy [39, Class I].

Standard dosage Oral: 2 mg/kg/day; intravenous: 1 g/m^2 administered monthly for 6–12 months.

Contraindications Pre-existing bone marrow disorder, bladder carcinoma, and pregnancy.

Main drug interactions Phenobarbital increases the rate of metabolism and leukopenic activity of cyclophosphamide. Succinylcholine inhibits cholinesterase activity, and this effect is potentiated by cyclophosphamide.

Main side effects Bone marrow suppression, risk of systemic infection, hemorrhagic cystitis, infertility, teratogenic effects, amenorrhea, nausea, vomiting, anorexia, and alopecia. There is higher risk of malignancy, especially lymphoma and leukemia, in patients receiving long-term cyclophosphamide therapy.

Special points Leukopenia is the most common adverse effect. A complete blood count (CBC) should be checked weekly after the first dose of intravenous cyclophosphamide; with subsequent cycles of therapy, the CBC should be measured after 2 weeks and the dosage adjusted to produce a transient reduction of the leukocyte count. Urinalysis should be monitored every few weeks for the first several months, then monthly thereafter. Intravenous fluid should be given at the time of cyclophosphamide infusion to reduce the risk of hemorrhagic cystitis; those on oral therapy should be encouraged to increase oral fluid intake. Nausea can be avoided by administering anti-emetics.

Cost/cost effectiveness A 1-month supply of 50 mg of oral cyclophosphamide costs approximately $450. An infusion of 1 g/m^2 of cyclophosphamide costs approximately $30. No cost effective analysis has been published.

Azathioprine

Azathioprine is used as adjunctive therapy for vasculitic neuropathy, usually with prednisone as a steroid-sparing agent or as an alternative to cyclophosphamide [40, Class I].

Standard dosage 2–3 mg/kg/day administered orally as a single daily dose. The drug should be started at 50 mg/day for several days and escalated by 50 mg every 3–5 days to the target dosage.

Contraindications Leukopenia (leukocyte count < 3 K/μL), thrombocytopenia (platelet count < 50 K/μL), systemic infection, and liver disease.

Main drug interactions Allopurinol blocks the metabolic pathway for detoxification of azathioprine; therefore, the dosage of azathioprine should be reduced by at least one third when used with allopurinol. Angiotensin-converting enzyme inhibitors should be avoided in patients treated with azathioprine because of the risk of leukopenia.

Main side effects An acute hypersensitivity reaction characterized by nausea, vomiting, diarrhea, and fever develops in some patients in the first several weeks of treatment. These symptoms resolve when the drug is discontinued. Drug-induced pancreatitis is rare. Delayed side effects include dose-dependent bone marrow suppression, risk of systemic infection, and hepatotoxicity with increased liver enzymes. The risk of neoplasia is another concern with long-term azathioprine therapy, although the exact incidence is unclear. Azathioprine is potentially teratogenic, and patients should use contraceptive measures during and at least 6 months after discontinuing treatment.

Special points CBC and liver enzymes should be monitored weekly during the first month of therapy, then monthly for 6 months, and then every 3 months. A disadvantage of azathioprine is the long interval, usually at least 6 months, between the initiation of treatment and a clinical response.

Cost/cost effectiveness	Azathioprine costs approximately $450/month. There are no studies assessing cost effectiveness.

Methotrexate

	Methotrexate has been used as adjunctive therapy in rheumatoid arthritis and inflammatory myositis, and as a steroid-sparing agent for patients with systemic vasculitis. It may be substituted for cyclophosphamide as primary treatment for antineutrophil cytoplasmic antibody–associated vasculitis [59, Class I].
Standard dosage	7.5–15 mg as a weekly oral dosage; the dosage may be increased to 20–25 mg/week based on the clinical response.
Contraindications	Methotrexate is teratogenic and contraindicated during pregnancy. Other contraindications include pre-existing blood dyscrasias, liver disease, immunodeficiency syndromes, and pulmonary fibrosis.
Main drug interactions	Concomitant use of NSAIDs may increase serum levels of methotrexate. Tetracycline and chloramphenicol reduce drug absorption. Penicillins reduce renal clearance. The risk of hepatotoxicity is increased when methotrexate is administered with other hepatotoxic drugs.
Main side effects	Ulcerative stomatitis, nausea, vomiting, leukopenia, fatigue, dizziness, rash, bone marrow suppression, and risk of infection.
Special points	Liver enzymes should be followed routinely, and the drug should be discontinued if liver function test results remain abnormal despite dose reduction; liver fibrosis has been reported rarely. CBC should also be monitored for thrombocytopenia and leukopenia. Stomatitis requires dose reduction. Folate (1 mg/day) should be administered concurrently. A rare but serious complication is interstitial pneumonitis, manifesting as dry cough, dyspnea, and fever; methotrexate should be used with caution in patients with pulmonary disease.
Cost/cost effectiveness	Methotrexate (15 mg/week) costs approximately $60/month. No studies assessing cost effectiveness in vasculitic neuropathy have been published.

