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Review on infectious causes of stroke

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Abstract
Stroke is one of the leading causes of mortality and disability around the globe. It is also known as cerebrovascular accident or apoplexy. Stroke can be ischemic or hemorrhagic. Established risk factors for stroke are hypertension, diabetes, obesity and physical inactivity. In addition to these traditional cerebrovascular risk factors, infections also become a major risk factor. In stroke patients without traditional risk factors, infections may play a major role particularly in low to middle- income regions. Infectious diseases such as neurosyphilis, neurocysticercosis, tuberculosis, and bacterial meningitis can induce a stroke. Recent reports show that COVID-19 can also increase the risk of stroke. The diagnosis is based on clinical, laboratory, and radiological findings. The burden of stroke is increasing day by day. There-fore infectious causes should be included in the differential diagnosis of stroke. The objective of this study is to review some infectious diseases causing stroke and its management.

Keywords: stroke, apoplexy, neurosyphilis, neurocysticercosis, COVID-19

1. Introduction
Stroke is the second leading cause of death and the third leading cause of disability worldwide [1, 2]. Stroke accounts for approximately 12% of total deaths worldwide. Stroke can be ischemic or hemorrhagic. The ischemic stroke occurs when a blood vessel supplying blood to the brain is obstructed. It accounts for 87 percent of all strokes. Hemorrhagic stroke occurs when a weakened blood vessel ruptures and bleeds in to the surrounding brain. The blood accumulates and compresses the surrounding brain tissue [3]. Several risk factors are associated with stroke. Unmodifiable risk factors are age, male sex etc. Modifiable risk factors are hypertension, diabetes mellitus, smoking, hyperlipidemia, obesity, physical inactivity, alcohol intake, cardiac causes(ischemic heart disease, atrial fibrillation, rheumatic heart disease, prosthetic valves) etc [3,4]. Apart from all these traditional risk factors, infections are also one of the risk factors for stroke [5, 6]. Infectious causes should be considered especially in patients with stroke of undetermined etiology and in certain patient populations, such as pediatrics and young adults without traditional risk factors. Evidence also suggests that systemic infection may trigger an acute stroke in patients with vascular risk factors [6].

The burden of stroke is increasing particularly in low and middle- income regions, where infection may play a major role [4, 5]. Recent studies have cast light on relationship between infections and stroke. Infectious agents associated with stroke include bacteria, viruses, fungi and parasites [7]. Several infectious diseases that can lead to stroke are meningitis, cerebral malaria, neurosyphilis, tuberculosis, cysticercosis and chagas' disease [4]. Recent reports suggested that novel Corona Virus Disease 2019 (COVID-19) can also cause stroke [8]. But the mechanisms are still under investigation. Stroke is an often devastating and not uncommon complication of many systemic infections. The pathogenesis varies with the pathogens. Infections increase the susceptibility to stroke by causing local inflammation of cerebral parenchyma and meninges, through systemic inflammation, by promoting atherosclerosis, causing coagulation, and endothelial dysfunction, and in some cases directly inducing ischemia [6]. Another proposed mechanism describes a direct pathogenic invasion of the vascular wall with smooth muscle cell proliferation or increased cytokine production. Inflammation is considered to be the main driver for stroke [7]. The burden of stroke is increasing day by day, therefore infectious causes should be considered in the differential diagnosis of stroke in certain population and appropriate treatment should be initiated to minimize adverse stroke related consequences or sequelae. The objective of this paper is a comprehensive review of some infectious causes of stroke and principles in its management.

Definition and classification of stroke
The World Health Organization (WHO) definition of stroke is that it is a syndrome characterized by rapidly developing clinical signs of focal disturbance of cerebral function, with symptoms lasting 24 hours or longer and/or leading to death, with no apparent cause other than of vascular origin. It is also called as cerebrovascular accident (CVA) or apoplexy. An acute stroke refers to the first 24 hour period of a stroke. The focal neurologic deficit lasting less than 24 hours (usually 5- 30 minutes) is known as Transient Ischemic Attack (TIA) [9].

Types of stroke
The two main types of CVA are ischemic (87%) and hemorrhagic (13%) stroke [10]. Ischemic stroke is produced by occlusion of a cerebral artery [thrombotic or atherosclerotic (50 %), embolic (25%) and micro artery occlusion, "lacunar stroke" (25%)] [10]. Hemorrhagic stroke is caused mainly by spontaneous rupture of blood vessels or aneurysms or secondary to trauma [11].

Hemorrhagic stroke are further subdivided into intracranial hemorrhage (ICH) or subarachnoid hemorrhage (SAH). Predisposing factors that significantly increase the risk of

developing a hemorrhagic stroke include myocardial infarction, hypertension and use of thrombolytics [12]. Clinical presentation of hemorrhagic stroke can vary on case basis. Generally patients present with a headache of an acute onset, along with severe high blood pressure. These clinical manifestations are accompanied with focal neurological signs that occur in minutes. These acute manifestations have been found to relate mostly to hemorrhagic strokes, although they can sometimes occur with any other type of stroke [13].

An ischemic stroke can originate from three main etiologies: thrombosis, hypo- perfusion and embolism. Thrombosis is considered to be the most common cause in ischemic stroke. The clinical manifestations of ischemic stroke progress relatively slowly (over hours) and vary in severity on compared with hemorrhagic stroke. Clinical manifestations of ischemic stroke can include paralysis, paresis, ataxia, vomiting and eye gaze. The specific site of the lesion will determine the symptoms and signs that will appear on the patient [14].

