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Review

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Stroke Care during the COVID-19 Pandemic: International Expert Panel Review

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Keywords

Stroke · Coronavirus disease 2019 · Management · Review

Abstract

Background: Coronavirus disease 2019 (COVID-19) has placed a tremendous strain on healthcare services. This study, prepared by a large international panel of stroke experts, assesses the rapidly growing research and personal experience with COVID-19 stroke and offers recommendations for stroke management in this challenging new setting: modifications needed for prehospital emergency rescue and hyperacute care; inpatient intensive or stroke units; posthospitalization rehabilitation; follow-up including at-risk family and community; and multispecialty departmental developments in the allied professions. ***Summary:*** The severe acute respiratory syndrome coronavirus 2 uses spike proteins binding to tissue angiotensin-converting enzyme (ACE)-2 receptors, most often through the respiratory system by virus inhalation and thence to other susceptible organ systems, leading to COVID-19. Clinicians facing the many etiologies for stroke have been sobered by the unusual incidence of combined etiologies and presentations, prominent among them are vasculitis, cardiomyopathy, hypercoagulable state, and endothelial dysfunction. International standards of acute stroke management remain in force, but COVID-19 adds the burdens of personal protections for the patient, rescue, and hospital staff and for some even into the postdischarge phase. For pending COVID-19 determination and also for those shown to be COVID-19 affected, strict infection control is needed at all times to reduce spread of infection and to protect healthcare staff, using the wealth of well-described methods. For COVID-19 patients with stroke, thrombolysis and thrombectomy should be continued, and the usual early management of hypertension applies, save that recent work suggests continuing ACE inhibitors and ARBs. Prothrombotic states, some acute and severe, encourage prophylactic LMWH unless bleeding risk is high. COVID-19-related cardiomyopathy adds risk of cardioembolic stroke, where heparin or warfarin may be preferable, with experience accumulating with DOACs. As ever, arteritis can prove a difficult diagnosis, especially if not obvious on the acute angiogram done for clot extraction. This field is under rapid development and may generate management recommendations which are as yet unsettled, even undiscovered. Beyond the acute management phase, COVID-19-related stroke also forces rehabilitation services to use protective precautions. As with all stroke patients, health workers should be aware of symptoms of depression, anxiety, insomnia, and/or distress developing in their patients and caregivers. Postdischarge outpatient care currently includes continued secondary prevention measures. Although hoping a COVID-19 stroke patient can be considered cured of the virus, those concerned for contact safety can take comfort in the increasing use of telemedicine, which is itself a growing source of patient-physician contacts. Many online resources are available to patients and physicians. Like prior challenges, stroke care teams will also overcome this one. ***Key Messages:*** Evidence-based stroke management should continue to be provided throughout the patient care journey, while strict infection control measures are enforced.

Introduction

The global COVID-19 pandemic due to a novel coronavirus has to date infected >57.8 million and taken the lives of >1.3 million [1], resulting in a tremendous strain on healthcare services worldwide. Long recognized as a medical emergency, the added burden of possible association with COVID-19 should not defer or substantially change the management directed at the stroke, even adding the unwelcome burden of protecting the patient and caregivers during and after the acute illness. The availability of evidence-based interventions has been shown to reduce death, disability, and recurrence and thus should continue to be provided [2]. However, the pandemic has added challenges to providing the best care for the stroke, both for those with or without COVID-19. Emerging knowledge for the management promoted this international expert panel to review the available evidence and offer guidance to clinicians on appropriate stroke management during the COVID-19 pandemic.

