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Article Topic: Neuropathies Due to Infections and Antimicrobial Treatments

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Abstract

Purpose of eview The aim of this review is to discuss the presentation, diagnosis, and management of polyneuropathy (PN) in selected infections. Overall, most infection related PNs are an indirect consequence of immune activation rather than a direct result of peripheral nerve infection, Schwann cell infection, or toxin production, though note this review will describe infections that cause PN through all these mechanisms. Rather than dividing them by each infectious agent separately, we have grouped the infectious neuropathies according to their presenting phenotype, to serve as a guide to clinicians. Finally, toxic neuropathies related to antimicrobials are briefly summarized.
Recent findings While PN from many infections is decreasing, increasing evidence links infections to variants of GBS. Incidence of neuropathies secondary to use of HIV therapy has decreased over the last few years.
Summary In this manuscript, a general overview of the more common infectious causes of PN will be discussed, dividing them across clinical phenotypes: large- and small-fiber polyneuropathy, Guillain-Barré syndrome (GBS), mononeuritis multiplex, and autonomic neuropathy. Rare but important infectious causes are also discussed.

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Introduction

Infectious diseases contribute to multiple polyneuropathy (PN) syndromes important to recognize insofar as they are treatable. Infectious diseases can cause prototypical sensorimotor large- and small-fiber axonal PN, acquired demyelinating PN, mononeuritis multiplex, and autonomic neuropathy. Recognition of these phenotypes as the presentation of an infectious disease has obvious implications in prompt treatment. When the phenotype is the consequence of an immune response to an infectious antigen, such as Guillain-Barré syndrome, diagnosis and recognition of the likely triggering microbe may lead to recognition of an epidemic and lead to changes in public health measures. Some of the infectious agents discussed in this manuscript may cause different phenotypes. Instead of using a "standard" approach of listing each of the infections individually, we thought it best to start with the phenotype, representing the way the patient presents to the clinician. Finally, we have briefly discussed the most common neuropathies related to antimicrobial use.

Polyneuropathy

HIV

PN is historically the most common neurological complication of HIV infection, and likely represents the most common PN associated with infection. It is generally a complication of chronic infection with low CD4 T cell counts (typically < 300), known as HIV-associated distal sensory polyneuropathy (HIV-DSP). A treatment-related toxicity related to older antiretroviral drugs, known as antiretroviral toxic neuropathy (ATN), may also occur but is not a recognized complication with current antiretroviral regimens.

Early after introduction of combination antiretroviral therapy (CART) (which commenced around 1996 with the introduction of protease inhibitors and continues to this day) approximately 35% of patients with moderate to severe immunodeficiency had symptomatic PN [1–4]. Asymptomatic neuropathy was additionally observed in up to 15%. These estimates represented an admixture of HIV-DSP and ATN. Currently in developed countries, symptomatic PN impacts only 10%, with earlier HIV diagnosis and faster initiation of non-neurotoxic therapy contributing to this trend [5].

Both HIV-DSP and ATN patients present with distal numbness and neuropathic pain, affecting quality of life and function [6–8]. Exam reveals stocking-distribution impairment of pain, temperature, or vibratory sensation with decreased or absent ankle reflexes [9]. Weakness is not prominent but when present is limited to distal lower extremity extensor muscles. These PNs may also be symptom-predominant with minimal, if any, abnormal exam signs, consistent with "small fiber" pathology.

Increased risk of HIV-DSP is conferred by older age, diabetes, and substance abuse. Multiple comorbidities can contribute to the development of HIV-DSP: malnutrition and vitamin (e.g., thiamine, B12) deficiencies, metabolic syndrome, and renal insufficiency. In considering extent of workup, the level of immunodeficiency during onset and evolution of PN symptoms is important: while with severe immunodeficiency in a treatment-naïve

patient, alternative causes are unlikely; however, if PN symptoms commence or evolve with mild immunodeficiency (e.g., CD4 > 500), or occur in the setting of suppressed viral load on non-neurotoxic CART, other etiologies should be considered.

