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Stroke from Infection

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Abstract

Background: Stroke related to infections represents a less common but significant cause, particularly in low- and middle-income countries. This review examines the pathophysiology of stroke from infections, involving both direct and indirect mechanisms.

Summary: Bacterial infections such as tuberculous meningitis and infective endocarditis can directly cause strokes through local inflammation, arteritis, and septic embolism. Viral infections like Varicella zoster virus and HIV increase stroke risk through chronic immune activation, vasculopathy, and endothelial dysfunction. Parasitic infections, particularly malaria and neurocysticercosis, can cause strokes via vascular occlusion and inflammatory responses. Fungal infections like aspergillosis and mucormycosis can lead to strokes through vasculitis and direct invasion of the CNS.

Key Messages: Understanding the mechanisms by which various infectious agents contribute to stroke pathogenesis is essential for developing targeted therapeutic strategies and improving patient outcomes. Further research is needed to establish effective prevention and treatment for infection-related strokes, especially in low- and middle-income countries.

Introduction

Stroke remains a leading cause of morbidity and mortality worldwide, posing significant challenges to healthcare systems [1]. While conventional risk factors such as hypertension, diabetes, smoking, and hyperlipidemia account for the majority of strokes, making over 80% of them preventable, stroke related to infections represents a less common but significant cause, particularly in low- and middle-income countries. The risk of stroke following an infection varies based on the type of infection and timing. Previous studies report prevalence of infection in the month before ischemic stroke ranges from 18% to 40% and from 10% to 35% in the week before stroke [2]. The Cardiovascular Health Study demonstrated that hospitalization for infection increases the risk of ischemic stroke within 90 days after infection (adjusted hazard ratio: 2.4; 95% CI: 1.6–3.4), with the risk being greater at shorter intervals after infection [3, 4]. Data from the New York State Inpatient and Emergency Department Databases (2006–2013) showed that all infection types, including skin, abdominal, urinary tract, respiratory tract infection, and septicemia, were linked to a higher risk of ischemic stroke, with urinary tract infection (UTI) showing the strongest association (OR: 5.32; 95% CI: 3.69–7.68) within 7 days. UTI was also associated with intracerebral hemorrhage, while respiratory tract infection was linked to subarachnoid hemorrhage [4]. Danish health records revealed an increased relative incidence of first strokes within 28 days of laboratory-confirmed respiratory infections, adjusted for age and season. The incidence ratios for strokes after *Streptococcus pneumoniae* infection were 25.5 (days 1–3) and 6.3 (days 8–14). For respiratory viruses (mainly influenza), the ratios were 8.3 (days

1–3), 7.8 (days 4–7), and 6.2 (days 8–14) [5]. Understanding the interplay between infectious processes and stroke pathogenesis is essential for comprehensive patient care and the development of targeted therapeutic strategies. The pathophysiology of stroke from infection involves two main mechanisms: direct and indirect. Direct involvement of the central nervous system (CNS) occurs in infections such as meningitis, where both bacterial and tuberculous etiologies trigger local inflammatory responses and arteritis, resulting in ischemic stroke. Indirect mechanisms are seen in chronic infections like HIV, syphilis, or herpes zoster, which can precipitate cerebral vasculitis through prolonged inflammatory processes. Moreover, infective endocarditis can cause septic emboli, where circulating microbial pathogens initiate vasculitis reactions and thrombogenesis within cerebral vasculature. The indirect mechanism involves both acute and chronic infections. Acute infections often precede stroke onset by days to weeks, suggesting a causative link. This association is particularly evident in pneumonia and urinary tract infections, where systemic inflammatory and coagulative responses are pronounced. Furthermore, the burden of chronic infections and the body's immune response to chronic infections such as *Chlamydia pneumoniae* and periodontal infections can create a pro-inflammatory state, promoting atherosclerosis and increasing stroke risk [6–9]. A summary of selected organisms related to stroke mechanisms is presented in Table 1, and the proposed mechanisms of stroke pathogenesis associated with infection are illustrated in Figure 1. This review focuses on the common infectious agents related to stroke, including bacteria, viruses, parasites, and fungi.

Bacterial Infections

Bacteria are the most common infectious agents responsible for causing strokes. Bacterial infections can lead to strokes through various mechanisms, including both direct and indirect pathways. Direct mechanisms, such as the contiguous spread of inflammation in the cerebrospinal fluid to brain arteries at the skull base in meningitis, trigger local inflammatory responses and arteritis. This can include direct invasion of the arterial wall or endotheliopathy caused by infections like tuberculous meningitis and syphilis. Indirect mechanisms, such as infective endocarditis, can lead to septic emboli, initiating vasculitis reactions and thrombogenesis. Acute systemic infections, such as respiratory or urinary tract infections, can trigger stroke through systemic inflammation, platelet activation, dehydration, and infection-induced cardiac arrhythmias. Chronic infections, such as *Chlamydia pneumoniae* and periodontal disease, contribute to chronic inflammation, promoting atherosclerosis and increasing stroke risk. Certain chronic infections, like syphilis, can also cause cerebral vasculitis.