Methodology

Stroke experts were approached to come together for the purpose of this study. The main areas of stroke care were identified that were then addressed by focus groups, from the pathobiology of COVID-19 infection, pathophysiology of stroke in COVID-19 patients, prehospital phase, through emergency and hyperacute care, imaging, revascularization, neurocritical care, stroke unit organization and care in patient isolation areas, investigations, stroke and medical management, rehabilitation, outpatient care, community support, continuing professional development, and stroke research, bearing on continuation of or changes occasioned by this new additional etiologic factor. The authors entered one or more focus groups, reviewed the available literature up till August 31, 2020, discussed, drew on their expertise, and formulated the recommendations presented below. All recommendations are empirical, congruent with recommendations published by other experts and societies, and based on best medical experience as no trial-based scientific evidence is yet available.

Pathobiology of SARS-CoV-2 Infection

In December 2019, several cases of atypical pneumonia of unclear etiology were reported in Wuhan, China [3]. On January 17, 2020, the complete genome of a novel beta-coronavirus suspected of causing "Wuhan pneumonia" was published [4]. Three weeks later, the virus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), and the World Health Organization proclaimed the "2019 novel coronavirus disease" as COVID-19.

The molecular immune pathogenesis of SARS-CoV-2 viral infection has been described [5]. Coronaviruses are enveloped virions, each of which contains a positive-sense, single-stranded RNA genome of 26–32 kb [6]. Within the triad of beta-coronaviruses that are phylogenetically similar and cause severe lower respiratory infections that may be fatal, the Asian epidemic initiated by SARS-CoV in 2002 had 10% case-fatality rate (CFR) but was exceeded by Middle East respiratory syndrome-CoV in 2012 with 34% CFR. To date, despite its demonstrable infectious properties, the worldwide CFR of COVID-19 caused by SARS-CoV-2 has not exceeded 6.5%.

Both SARS-CoV and SARS-CoV-2 use their respective spike proteins to bind to the angiotensin-converting enzyme (ACE)-2 (ACE2) receptor [7, 8], thereby gaining access to host target cells in the human body, and the common pathway is via inhalation. The ACE2 receptor binding affinity of the SARS-CoV-2 spike protein is 10- to 20-fold greater than that of SARS-CoV [9], perhaps accounting for its exceptional virulence.

Unsettled concerns that SARS-CoV-2 may be a neurotropic virus raise this possible capacity to augment the risk of stroke or other neurological complications that have been reported in COVID-19. The path of viral invasion is dictated by cellular tropism, following the distribution of target receptors in host tissues. In the human brain, both neurons and glia display ACE2 receptors. Evidence of neuronal uptake of SARS-CoV was demonstrated at autopsy and in cerebrospinal fluid of human victims of the 2002 SARS epidemic. Although the first reported autopsy studies of fatal COVID-19 did not show viral invasion of any neural element [10], it remains unknown whether SARS-CoV-2 shares the capacity for neurotropism with its sister virus, SARS-CoV, at the present stage of the COVID-19 pandemic, but both have been associated in the occurrence of stroke in infected individuals [11].

Mechanisms of Stroke in COVID-19

SARS-CoV-2 that causes COVID-19 may predispose to stroke by several direct and indirect mechanisms that induce new cerebrovascular pathologies, among them are primary vasculitis, cardiomyopathy, hypercoagulable states, and endothelial dysfunction, carrying risks of systemic embolism and local thrombosis. The coronavirus surface spike protein binds to the ACE2 receptor on human vascular endothelial cells and smooth muscle. It invades the host cells and can cause systemic vasculitis at any sites of the vascular tree, including cerebral vessel with possible local thrombosis and artery-to-artery embolism, that may lead to symptomatic cerebrovascular occlusion (ischemic stroke) or rupture (hemorrhagic stroke) or a coronary vasculitis resulting in acute coronary syndrome and subsequent cardioembolic ischemic stroke [12]. Direct effects of the virus on the myocardium, also mediated by ACE2, adds to the risk of embolic stroke via myocarditis, left ventricular systolic dysfunction, and cardioembolism and even stimulates the sympathetic nervous system, predisposing to stress cardiomyopathy and cardiac arrhythmias [13, 14].