ATN is classically associated with the HIV dideoxynucleoside reverse transcriptase inhibitors, including zalcitabine, didanosine, and stavudine. Commonly used drugs up to the early 2000s for the treatment of HIV/AIDS, introduction of newer antiretrovirals have supplanted their clinical use though patients who were exposed to these medications may have ongoing neuropathic symptoms despite stopping the offending agent. ATN diagnosis depends on the timing of symptom onset (generally within 3 months to 1 year of starting the medication) or clinical worsening related to drug exposure, or the patient's improvement after drug withdrawal [10]. The underlying pathophysiology is thought to be inhibition of mitochondrial DNA polymerase, with subsequent mitochondrial toxicity [11]. At times the neuropathic symptoms of ATN may continue to progress for weeks after drug withdrawal, commonly referred to as "coasting," which is a phenomenon less relevant today given that they are not frequently utilized.

No large-scale trial shows meaningful improvement of symptomatic HIV-DSP after initiation of CART therapy; as such, though CART is indicated in untreated patients, management strategies focus on analgesic therapy for neuropathic pain to improve quality of life and function [12–14]. There is, unfortunately, a paucity of data supporting the efficacy of many analgesic regimens for the treatment of HIV-associated neuropathic pain. Despite this, use of medications utilized in other neuropathic pain conditions is common. For a recent review of analgesic treatment of neuropathic pain, see Finnerup et al. [15].

Uncommon causes of polyneuropathy in HIV

Diffuse infiltrative lymphomatosis syndrome (DILS) is characterized by multisystem CD8 lymphocytic visceral infiltration primarily involving salivary glands and lungs, but also the kidney, gastrointestinal system, and peripheral nerve. The combination of parotid enlargement, sicca symptoms, and CD8 hyperlymphocytosis is classic. Salivary biopsy or gallium scintigraphy may show evidence for lymphocytic infiltration. Polyneuropathy typically presents as acute-to-subacute painful sensorimotor axonal PN [16]. Nerve biopsy shows angiocentric peripheral nerve infiltration of T lymphocytes, mimicking that seen with T cell lymphoma [17]. Treatment of DILS-related neuropathy includes initiation of CART with or without low to moderate doses of oral corticosteroids.

GBS, mononeuritis multiplex, and autonomic neuropathy in the setting of HIV will be discussed in the following sections.

Mononeuritis multiplex

Hepatitis B

An estimated 296 million people are chronically infected with HBV worldwide, combined with an estimated 1.5 million new infections annually in 2019 [18]. Hepatitis B causes chronic infection in approximately 10%, and of those with chronic HBV infection, approximately 20% may develop extrahepatic disease.

The most serious presentation of extrahepatic disease is polyarteritis nodosa (PAN), a vasculitis preferentially affecting medium-sized arteries. The pathogenesis of PAN is related to the deposition of immune complexes containing HBSAg or HBEAg triggering activation of the complement cascade and neutrophils. PAN generally occurs within 6 months of infection with prominent constitutional symptoms of fever, weight loss, arthralgia, and myalgia [19]. Markers of inflammation and acute phase reactants may be elevated, transaminases typically are not markedly elevated, HbSAg is almost always present, and ANCA as well as cryoglobulins are negative. PN is the most frequent finding in PAN, seen between half to three quarters of patients, and it should be recognized that up to 25% of those with apparently isolated cutaneous PAN may also have electrodiagnostic evidence of PN [20, 21]. The classic presentation is a painful mononeuropathy multiplex (MM), though may present as a subacute stocking-distribution painful PN. Rash predominately affects the legs and presents in a protean fashion: livedo reticularis, painful subcutaneous nodules, skin ulcers or infarcts, or purpura. Nerve conduction studies typically show evidence for an asymmetric, non-length dependent sensorimotor axonal PN. Needle exam typically shows ongoing denervation coupled with reinnervation changes that may vary from acute to chronic. Concomitant irritable myopathy may be observed. Skin biopsy may reveal leukocytoclastic vasculitis. In suspected peripheral nervous system (PNS) vasculitis, nerve biopsy (generally sural, superficial peroneal or radial), combined with muscle biopsy (gastrocnemius, peroneus brevis, or deltoid) may increase diagnostic sensitivity given frequent vascular involvement of intramuscular arteries.

Given the rarity of this disease, randomized controlled trials are limited. Current treatment aims for suppressing viral replication in combination with clearance of pathogenic immune complexes, the latter typically with plasma exchange (for a review, please refer to Hocivar et al. [22••]) [23, 24]. If steroids are used, short (2-week) course is generally recommended.

