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Management of acute ischemic stroke in patients with COVID-19 infection: Report of an international panel

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Abstract

Background and purpose: On 11 March 2020, World Health Organization (WHO) declared the COVID-19 infection a pandemic. The risk of ischemic stroke may be higher in patients with COVID-19 infection similar to those with other respiratory tract infections. We present a comprehensive set of practice implications in a single document for clinicians caring for adult patients with acute ischemic stroke with confirmed or suspected COVID-19 infection.

Methods: The practice implications were prepared after review of data to reach the consensus among stroke experts from 18 countries. The writers used systematic literature reviews, reference to previously published stroke guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate practice implications. All members of the writing group had opportunities to comment in writing on the practice implications and approved the final version of this document.

Results: This document with consensus is divided into 18 sections. A total of 41 conclusions and practice implications have been developed. The document includes practice implications for evaluation of stroke patients with caution for

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stroke team members to avoid COVID-19 exposure, during clinical evaluation and performance of imaging and laboratory procedures with special considerations of intravenous thrombolysis and mechanical thrombectomy in stroke patients with suspected or confirmed COVID-19 infection.

Conclusions: These practice implications with consensus based on the currently available evidence aim to guide clinicians caring for adult patients with acute ischemic stroke who are suspected of, or confirmed, with COVID-19 infection. Under certain circumstances, however, only limited evidence is available to support these practice implications, suggesting an urgent need for establishing procedures for the management of stroke patients with suspected or confirmed COVID-19 infection.

Keywords
Coronavirus, COVID-19, acute stroke, mechanical thrombectomy, thrombolysis, ischemic stroke

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Introduction

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) as a pandemic on 11 March 2020. As of 27 April 2020, a total of 3,064,895 patients had been diagnosed globally, with 211,609 deaths. Most patients with confirmed COVID-19 developed fever, cough, and/or dyspnea. Pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), cardiac injury, renal failure, and encephalitis[1] have been reported. Some patients do have Transient Ischemic Attack (TIA) or Stroke as their initial presentation. A comprehensive document providing up-to-date data and guidance to healthcare providers involved in management of acute stroke is needed to meet the new challenges to acute stroke care posed by COVID-19 pandemic.

To develop a comprehensive document, panel members from 18 countries were identified on the basis of their previous work in relevant topic areas. Preference was given to members from countries with large proportion of COVID-19 infected patients and those from countries with previous corona virus infection outbreaks such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). The panel used systematic literature reviews using key words "COVID-19," AND "corona virus," OR "stroke," AND "cerebrovascular disease" from 1 November 2019 to 5 April 5 2020. Additional reference to previously published stroke guidelines, WHO, and Centers for Disease Control and Prevention (CDC) recommendations, relevant non-stroke-related professional guidelines, personal files, and expert opinion were made (see supplemental material for literature reviewed). The report summarized existing evidence, indicated gaps in current knowledge, and when appropriate, formulated practice implications.

Section 1. Acute stroke in patients with COVID-19 infection

A single center study of 221 consecutive hospitalized patient with COVID-19 infection reported that 11 (5%) developed acute ischemic stroke, 1 (0·5%) cerebral venous sinus thrombosis, and 1 (0·5%) cerebral hemorrhage.[2] The mean age of patients who developed stroke (72 years) was higher (52 years) and the stroke group had higher frequency of hepatic and renal dysfunction. The frequency of hypertension, diabetes mellitus, and previous history of cerebrovascular disease were higher among those who developed stroke. The median duration from first symptoms of COVID-19 infection to stroke was 10 days (interquartile range 1–29 days). Of the 11 patients with ischemic stroke, five were related to large artery disease, three small artery disease, and three cardioembolic events. The fibrin D-dimer levels were 12-fold higher in patients who developed stroke indicating a hypercoagulable state. Of 11 patients with ischemic stroke, 6 received antiplatelet treatment with aspirin or clopidogrel, and 5 received anticoagulant treatment with enoxaparin. The overall mortality rate was 38.5% (5/13); 50% and 20% in those treated with antiplatelet or anticoagulant, respectively. Another study reported occurrence of cerebrovascular disease in 5 (5.7%) of 88 patients with severe COVID-19 infection and 1 (1%) of 126 patients with mild infection.[3,4] Cerebrovascular events were more common in older patients with stroke risk factors such as hypertension and diabetes mellitus, and those who had elevated fibrin D-dimers.[2,3]

The proportion of COVID-19 infected patients who are expected to have acute stroke is 4.9% (95% confidence interval: no continuity correction 2.8%–8.7%).[2] The estimated number ranges between 7820 and 35,867 under the assumption that 1,329,877 patients are infected as of 6 April 2020, and an estimated 21% to

31% of COVID-19 infected patients requiring hospitalization. There is a possibility that COVID-19 infection increases the risk of stroke because the risk is increased 3.2 to 7.82 folds within first three days after other respiratory tract infections.[5,6] If the risk of stroke is increased with COVID-19 infection, an increase in number of acute strokes can be expected during the COVID-19 pandemic. Concurrently, the number of patients with transient ischemic attack and minor stroke presenting to hospital may decrease as those patients may avoid hospitalization.