Therapies for viral-associated vasculitic neuropathy

Interferon-α

	Injections of interferon-α have been demonstrated to be effective in the treatment of hepatitis B and C [48, Class I], and may be useful therapy in patients with cryoglobulinemia and vasculitic neuropathy [12,49, Class III].
Standard dosage	0.5 mL intramuscularly, three times weekly (interferon-α 2b).
Contraindications	Bone marrow suppression, liver failure, and pregnancy.
Main drug interactions	Colchicine decreases the effectiveness of interferon-α. Interferons inhibit the metabolism of theophylline and lead to theophylline toxicity.
Main side effects	Flu-like symptoms, headache, chills, myalgias, nausea, fatigue, injection site reaction, anorexia, diarrhea, dizziness, depression, hypothyroidism, and rash.
Special points	Injection sites should be rotated to minimize skin reactions. The flu-like reaction usually resolves after several injections and can be minimized if acetaminophen is administered with each injection.
Cost/cost effectiveness	A 1-month supply of interferon-α 2b costs approximately $450.

Interventional procedures

Plasma exchange

	PE may be an effective therapy for hepatitis B infection (associated with polyarteritis nodosa) and hepatitis C with cryoglobulinemia [60,61, Class III]. The beneficial effect of PE results from removal of pathogenic humoral factors, such as circulating immunoglobulins or auto-antibodies. A single exchange removes 3–5 L of plasma and reduces circulating IgG by approximately 45%; a typical course involves 10–15 exchanges based on the plasma volume of the patient. A common treatment regimen is three

exchanges/week for 3 weeks, followed by two/week for 3 weeks, then weekly for several weeks or until there is a clinical response. Prednisone or other immunosuppressive regimens usually are administered concurrently.

Standard procedure No specific guidelines have been established for patients with vasculitic neuropathy caused by hepatitis B or C. Patients with severe disability (eg, those who are nonambulatory) can be treated with five exchanges performed over 7–10 days on an inpatient basis. Improvement usually occurs within several weeks followed by a plateau of weeks to months; exchanges may be repeated periodically to maintain improvement.

Contraindications Hemodynamic instability, coagulation disorders, and thrombocytopenia.

Main drug interactions The use of angiotensin-converting enzyme inhibitors leads to symptomatic hypotension and should be avoided for at least 1 day before PE. Other essential medications should be administered well before or after completion of an exchange.

Complications Hypotension, cardiac arrhythmia, vasovagal reaction, citrate toxicity with nausea and vomiting, electrolyte imbalance (citrate-induced hypocalcemia), allergic reactions to infused plasma or plasma substitutes, anemia, thrombocytopenia, muscle cramps, paresthesias, and infection, bleeding, venous thrombosis, and pneumothorax as a complication of the use of indwelling venous catheters.

Special points The response to PE is usually rapid but less sustained than other therapies. Accordingly, PE usually is reserved for those with fulminant, rapidly progressive disease and used with other immunomodulating regimens. Patients with poor peripheral venous access require placement of a central venous catheter. Intravenous saline (0.5–1 L) administered several hours before an exchange reduces the risk of hypotension and vasovagal symptoms. PE is generally safe and well-tolerated, but it is cumbersome, invasive, and requires expensive equipment and ancillary personnel and is usually used only in specialized medical centers familiar with the procedure.

Cost effectiveness PE costs approximately $5000 to $10,000/series of exchanges.

Assistive devices

- Patients may benefit from canes, walkers, ankle-foot orthotics, and other rehabilitation devices and strategies to assist ambulation and other activities of daily living.

Physical/occupational therapy and exercise

- Physical and occupational therapy may be helpful to maintain range of motion, prevent joint contractures in paretic limbs, and assist in gait retraining.
- Modest exercise regimens may help reduce physical fatigue and increase endurance.

Emerging therapies

Mycophenolate mofetil

MMF is a novel immunosuppressant that, like azathioprine, has been used successfully for prevention of acute rejection after organ transplantation and has been used in immune-mediated neuropathies [62, Class III]. A pilot study indicated that MMF maintained remission in patients with Wegener's granulomatous and microscopic polyangiitis, yet another study indicated that patients treated with MMF had a higher relapse rate [63,64, Class III]. An international trial comparing MMF with azathioprine for maintenance therapy in renal vasculitis is ongoing.

Standard dosage 1 g administered orally twice/day.

Contraindications Hypersensitivity to MMF.

Main drug interactions The concurrent administration of MMF and cholestyramine may decrease the levels and clinical effects of MMF.

Complications Susceptibility to infection; increased risk of lymphoma or other malignancies, particularly of the skin, related to intensity and duration of immunosuppression; diarrhea, leukopenia, sepsis, and vomiting.