Hepatitis C

Globally, an estimated 58 million people are infected with hepatitis C, with an estimated 1.5 million new infections annually [25]. In the absence of treatment, 55% to 85% of acute HCV infections will become chronic. While 95% of infections can be successfully treated with antiviral medications, many

patients face barriers to diagnosis and access to treatment. Chronic HCV infection is related to several extrahepatic syndromes, including mixed cryoglobulinemia, renal impairment, polyarthralgia, and sicca syndrome. PN is considered one of the most common neurological complications of chronic HCV, affecting approximately 10% or more [26–28].

Up to 50% of chronically infected patients develop mixed cryoglobulinemia [26]. Cryoglobulins represent immunoglobulins that precipitate in vitro at temperatures ≤ 37 °C, generated by clonal expansion of B cells in the setting of persistent immune stimulation. HCV-related cryoglobulinemia is generally comprised of "mixed" cryoglobulin, consisting of either monoclonal IgM with polyclonal IgG (type II) or polyclonal IgM and IgG (type III). Mixed cryoglobulinemic vasculitis affects small- to medium-sized arteries.

Low complement levels (C4 and CH50) and rheumatoid factor activity may suggest cryoglobulinemia. False negative lab results for cryoglobulinemia may reflect problems with collection and/or laboratory processing [29]. Treatment of HCV-associated PN focuses on treatment of the infection with direct-acting antivirals [30]. There is, additionally, evidence to suggest that rituximab may be safe and efficacious [31••].

HIV

PNS vasculitis is rare in HIV. When identified, it presents early after initial infection or in the setting of severe immunodeficiency, at which time opportunistic infections may be the driving force for the syndrome. Acute or subacute onset of painful asymmetric PN helps distinguish this entity from HIV-DSP.

Vasculitis affecting all vessel types have been reported, with the pathological hallmark being necrotizing thrombosis or inflammatory infiltration of vessels on nerve biopsy. Early in HIV with mild to moderate immunosuppression, vasculitis may be associated with immune complex deposition or infiltrating CD8 T cells. This may reflect a reaction to HIV infection of endothelial cells or neoplasm. Other potential causes that are important to consider include HBV or HCV co-infection, cryoglobulinemia, immune complex disease, and drug-induced vasculitis. Serum autoantibodies (e.g., ANA, RF, ANCA), when present, are nonspecific given the polyclonal B cell activation given abnormal T cell regulation in HIV infection. With severe immunodeficiency, CMV is the classic vasculitis pathogen, and particularly so with a history of CMV infection (i.e., prior or concurrent CMV retinitis, gastroenteritis, or pneumonia). The diagnostic utility of plasma CMV PCR in this setting is unclear, being insensitive and non-specific for nervous system involvement.

Management depends mostly on the severity of prevailing immunodeficiency. Early vasculitis may therefore be treated with CART, whereas in the setting of concomitant/opportunistic infection therapy is directed toward the underlying co-infection. Clinical trial data is limited given the rarity. For those with advanced immunodeficiency and CMV infection, ganciclovir with or without foscarnet is favored, though the toxicity profiles of these medications in the individual circumstances must be considered (e.g., hematopoietic, renal). Immunosuppressive mediations such as steroids may potentially worsen outcomes in severe immune deficiency.

Leprosy

Mycobacterium leprae and *Mycobacterium lepromatosis* (together referred to as the *M. leprae* complex) cause chronic mycobacterial infection of skin and nerve. Familiarity with the signs of lepromatous polyneuropathy (Hansen's disease) is important as early diagnosis and treatment prevents disability. Leprosy remains an important cause of PN and disability worldwide, with approximately 200,000 cases annually [32]. An asymmetrical, non-length dependent MM is the most common pattern though generalized PN may also be seen.

Predominately in tropic and subtropic regions, most cases are currently reported in South-East Asia and Brazil. In the USA, there are pockets of endemism in Texas, Louisiana, Hawaii, and California. Humans are the principal reservoir, though armadillos also serve as reservoirs in the western hemisphere. Transmission occurs primarily via respiratory or nasal droplets; cutaneous transmission can occur if the skin barrier is not intact. A long interval between infection and clinical symptoms, up to decades, is common as *M. leprae* is slow growing (with a doubling time of almost 2 weeks) [33].