Tuberculous Meningitis

Tuberculosis (TB) is a preventable and usually treatable disease; however, it remains a serious communicable disease causing high morbidity and mortality, particularly in developing countries [10]. TB is primarily caused by *Mycobacterium tuberculosis*. Tuberculous meningitis (TBM) accounts for 1–2% of active TB cases and can lead to severe neurologic impairment [11]. Stroke is a common complication of TBM, with a global frequency of approximately 30% (8% to 56%), and is more prevalent in Africa, Latin America, and Asia, where it can result in poor clinical outcomes [12]. The main pathophysiology of TBM-related strokes involves leptomeningeal exudation at the base of the brain, including regions such as the interpeduncular fossa, suprasellar cistern, and ambient cistern. This exudation can cause inflammation in the vessel walls around the circle of Willis, leading to vasculitis, intimal proliferation, and fibrinoid necrosis. Moreover, hemodynamic hypoperfusion, resulting from a combination of intimal thickening and vasospasm, can lead to infarction. Less common mechanisms include aneurysmal dilatation, mycotic aneurysms, and venous sinus thrombosis. During acute infection, a hypercoagulable state may increase the risk of infarction by decreasing protein S, increasing Factor VIII and plasminogen activator inhibitor-1 (PAI-1). In addition, high level of cytokines in the cerebrospinal fluid such as interleukin-8 (IL-8) and interleukin-10 (IL-10) have been linked to cerebral infarction in TBM [13–17]. Focal weakness is the most common clinical feature of stroke in TBM. Other symptoms, such as cortical signs and seizures, are less common [13]. Infarcts in TBM (70–75%) are primarily located in the tubercular zone, which includes the caudate nucleus, anteromedial thalami, and the anterior limb or genu of the internal capsule. This zone, also known as the anterior zone, is supplied by the medial striate, thalamotuberal, and thalamostriate arteries. In contrast, infarcts from degenerative causes typically occur in the posterior zone, which includes the lenticular nuclei, posterolateral thalami, and the posterior limbs of the internal capsules, and is supplied by the lateral striate, anterior choroidal, and

thalamogeniculate arteries [18, 19]. For TBM treatment, the World Health Organization (WHO) recommends a 6-month regimen of rifampicin, starting with 2 months of a combination of rifampin, isoniazid, pyrazinamide, and ethambutol, followed by 4 months of isoniazid plus rifampin (2HRZE/4HR). Some patients may require longer therapy. Additionally, initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks is recommended. Adjuvant steroids have been shown to reduce mortality, severe disability, and disease relapse [20, 21]. A meta-analysis found that adding aspirin to TBM treatment regimens significantly reduced the risk of new infarctions, though it did not significantly reduce mortality [22].

Syphilis

Syphilis, caused by *Treponema pallidum*, has seen a recent resurgence despite previous declines in its rate. Neurosyphilis can be asymptomatic or manifest in various forms including meningitis, meningovascular disease, general syphilitic paresis, and tabes dorsalis. A study conducted in a US hospital revealed that nearly 3% of syphilis patients and 10% of those with neurosyphilis experienced a stroke [23]. Another study in Taiwan highlighted significantly increased risks of both ischemic and hemorrhagic strokes among syphilis patients [24]. Stroke can occur months to years after syphilis infection, with an average interval of approximately 7 years in the prepenicillin era [25]. Infectious arteritis due to syphilitic meningitis can affect any cerebral or spinal vessel, with the middle cerebral artery being the most commonly affected, followed by the basilar artery. Symptoms of stroke in meningovascular syphilis vary depending on the vascular involvement. Focal weakness is the most common manifestation (55%), followed by movement disorders (28%) and ataxia (21%), as observed in a study of 53 patients with stroke and syphilis [26]. Vascular imaging typically reveals focal segmental arterial narrowing, dilatation, or total occlusion, akin to other forms of infectious vasculitis [25]. Syphilis can trigger obliterative endarteritis in medium-sized and large-sized vessels, characterized by intimal fibroblast proliferation, medial thinning, and adventitial inflammation and fibrosis, resulting in progressive luminal stenosis and thrombosis leading to ischemic stroke [27]. The recommended treatment for neurosyphilis is intravenous aqueous crystalline penicillin G administered for 10 to 14 days.

Bacterial Meningitis

Acute bacterial meningitis (ABM) has a significantly higher incidence in developing countries (40 per 100,000) compared to developed countries (0.7 to 0.9 per 100,000). Neurological complications occur in 50–75% of patients with ABM, with ischemic stroke affecting 15–25% of cases, leading to morbidity rates of 38–62% and a mortality rate of 46% [28]. Risk factors for ischemic stroke in ABM include otitis or sinusitis and immunocompromised status [29]. *Streptococcus pneumoniae* is the most common pathogen responsible for ABM (67%), followed by Group B *Streptococci*, *Staphylococcus aureus*, and *Neisseria meningitidis* [17]. Abnormal angiographic findings are found in approximately 50% of acute ABM cases, which can include arterial narrowing, irregularities in vessel walls, focal dilatations, arterial occlusions, focal arterial beading, and thrombosis of venous sinuses and cortical veins [30]. In meningitis caused by Group B *Streptococcus* or *Streptococcus pneumoniae*, vascular involvement primarily affects small perforating arteries such as the lenticulostriate and thalamostriate arteries, which supply the thalamus and basal ganglia. In contrast, *Hemophilus influenzae* meningitis tends to involve the supraclinoid portion of the internal carotid artery [31]. Delayed cerebral infarction (DCI) occurs in 1–4% of ABM cases, characterized by initially good clinical recovery followed by acute changes in consciousness or new focal neurological signs after the first week. Vasculopathy and hypercoagulation are significant contributors to cerebral infarction and DCI [28]. Intracranial hemorrhage occurs in 1–3% of ABM cases [17]. Early and appropriate antibiotic treatment is crucial for managing ABM. Adjunctive corticosteroid therapy has been shown to reduce mortality and hearing impairment in adults with ABM [32].