Conclusion and practice implications

1. Patients with COVID-19 infection carry a high risk of developing acute stoke especially in those with multiple organ dysfunctions.
2. It remains unclear as to the underlying cause of developing acute stroke in patients with COVID-19 infection. There is preliminary evidence of hyper coagulopathy in association with increased risk of developing stroke in patients with COVID-19 infection. An increased risk of acute ischemic stroke has also been noted in patients with other respiratory tract infections.
3. Further studies should be undertaken to assess the risk of acute ischemic stroke which is likely increased in patients with COVID-19 infections and to establish evidence of increased stroke incidence during the COVID-19 pandemic.[7]

Section 2. Risk to stroke team members

Healthcare providers in contact with patients who have confirmed or possible COVID-19 infections have an increased risk of exposure to this virus. Basic principles of transmission and protection against transmission are summarized in Table 2 and Figure 1. A Chinese report concluded that 3300 health-care workers have been infected as of early March with 22 deaths.[8] The Chinese Center of Disease Control and Prevention reported that 1716 (3.8%) of 44,672 laboratory confirmed COVID-19 infections were healthcare workers with highest occurrence reported in Wuhan before precautionary measures were taken.[9] In Italy, as of 15 March 2020, there had been 2026 documented COVID-19 cases among healthcare providers.[10]

Conclusion and practice implications

1. Healthcare providers engaged in acute stroke care are at risk of acquiring COVID-19 infection from stroke patients with COVID-19 infection.
2. The exact risk of COVID-19 infection transmission during acute stroke care has not been established. It is likely that the risk of contracting COVID-19 infection is lower among providers taking care of acute stroke than those who are involved in evaluation of respiratory or infectious diseases and those who perform aerosol-generating procedures.

Figure 1. Flowchart suggesting strategy to minimize exposure from COVID-19 infection during evaluation of stroke patients. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

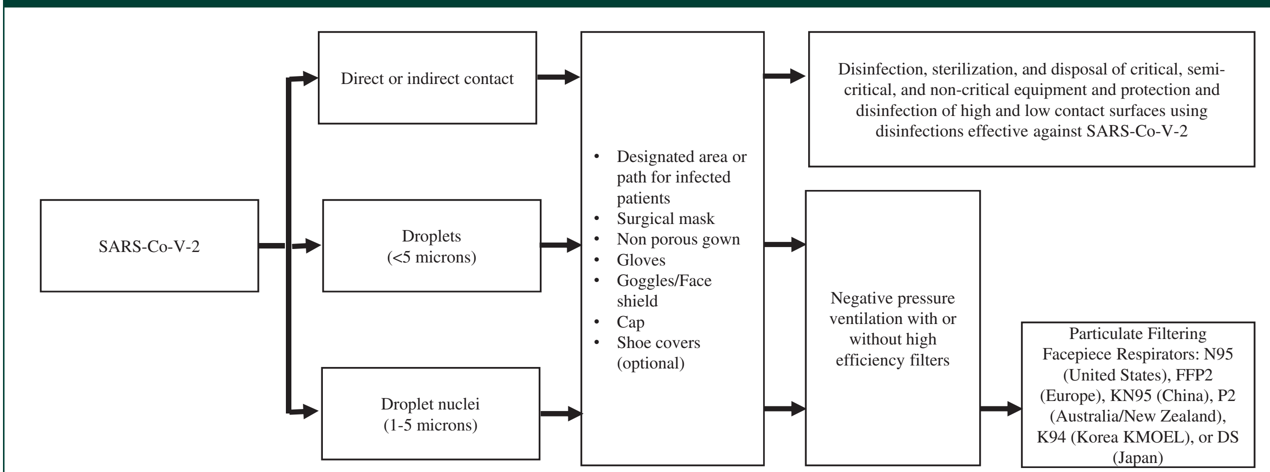


Table 1. World Health Organization case definitions of COVID-19 case surveillance.[24]

Suspected case	A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath), AND a history of travel[a] to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset. OR B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset. OR C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.
Probable case	A. A suspect case for whom testing for the COVID-19 virus is inconclusive. OR B. A suspect case for whom testing could not be performed for any reason.
Confirmed case	A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

[a]History of travel may lose significance as cases are reported in larger geographic areas.

Section 3. Types of COVID-19 infected stroke patients

The stroke team may be involved in evaluation of three categories of patients:

Patients with known COVID-19 infection

The current data suggest that patients with COVID-19 infection developed stroke in advanced stages of COVID-19 infection. The median duration from first symptoms of COVID-19 to the development of stroke was 10 days in one study.[2] Therefore, whether the patients are being evaluated in the emergency department (ED) or within the hospital, the institutional screening protocols would have already identified COVID-19 infection in these patients.

Patients with suspected COVID-19 infection

Almost all institutional screening protocols are based on the recommendations of WHO and CDC (Table 1). One of the challenges in identifying COVID-19 infection in acute stroke patients is an inability to get an accurate history of clinical symptoms due to underlying aphasia, dysarthria, and confusion. Cognitive incompetency and lack of availability of next of kin together are seen in 10%–12% of acute stroke patients depending upon stroke severity.[11,12] Some of the disease features, such as fever and cough are seen in 44% and 68% of the patients, respectively on admission.[13] Radiographic or computed tomography (CT) chest abnormalities may be found in 82% of the COVID-19 infected patients on admission.[14]

The time constraints for confirming a COVID-19 infection need to be understood. Confirmation of COVID-19 infection requires detection of unique sequences of virus RNA using real-time reverse-transcription polymerase chain reaction (rRT-PCR) from nasopharyngeal and oropharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage. The time required to get the results vary depending upon what kit is being used (5 min to 8 h for rRT-PCR and three days for serological enzyme-linked immunosorbent assays) and whether the specimen has to be sent to a laboratory outside the hospital. Repeat testing may be necessary due to poor quality of the specimen, limited patient specimens, the inappropriate timing of specimen collection (to early or too late) during the infection process.