Neuropathy may result from either direct infection of Schwann cells or the immune response to mycobacterial antigens. Sensory symptoms and signs are more common than motor symptoms, with "negative" sensory symptoms predominating. Temperature and pain sensation are disproportionately affected compared to vibratory sensation and joint proprioception [34]. Commonly affected nerves include superficial nerves such as the sural, fibular, posterior tibial, ulnar, and superficial radial sensory nerves as *M. leprae* preferentially replicates in cooler temperatures. As such, clinical stigmata tend to be found in cooler regions of the body: nose, ears, tips of fingers, and toes. In up to 10%, skin lesions may be absent with PN being the only symptom.

Clinical diagnosis is made by the presence of typical skin lesions (e.g., hypopigmented or reddish skin patch with definite hypesthesia), thickened or enlarged nerves with sensory loss in the distribution of that nerve, and skin smear or biopsy documenting acid-fast bacilli. Clinical and histological features (Table 1) may be used to classify leprosy patients, with the WHO classification being most employed.

The WHO recommendations for treatment for paucibacillary disease are rifampin and dapsone for 12 months while multibacillary disease is treated with rifampin, clofazimine, and dapsone for 24 months. Screening of contacts and chemoprophylaxis with single-dose rifampin is recommended to reduce transmission to household and near contacts of infected individuals.

Host immune responses are felt to play a large role in development of neuropathy, particularly in paucibacillary disease, and continued evolution of nerve injury is common after initiation of treatment [35]. Two basic types of immune responses, or "reactions" are recognized: (1) a type I or "reversal" reaction (RR); and (2) a type II reaction, or "erythema nodosum leprosum" (EHL) reaction. These reactions can occur before, during, or after introduction of multidrug therapy. The RR represents an increase in cell-mediated immunity and presents with erythematous skin lesions coupled with nerve swelling (particularly the ulnar nerve at the elbow and tibial nerve at the tarsal tunnel/medial malleolus). EHL is distinguished from reversal reactions by subcutaneous red nodules (panniculitis), arthralgia or frank arthritis, and fever.

Table 1. Classification of leprosy based on clinical and histopathological findings from the skin lesions.

WHO Classification	Paucibacillary		Multibacillary		
HRSA Classification	**Tuberculoid**	**Borderline tuberculoid**	**Borderline-borderline**	**Borderline lepromatous**	**Lepromatous**
Quantity of Lesions	≤5 (often one)	Variable			6 or more
Shape/Size	Macules or plaques, asymmetric with defined edges, less than 10 cm before healing	Variable, plaques are larger with satellite lesions	Macular, popular, and/or plaque like, may be annular in shape	Symmetrical macular lesions, well-defined nodular areas	Macules with poorly defined margins, advanced infection associated with nodules and/or plaques
Color	Hypopigmented or red	Variable			Skin-colored or red, variations present with advanced disease
Sensation	Definite loss of sensation, thickened cutaneous nerves in proximity to lesion	variable			Less likely to have severe sensory loss
Location	Anywhere	Tend to involve larger part of extremities or trunk	Variable	Symmetrical distribution	
Acid-fast smear from slit skin samples	Negative	Variable		Positive	
Histology	Epithelioid noncaseating granulomas	Mixed		Foamy macrophages and histiocytes	

Health Resources and Services Administration, US Department of Health and Human Services

Steroids improve neurologic outcome of reversal reactions, with current recommendations endorsing prednisolone 40 mg daily, generally for about 12 weeks [36]. No conclusive evidence, however, shows steroids can prevent neuropathy [37]. Shorter courses of steroids are generally used for EHL, but with severe and/or recurrent reactions thalidomide may be considered. For further discussion about treatment options, the interested reader may refer to the recent review by Ebenezer and Scollard [38•].

Infections triggering Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) consists of a monophasic acute generalized weakness with mild sensory symptoms and hypo/areflexia localizing to the spinal roots and peripheral nerves, which progresses for four weeks and is followed by a plateau phase. Close to a third of the patients develop respiratory failure [39]. GBS is the most common cause of acute neuromuscular paralysis worldwide, with an annual incidence estimated between 0.4 and 4/100,000 [40–43]. Incidence increases during the rainy season in tropical countries [43, 44]. At least two-thirds report having either a respiratory or gastrointestinal illness in the preceding 6 weeks [41, 45, 46].