Infective Endocarditis

Neurologic complications of infective endocarditis (IE) occurs in 25–70% of cases, including ischemic stroke (20–40%), intracerebral hemorrhage (4–27%), and infectious intracranial aneurysms (2–4%). Asymptomatic ischemia detected by MRI is found in an additional 30% to 40% of patients [33]. Clinically, focal neurological symptoms are present in 40% of IE patients, with non-focal presentations occurring in one-third. Ischemic strokes in IE are primarily due to cardiac embolism, most commonly affecting the middle cerebral artery

territory. Histopathologically, cardiac valve vegetations consist of microorganisms, inflammatory cells, platelets, and fibrin. These vegetations are fragile and can fragment, leading to embolization to the brain [34]. Risk factors for cerebral embolization in IE include endocarditis caused by certain bacteria, larger vegetation size, greater vegetation motion, and involvement of the mitral valve. A diffusion-weighted magnetic resonance imaging study have identified distinct patterns of stroke in patients with IE and nonbacterial thrombotic endocarditis (NBTE). Embolic strokes in IE typically present with multiple lesions distributed in different vascular territories, often affecting both cortical and subcortical regions. In contrast, NBTE generally results in larger, more confluent infarcts, frequently involving the middle cerebral artery territory. Early initiation of antibiotic therapy is crucial in IE and significantly reduces the incidence of stroke, decreasing from 4.82/100 patient days within the first week to 1.71/100 patient days in the second week [35, 36]. Thrombolytic therapy is not recommended for acute ischemic stroke in IE due to the heightened risk of intracranial hemorrhage, while mechanical thrombectomy may be considered [37, 38]. IE can lead to intracranial hemorrhages through several mechanisms. These include hemorrhagic transformation of ischemic strokes, primary hemorrhages due to vascular friability, or subarachnoid hemorrhage resulting from the rupture of mycotic aneurysms [8]. Among the organisms associated with intracerebral hemorrhages, *Staphylococcus aureus*, β -haemolytic streptococci, and *Streptococcus viridans* are the most common causes [27]. Infectious intracranial aneurysms (IIAs), also known as mycotic aneurysms, are abnormal dilations of arteries resulting from the destruction of the arterial wall by bacteria or septic emboli, which provoke immune-mediated inflammation. These aneurysms most frequently occur in the distal branches of the middle cerebral artery [27].

Pneumonia

A recent systematic review and meta-analysis showed that community-acquired pneumonia (CAP) significantly increases the risk of developing a first stroke event (OR 2.88) [39]. The mechanisms linking CAP to stroke include systemic inflammation, increased procoagulant activity, endothelial dysfunction, and the potential for direct microbial invasion of vascular tissues. However, the efficacy of the 23-valent polysaccharide-based vaccine (PPSV23) in reducing stroke risk remains inconclusive [40].

Treatment: Treating the underlying bacterial infection with appropriate antimicrobial drugs is essential. There is limited evidence supporting antiplatelet or anticoagulant therapy for strokes caused by bacterial infections. However, in cases of neurosyphilis with vasculopathy, studies suggest long-term low-dose aspirin as a potential strategy for secondary stroke prevention [25].

Intravenous alteplase is contraindicated in patients with acute ischemic stroke and symptoms suggestive of infective endocarditis due to the high risk of intracranial hemorrhage [41].

Viruses

Varicella Zoster Virus

Primary infection with Varicella zoster virus (VZV), typically occurring in children as varicella (chickenpox), leads to the virus remaining latent in neuronal ganglia. Reactivation can occur when there is a decline in cell-mediated immunity, such as with aging or immunosuppression, resulting in shingles (herpes zoster). VZV reactivation can also cause neurological complications, including cerebral infarction [42]. VZV is a common cause of strokes in both pediatric and adult populations, with a 1.5-fold increase in stroke risk in the first month following a zoster infection, and this risk may persist for several years [8]. Patients with herpes zoster ophthalmicus due to reactivation of VZV along the V1 distribution of the trigeminal nerve, have a high risk of later cerebrovascular complications [25]. Ischemic stroke is the most common cerebrovascular complication of VZV vasculitis, but intracerebral hemorrhage, dissection, aneurysm formation, and venous sinus thrombosis can also occur [42]. In VZV vasculitis, infarct lesions are typically ovoid, well-defined, involve both cortical and deep structures, the gray-white matter junction, and can be single or multifocal [42]. Angiographic changes often show a "beading" appearance with segmental stenosis, occlusion, and poststenotic dilatation, most commonly affecting the middle cerebral artery or anterior cerebral artery. High-resolution MRI with vessel wall imaging often demonstrates vessel wall thickening, irregularity, and enhancement [25]. For VZV vasculopathy, antiviral treatment with intravenous acyclovir is recommended for at least 14 days, and some studies suggest a short course of high-dose steroids

combined with antiviral therapy in selected cases. Secondary stroke prevention with antiplatelet therapy in ischemic stroke due to VZV vasculitis has not been well studied [42]. Vaccination against VZV reduces the incidence of herpes zoster and the associated stroke risk. A population-based cohort study in the US found that VZV-vaccinated individuals had lower incidences of stroke, ischemic stroke, and hemorrhagic stroke compared to non-vaccinated individuals [43].