Patients with undiagnosed COVID-19 infection

Acute stroke patients may be asymptomatic carriers, in the prodromal period, or neurological deficits is the first manifestation. The time between transmission and symptoms onset ranges between 2 and 14 days.[15] The viral load that was detected in the asymptomatic patients was similar to that in the symptomatic patients, highlighting the transmission potential of asymptomatic or minimally symptomatic patients.[16] The estimated asymptomatic patient proportion ranges between 17.9% to 30.8% of all infected patients.[17,18] The possibility of isolated neurological symptoms as presenting symptoms in COVID-19 infected patient such as confusion (8%), headache (8-13%) and dizziness (17%) may prompt a stroke evaluation.[3]

Conclusion and practice implications

1. COVID-19 infected patients may develop stroke after the diagnosis of infection had already been made. This sequence of events is consistent with

Table 2. Basic principles of transmission and prevention of COVID-19 infection.[18]

Size of corona virus (SARS – CoV & MERS – CoV)	0.125 μm
Route of infection	Inhalation and mucous membrane penetration
Method of transmission	Contact (direct-touching the skin of other people or indirect-objects contaminated with infectious droplets and then touching the eyes, nose, or mouth) Droplets (>5 μm) through coughs or sneezes droplets onto themselves, other people, or nearby surfaces Droplet nuclei (1–5 μm) unclear if role in transmission
Penetration through respiratory tract	Particles < 100 μm in size can enter the nose, mouth and throat and are considered "inhalable." Particles < 10 μm can reach the large bronchioles and are considered the "thoracic" fraction, and particles < 5 μm can enter the deep lung and are considered the "respirable" fraction
Close contact	Approximately 6 feet (2 m) of a COVID-19 case for a prolonged period of time; close contact can occur while caring for COVID-19 infected patient; or having direct contact with infectious secretions of a COVID-19 infected patient
Maximum risk	Performance of aerosol-generating procedures
Intermediate risk	Entering the room of a COVID-19 infected patient. The risk may vary depending upon the room. Isolation rooms, angiographic suites, and operating rooms already have a set up for infection control. Medical transport workers transporting patients with suspected COVID-19 infected patient
Low risk	Other parts of hospitals or other health care facilities where there is no direct contact with patients
Basic protection	Surgical masks, safety glasses or goggles, (capable of protection from aerosols from all sides) and face shields shield the healthcare worker's mucous membranes (eyes, nose, and mouth) from large sprays of blood and other body fluids
Advanced protection	Particulate respirators if transmission via droplet nuclei or in close proximity to droplets: 1. A filtering half facepiece (sometimes called a disposable respirator), where the filter is virtually the entire respirator 2. An elastomeric (reusable) half facepiece with a particulate filter 3. An elastomeric (reusable) full facepiece with a particulate filter 4. A powered air purifying respirator that includes a particulate filter
Rating of respirators	"**N**," if they are **N**ot resistant to oil, "**R**" if somewhat **R**esistant to oil, and "**P**" if strongly resistant (oil **P**roof)
Implications for corona virus	The SARS virus has a "shell" composed of lipids, which are fats and oils. However, the amount of fat and oil in these tiny virus particles is extremely low and is not enough to affect the filter in the N-series respirator
Levels of filter efficiencies	95% (N95), 99% (N99), and 99.97% (N100 or high-efficiency particulate air filter) tested against aerosol (fine mist) droplets 0.3 μm in diameter
Strategies for effectiveness	Fit-testing and training of each worker in the use, maintenance, and care of the respirator
Complimentary strategies	Adequate ventilation Disinfection of contaminants

acute stroke seen in the setting of other respiratory tract infections.
2. A COVID-19 infection is unlikely to be confirmed or excluded using laboratory assessment during the time frame for initial evaluation and decision making in acute stroke patients. Therefore, a clinically suspected COVID-19 infected patient with stroke has to be evaluated under the assumption that the patient has COVID-19 infection.
3. There is a possibility that acute stroke patients may have undiagnosed COVID-19 infection because: 1. Appropriate screening was not possible due to inadequate history from patient, due to stroke-related neurological deficits and lack of relatives; 2. Patients with COVID-19 infection being in prodromal period; 3. Patient is an asymptomatic carrier; and 4. Neurological deficits seen in early period of COVID-19 infection prompting a stroke evaluation.
4. If a stroke patient is suspected to have COVID-19 infection, pulmonary imaging using chest computerized tomography (CT) scan and/or radiograph may be helpful in identifying radiological abnormalities suggestive of COVID-19 infection.

Section 4. Transmission risk during evaluation of acute stroke patients

The principles of transmission and protection are summarized in Table 1 and Figure 1. Published data[19] show that SARS-CoV-2 virus maybe present and can survive in droplet nuclei up to 3 h. However, the contribution of droplet nuclei in transmission is currently uncertain. Standard surgical masks may not be effective in preventing inhalation of droplet nuclei because they are not designed to provide a tight face seal and to filter out particulates in the droplet nuclei. Particulate filtering facepiece respirator which include N95 (United States), FFP2 (Europe), KN95 (China), P2 (Australia/New Zealand), K94 (Korea KMOEL), or DS (Japan) are preferable. Using surgical mask, gloves, gowns, and hand-washing was effective in the prevention of nosocomial transmission of severe acute respiratory syndrome in 2003[20] with no superiority demonstrated for particulate filtering facepiece respirator.[21] The Surviving Sepsis Campaign Guidelines on the Management of Critically Ill Adults with COVID-19[22] recommend a minimum of a surgical/medical mask for healthcare providers caring for non-ventilated COVID-19 infected patients and during performance of non-aerosol-generating procedures on mechanically ventilation (closed circuit). The risk for severe COVID-19 infection may be higher in healthcare providers with advanced age or underlying medical comorbidities including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, chronic renal disease.[4,9]