Electrophysiologically, GBS has been divided into different subtypes that have different prognoses and pathophysiology, as well as different associations with distinct infections. These electrophysiological variants are acute inflammatory demyelinating inflammatory polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN). GBS pathophysiology is thought to be explained by a post-infectious immune reaction targeting peripheral nervous system antigens [39]. Some of the most commonly associated pathogens are *Campylobacter jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr virus, Dengue virus, and Chikungunya virus. In some cases, evidence of co-infection has been found [41]. Interestingly, prospective studies have shown that asymptomatic infections with these pathogens are also associated with GBS [41, 47]. Conversely, a significant proportion of GBS patients with prodromal symptoms does not show serological evidence of infection [47].

Campylobacter jejuni, a gram-negative rod, is an important cause of bacterial gastroenteritis worldwide [41, 48, 49]. Gastroenteritis from *C. jejuni* consists of fever, abdominal pain, and diarrhea [49]. *C. jejuni* has been implicated in a third of GBS cases in prospective series [41, 45, 46, 50]. Associations between GBS and asymptomatic *C. jejuni* infection have also been found [41]. *C. jejuni* is thought to cause GBS via molecular mimicry between the bacteria lipooligosaccharide and GM1, GM1b, GD1a, and/or GalNac-GD1a gangliosides located in the node of Ranvier of the axolemma [51–53]. This leads to IgG deposition and membrane attack complex formation in the node of Ranvier causing paranodal myelin detachment that progresses to axonal degeneration [54]. Consequently, *C. jejuni* infection is more likely to cause the AMAN variant, which carries a worse prognosis [41, 45, 47, 48].

The most common virus associated with GBS is cytomegalovirus (CMV), followed by hepatitis E virus (HEV) and Epstein-Barr virus (EBV) [41, 45, 50]. CMV IgM targets the GM2 ganglioside, and it is the most common cause of GBS following renal transplant [55]. In HEV-GBS, there is some weak

evidence of molecular mimicry with GM1 or GM2 gangliosides [56, 57]. CMV- and EBV-related GBS most commonly cause sensory symptoms and may be associated with a milder form (e.g., slower time to nadir, capable of ambulating at nadir, normal strength at 6 months) [41, 58]. On the other hand, HEV-GBS may portend a worse prognosis [41]. HEV-GBS may also be accompanied by transient transaminase elevation, which likely reflects the down trending phase of the preceding, usually asymptomatic, infection [59]. In some HEV-GBS cases, a positive HEV RNA in CSF has been detected, suggesting a para-infectious or directly infectious pathophysiology [49]. It must be noted that for CMV- and EBV-related GBS, serological diagnosis necessitates not only a positive IgM, but also IgG titers that are not indicative of a prior infection [41]. *M. pneumoniae* is an atypical bacterium causing respiratory infections. GBS-associated *M. pneumoniae* is more common in children, and more frequently involves the cranial nerves [41, 45, 60]. Antibodies against Gal-C, a major component of myelin, are found in most of the patients [60].

Arboviruses (Zika virus, Dengue virus, and Chikungunya virus) have been associated with GBS development in the context of epidemic outbreaks. Of these, the strongest association was found for Zika virus [61, 62]. These patients may develop GBS concomitantly with the Zika infection [61]. About half have facial paresis [61, 62]. Subsequent research using strict serological criteria and performed in endemic countries outside of the epidemic outbreaks did not show a strong association of these viruses and GBS, although this could have been due to low statistical power [47]. Contrary to the infectious agents mentioned earlier, molecular mimicry with gangliosides has not been found with arboviruses epitopes [63]. Table 2 summarizes infectious agent, affected ganglioside(s), and clinical features in GBS.

Different population-based studies have failed to find an association between SARS-CoV-2 infection and GBS [42, 64••, 65]. In fact, the incidence of GBS decreased during the first months of the pandemic despite rising numbers of SARS-CoV-2 infection [64••, 65]. This decrease has been attributed to lockdown measures preventing transmission of known GBS triggers.

Table 2. Summary of infectious agent, affected ganglioside(s), and clinical features in GBS

Infectious agent	Ganglioside	Clinical features
C. jejuni	GM1, GM1b, GD1a, GalNac-GD1a	AMAN most commonly; worse prognosis
CMV	GM2	AIDP; good prognosis
HEV	GM1/GM2?	AIDP most common
M. Pneumoniae	Gal-C	AIDP; facial paresis
EBV	Unknown	AIDP; good prognosis
Arboviruses	Unknown	Facial paresis for Zika

Infectious neuropathies presenting with GBS-like phenotypes

The HIV seroconversion syndrome, usually presenting with fever, headache, myalgia, arthralgia, rash, or diarrhea, may also present with GBS. It affects 30–50% of patients with acute HIV infection around 3–9 weeks after viral exposure [66]. When GBS accompanies this syndrome, it is otherwise clinically and electrophysiologically indistinguishable from non-HIV-GBS. The differentiating feature that prompts the clinician to consider HIV is the presence of lymphocytic pleocytosis in the CSF, instead of the expected albuminocytologic dissociation of non-HIV-GBS cases [66]. GBS-phenotype may also be part of the immune reconstitution inflammatory syndrome [67].