Herpes Simplex Virus

Herpes simplex virus (HSV-1 and HSV-2) is a common cause of acute viral encephalitis, which predominantly affects the temporal lobes and limbic system. Cerebral vasculitis was present in 63% of cases, primarily affecting large-sized vessels. HSV-1 is more commonly associated with hemorrhage, whereas HSV-2 is linked to ischemic stroke. A systematic review found that patients with temporal lobe hemorrhage as a complication of HSE had a worse prognosis, while infarctions, which were often multifocal, were less severe [44].

Dengue Virus (DENV)

Dengue is a significant mosquito-borne viral infection worldwide, particularly prevalent in tropical and subtropical regions. It is transmitted through the bites of infected female mosquitoes, primarily *Aedes aegypti*. Clinical manifestations of dengue infection range from asymptomatic cases to severe hemorrhagic fever. Central nervous system involvement is a criterion for severe dengue, as per the WHO's 2009 classification [45, 46]. Patients with dengue have an increased risk of both hemorrhagic and ischemic strokes, especially within the first two months post-infection [45]. Hemorrhagic strokes may result from thrombocytopenia, coagulopathy, elevated vascular permeability, plasma leakage, and vasculitis. Combination of dengue fever with thrombocytopenia and ischemic stroke is relatively rare [46].

Influenza

Influenza is a widespread virus that causes seasonal outbreaks, with severity ranging from asymptomatic cases and upper respiratory tract infections to life-threatening respiratory failure, particularly in compromised patients. Several studies have linked respiratory tract infections and influenza-like illness to short-term stroke risk, especially in individuals under 45 years of age [47]. Proposed mechanisms for stroke include platelet activation and aggregation, inflammation or dehydration inducing thrombosis, impaired endothelial function, arterial dissection, and infection-induced cardiac arrhythmias. A large population-based study in Canada showed a significant reduction (22%) in stroke risk in the six months following influenza vaccination, consistent across all stroke subtypes, age groups, and sexes, regardless of risk factors. Influenza vaccination also significantly reduced the risk of recurrent stroke by 25% [48]. Thus, influenza vaccination appears to offer potential benefits for both primary and secondary prevention of stroke [40].

Human Immunodeficiency Virus (HIV)

The increased risk of stroke in HIV patients has been known since the 1980s. Approximately 1-5% of patients with HIV develop a stroke, and 4-34% of patients who die from HIV-related complications have cerebral infarct lesions at autopsy [49]. Since HIV has become a chronic, controllable disease with the advent of highly active antiretroviral therapy (HAART), stroke rates have remained high [17]. The incidence of stroke in HIV patients is three times higher than in uninfected controls. Possible causes for stroke in HIV patients include conventional vascular risk factors, effects of antiretroviral therapy that might cause metabolic syndrome, opportunistic infections, neoplasms, and vasculopathy [27]. The direct effects of HIV infection, including viremia, introduce chronic immune activation, increased cell and monocyte/macrophage activation, and increased proinflammatory cytokines, adipokines, and profibrotic cytokines, ultimately causing hypercoagulation and endothelial dysfunction, resulting in strokes [49]. High viral load and lower CD4 counts are associated with an increased stroke risk in HIV patients [17].

Patients with HIV are at increased risk for both hemorrhagic and ischemic strokes. Ischemic strokes in these patients can result from cardiac embolism (such as infective endocarditis, marantic endocarditis, HIV-associated cardiomyopathy), thrombosis (HIV vasculitis and vasculopathy), drug-induced vasculopathy from substances like amphetamines and cocaine, infectious diseases (such as VZV, *Treponema pallidum*),

and hypercoagulable states (such as protein S deficiency, antiphospholipid antibody syndrome, and hyperviscosity syndrome). Hemorrhagic stroke can be caused by factor VIII deficiency, thrombocytopenia, intracranial malignancies (primary CNS lymphoma), intracranial infections, drug-induced vasculopathy, and ruptured mycotic aneurysms [17]. Additionally, 50% of stroke in HIV patients on HAART are caused by large vessel atherosclerosis. Prolonged use of some HAART medications, such as darunavir and abacavir, can also induce stroke. During the first six months of HAART, the Immune Reconstitution Inflammatory Syndrome (IRIS) can occur and is associated with a high risk of stroke [49].

COVID-19

COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). A meta-analysis found that the incidence of stroke in COVID-19 patients is 1.4%, with ischemic strokes being more common than hemorrhagic strokes [27]. Patients with COVID-19 (1.6%) appear to have a sevenfold higher risk of acute ischemic stroke compared to patients with influenza (0.2%) [50]. Several mechanisms have been proposed for stroke in COVID-19. These include endothelial dysfunction from the alternative renin-angiotensin system (RAS), leading to vasoconstriction and increased blood pressure, a hypercoagulable state promoting venous thromboembolism, and a hyperinflammatory state due to elevated cytokines, promoting atherosclerosis, plaque rupture, and thrombosis. Hypoxemia due to respiratory dysfunction can lead to hypoperfusion, and traditional stroke risk factors, cardioembolism, or cardiopathy also contribute [17]. Strokes in COVID-19 patients tend to be more severe, predominantly cryptogenic or cardioembolic, and involve large vessels more often than strokes in non-COVID-19 patients. In cases of acute ischemic stroke related to COVID-19, the use of thrombolytics and thrombectomy remains the standard of care following international recommendations. However, caution is advised with thrombolysis due to the potential increased risk of intracerebral hemorrhage. It is also important to consider potential drug interactions between antiplatelet/anticoagulant therapies and antiviral treatments for COVID-19.