The main factors that diminish the rate of complications and permanent morbidities are early diagnosis of stroke, determination of the type and etiology of the stroke. A thorough history with a proper physical examination will help determining the type of the stroke [15]. However, imaging is still required to establish a diagnosis. The imaging modality of choice to distinguish a hemorrhagic from an ischemic stroke is non- contrast CT scan. However, it is not always available in hospitals and emerging departments. Therefore, studies have attempted to give protocols to be able to distinguish between the two types based solely on clinical manifestations. Characteristics that help determining the type include focal versus diffuse symptoms, positive versus negative symptoms, and gradual versus sudden onset of symptoms [16]. Moreover, some studies suggested that pupil size and eye gazes can help distinguish between types [17].

Pathophysiology

Ischemic stroke

Ischemic stroke (87% of all strokes) is due to either local thrombus formation or emboli occluding a cerebral artery. Cerebral atherosclerosis is a cause in most cases, but 30% are of unknown etiology. Emboli arises either from intra or extra cranial arteries. Twenty percent of ischemic strokes arises from the heart. Carotid atherosclerotic plaques may rupture, resulting in collagen exposure, platelet aggregation and thrombus formation. The clot may cause local occlusion or dislodge and travel distally, eventually occluding a cerebral vessel. In cardiogenic embolism, stasis of blood flow in the atria or ventricles lead to formation of local clots that can dislodge and travel through the aorta to the cerebral circulation. Thrombus formation and embolism result in arterial occlusion, decreasing cerebral blood flow and causing ischemia and ultimately infarction distal to the occlusion.

Hemorrhagic stroke

Hemorrhagic strokes (13% of strokes) include subarachnoid hemorrhage (SAH), intracerebral hemorrhage, and subdural hematomas. SAH may result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation (AVM). Intracerebral hemorrhage occurs when a ruptured blood vessel within the brain causes a hematoma. Subdural hematomas are usually caused by trauma. Blood in the brain parenchyma damages surrounding tissue through a mass effect and the neurotoxicity of blood components and their degradation products. Hemorrhagic stroke can result in abrupt increased intracranial pressure leading to herniation and death.

Epidemiology

Infectious diseases are more common in tropical regions of the world. The tropic or torrid zones are the areas between two parallels of latitude (Tropic of Cancer and Tropic of Capricorn) on the earth. The latitudes are located 23.5^{o} north and south of the equator. The peculiarity of this region is that it receives more direct sunlight causing high temperature in these areas. Direct sun shine, warm weather, abundant rainfall, distance from ocean and warm humid climate of those regions may predispose them to some infectious diseases more than other regions. The main countries located in the tropical zone are Latin and Central America, Sub-Saharan Africa, Middle East, India, South Eastern countries of Asia [4]. Therefore infection induced stroke is more common in these regions of the world.

Risk factors

The risk factors for stroke can be subdivided into non-modifiable, modifiable and potentially modifiable. The recommendations for risk factor reduction aggressively target the modifiable, well documented risk factors, even in individuals with non-modifiable risk [18]. The non-modifiable risk factors are age, race, sex, low birth weight and family history [18]. An individual risk of having a stroke increase substantially as he or she ages, with a doubling of risk for each decade older than 55 years of age [18]. African Americans, Asian- Pacific Islanders, and Hispanics experiences higher death rate than their white counter parts [19]. Men are at a higher risk of stroke than women when matched for age, but women who suffer from a stroke are more likely to die from it [19].

The most common modifiable, well documented risk factors for stroke include hypertension, cigarette, smoking, diabetes, atrial fibrillation and dyslipidemia. The treatment of hypertension, beginning in the mid-20th century is thought to be primarily responsible for drastic reduction in stroke death rates between 1950 and 1980 in the United States [20]. A second very risk factor for stroke is cardiac disease [18]. Patients with coronary artery disease, congestive heart failure, left ventricular hypertrophy and especially atrial fibrillation are at increased risk of stroke [18]. Other known risk factors for atherosclerosis are also known to place patients at risk of stroke [18]. Diabetes mellitus, dyslipidemia, and cigarette smoking are known atherogenic states that lead to cerebrovascular disease and ischemic stroke [18].

Other than the modifiable and non-modifiable risk factors, the less well documented risk factors i.e., the infectious disease also result in additional risk. It is estimated that about 6% to 12% of the vascular accident in the tropical countries are mainly due to cerebral malaria, tuberculosis, neurosyphillis, cysticercosis, chaga's disease and brucellosis [21].

Infectious organism causing stroke

Many CNS infections can directly cause stroke, including bacterial (i.e., syphilis and tuberculosis), fungal (i.e.,

cryptococcus, aspergillus, mucormycosis), parasitic (neurocysticercosis) and numerous viruses. Table 1 show various infectious agents along with its mechanism causing stroke.

Table 1: Mechanism of infectious causes and triggers of stroke (Fugate *et al*. Lancet 2014).

Mechanism	Infectious casuses
Preceding or concomitant systemic infection, outside the CNS	Influenza *Chlamydia pneumonia* *Helicobacter pylori* *Porphyromonas gingivatis*
Preceding or concomitant systemic infection, contigious with the CNS	*Streptococcus pneumoniae sinusitis* *Haemophilus influenza sinusitis* *Moraxella catarrhalis sinusitis* *Aspergillus fumigates sinusitis*
Vasculitis and mycotic aneurysm	*Varicella zoster* virus *Syphilis* *Epstein-barr virus* *Tuberculosis* *neurobrucellosis*
Vascular remodelling	*Syphilis* HIV
Promotion of a hypercoagulable state	Hepatitis C
Infectious endocarditis	*Staphylococcus aureus* *Coagulase-negative staphylococci* *Escherichia coli*

Infectious diseases leading to stroke

The common infectious diseases causing stroke are as follows:

- **Syphilis**

The syphilis is a chronic sexually transmitted infection caused by the spirochete *Treponema pallidum*. The CNS involvement of syphilis is referred to as neurosyphilis [6]. Cerebral infarction occurs in approximately 15% of neurosyphilis cases. The neurosyphilis should be considered in young adults with stroke who lacks traditional cerebrovascular risk factors (atherosclerosis) [6, 22]. Inflammatory infiltration of the cerebral artery is thought to be the mechanism underlying the cerebral infarcts in neurosyphilis [22]. Two types of vascular pathology have been described in meningovascular syphilis [4]. Hubner arteritis is the most common type and it involves large and medium sized blood vessels. The other pathology is Nissl's endarteritis characterized by intimal and adventitial proliferation, mainly of small blood vessels [4]. Mostly middle cerebral artery is affected [4, 22]. Compression of the left carotid artery by an enlarged aortic aneurysm is also one of the reported causes of stroke in patients with syphilis [22]. Individuals with stroke caused by neurosyphilis may show prodromal symptoms over weeks to months, including headache, malaise, personality and behavioural changes [4].

- **Bacterial meningitis**

Acute Bacterial Meningitis (BM) is one of the most common infectious causes of death worldwide [6]. Eighty percent of the community acquired cases are caused by *Streptococcus pneumoniae* and *Neisseria meningitides* [6, 23]. The major cause of the disability and mortality associated with bacterial meningitis (BM) are the cerebrovascular complications that arises in the acute phase of BM and in the end causing secondary brain damage [24]. The rate of stroke depends upon the specific pathogen. The rate is higher from *Streptococcus pneumonia* (36%) and rate is lower with *Neisseria meningitides*(9%) [6]. Ischemic stroke are reported more frequently than hemorrhagic strokes in BM [24]. The BM is one of the leading causes of stroke in children. About 5- 12% children with BM will have a stroke due to local vasculitis and thrombosis [25]. The ischemic complications usually occur due to arteritis in large and medium sized cerebral blood vessels [24]. The bacterial pathogens evokes the formation and release of inflammatory cytokines that damage the endothelium of blood vessels (vasculitis) [6]. The pathogenic mechanism in the development of cerebral hemorrhage include a process that is destructive to the blood vessels, secondary to the inflammatory response produced in subarachnoid space. This process may lead to the formation of aneurysms with fatal rupture resulting in cerebral hematomas and subarachnoid hemorrhage. The cerebrovascular disease manifest clinically as focal neurological deficits [24, 25].

- **Tuberculosis**

Central Nervous System (CNS) tuberculosis (TB) is a serious type of extrapulomonary TB, and remaining as a serious health problem in most of the developing countries [4]. World Health Organization (WHO) estimates that one-third of the world's population has infected with *Mycobacterium tuberculosis* (MTB), with highest prevalence in the south East Asia [26]. Different forms of CNS tuberculosis may cause motor neuron deficit, however the main cause of stroke is tuberculous meningitis (TBM). Stroke in TB occur in 15% to 60% of people with TBM [6]. Infarcts are one of the characteristic imaging abnormalities of the TBM. Infarcts can either be asymptomatic or symptomatic [27]. The majority of stroke may be asymptomatic, because of being in a silent area or patient is in deep coma. Symptomatic stroke in TBM often present with dense hemiplegia [27]. In all cases of MTB, the bacterium settled in the lungs disseminated to the nervous system through the hematogenous system [4, 28]. Polymorphism in the toll- like receptor 2 (TLR-2) gene influence the bacterial dissemination and development of TBM [28]. Rupture of rich nodules into the subarachnoid space is the beginning phase of meningitis. It induces lymphocytic infiltration around the meningial blood vessels and causing arteritis in almost all cases [4]. The vasculitis involving perforating blood vessels of the brain is the characteristic hallmark of TBM - associated stroke [28].

Small, medium and large arteries of the anterior circulation may be involved. Lenticulostriate branches of the middle cerebral artery are frequently affected [4]. Most of the infarctions are located in the tubercular zone, including basal ganglia, internal capsule, thalamus and the brain stem [6]. Posterior circulation infarctions are less common. Tuberculous infiltration and occlusion of venous sinus can provoke hemorrhagic infarction. Although intracranial hemorrhages are uncommon, the leptomeningeal exudate can produce changes in the artery wall with the formation of aneurysms that may rupture [28]. The symptoms of stroke in TBM manifests as sudden onset of focal motor weakness [27].

- **Malaria**

Malaria is a parasitic disease with high prevalence in several regions of the world [29]. Malaria itself causes 0.5 to 2 million death each year. Cerebral malaria is the most severe complication of malaria associated with *Plasmodium falciparum* infection. It is responsible for up to 10% of stroke in the endemic regions [4]. The main pathological findings of the cerebral malaria are diffuse cerebral edema, perivascular ring hemorrhages, white matter necrosis, and occlusion of brain vessels and sequestration of infected erythrocytes in the cortical and perforating arteries [28]. The exact pathophysiological mechanism behind the stroke in cerebral malaria is not clear but a mechanical theory can explain the mechanism of infarction [29]. According to the mechanical theory the obstruction of the capillaries and the cerebral venules by parasitized erythrocytes is caused by direct action of parasites on the erythrocytes, distorting its morphology, diminishing its elasticity and plasticity and changing its surface proteins. The adherence of infected erythrocytes to the endothelium of the blood vessels and other blood cells impairs the blood flow and the obstruction supervenes. The results are thrombosis, stroke and tissue necrosis [29]. The clinical manifestations of stroke are focal motor deficits (hemiparesis, aphasia, ataxia and tremor), epilepsy, cognitive dysfunction, visual and language disturbances [28].