Corynebacterium diphtheria is an exotoxin-producing gram-positive bacterium that causes local infection of the upper respiratory tract or skin [68]. It presents as pharyngitis associated with a grayish-while membranous exudate, a "pseudo-membrane" of the posterior pharynx [68]. This may be followed by diphtheritic polyneuropathy (DP) after a latent period of 3–6 weeks. *C. diphtheria* produces a protein exotoxin which causes segmental demyelination of nerve roots and proximal peripheral nerves. Most pathology is observed at the level of roots and dorsal root ganglia, likely due to fenestrated capillaries at the blood-nerve barrier. DP has two phases, affecting initially the cranial nerves, and evolving 2 weeks later to a generalized demyelinating polyneuropathy, similar to GBS [69, 70]. Autonomic dysfunction is common, usually manifesting as tachycardia, accommodation paresis, and/or urinary retention [71]. CSF analysis may also show albuminocytologic dissociation [69]. The biphasic course of DP helps differentiating it from GBS. Interestingly, the cranial nerve deficits start to recover while the limb deficits are still worsening. Overall, recovery is seen after 2 months on average [69]. Once DP is established, the management is conservative. Thus, treatment with diphtheria antitoxin plus penicillin or macrolides should be started during the acute sore throat phase to prevent complications and patients are isolated until they have two negative throat swab cultures [68].

Small fiber neuropathies: sensory and autonomic neuropathy

The unmyelinated type C fibers can be the target of infections. When the sensory fibers are affected, the patient will experience positive sensory symptoms which are often described as tingling, burning, sharp, or stabbing pain. If the autonomic fibers are affected, then the patient can experience a wide spectrum of symptoms including resting tachycardia, orthostatic hypotension, genitourinary symptoms such as impotence and urinary dysfunction, gastrointestinal symptoms such as early satiety, constipation and/or diarrhea, and abnormal sweating (including hypo/anhidrosis). Diagnosis of small fiber sensory neuropathy is usually done with a skin biopsy to quantify nerve fiber density. For autonomic neuropathy, skin biopsy may also be utilized to evaluate for sweat gland nerve fiber density. Furthermore, bedside evaluation may reveal a >20 mmHg drop in systolic or >10 mmHg drop in diastolic blood

pressure without an adequate rise in heart rate. The sympathetic skin response evaluates small fiber sudomotor function and may be available on standard EMG equipment but is not sensitive. Parasympathetic function can be evaluated by heart rate variability with Valsalva maneuver or deep breathing on standard EMG equipment, but these assessments are compared to autonomic lab batteries (for a detailed review, please see Kaur et al. [72]).

HIV

Although autonomic and neuropathic pain symptoms are frequent in HIV, particularly with severe immunodeficiency, the prevalence of small fiber sensory and autonomic neuropathy is not known [73–76]. This is not surprising given that clinical and subclinical autonomic dysfunction is frequent with other generalized PNs which feature involvement of small, thinly myelinated, or unmyelinated nerve fibers. Study of sympathetic ganglia shows neuronal degeneration coupled with perivascular mononuclear cell infiltration with T cells and macrophages [77]. Reduced intraepidermal nerve fibers correlate with neuropathic pain, HIV viral load, and CD4 count [78].

The contributions of anemia and/or hypovolemia, both of which are common in symptomatic AIDS, should be considered. Cardiomyopathy and adrenal insufficiency may also result in similar symptoms. In the appropriate clinical context, a random cortisol level and a cosyntropin stimulation test may be performed. Medication side effects must be considered, particularly in the context of polypharmacy. Treatment of orthostatic hypotension with autonomic dysfunction may include liberal fluids, NaCl supplementation, thigh-high compression stockings, elevation of the head-of-bed, the mineralocorticoid fludrocortisone, midodrine, or droxidopa [79].