Treatment: Managing viral infection-related strokes includes treating the underlying infection and preventing medical complications. There is no strong evidence to recommend antiplatelet or anticoagulant therapy for stroke caused by viral infections. However, some studies and guidelines suggest antithrombotic use for specific viral pathogens. In patients with ischemic stroke or TIA and HIV vasculopathy, the American Heart Association/American Stroke Association recommends daily aspirin in combination with antiretroviral therapy to reduce the risk of recurrent stroke [51]. In patients with stroke and COVID-19, the benefits of secondary prevention remain unclear. For most patients with stroke and COVID-19 without alternative indications for anticoagulation, single antiplatelet therapy or short-term dual antiplatelet therapy is considered safe and potentially effective. In cases of embolic cryptogenic infarcts linked to COVID-19 hypercoagulability, particularly in non-critically ill patients with elevated D-dimers, short-term anticoagulation (1–2 months) with heparin, followed by direct oral anticoagulants and later antiplatelet monotherapy, may be appropriate. For patients with incidentally detected SARS-CoV-2 and no signs of hypercoagulability, antiplatelet monotherapy or short-term dual antiplatelet therapy is reasonable for secondary stroke prevention. The potential benefits of antithrombotic therapy must always be weighed against the risk of hemorrhage. Notably, acute ischemic stroke in patients with COVID-19 (or suspected COVID-19) is not a contraindication for systemic thrombolysis [52].

Parasites

Malaria

Malaria is caused by parasites of the genus *Plasmodium*, which are transmitted to humans through the bite of an infected female *Anopheles* mosquito. Cerebral malaria [21], a severe neurological complication primarily caused by *Plasmodium falciparum*, carries a mortality rate of 10–30%. The proposed pathogenesis of CM includes (a) vascular occlusion resulting from the clogging of microvasculature by parasitized erythrocytes, leading to reduced tissue perfusion, and (b) inflammatory responses due to excessive release of proinflammatory cytokines by hyperactivated host immune cells [15, 53]. Large intracranial hemorrhages and cerebral infarcts are not typically observed in cerebral malaria [27].

Neurocysticercosis

Cysticercosis, caused by the larval stage of *Taenia solium*, is the most common parasitic infection of the CNS. CNS infection occurs when cysticerci lodge in the brain parenchyma, subarachnoid space, or cerebral ventricles, leading to inflammation. Stroke occurs in 21-53% of patients with subarachnoid neurocysticercosis and 4-12% of those with active neurocysticercosis [17]. Strokes are more frequent in patients with cysticerci in the subarachnoid space, basal cisterns, or sylvian fissure. Mechanisms include superficial cortical vessel thrombosis, occlusive endarteritis from adventitial thickening of small perforating arteries bathed in subarachnoid inflammatory exudate, focal arteritis, and inflammatory aneurysms [16]. Both aneurysmal and non-aneurysmal subarachnoid hemorrhage and parenchymal hemorrhage are often linked to cysticercotic angiitis [27].

Gnathostomiasis

Gnathostomiasis, caused by the nematode *Gnathostoma spinigerum*, is a common cause of eosinophilic meningitis in Mexico, South America, East Asia, and Southeast Asia. Humans are infected by consuming raw or undercooked fish or poultry or drinking copepod-contaminated freshwater. Once ingested, the larvae cross the intestinal wall, migrating to subcutaneous tissues or organs like the eye, spinal cord, brain, and nerve roots. In the brain, larval migration creates hemorrhagic and necrotic tracts with surrounding inflammatory infiltrates, and the host's immune response triggers leptomeningeal inflammation [54, 55]. Intracranial hemorrhages occur in 15–30% of cases with cerebral involvement. In northeastern Thailand, *G. spinigerum* infection accounts for 18% of subarachnoid hemorrhages in children and 6% in adult [56].

Chagas disease (American Trypanosomiasis)

Chagas disease (CD), caused by the protozoan *Trypanosoma cruzi*, is a significant health concern in South America, the United States, and Western Europe [55, 57]. The primary mode of transmission is through the bite of triatomine bugs (Reduviidae), with trypanosome entry facilitated by scratching the bite site. CD pathogenesis involves multiple organ systems and may lead to life-threatening complications. The disease progresses from an acute phase, often asymptomatic or with mild, nonspecific symptoms, to an indeterminate phase with undetectable parasitemia, and finally to a chronic phase if untreated. Chronic cardiomyopathy, affecting ~30% of patients, is the most common clinical form and is associated with cardiac arrhythmias, congestive heart failure, apical aneurysm, and mural thrombus [55]. Cardioembolic stroke, most commonly involving the middle cerebral artery, occurs in 70% of patients with Chagas cardiomyopathy [58]. Additionally, large and small vessel atherothrombosis is more prevalent in CD, likely due to chronic inflammation and endothelial damage [59]. Recurrent stroke affects 20% of CD patients with stroke, highlighting the need for secondary prevention [58]. Secondary prevention with oral anticoagulation should be considered for CD patients with stroke and associated conditions such as heart failure, atrial fibrillation, mural thrombus, or apical aneurysm [55].