One of the unique aspects of evaluation of acute stroke is that such evaluation can be performed remotely using Telestroke; and several guidelines identify Telestroke as an integral part of stroke systems of care.[23,24] Telestroke has demonstrated equivalence to that of a bedside assessment[23,24] for immediate assessment of stroke severity using National Institutes of Health Stroke Scale (NIHSS) and to determine intravenous recombinant tissue plasminogen activator (rt-PA) and/or thrombectomy eligibility.[23,24] Use of the low-cost smartphone application system is another option for the rapid clinical assessment in acute stroke care.[25]

Conclusion and practice implications

1. Members of stroke team must use basic principles targeting prevention of disease transmission, including maintaining a distance of 2 m from patient (unless absolutely necessary) and combining the use of surgical mask, gloves, gowns, and handwashing. Whether a particulate filtering facepiece respirator is necessary is not clear as stroke evaluation does not require aerosol-generating procedures. The use of particulate filtering facepiece respirator may depend upon availability, institutional policy, and regional prevalence of COVID-19 infection.
2. The stroke team evaluating the patient should comprise of the minimum number of healthcare providers and those who meet the high-risk criteria of contracting COVID-19 infection should preferably not be involved in the evaluation of stroke patients.
3. The most effective strategy to avoid transmission is by not being in the same room or space with a stroke patient with suspected or confirm COVID-19 infection. The use of Telestroke must be maximized in the current situation because all aspects of acute stroke evaluation can be performed. Institutions may explore with the ethics committee or Institutional Review Board whether commercially available low-cost smartphone application systems can substitute when Telestroke networks are not available.

Section 5. Environmental contamination

Centralized air conditioning may re-circulate viral materials in droplets from patients to unaffected individual and care providers due to inward direction of airflow.[26] SARS-CoV-2 has been detected in other body fluids such as fecal specimens of infected patients.[27] Significant contamination (SARS-CoV-2 viral RNA)[28] from patients was seen in air samples and surface samples from personal items (spirometer, pulse oximeter, nasal cannula), personal computers, iPads and reading glasses), room surfaces, and toilets. Viral RNA was also identified in bedside tables and beds, window ledges, and the floor beneath patients' beds.

Conclusion and practice implications

1. To avoid contamination of the environment and exposure to staff, it is advisable to create a stroke green pathway (including consultation rooms, CT/magnetic resonance imaging (MRI) rooms, and angiographic suite) that is separated from potentially contaminated ED to avoid direct interaction between the stroke team and patients with COVID-19 infection. The stroke green pathway can be based on a pre-hospitalization screening.
2. In the case of a patient with confirmed or suspected COVID-19 infection, an ad hoc pathway must be followed and the environment must be sanitized. The suspected or ascertained case must then be admitted in an isolation ward after treatment (suspected cases should be kept separated from the confirmed), in isolation room with precautions against transmission.

Section 6. Overall management plan for acute stroke patient

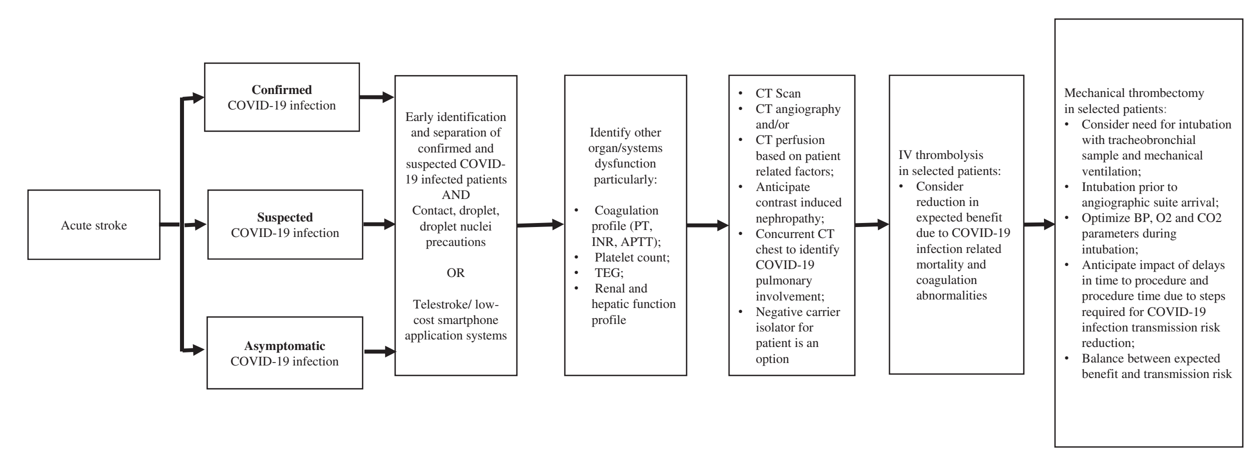
A management algorithm is summarized in Figure 2. The mortality was very high (38%) in stroke patients with COVID-19 infections.[2] The mortality was much higher than the mortality observed for hospitalized stroke patients in China ranging from 1.5 to 2.3% for ischemic stroke and 2.3–3.2% for all strokes.[29] Therefore, the outcome of patients with COVID-19 infection and stroke is heavily determined by the severity of underlying COVID-19 infection. The mortality rates among hospitalized patients with COVID-19 infection without stroke range from 22% to 45%.[4,30,31] Several factors in patients with COVID-19 infection have been established which can identify the patients at risk for in-hospital mortality such as older age, high Sequential Organ Failure Assessment (SOFA) score, cardiovascular diseases, secondary infections, ARDS, acute renal injury, and laboratory findings of lymphopenia and elevated hepatic enzymes, C reactive protein, ferritin, creatinine phosphokinase, and fibrin D-dimers.[4,30–32]