Chagas disease

Chagas disease, also known as American trypanosomiasis, is caused by infection with the parasite *Trypanosoma cruzi*, which results in human infection via exposure to the bite of the *Triatominae* (*aka* conenose or kissing bug) insect or through mucous membrane exposure to infected *Triatominae* feces. Prevalence is highest in Latin America; in the USA, cases are typically identified in migrant populations. After the acute infection (which can be asymptomatic but may result in nonspecific malaise, fatigue, and anorexia) the disease becomes latent. During acute infection, parasitemia can be detected by peripheral blood smear or PCR testing. About one-third of patients who are not treated in the acute phase may develop chronic disease with cardiomyopathy or a digestive form (with megacolon and/or megaesophagus) due to involvement of the autonomic nervous system. Diagnosis at this stage is based primarily on serology (e.g., *T. cruzi* IgG antibodies), with blood smear being negative and PCR of variable sensitivity. The parasite invades the muscular tissue which leads to destruction of the myenteric plexus. The parasite also affects the cardiac tissue but the role of autonomic dysfunction in the development of cardiomyopathy is not well understood. The autonomic

Table 3. Antimicrobials associated with PN

Medication	Indication	Notes
Benznidazole	Chagas disease	Sensory polyneuropathy
Chloroquine/Hydroxychloroquine	Malaria	Sensory polyneuropathy
Chloramphenicol	Broad spectrum antibiotic	Painful sensory polyneuropathy
Clioquinil	Antifungal, antiprotozoal	Subacute myelo-optic neuropathy in Japan, since then its use has been limited, unclear association
Dapsone	Leprosy	Motor-predominant neuropathy, non length-dependent. Toxicity is dose-related, after chronic ingestion of greater than 300 mg/d
Ethambutol	Tuberculosis	Optic neuropathy
Ethionamide	Tuberculosis	Sensory neuropathy
Fluoroquinolones	Broad spectrum antibiotic	Sensorimotor axonal polyneuropathy. Overall risk is small, unclear if causal relationship
Griseofulvin	Antifungal	Sensory polyneuropathy
Isoniazid	Tuberculosis	Pyridoxine (B6) 100 mg daily prevents toxicity
Mefloquine	Malaria	Sensory polyneuropathy
Metronidazole	Anaerobic infections	Predominantly sensory axonal neuropathy
Nitrofurantoin	Urinary tract infections	Patients with impaired renal function are at greater risk
Podophyllin resin	Treatment of warts	Sensorimotor and autonomic neuropathy
Voriconazole/Posaconazole	Antifungal	Painful neuropathy
Linezolid	Methicillin resistant staphylococcus aureus (MRSA), Vancomycin-resistant enterococcus (VRE)	Polyneuropathy risk increased with long term use, may be due to mitochondrial toxicity
Thalidomide	Leprosy	Sensorimotor polyneuropathy

involvement is limited to the end organ and there is no evidence of a more diffuse autonomic dysfunction in Chagas disease [80].

The antiparasitic drugs benznidazole and nifurtimox are approved for treatment in Chagas disease, but treatment is generally considered for acute and congenital infection, while treatment may be considered for chronic forms in those under 18 years of age [81]. There is a paucity of evidence that anti-protozoal therapy improves outcomes in chronic forms of Chagas [82••, 83].

Treatment-associated toxic polyneuropathy

Antivirals

Antimicrobials

Many antibiotics and antifungals have been associated to the development of neuropathy. The prevalence of antimicrobial-induced neuropathy is unknown and in many of them, the reason for the neurotoxicity is unknown. One of the most widely prescribed antibiotic groups that are most commonly linked to neuropathies are the fluoroquinolones. An increased incidence of neuropathy was found in a large study of patients exposed to quinolones versus amoxicillin-clavulanate; this risk increased with each additional day of therapy [84]. Nitrofurantoin has also been reported to cause neuropathy; there are no large studies evaluating the risk for neuropathy. The neuropathy from nitrofurantoin can be acute to subacute and can be severe; initial reports suggested that abnormal renal function was a risk factor, but more recent publications suggest that the development of neuropathy is independent of cumulative dose or renal function [85]. We summarize the different antimicrobials that have been associated with development of neuropathy in Table 3.

Conclusion

The clinical presentation of infectious neuropathies is varied. Prompt recognition is key for initiation of proper treatment and isolation measures as needed, where approriate.

Compliance with Ethical Standards

Conflict of Interest
The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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