Schistosomiasis

Schistosomiasis is caused by trematode worms of the genus *Schistosoma*, with a varied geographic distribution. Humans become infected through contact with freshwater contaminated by free-swimming cercariae, the infectious stage of schistosomes. These cercariae are released by infected snails, the intermediate host, and penetrate intact human skin [60]. Stroke can occur at any stage of schistosomiasis but is most common during the subacute and chronic phases [27]. Schistosomal ectopic eggs reach the central nervous system via retrograde flow through the venous plexus. During the chronic stage of infection, intracranial hemorrhage is more common in *Schistosoma japonicum* infections than in other schistosomal species, likely due to its smaller ova size, which facilitates brain penetration. Cerebral hemorrhage typically occurs as part of a meningitic granulomatous reaction around schistosomal ova [27]. Although rare, cerebrovascular events can occur during the acute stage of schistosomal infection due to cerebral vasculitis caused by eosinophil-mediated toxicity or distal ischemic infarctions associated with hypereosinophilic syndrome [27]. Patients with schistosomal infection often present with watershed infarction or intracranial vasculitis. Stroke mechanisms include hemodynamic impairment, direct arterial wall damage (vasa vasorum obliterative endarteritis), inflammatory intimal damage, or direct injury from adjacent inflamed tissue [60].

Toxocariasis

Toxocariasis is an infection caused by the roundworm *Toxocara* spp., with *Toxocara canis* being more common than *Toxocara cati*, which primarily infect dogs and cats, respectively. Humans contract toxocariasis by ingesting embryonated eggs from contaminated soil, unwashed hands, or, less commonly, raw liver or meat containing *T. canis* larvae [61]. After ingestion, larvae penetrate the intestinal wall and spread via circulation to tissues such as the heart, brain, and eyes. *Toxocara* larvae release enzymes and waste products that cause tissue damage, necrosis, and marked inflammatory responses, predominantly eosinophilic [62]. Cerebral infarction may result from larval invasion of brain parenchyma, cerebral vessel occlusion (mimicking microemboli), or secondary hypereosinophilia, which can induce left ventricular mural thrombi or endomyocardial fibrosis through endocardial infiltration [63]. Eosinophilic toxicity to the vascular wall has also been proposed [61]. Diagnosis relies on patient history, hypereosinophilia, and/or positive serology for *T. canis* IgG.

Toxoplasmosis

Toxoplasmosis, caused by the parasite *Toxoplasma gondii*, is a common worldwide infection. Humans acquire it through ingestion of tissue cysts in infected meat, infective oocysts in soil, transplacental transmission, organ transplantation, or blood transfusion [64]. Cerebral toxoplasmosis is more common in immunocompromised individuals, particularly those with HIV, than in immunocompetent hosts. A stroke-like presentation, with or without headache, is one of the manifestations of cerebral toxoplasmosis [65, 66]. Additionally, a correlation has been reported between serological evidence of prior *T. gondii* or *Toxocara* infection and stroke [67, 68].

Treatment: Treating the underlying parasitic infection and its complications is essential. Secondary prevention with oral anticoagulation should be considered for Chagas disease patients with stroke and associated conditions, including heart failure, atrial fibrillation, mural thrombus, or apical aneurysm [51, 55]. However, there is no strong evidence supporting the use of antiplatelet or anticoagulant therapy for stroke caused by other parasitic infections.

Fungal Infections

Aspergillosis

Aspergillus spp. are the most common pathogenic fungal infection associated with stroke, particularly in immunocompromised patients. CNS involvement by *Aspergillus* carries a very high mortality rate in this population. The fungus can invade the CNS through hematologic spread via septic emboli, leading to hemorrhagic or ischemic stroke, with or without mycotic aneurysm or arteritis. Direct extension from paranasal sinuses, orbits, inner ear, or following trauma or neurosurgery is also possible. Vasculitis results from elastase produced by *Aspergillus*, arterial infiltration, and intramural hyphae deposits, typically affecting the anterior circulation [17]. Fungal aneurysms, though rare, are often fusiform and involve proximal segments of intracranial vessels, most commonly the intradural internal carotid artery [25].

Mucormycosis

Rhinocerebral mucormycosis, caused by Zygomycetes class, including *Mucor* spp. or *Rhizopus* spp., primarily affects patients with diabetes, immunocompromised conditions, or severe trauma. It can lead to ischemic or hemorrhagic stroke. CNS involvement typically occurs through spread from the paranasal sinuses and orbits, with some cases involving hematogenous spread from the lungs [17]. These fungi invade large blood vessels, triggering an inflammatory cascade that causes endothelial injury, vascular thrombosis, rupture aneurysm, subarachnoid hemorrhage, and infarction. They also directly infiltrate the vessel lumen and surrounding structures with their hyphae [8, 16]. Commonly affected structures include the cavernous sinus and the internal carotid artery, particularly the supraclinoid portion. Posterior circulation involvement is rare and indicates advanced infection [16].