Therefore, assessment of dysfunction in other organs using validated systems such as SOFA appears to be important to provide overall prognosis prior to determining the appropriate acute stroke treatment. The SOFA assesses respiration (PaO2/FiO2 ratio), coagulation (platelet count strata), hepatic enzymes (bilirubin concentration strata), cardiovascular (hypotension and treatment), neurological function (Glasgow Coma Scale/Score strata), renal (serum creatinine/urine output strata), and sepsis (present/absent) and assigns a score of 0–4. The mortality rates range from 3.2% in patients without organ failure to 91.3% in patients with failure of all the six organs analyzed in patients with sepsis.[33]

Conclusion and practice implications

1. The high rate of mortality in COVID-19 infected patients who have multiple organ dysfunctions/failure needs to be recognized and is unlikely to be

Figure 2. Proposed workflow of hyper acute stroke care in era of COVID-19 infection pandemic.



PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; TEG: thromboelastography; CT: computerized tomography; IV: intravenous; BP: blood pressure; O_2: oxygen; CO_2: carbon dioxide.

influenced from acute treatment of stroke. An assessment of the magnitude of organ dysfunction using SOFA score maybe helpful in delineating the overall care paradigm in acute stroke patients in accord with the expected prognosis in addition to stroke-related factors.

Section 7. Neurovascular imaging

Current guidelines for acute stroke management[34] recommend that all suspected stroke patients should receive brain imaging (non-contrast CT scan) on arrival to hospital preferably within 20 min of arrival in the ED. Patients in whom mechanical thrombectomy is being contemplated may require CT angiography and patients presenting between 6 and 24 h may require CT perfusion, or multimodal MRI. Current guidelines[34] recommend to proceed with contrast imaging prior to acquiring serum creatinine concentration in patients without a history of renal impairment. Both COVID-19 infection and stroke carry a high probability of renal impairment and perhaps higher probability when both occur together.[35] Contrast exposure required for CT angiography and perfusion images may precipitate acute kidney injury (AKI) in a highly vulnerable COVID-19 infected patient and increase risk of mortality.

Negative pressure carrier isolators have been used to isolate the patient during neurovascular imaging. The isolator consists of non-porous vinyl material that encapsulates the patient and the negative pressure and the outlet filters prevent contaminated air to escape from the isolator. Concurrent chest CT scan may be obtained at the time of neurovascular imaging may identify CT chest abnormalities (consolidation, ground glass opacity and reticular opacity in the presence of architectural distortion) that may be seen in up to 82% of patients with COVID-19 infection on admission.[13]

Conclusion and practice implications

1. The relatively high rate of renal insufficiency with subsequent AKI in patients with COVID-19 infection needs to be recognized. Renal insufficiency and/or AKI increase the risk of mortality in patients with COVID-19 infection and those with stroke. It is reasonable to ascertain the presence of other risk factors for contrast-induced nephropathy in patients with COVID-19 infection prior to administration of contrast for CT angiography and/or perfusion to appropriately identify the risk benefit ratio.
2. The purpose of CT angiography and perfusion images is to select patients for mechanical thrombectomy and can be avoided if mechanical thrombectomy is not going to be considered due to poor patient condition or patient/family wishes.
3. Concurrent pulmonary imaging using chest CT scan for identifying radiological abnormalities suggestive of COVID-19 infection may be incorporated as part of initial imaging in patients with acute stroke. The extent of pulmonary involvement may impact the therapeutic decisions in acute stroke management including the need for intubation. However, chest CT scan may be normal in the early phase of COVID-19 infection.
4. Negative pressure carrier isolators may be used to isolate patient with COVID-19 infection during neurovascular imaging.

Section 8. Intravenous thrombolysis

Intravenous rt-PA is recommended for selected patients who may be treated within 3 h and for highly selected patients who can be treated within 3 and 4.5 h of symptom onset or last known well.[34] Current guidelines do not recommend treatment with intravenous rt-PA in patients with acute ischemic stroke and infective endocarditis, because of the increased risk of intracranial hemorrhage (ICH).[34] There are no septic emboli generated in COVID-19 infection but perhaps a generalized pro-coagulable state similar to sepsis may exist. Patients with sepsis and systemic inflammatory response can be either hypercoagulable or hypocoagulable.[36] Leukocytosis (with lymphocytopenia), with elevation in neutrophil counts, the level of C reactive protein, and fibrin D-dimers, a fibrin degradation product, have been identified in patients with COVID-19 infection.[13] Previous studies in patients without COVID-19 infection have demonstrated a higher rate of death[35] or more severe disability and higher risk of ICH among ischemic stroke patients with leukocytosis, elevated levels of C reactive protein,[37] and fibrin D dimers[38] who were treated with intravenous rt-PA.

Another aspect to consider is hepatic dysfunction manifested by elevation in the transaminases level in patients with COVID-19 infection.[13] Intravenous rt-PA undergoes hepatic clearance which may be reduced in hepatic dysfunction with potential increase serum levels and risk of ICH. Advanced hepatic dysfunction may be associated with coagulopathy with elevation in prothrombin time (PT), international normalized ratio (INR), and thrombocytopenia. However, in acute hepatic dysfunction, either a prothrombotic state or coagulopathy can exist which is not fully identified by PT and INR values.[39] Therefore, a rapid bedside tool of thromboelastography may provide assessment of hemostatic characteristics in patients with hepatic dysfunction and sepsis[40] be measuring maximum clot firmness, maximum clot lysis, maximum elasticity, and clot strength reduction.