- **Neurocysticercosis**

Cysticercosis is a parasitic infection causesd by the larval form of the tapeworm, *Tenia solium* [28, 30]. The cysticercosis affecting brain, optic nerve or spinal cord is known as neurocysticercosis (NCC) [31]. A high prevalence has been reported from the developing countries because of the co-existence of the poor sanitation and domestic pig raising without veterinary control. *Tenia solium* infestation is endemic in Africa, Asia and South America [28, 31]. The neurological symptoms of NCC include seizures, cognitive dysfunction and focal deficits. Common clinical topo-graphical syndromes include chronic meningitis, parenchymal cysticercosis, subarachnoid cysticercosis and intraventricular cysticercosis [28]. The association of cerebral cysticercosis and stroke has been widely accepted [32]. NCC is one of the independent risk factor for stroke in young and middle –aged adults [4]. Ischemic and hemorrhagic lesions can be observed in NCC and are associated with cerebral vasculitis. Cerebrovascular complications of NCC include Transient Ischemic Attack (TIA), ischemic stroke and intracranial hemorrhages [28]. The frequency of cerebral infarction due to NCC varies between 2% and 14% [28, 31]. Subarachnoid NCC is the more complex form of disease [28]. The pathological mechanism behind the stroke is the presence of an inflammatory reaction. The meningeal cysticerci elicits a severe inflammatory reaction in the subarachnoid space with formation of an exudate composed of collagen fibres, lymphocytes, eosinophils leading to abnormal thickening of the leptomeninges [32, 33]. This inflammation may be disseminated inducing damage in the optic chiasm and cranial nerves arising from the brain stem as well as from the Circle of willis. The latter may cause occlusion of the lumen of vessel with subsequent development of ischemic stroke [33]. Hemorrhagic stroke due to NCC include intracystic hemorrhages, cerebral hemorrhages secondary to an inflammatory arteritis and subarachnoid hemorrhage secondary to the rupture of mycotic aneurysms [28].

- **COVID-19**

The COVID-19 outbreak is currently the major public health concern worldwide. A novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has emerged in Wuhan, China, in December 2019 [34]. The World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) as a pandemic on 11 March 2020 [35]. As of 9th October 2020, a total of 36,361,059 patients had been diagnosed globally, with 1,056,186 deaths [53]. COVID- 19 mainly affects the respiratory system, but there is increased evidence of cerebrovascular accidents and neurologic involvement [36]. From the initial outbreak in China, transmission was identified from respiratory droplets and fomities with symptoms initially reported as fever, dyspnea, cough and severe hypoxia. With greater clinical experience, a broader spectrum of symptoms has emerged, such as gastrointestinal disease, headache, altered mental status, anosmia, and confusion [34]. Some patients do have Transient Ischemic Attack (TIA) or Stroke as their initial presentation. The pandemic epicenter in Wuhan, China, reported 36% of neurological complications in 214 patients with COVID-19 [37]. A review by a panel of the World Stroke Organization reported that the risk of ischemic stroke during COVID-19 is around 5% (95%confidence interval (CI: 2.8 to 8.7%). COVID-19 related hemorrhagic strokes are far less common than ischemic stroke, but a few cases have been reported [38]. Stroke in COVID 19 mostly occur in patients(> 55 years of age) with previous vascular risk factors (Hypertension, Diabetes Mellitus, Atherosclerosis, Myocardial Infarction and previous history of stroke) [39]. But few case reports described the development of large vessel stroke in patients younger than 50 years of age without previous vascular risk factors [40]. Some studies have been conducted to find the association between stroke and COVID-19. Alexander. E. Merlder *et al*. conducted a retrospective cohort study at 2 academic hospitals in New York City, New York. He found that approximately 1.65% of adults with COVID-19 experienced ischemic stroke, which is a higher rate of stroke when compared with a cohort of patients with Influenza [41]. Another retrospective case control study conducted by P. Belani *et al*. at 6 hospitals in New York City confirmed that there was significantly greater incidence of Acute Ischemic Stroke in patients with COVID-19 infection when compared with those without infection [34]. The mechanism through which SARS-CoV-2 attacks the neurologic system or can cause stroke is still a matter of debate. Further investigations are needed in this area. Because of the recency of the pandemic, most studies should be regarded as preliminary. It is suggested that several mechanisms are associated with stroke in COVID- 19. Neurological complications including

stroke have been reported in severe form of COVID-19. Pathophysiologic changes contributing to neurologic complications include hyperinflammation, blood-brain barrier (BBB) dysfunction and hypoperfusion. Autopsy reports in COVID-19 described some vascular alterations which can contribute to neurological complications [42]. One of the suggested mechanism for Ischemic Stroke is that SARS-CoV-2 infection is linked to a prothrombotic state causing venous and arterial thromboembolism and elevated D- dimer levels (normal value is <500 microgram per liter) [37]. Severe COVID-19 is associated with a systemic immune response to the pathogen by proinflammatory cytokines (Cytokine Rush or Cytokine Storm) induce endothelial and mononuclear cell activation with expression of tissue factor leading to coagulation activation and thrombin generation [37, 38]. In the case of COVID-19 several cytokines, including IL1B, IFN gamma and MCP1 have been found to be markedly elevated [38]. Circulation of free thrombin, uncontrolled by natural anticoagulants, can activate platelets and lead to thrombosis [37]. This is the possible mechanism for Ischemic Stroke. While the pathogenesis of Hemorrhagic stroke has not been fully elucidated, it is possible that the affinity of SARS- CoV-2 for Angiotensin Converting Enzyme 2 receptors (a surface protein) which are expressed mainly in the lungs but it is also present in the endothelial and arterial smooth muscle cells of the brain. These ACE 2 receptors allow the entry of virus in to the CNS and thus causing damage to the intracranial arteries which leads to vessel wall rupture. In addition it is possible that, the cytokine storm that accompanies this disorder could be the cause of Hemorrhagic Strokes [34, 38]. The massive release of cytokines may also damage blood brain barrier and cause hemorrhage. Secondary hemorrhagic transformation of the acute infarct can also occur. This is only preliminary evidence and further investigations are needed. But it is certain that patients with severe COVID-19 must undergo aggressive monitoring for stroke.