Cryptococcosis

Cryptococcus neoformans is the leading cause of fungal meningitis. The variety *neoformans* accounts for most cryptococcal infections in the United States, particularly in patients with HIV. In contrast, the variety *gattii* primarily causes meningitis in immunocompetent individuals in tropical and subtropical regions.

Cerebral infarction is less common in cryptococcal meningitis compared to other chronic meningitides, but vascular involvement remains a serious complication. *Cryptococcus* spp. invade the meninges and brain parenchyma, causing meningitis and abscess formation. Subarachnoid blood vessels passing through the exudate in the basal meninges become irritated, compressed, and inflamed, leading to vasospasm, stenosis, necrosis, and thrombosis. The Circle of Willis is often heavily affected by this inflammatory exudate, resulting in infarctions commonly located in the basal ganglia, internal capsule, and thalamus due to endarteritis of small vessels [6, 17]. Cerebral infarctions may occur early in the illness, especially in severe cases, or later in its progression [16]. Infarction can occur as a delayed complication of persistent inflammatory basilar arachnoiditis, even after appropriate antifungal therapy and sterile CSF are achieved [69]. Hydrocephalus, a common complication of chronic meningitis, can further compress vessels, leading to ischemia and stroke [16].

Candidiasis

Candida is the most common opportunistic fungus in humans. Both immunocompromised individuals and immunocompetent patients with risk factors such as intravenous drug use, catheterization, prolonged antibiotic use, extensive wounds from burns, surgery, traumatic brain injury, or premature infant are susceptible to candidiasis. Vascular invasion and hematogenous spread can cause arteritis, mycotic aneurysms, and lead to ischemic stroke, subarachnoid hemorrhage, or intracerebral hemorrhage [55, 70]. *Candida* accounts for 1% of infective endocarditis cases in the U.S. and up to 6.5% in China [71, 72]. Species such as *C. parapsilosis*, *C. albicans*, and *C. glabrata* have been linked to infective endocarditis and pacemaker wire vegetations, followed by cardioembolic stroke [73, 74].

Treatment: Managing the underlying fungal infection and its associated complications is essential. There is no strong evidence to recommend antiplatelet or anticoagulant therapy for treating stroke caused by fungal infections.

Conclusion

Infectious agents significantly contribute to the pathogenesis of both ischemic and hemorrhagic strokes through various direct and indirect mechanisms. Bacterial infections like tuberculous meningitis and infective endocarditis, viral infections such as HIV and VZV, and parasitic and fungal infections like malaria and aspergillosis all illustrate the diverse ways in which infections can lead to stroke. Understanding these interactions is crucial for improving clinical outcomes through timely diagnosis, targeted treatments, and effective prevention measures. Treating the underlying infectious cause is essential to reduce the risk of recurrent stroke. In ischemic stroke, antithrombotic drugs are recommended for specific pathogens but must be carefully weighed against the risk of bleeding. Future research should focus on elucidating mechanisms, optimizing treatments, and developing innovative prevention strategies to reduce the global burden of infection-related strokes.

Statement of Ethics

No approval from Ethics Committees is required in this paper, which is based on publicly available publications.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability Statement

All data were extracted and presented in this review. Further inquiries can be directed to the corresponding author.

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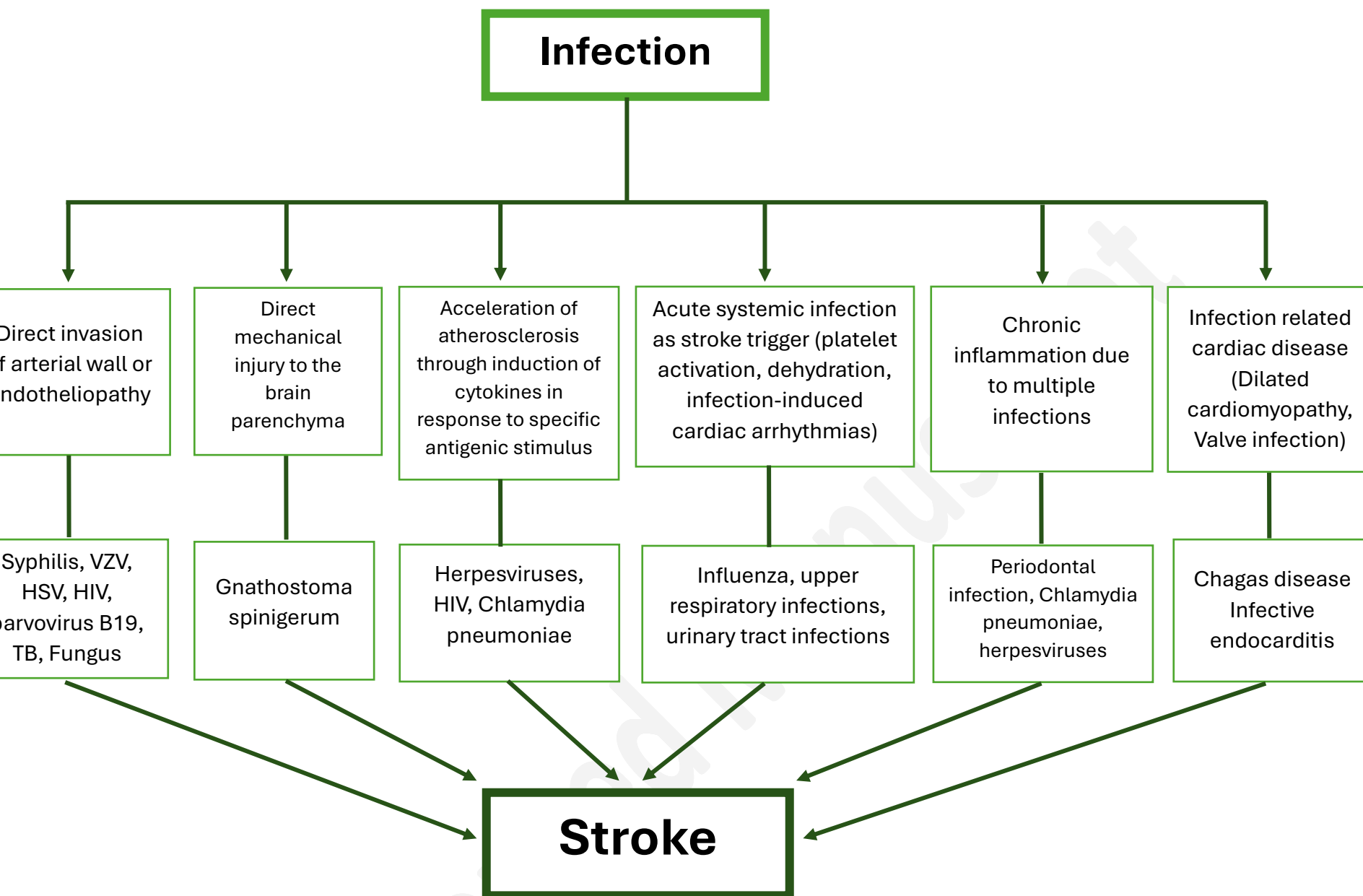
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Figure 1. Proposed mechanisms of stroke pathogenesis associated with infection