The relationship between low platelet counts, elevated PT or activated partial thromboplastin time (APTT), and risk of hemorrhagic complications in ischemic stroke patients receiving intravenous rt-PA is unclear. Current guidelines state[34] that intravenous rt-PA may be considered on a case-by-case basis and is reasonable in patients who have a history of warfarin use and an INR $\leq$1.7 and/or a PT < 15 s, or those with end-stage renal disease on hemodialysis or systemic malignancy with normal INR and APTT.

Conclusion and practice implications

1. The relatively high prevalence of elevated concentration of inflammation and hypercoagulabilty markers such as leukocytosis, and C reactive protein and D dimers in patients with COVID-19 infection need to be recognized. While none of these laboratory abnormalities are a contraindication to intravenous rt-PA, previous studies conducted in patients with acute ischemic stroke but without COVID-19 infection demonstrated a higher rate of death or disability and post thrombolytic ICH.
2. Hepatic dysfunction (transaminases elevation) without coagulopathy (normal PT, INR, APTT, platelet count) can occur in patients with COVID-19 infection. Despite the concern of impaired rt-PA hepatic clearance, no data are available to suggest a greater risk or benefit with intravenous rt-PA.
3. Hepatic dysfunction manifesting with coagulopathy (elevated prothrombin time, INR, activated partial thromboplastin time, or reduced platelet count) can occur in patients with COVID-19 infection. The current guidelines specify certain eligibility thresholds based on PT, INR, APTT, or reduced platelet counts although there is ambiguity regarding thresholds associated with greater risk or benefit with intravenous rt-PA.
4. Additional tests for assessing coagulation profile such as thromboelastography and serum concentration of D-dimers have been useful in sepsis and hepatic dysfunction and may be considered as needed. For patients with COVID-19 disease and other organ involvement, a detailed assessment of coagulation profile to determine risk benefit ratio is preferable prior to intravenous rt-PA administration.

Section 9. Mechanical thrombectomy

Current guidelines[34] recommend mechanical thrombectomy with a stent retriever in adult patients with ischemic stroke caused by the internal carotid artery or proximal middle cerebral artery (identified by CT angiogram) occlusion, have a NIHSS score $\geq$6, do not have extensive ischemic changes on CT scan, and if they can be treated within 6 h of symptom onset.[34] Mechanical thrombectomy is recommended in selected acute stroke patients within 6–16 h of last known normal and is considered reasonable in selected acute stroke patients within 6–24 h of last known normal but requires CT perfusion or MRI to identify potentially salvageable tissue.[34] During the COVID-19 pandemic, there will be new challenges in triaging stroke patients with suspected or confirmed COVID-19 infection, who cannot be transferred rapidly to angiographic suite from ED or from outside the hospital due to added requirements. Inter-facility transfer, which occurs in 44%–72% of acute ischemic stroke patients[41,42] may require special equipment and personnel that are likely to delay the procedure. Due to expected challenges, intravenous rt-PA in an isolation ward, rather than percutaneous coronary intervention has been recommended for patients with acute myocardial infarction.[43,44]

Conclusion and practice implications

1. New challenges in existing triage protocols for facilitating rapid transfers from ED to angiographic suite and between facilities should be anticipated because of new protocols to ensure early detection of COVID-19 infection and reduction in transmission.
2. Given the complexities associated with performing invasive procedures in patients with suspected or confirmed COVID-19 infection, a stringent policy is required to select acute ischemic stroke patients for mechanical thrombectomy. Although decisions need to be made on a case-by-case basis, the highest rates of favorable outcomes are expected in those who meet inclusion criteria used in clinical trials and when procedures can be initiated and performed rapidly.
3. In appropriate candidates, it may be reasonable to initiate mechanical thrombectomy assuming the patient has COVID-19 infection with appropriate precautions to avoid delays in mechanical thrombectomy.
4. Obtaining informed consents in light of "no visitor hospital policies" may require advanced consenting methods like waiver of consent or remote electronic informed consent.

Section 10. Intubation and mechanical ventilation

Current guidelines recommend the selection of general anesthesia or conscious sedation to be based on individual patient risk factors, technical aspects of the procedure, and other clinical characteristics.[34] Approximately 28–38% of the patients with acute ischemic stroke (prior to emergence of COVID-19 pandemic) who underwent mechanical thrombectomy received general anesthesia due to high stroke severity, poor respiratory status, altered level of consciousness, or inability to follow commands with variations noted among institutions.[45] Approximately 6–14% of acute ischemic stroke patients required unplanned intubation during mechanical thrombectomy[46] due to severe agitation, apnea after sedation bolus, and respiratory insufficiency. Patients with COVID-19 infection may be at higher risk for intubation because of respiratory failure with almost 20% having hypoxic respiratory failure.[9] Cardiac guidelines during the COVID-19 pandemic[43] recommend a low threshold in considering intubation in a patient with borderline respiratory status to avoid emergent intubation and reduce transmission risk to staff in the catheterization laboratory by managing ventilation through a closed circuit.

Conclusion and practice implications

1. A low threshold for initiating intubation, mechanical ventilation, and general anesthesia may be required in patients with COVID-19 infection who are selected for mechanical thrombectomy to reduce exposure risk during procedure by maintaining ventilation through closed circuit and avoiding unplanned intubations.
2. A tracheobronchial specimen for confirmation of suspected COVID-19 infection may be obtained at the time of intubation.