Diagnosis

The diagnosis of infectious causes of stroke is based on clinical, laboratory and radiologic findings [4].

- Clinical Findings: The clinical findings include signs and symptoms:
- Fever
- Headache
- Nausea/vomiting
- Tiredness
- Blurred vision
- Convulsions
- Unconsciousness
- Paresis
- Hemiplegia
- Neck stiffness
- Cranial nerve palsy
- Laboratory Findings:
- Complete blood count(CBC)
- Serum biochemistry
- Erythrocyte Sedimentation Rate(ESR)
- C-Reactive Protein(CRP)
- Blood culture
- CSF fluid analysis
- Sputum culture (for TB)
- Serological Tests
- Blood clotting profile
- PCR
- ELISA
- Imaging studies:
- Computed tomography(CT BRAIN)
- Magnetic resonance imaging (MRI BRAIN)
- Transcranial Doppler
- Carotid Ultrasonography
- Cerebral Angiography
- Echocardiography
- Chest X ray
- ECG
- EEG

Management of stroke

The goals of treatment are to (1) reduce ongoing neurologic injury and decrease mortality and long term disability (2) prevent complications secondary to immobility and neurologic dysfunction and (3) prevent stroke recurrence [49]. Management consists of drug therapy, physical rehabilitation, control of risk factors and good nursing care [4]. Ensure adequate respiratory and cardiac support and determine quickly from CT scan whether the lesion is ischemic or hemorrhagic [3]. American Stroke Association (ASA) has established guidelines on the management of both Ischemic and Hemorrhagic stroke [43].

- **Ischemic stroke**

If a patient is admitted with ischemic stroke within 4.5 hours of symptom onset, acute treatment includes initiation of Tissue Plasminogen Activator (t-PA) and Aspirin [3, 43, 44]. But before initiation of t-PA therapy me*et al*l inclusion and no exclusion criteria [3, 43]. Avoid antiplatelet and anticoagulant therapy for 24 hours after administration of Alteplase (t-PA) to avoid the risk of bleeding. Aspirin 160 to 325 mg/day should be started between 24 and 48 hours after completion of Alteplase to reduce long tern death and disability [43]. For secondary prevention of stroke use antiplatelet agents, anticoagulants and statins [43]. Antiplatelet drugs include Aspirin, Clopidogrel, Ticlopidine and Dipyridamol [4]. For patients with embolic diseases due to cardiac problems or vascular atherothrombotic plaques anticoagulant drugs such as Heparin or Warfarin could be used [4]. Treat ischemic stroke patients with high- intensity statin therapy to achieve a reduction of at least 50% LDL for secondary stroke prevention [43]

Table 2: Evidence - based recommendations for pharmacotherapy of ischemic stroke [43].

	Recommendation	Evidence
Acute treatment	t-PA 0.9 mg/kg IV (maximum 90 kg) over 1 hour in selected patients within 3 hours of onset ASA 160–325 mg daily started within 48hours of onset	IA IA
Secondary prevention Non-cardioembolic	Antiplatelet therapy Aspirin 50–325 mg daily Clopidogrel 75 mg daily (over aspirin)	IA IA IIb B

	Aspirin 25 mg + extended release dipyridamole 200 mg twice daily	IB
Cardioembolic (esp. Atrial fibrillation)	Warfarin (INR = 2.5) Dabigatran 150mg twice daily	IA
Atherosclerosis	Intense statin therapy	IB
All patients	BP reduction	IA

- **Hemorrhagic stroke**

There is no current pharmacologic strategy for treating intracerebral hemorrhage. Follow medical guidelines for managing BP, increased intracranial pressure, and avoid other medical complications in acutely ill patients in neurointensive care units [43, 45]. Subarachnoid hemorrhage (SAH) due to aneurysm rupture is often associated with delayed cerebral ischemia in the 2 weeks after the bleeding episode [43]. The calcium channel blocker Nimodipine 60mg every 4 hours for 21 days is recommended to reduce the incidence and severity of neurologic deficits resulting from delayed ischemia. In SAH, surgical intervention to clip or ablate the vascular abnormality reduces mortality from rebleeding [43].

Other approaches for care

Nursing care include early rehydration, prevention of bedsores, protecting from aspiration pneumonia and rehabilitation. The rehabilitation is a combination of physical, occupational and speech therapy [4]. Treatment of the risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia, and smoking cessation are important features of the stroke management. Decreasing salt intake as well as weight reduction and increase in physical activity also are the other important aspects of stroke management [4, 43].

Treatment

- **Neurosyphilis**

According to the treatment guidelines of Centers For Disease Control And Prevention (CDC), the recommended regimen for treatment of neurosyphilis is Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion for 10-14 days [46]. Alternative regimen include procaine penicillin G 2.4million units IM once daily plus probenecid 500mg orally 4 times a day (both for 10-14 days) [4, 46]. The durations of the recommended and alternative regimen of the neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore Benzathine penicillin, 2.4 million units IM once per week for up to 3 week, can be considered after these neurosyphilis treatment regimen to provide a comparable total duration of therapy [46]. All patients should be treated with long term aspirin or other antiplatelet agents to prevent the endothelial proliferation in Nissl's endarteritis [4].