Special Points	MMF usually is administered in combination with prednisone. This agent should not be used in pregnant women because of its potential teratogenic effects. CBC should be monitored for neutropenia monthly for the first few months and then every 3 months.
Cost/cost effectiveness	The cost of MMF is approximately $450/month. No cost analysis has been performed.

Intravenous immune globulin

	IVIG has been reported to be effective in some patients with vasculitic neuropathy [41,42, Class III]. Those who improve may relapse and require periodic treatment at intervals from 1–4 weeks to maintain improvement.
Standard dosage	2 g/kg intravenously over 2–5 days. The frequency needs to be individualized depending on the duration of improvement.
Contraindications	Absolute IgA deficiency, hypersensitivity or anaphylactic reaction after exposure to human immune globulin.
Main drug interactions	None.
Main side effects	Headache, aseptic meningitis, flu-like reaction, rigors, myalgias, flushing, fluid overload with edema or congestive heart failure, renal insufficiency, transient neutropenia, back, chest, leg or abdominal pain, and eczematous rash. Rarely, IVIG induces a hyperviscosity syndrome with increased risk for stroke, myocardial infarction, or deep venous thrombosis. In patients with absolute IgA deficiency, an anaphylactic reaction may occur. The risk of hepatitis C and HIV transmission has been eliminated through effective processing techniques.
Special points	IVIG may be administered by rapid infusion (1 g/kg/day over 4–6 hours, for 2 days) in younger and otherwise healthy patients, and is generally well tolerated. The drug should be given at a slow rate to the elderly or those with vascular disease, or cardiac or renal insufficiency. Headache, fluid overload, and flu-like symptoms are more likely to occur at higher infusion rates. Pretreatment with 60 mg of intravenous methylprednisolone may reduce the severity of headaches in headache-prone patients. The first treatment should be monitored in a supervised setting (hospital, office, or outpatient clinic), and if well tolerated, subsequent infusions may be provided safely in the home. An IgA level and renal function studies should be checked before IVIG administration.
Cost/cost effectiveness	IVIG is very expensive ($8500 to $20,000/infusion), and the cost may vary depending on drug availability.

Rituximab

	Rituximab is a chimeric monoclonal immunoglobulin that binds to the CD20 transmembrane antigen expressed by mature B cells. It is an effective therapy for non-Hodgkin's lymphoma and has been used in patients with autoimmune diseases and paraproteinemic neuropathies with some success [65,66, Class III]. There are a few reports of efficacy in patients with systemic vasculitis [43,67–69, Class III].
Standard dosage	375 mg/m^2 intravenously, weekly for 4 weeks.
Contraindications	This agent should not be used in women who are breastfeeding.
Main drug interactions	Renal toxicity when administered concurrently with cisplatin.
Main side effects	Hypotension, nausea, vomiting, chills, dyspnea, fever, flushing, fatigue, angioedema, headache, urticaria, pruritus, and pulmonary disease.
Special points	Rituximab is generally well tolerated. Most side effects are related to the rate of the infusion—this drug should never be administered as a bolus infusion because of the high risk of a hypersensitivity reaction. The initial rate should be 50 mg/hour and increased incrementally every half hour up to 400 mg/hour.
Cost/cost effectiveness	A course of rituximab (four weekly infusions) costs approximately $12,000.

Infliximab

	Infliximab is an IgG kappa monoclonal antibody that inhibits tumor necrosis factor–α (TNF-α) by high affinity binding to TNF-α and by blocking binding to its transmembrane receptor. Infliximab is indicated for rheumatoid and psoriatic arthritis,

	ankylosing spondylitis, and Crohn's disease. A few case reports and one prospective, open trial have indicated that infliximab was effective in patients with systemic vasculitis who were refractory to standard therapies [70, Class I; 71,72, Class III]. There are no studies of infliximab in patients with vasculitic neuropathy.
Standard dosage	3–5 mg/kg as a single intravenous infusion, repeated 2 and 6 weeks later and then every 8 weeks.
Contraindications	Moderate to severe congestive heart failure.
Main drug interactions	Live vaccines should not be administered concurrently to patients who are receiving infliximab therapy.
Main side effects	Abdominal pain, nausea, diarrhea, upper respiratory and urinary tract infections, pharyngitis, sinusitis, rash, fever, headache, arthralgias, back pain, cough, and fatigue.
Special points	Infliximab should not be used in patients with an active infection, and it should be used with great caution in those at high risk for infection. Tuberculosis and fungal and opportunistic infections have been observed in patients who received infliximab; some of these infections have been fatal. Patients should have tuberculin skin testing before initiating therapy.
Cost/cost effectiveness	The cost of infliximab is $691/100-mg vial; therefore, each infusion costs approximately $1500.

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