Section 11. Timing of intubation and mechanical ventilation

Endotracheal intubation, open suctioning, administration of nebulized treatment, manual ventilation before intubation, placing patient in prone position, and non-invasive positive pressure ventilation are all aerosol generating procedures that increase risk of transmission to healthcare professionals.[47] Therefore, intubation in a negative-pressure room in teams of two to four experienced members with enclosed, ventilated protective suits, with video-guided laryngoscopy is recommended[22,48] with minimum number of attempts to reduce duration of exposure to the patient. The cardiac guidelines during the COVID-19 Pandemic[43] recommended patients should be intubated prior to arrival to the catheterization laboratory to reduce exposure to personnel in angiographic suite.

Conclusion and practice implications

1. Several components of endotracheal intubation are aerosol-generating procedures that increase the risk of transmission of COVID-19 infection. Therefore, intubation and mechanical ventilation should be performed in the most optimal settings, which may not possible in the angiographic suite. It may be best for intubation and mechanical ventilation to be completed prior to arrival at an angiographic suite.

Section 12. The risk of intubation and general anesthesia

A greater proportion of acute ischemic stroke patients receiving general anesthesia due to COVID-19 infection also requires recognition that mechanical thrombectomy had higher odds of death, disability, or respiratory complications (pneumonia and prolonged mechanical ventilation) when used in acute ischemic stroke patients in previous studies.[45] The increase in death or disability rates associated with general anesthesia were attributed to intraprocedural hypotension[49] and hypocapnia due to hyperventilation at the time of intubation.[50] Patients with COVID-19 infection may be at higher risk for hypotension, due to underlying volume depletion (reduced fluid intake, fever and tachypnea), sepsis, or multiple organ dysfunctions. Strict parameters for intubation/anesthesia protocol used in three randomized clinical trials reduced the risk of death or disability to values comparable to local anesthesia.[51–53] All three trials used short acting anesthetic agents and blood pressure goals were prespecified and any hypotension during the intubation process was treated with intravenous vasopressors[51–53] (Table 3).

Table 3. Parameters used in the SIESTA trial[46] to reduce minimize risk of death or disability in acute ischemic stroke patients undergoing intubation and mechanical ventilation.

Parameters	Target	Limit
Systolic blood pressure	140–160 mm Hg	120–180 mm Hg
End tidal carbon dioxide	40–45 mm Hg	34–45 mm Hg
Percutaneous oxygen saturation	95–98	90–100
Richmond Agitation and Sedation Scale	−2 – 3	−5 – 3

Conclusion and practice implications

1. Strict parameters for systolic blood pressure or mean arterial pressure and end tidal CO_2 should be used to reduce the risk of death or disability in patients who require intubation and mechanical ventilation prior to mechanical thrombectomy, particularly in patients with suspected or confirmed COVID-19 infections.

Section 13. Personnel in angiographic suite

Standard precautions prior to emergence of COVID-19 infection included the use of personal protective equipment that consisted of a cap, standard surgical/medical masks mask, eye protection (proper splash protection), sterile (non-porous) gown, and sterile gloves, for anyone involved in the insertion of catheters or for guidewire exchange,[54] shoe covers were optional. The Surviving Sepsis Campaign Guidelines[22] recommend using standard masks, due to lack of evidence of superiority of particulate filtering facepiece respirator. This is in addition to standard, personal, protective equipment for healthcare providers who are performing non-aerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19 infection and are eligible for mechanical thrombectomy. Cardiac guidelines during the COVID-19 Pandemic[43] recommended particulate filtering facepiece respirator and eye protection for all catheterization laboratory personnel due to the risk of emergent intubation, suctioning, and/or cardiopulmonary resuscitation.

Conclusion and practice implications

1. All healthcare providers within the angiographic suite should wear surgical/medical masks, gloves, gown, and eye protection, such as a face shield or safety goggles at the minimum. The preferential use of particulate filtering facepiece respirator may depend upon availability and institutional policy. The limitations posed by additional personnel protective equipment in communication and technical aspects during procedure need to be considered.

Section 14. Surface contamination and transmission in the angiographic suite

The transmission of SARS-CoV-2 virus from contaminated environmental surfaces and equipment to healthcare providers and other patients is a serious concern in the angiographic suite. The SARS-CoV-2 can survive in aerosol up to 3 h, on copper up to 4 h, on cardboard up to 24 h, on stainless steel metal and plastic surface up to 72 h.[19] Mechanical thrombectomy procedures are performed in a radiographic-fluoroscopic room, usually equipped with biplane floor-mounted and ceiling-mounted C-arm angiography systems with two flat detectors. The patients are placed on a floor-mounted patient table with cantilevered carbon-fiber tabletop with a special, contoured foam mattress placed on the table. Use of non-porous sterile coverings on all areas in the procedure field is the currently acceptable procedure.[54] The area that requires such preparation may be increased in patients with suspected or confirmed COVID-19 infection. There are existing protocols for critical (introduced directly into the bloodstream or into other normally sterile areas of the body), semi critical (contact with mucous membranes), and non-critical (contact with intact skin), high touch (frequent touch by patients and health care workers) and low touch (infrequent touch) surfaces and spills. These protocols are likely to be modified requiring decontamination of work surfaces and equipment with designated hospital disinfectants (quaternary ammonium compounds, hydrogen peroxide, chlorine releasing agents, and alcohols 60-80% concentration) effective against SARS-CoV-2 with recommended contact time. Saline or contrast that may have contact with patient's blood or secretion may need to discard using closed systems. Terminal cleaning requiring decontamination of patient area and surrounding zone and equipment between procedures may be required by specialized teams[43] to avoid transmission to the next patient.