- **Bacterial meningitis**

Bacterial meningitis is a neurologic emergency that is associated with significant morbidity and mortality. Therefore it is vital to begin the treatment as early as possible in the disease course. The goals of treatment are: (1) eradication of infection with amelioration of signs and symptoms (2) preventing morbidity and mortality (3) initiating appropriate antimicrobials and (4) providing supportive care [47]. Figure 1 explains the management algorithm for bacterial meningitis in adults. Figure 1

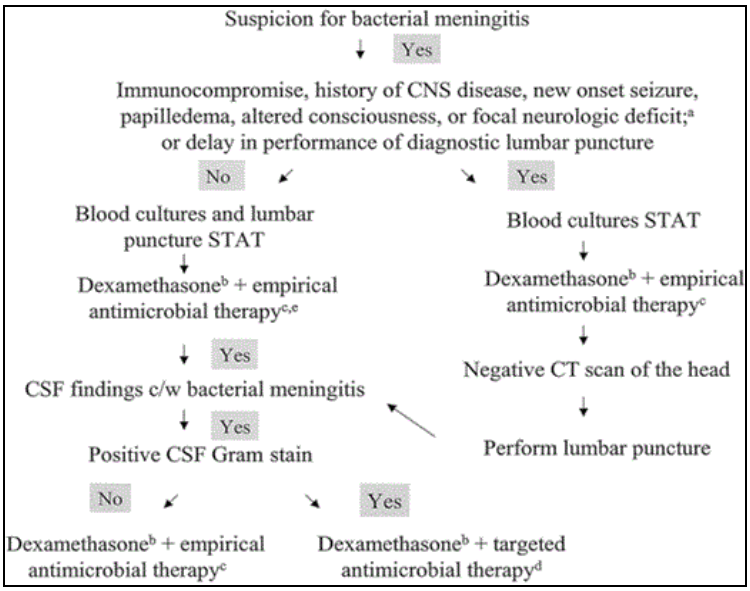

Fig 1: Management algorithm for bacterial meningitis in adults adapted from IDSA guidelines: [48]

Once there is suspicion of acute bacterial meningitis, blood samples must be obtained for culture and a lumbar puncture should be performed immediately to determine whether the CSF formula is consistent with the clinical diagnosis [48]. If there is any delay occurs in performing lumbar puncture, empirical antimicrobial therapy should be instituted as soon as possible to eradicate the causative organism [46, 48]. Empirical antibiotic therapy should last at least 48 to 72 hours or until the diagnosis of bacterial meningitis can be ruled out. Continued therapy should be based on the assessment of clinical improvement, cultures and susceptibility testing results [46]. The choice of empirical

antibiotic therapy in this situation should be governed by the patient's age and by various conditions that may have predisposed the patient to meningitis [48]. Delay in the initiation of therapy introduces potential for increased morbidity and mortality. Once the pathogen has been identified through CSF Gram stain, targeted antibiotic therapy can be initiated in patients with bacterial meningitis [46]

Table 3: Recommended empirical antibiotic therapy based on age and predisposing factors: [48]

Predisposing factor	Common bacterial pathogens	Empirical therapy
AGE		
< 1month	*Streptococcus agalactiae, E. coli, Listeria monocytogenes, Klebsiella species*	Ampicillin plus Cefotaxime or Ampicillin plus an Aminoglycoside
1-23 months	*Streptococcus pneumoniae, Neisseria meningitidis, S.agalactiae, H. influenzae, E.coli*	Vancomycin plus third- generation cephalosporin
2-50 years	*N. meningitidis, S. pneumoniae*	Vancomycin plus third- generation cephalosporin
>50 years	*N. meningitidis, S. pneumoniae, L. monocytogenes*	Vancomycin plus Ampicillin plus third- generation cephalosporin
HEAD TRAUMA		
Basilar skull fracture	*S. pneumoniae, H. influenzae,* group A *β-hemolytic streptococci*	Vancomycin plus a third generation Cephalosporin
Penetrating trauma	*Staphylococcus aureus,* coagulase-negative staphylococci, aerobic gram- negative bacilli*(P. aeuruginosa*)	Vancomycin plus cefipime, vancomycin plus ceftazidime or vancomycin plus Meropenum
CSF SHUNT	Coagulase-negative staphylococci, aerobic gram- negative bacilli*(P. aeuruginosa), S. aureus*	Vancomycin plus cefipime, vancomycin plus ceftazidime or vancomycin plus Meropenum

Table 4: Recommended specific antimicrobial therapy in bacterial meningitis based on isolated pathogen: [48]

Microorganism	Recommended therapy	Alternative therapy
Streptococcus pneuoniae	Vancomycin plus a third- generation cephalosporin (ceftriaxone or cefotaxime)	Meropenum or fluoroquinolone(gatifloxacin or moxifloxacin)
Neisseria meningitidis	Third-generation cephalosporin(ceftriaxone or cefotaxime)	Penicillin G, ampicillin, chloramphenicol, fluoroquinolone
Listeria monocytogenes	Ampicillin or penicillin G	Trimethoprim -sulphamethoxazole, meropenem
Haemophilus influenzae	Third-generation cephalosporin (ceftriaxone or cefotaxime)	Chloramphenicol, cefepime, meropenem, fluroquinolone
Escherichia coli	Third-generation cephalosporin (ceftriaxone or cefotaxime)	Cefepime, meropenem, fluroquinolone, aztreonam, trimethoprim-sulphamethoxazole

Table 5: Recommended dosages of antimicrobial therapy in patients with bacterial meningitis [48]