VZV = Varicella zoster virus, HSV = Herpes simplex virus, HIV = Human Immunodeficiency Virus, TB = Tuberculosis

Table 1. Selected Organisms Linked to Stroke Pathogenesis

Infectious types	Organisms	Infection	Mechanism
Bacterial infections	<i>Mycobacterium tuberculosis</i>	Tuberculous meningitis	Vasculitis/arteritis
	<i>Treponema pallidum</i>	Neurosyphilis	Arteritis, direct invasion of arterial wall, endotheliopathy
	<i>Streptococcus pneumoniae</i>	Bacterial Meningitis	Vasculopathy, hypercoagulability
	<i>Staph. Aureus</i>	Infective endocarditis	Cardiac embolism
	<i>Staphylococcus aureus</i>		
	<i>Staphylococcus epidermis</i>		
	<i>Streptococcus bovis</i>		
	<i>Streptococcus viridans</i>		
	<i>Enterococci</i>		
Viral infections	<i>Chlamydia pneumoniae</i>	Acute or chronic respiratory infections	Accelerated atherogenesis, enhanced platelet aggregation
	<i>Porphyromonas gingivalis</i> (and other periodontal pathogens)	Periodontal disease	Chronic inflammation due to infectious burden; prothrombotic state
	<i>Varicella zoster</i>	Chickenpox, shingles	Arteritis or noninflammatory vasculopathy, direct invasion of arterial wall, endotheliopathy
	<i>Herpes simplex</i>	Oral and genital infections	Noninflammatory vasculopathy, direct invasion of arterial wall, endotheliopathy, chronic inflammation due to infectious burden
	<i>Dengue virus</i>	Dengue fever	Thrombocytopenia, coagulopathy, elevated vascular permeability, plasma leakage, vasculitis
	<i>Influenza</i>	Upper respiratory infection	Acute systemic infection as stroke trigger (platelet activation, dehydration, infection-induced cardiac arrhythmias)
	Human immunodeficiency virus (HIV)	HIV disease/AIDS	Noninflammatory vasculopathy; susceptibility to opportunistic CNS infections, possible direct invasion of arterial wall,

	SARS-CoV-2	COVID-19	endotheliopathy Hypercoagulability, endotheliopathy, hyperinflammation, myocarditis, arrhythmia, complications of critical illness (renin-angiotensin system dysregulation, hypotension, hypoxemia)
Parasitic infections	<i>Taenia solium</i>	Neurocysticercosis	Arachnoiditis/small vessel arteritis; direct compression of large arteries by cysts
	<i>Plasmodium falciparum</i>	Cerebral malaria	Occlusion of cerebral arteries by infected erythrocytes
	<i>Gnathostoma spinigerum</i>	Gnathostomiasis	Hemorrhagic and necrotic tracts, leptomeningeal inflammation
	<i>Trypanosoma cruzi</i> <i>Schistosoma mansoni</i>	Chagas disease Schistosomiasis	Cardioembolism Microembolic borderzone infarction
	<i>Toxocara canis</i>	Toxocariasis	Arachnoiditis; vasculitis
Fungal infections	<i>Aspergillus</i>	Systemic and CNS infections	Arteritis, infectious vasculopathy
	Mucorales (including <i>Rhizopus</i> , <i>Mucor</i>)	Mucormycosis	Vascular invasion of fungus with vascular necrosis, aneurysmal dilatation
	Cryptococcus	Cryptococcus meningitis	Meningitis; arteritis