Conclusion and practice implications

1. Angiographic suites must have a policy that identifies the principles of decontamination and disinfectants for various categories of items (critical items, semi-critical items, and noncritical items) and surfaces (high touch and low touch) in the event a patient with suspected or confirmed COVID-19 infection undergoes mechanical thrombectomy.
2. A protocol for terminal cleaning is required to ensure that there is no transfer of COVID-19 infection to the next patient.
3. Institutional strategies must be developed to reduce longer than anticipated procedure times due to new precautionary measures for decontamination in angiographic suites.

Section 15. Ventilation and airflow in angiographic suite

Current guidelines recommend negative-pressure rooms with anterooms or industrial-grade, high efficiency particulate air filter units for patients with airborne viral diseases. The negative-pressure room ensures that air flows into the angiographic suite towards the patient by using a > -2.5 Pa (0.01″ water gauge) pressure differential and ≥ 12 air changes per hour. The filtration efficiency of 99.97% for particles of 0.3 μm diameter is recommended. Cardiac guidelines during the COVID-19 Pandemic[43] recommend negative pressure angiographic suite but acknowledge that most catheterization labs have either normal or positive ventilation systems.

Conclusion and practice implications

1. Although it is preferable to use negative pressure angiographic suites for mechanical thrombectomy, the lack of such angiographic suites in most institutions may make any recommendation impractical.

Section 16. Use of aspirin, P2Y12 receptor inhibitors, and heparin

Currently, guidelines[34] recommend immediate oral administration of aspirin or a combination of aspirin and clopidogrel after minor ischemic stroke or TIA, or after 24 h in patients treated with intravenous rt-PA. The possibility as to whether anticoagulants or antiplatelet agents may be superior in stroke patients with COVID-19 infection requires consideration. In sepsis, lipopolysaccharide triggers a procoagulant state via the tissue factor-dependent pathway of coagulation, which is reduced by heparin and hirudin[55] but not aspirin.[55] In patients with infections, platelet hyperactivity via ADP signaling is reported.[56] It remains unclear whether there is a superiority of P2Y12 receptor ADP antagonist such as clopidogrel or ticagrelor in such settings.[56]

Conclusion and practice implications

1. Consistent with existing data, antiplatelet medication may be avoided if possible for the first 24 h after receiving intravenous rt-PA and mechanical thrombectomy in stroke patients with suspected or confirmed COVID-19 infection until the risk can be better defined.
2. Single or dual antiplatelet medication may be considered in acute ischemic stroke who do not receive intravenous rt-PA and/or mechanical thrombectomy in patients with suspected or confirmed COVID-19 infection. No clinical data suggest superiority of one antiplatelet agent over another in secondary prevention of ischemic stroke in these patients. It may be valuable to identify underlying coagulation profile by laboratory testing as mentioned in previous section.

Section 17. Additional considerations

Comprehensive and designated stroke centers have a high volume of stroke patients with some receiving intravenous rt-PA, mechanical thrombectomy, or requiring longer hospital stay. A high number of other procedures such as endovascular treatment of intracranial aneurysms, carotid stenosis, and arteriovenous malformations are performed as well. Designated stroke centers are more likely to be large volume, level I or II trauma centers, and teaching hospitals. Therefore, such centers may become the designated center for the management of stroke patients with COVID-19 infection. A dedicated angiographic suite equipped with personal protective equipment, terminal cleaning supplies, anesthesia machines, and ventilators may have to be installed. Several organizations are anticipating the challenge[43,57] and have recommended downsizing case volumes (e.g. deferral of elective cases) and or shift-based allocation of staff/physicians to operate the angiographic suite with lower staffing. Staff shortage could be anticipated based on the possibility that some members in the stroke team may be infected or exposed or quarantined with suspected or confirmed COVID-19 infection. Exposure is also reduced by avoiding use of overlapping skills such as two neuro interventionalists in the same unit simultaneously.[43]

Conclusion and practice implications

1. Comprehensive and designated stroke centers must anticipate new challenges because of mismatch between demand and resources. It can be expected that there will be a deviation of resources from service lines responsible for management of stroke patients to those responsible for management of COVID-19 infection because of the concurrent engagement of two separate specialties in comprehensive and designated stroke centers.
2. A high volume of elective neuro-endovascular procedures may need to be deferred to meet new demands placed on comprehensive or designated stroke centers. Institutional policies and triage pathways can ensure standardized resource allocation.

Table 4. Research questions for defining the best management paradigm for patients with COVID-19 infection and ischemic stroke

Questions	Designs
Is the risk of ischemic stroke higher in patients with COVID-19 infection?	Case–control studies
What are the changes in hospitalization of ischemic stroke patient population (transient ischemic attack or minor stroke related admissions) during COVID-19 infection pandemic?	Hospital-based registries
What are underlying factors underlying changing characteristics of hospitalized ischemic stroke patients?	Hospital-based registries
What is the risk of transmission and optimal protection strategies for stroke team?	New studies on methods of transmission of COVID-19 infection to health care providers during steps specific for acute stroke management
What is the yield of additional tests such as thromboelastography and chest-computed tomographic scan in initial evaluation of acute stroke patients?	Hospital-based registries; clinical utility analysis
What is the risk benefit ratio of intravenous rt-PA in acute ischemic stroke patients with COVID-19 infection?	Single or multicenter case series
What is the risk benefit ratio of mechanical thrombectomy in acute ischemic stroke patients with COVID-19 infection?	Single or multicenter case series

Section 18. Need for additional data

A range of issues regarding acute ischemic stroke management can be confounded by stroke patients with suspected or confirmed COVID-19 infection and deserve further analysis (Table 4).

Conclusion and practice implications

1. Prospective registries may help to understand whether there are differences in risk, manifestations, response to treatment strategies, and outcomes in stroke patients with COVID-19 infection.

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