Antibiotics	Total Daily Dosing (Dosing Interval in Hours)			
	Neonates, age in days		Infants and children	Adults
	0-7 days	8-29 days		
Ampicillin	150mg/kg(8)	200mg/kg (6-8)	300mg/kg(6)	12g(4)
Aztreonam	-	-	-	6-8g(6)
Cefepime	-	-	150mg/kg(8)	6g(8)
Cefotaxime	100-150 mg/kg(8-12)	150-200 mg/kg(6-8)	225-300 mg/kg(6-8)	8-12g(4-6)
Ceftriaxone	-	-	80-100mg/kg (12-24)	4g(12-24)
Chloramphenicol	25mg/kg(24)	50mg/kg (12-24)	75-100 mg/kg(6)	4-6g(6)
Meropenem	-	-	120mg/kg(8)	6g(8)
Penicillin G	0.15mU/kg (8-12)	0.2mU/kg (6-8)	0.3mU/kg(4-6)	24 mU/kg (4)

The Infectious Diseases Society of America (IDSA) guidelines recommend use of adjunctive Dexamethasone in patients with suspected or proven community- acquired bacterial meningitis [48]. The first dose of Dexamethasone 0.4mg/kg IV every 12 hours for 2 days (in adults) or 0.15mg/kg every 6 hours for 4 days (in children) should be given 15-20minutes before the first dose of antibiotics [46, 48, 49]. Dexamethasone should be continued if the culture grows either *S. pneumoniae or H. influenzae*. The administration of dexamethasone can prevent the deafness in children. The rationale for the use of Dexamethasone is that it can attenuate the inflammatory response. This may be effective in reducing many of the pathophysiological consequences of bacterial meningitis, such as cerebral edema, increased intracranial pressure, altered blood flow, cerebral vasculitis and neurological injury mediated by proinflammatory cytokine expression [48]. The patient must also be monitored for complication from the disease like hydrocephalus, seizures and hearing defects. The administration of fluids, electrolytes, antipyretics and other supportive measures include treatment of seizures and monitoring of intracranial pressure are also important for patients present with acute bacterial meningitis [46].

- **Cerebral malaria**

Patients with malaria should be treated early with antimalarial drugs. Quinine is the main stay of treatment [4]. Quinine dihydrochloride (loading dose: 20mg/kg over 4 hours; maximum dose: 600mg; and maintenance dose: 10mg/kg every 8 hours) is commonly used. The loading dose is associated with faster clearance of parasitemia and resolution of the impaired state of consciousness [28]. Artemisin derivatives (eg: artesunate and artemether) are also good alternatives [4]. The artemisin derivatives reduce paresitemia faster and diminish mortality in adults with

severe malaria, and therefore these are preferred in patients with parasite count > 10% [28]. Artemisins are generally well tolerated. Artemisins should be used in malaria stroke patients with associated cardiac conditions since Quinine is proarrythmogenic. The dose used in cerebral malaria is as follows: 1) Artesunate, 2.4mg/kg given IV at 0, 12 and 24 hour and then daily. 2) Artemether, 3.2mg/kg given IM as loading dose, followed by 1.6mg/kg IM daily to a total of 640mg. Artemisins should be followed by doxycycline (100mg daily for 7 days) [28]. Fluid, electrolyte balance and acid-base correction are important cornerstone of treatment. Some clinical trials found that corticosteroids (eg: Dexamethasone) may increase the stupor period as well as may prolong the coma in survivors, and therefore it should not be used in cerebral malaria (CM) [4].

- **Tuberculous meningitis (TBM)**

Early treatment is mandatory, and delayed treatment is associated with a higher rate of morbidity and mortality [4]. The main stay of treatment remains anti-tuberculous therapy. Antituberculous regimen included 2 month intensive therapy comprising Isoniazid (5mg/kg of body weight; maximum dose, 300mg), Rifampicin (10mg/kg; maximum, 600mg), Pyrazinamide (25mg/kg; maximum, 2g/day) and Ethambutol (20mg/kg; maximum, 1200g/day), followed by a continuation phase comprising of Isoniazid and Rifampicin for 6 months. Prior studies have shown that corticosteroids may affect outcome from TBM by reducing hydrocephalus and preventing infarction [28]. Dexamethasone appears useful as an adjunctive treatment [4]. Dexamethasone should be given IV for 4 weeks (0.4mg/kg/day for week 1, 0.3mg/kg/day for week 2, 0.2mg/kg/day for week 3, and 0.1mg/kg/day for week 4) and then oral treatment for 4 weeks starting at 4mg/day and decreasing by 1 mg each week. Pyridoxine should be given orally 20-40mg/day [27]. The Aspirin has anti-platelet, anti-inflammatory and anti- oxidant properties. In a study evaluating the effect of Aspirin in the prevention of stroke in patients with TBM, there was a significant reduction in the number of stroke and significant reduction in the three month mortality. The Aspirin at a dose of 150mg/day is preferred in TBM with stroke [50].

- **Neurocysticercosis (NCC)**

The goals of therapy for neurocysticercosis are to reduce the morbidity, to prevent the complications and to eradicate the infestation. Treatment depends upon the viability of cyst and its complications. Management includes symptomatic treatment as well as treatment directed against the parasite [51]. If the parasite is dead, symptomatic treatment can be initiated (eg: anticonvulsants for management of seizures). Monotherapy with first –line antiepileptic drugs like phenytoin, carbamazepine and phenobarbital is usually sufficient for management of seizures [30, 51]. If the parasite is viable or active, administration of anticysticercal drugs are beneficial to achieve better control of seizures. The two anticysticercal drugs used to treat NCC are Albendazole (15-30mg/day for 8-15 days) and Praziquantal (50mg/kg/day for 15 days) [4, 28]. Both agents eliminate the cysticerci or markedly reduce their number. Albendazole is superior to praziquantal and seems to be more effective in giant cyst and subarachnoid, intraventricular or spinal NCC. Corticosteroids like Dexamethasone (16-32mg/day) should be used to reduce the inflammatory reactions before and during the cysticidal therapy and in conditions like vasculitis, arachnoditis and encephalitis [28, 30, 51]. In the presence of hydrocephalus due to an intraventricular cyst, placement of a ventricular shunt is recommended, followed by surgical extirpation of the cyst and subsequent medical treatment [51]. In cases of multiple cysts in the subarachnoid space, surgical extirpation is recommended.

- **Corona virus disease 2019**

Following the declaration of Corona virus Disease 2019 (COVID-19) as a pandemic, and reports describing some patients presenting with transient ischemic attack or stroke, a panel of international experts from 18 countries prepared a comprehensive set of practical implications for the management of stroke in patients with confirmed or suspected of having COVID-19 [35]. While the underlying cause is unclear, patients with COVID-19 are at increased risk of developing acute stroke. Several factors may impair the possibility to complete appropriate screening of patients with stroke for COVID-19. Therefore, patients with stroke suspected of having COVID-19 should be evaluated under the assumption that they have COVID -19. The available data suggest that healthcare providers treating patients with acute stroke are at risk of acquiring COVID-19, though the risk for infection is probably lower compared to the risk of providers involved in the evaluation of respiratory or infectious diseases. The stroke team must use every precaution to reduce the transmission risk during evaluation of acute stroke patients, including maintaining a distance of 2 meters, using surgical masks, gloves, gowns, goggles or face shielding and hand washing, along with minimizing the number of providers and the use of Telestroke, when appropriate [35, 52]. To avoid contamination of the environment and exposure to staff, it is advisable to create a stroke green pathway that is separated from potentially contaminated emergency department, along with ad hoc pathway in the case of a patient with confirmed or suspected COVID -19 [35]. Figure 2 shows the proposed workflow of hyper acute stroke patients.

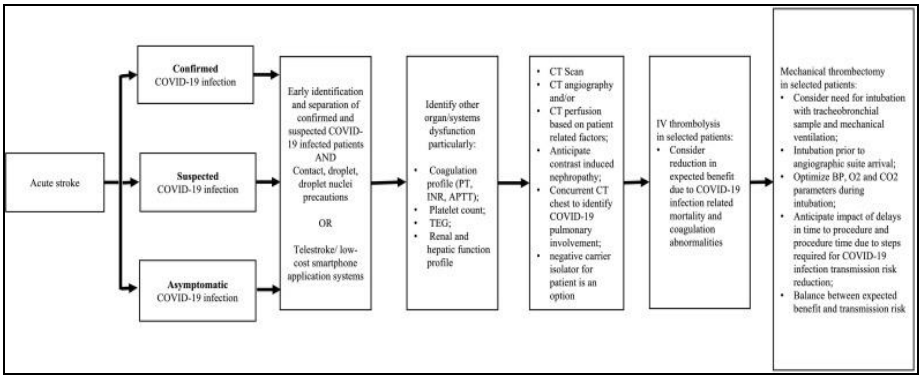

Fig 2: Proposed workflow of hyper acute stroke care in era of COVID- 19 pandemic [35]

Rapid screening should be done in screening area for patients present with stroke. Intravenous thrombolysis in the absence of any major contraindications should be provided with either IV Alteplase or IV Tenecteplase in standard doses followed by post thrombolysis monitoring to all eligible patients [35]. Mechanical thrombectomy should be provided to eligible patients with large vessel occlusion if the facility is available at the designated hospital. The challenge will remain for either designating a particular angiosuite if feasible or sanitizing the angiosuite used when treating a COVID-19 suspected or positive case [35, 52]. While considering mechanical thrombectomy the standard recommendations for managing stroke due to large vessel occlusion as per the AHA, ASA and National Stroke Guidelines need to be followed. Secondary prevention is also very important. Risk factors, routine blood investigations, ECG and the pattern of ischemia on imaging, may help discerning the stroke mechanism [52]. Patients should be started on Aspirin, statin and other specific medications as per risk factors and possible etiology. Anticoagulation should be only started if there is a cardioembolic stroke and after considering any exclusions among the patients [52]. Compliance should be encouraged. The patients should be discharged as per the guidelines and stability with optimum advice [35, 52]. In case of hemorrhagic stroke, the treatment and management depends on the cause and severity of bleeding. Basic life support, as well as control of bleeding, blood pressure and intracranial pressure are critical [43]. Patients requiring urgent neurosurgical interventions should be provided with a standard of care. For COVID-19 positive patients, neurosurgery facilities should be provided in designated places as per guidelines. Separate operation theatres (OT) for COVID-19 suspect and positive patients and sanitization after every procedure is required [52].

Conclusion

Stroke is a neurologic emergency. Several definite risk factors have been identified for stroke, although infectious factors might also contribute to stroke episodes through increased susceptibility or direct induction. For stroke patients without traditional cerebrovascular risk factors but with signs of infection, then infectious causes should be considered. Identifying infectious causes can be challenging and so a high index of suspicion and a low threshold for obtaining additional non-traditional stroke investigations are necessary. These investigations can include contrasted cerebral imaging, cerbrospinal fluid analysis and high resolution vessel imaging modalities that may facilitate an early diagnosis and prompt initiation of targeted antimicrobial therapy. The antimicrobial therapy is the cornerstone of management in stroke associated with infections. Appropriate anti-infective therapy should be given in addition to traditional treatment for storke. Preventive and therapeutic interventions through the use of vaccinations and antimicrobial therapy along with infection evaluation may help in reducing stroke incidence going forward.

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