The coronavirus evokes a systemic inflammatory response, with reports of proinflammatory cytokines (cytokine storm) that manifest as elevated levels of inflammatory biomarkers (interleukin-6, ferritin, lactate dehydrogenase, and D-dimer). This reaction predisposes to inflammation and rupture of prevalent atherosclerotic plaque and injury to the left atrium, left ventricle, and cerebral blood vessels [13–15].

The coronavirus can also produce an acquired hypercoagulable state with hyperviscosity and the production of antiphospholipid antibodies, predisposing to thrombosis in the leg veins (with embolism to the lungs and to the brain via patent foramen ovale) and also to cerebral venous thrombosis, marantic vegetations on the mitral and aortic valves, and thrombosis in the left atrium, coronary arteries, and extracranial and intracranial cerebral arteries and arterioles [16, 17]. Severe COVID-19 has even been associated with progression to disseminated intravascular coagulation, which may also predispose to intracerebral hemorrhage, via necrotizing encephalopathy and perhaps thrombocytopenia. Occlusion of multiple large cerebral arteries is likely to be related to cardioemboli.

More recently, in addition to endothelitiis, endothelial dysfunction is also being implicated in the pathophysiology of COVID-19 [18]. The binding of SARS-CoV-2 to surface ACE2 receptors leads to a depletion of membrane-bound ACE2, disruption of the protective effects of the renin-angiotensin system, decreased production of the protective peptides, and decreased stimulation of the receptor Mas and angiotensin AT2 receptors with overstimulation of angiotensin AT1 receptors. The dysfunctional endothelium contributes to thrombotic processes at the endothelial surface that could result in thromboembolism [19]. The systemic inflammatory state also impairs neurovascular endothelial function and contributes to subsequent central nervous system complications [20].

Patients with COVID-19 requiring prolonged intensive care and mechanical ventilation are also at risk of complications associated with critical illness including hypotension with inadequate cerebral perfusion; deep venous thrombosis; hypertension with intracerebral hemorrhage; stress cardiomyopathy; and septic embolization of any concurrent bacterial infection [21].

Prehospital Stroke Care

During the initial outbreak of COVID-19, decreased admission volume was noted because patients feared infection if referred to a hospital during a period of distancing and lockdown [22]. Some countries reported the number of acute stroke admissions reducing by 50–80% [23], indicating that many patients with moderate and even severe stroke were avoiding presentation. It is important, however, that patients continue to understand that stroke is an emergency and that when there is suspicion of stroke, the emergency medical services must be immediately called for help.

Also, during the pandemic, stroke must continue to be viewed as an emergency. Current stroke clinical guidelines are based on the "time is brain" concept, which remains valid. While time consuming, measures taken to obtain a detailed history and diagnostic measures are not appropriate during COVID-19, and an initial evaluation for key features of possible infection now has to be combined with ongoing rapid acute stroke assessment and treatment. At the same time, all safety requirements for management of COVID-19 patients have to be respected. Thus, it is recommended that measures be taken to protect both healthcare professionals and patients from infection. As point-of-care diagnosis of SARS-CoV-2 is not yet widely available, the policy is for all patients in the prehospital setting to be treated as potential COVID-19 cases until the results of subsequent COVID-19 screening in the hospital are negative. Thus, current safety measures being applied in the emergency room (ER) are also valid for prehospital patient management [24]. In detail, for each member of the Emergency Medical Service (EMS) staff, the use of protective wear and devices is mandatory. There may be regional adaptations, but a basic protection consists of nonporous gowns, gloves, goggles/face shields, caps, and shoecovers. When facing patients at high risk of COVID-19, particulate filtering facepiece respirators should be used. EMS staff must be trained in using this equipment, which should be sufficiently stocked.

Apart from the usual recording of neurological symptoms and signs, stroke history taking should additionally include several questions focused on key red flags for COVID-19 – fever, infection symptoms and any contact with a COVID-19 patient or anyone with suspected infection, or travel to high-risk areas within the previous 14 days – in order to estimate infection risk without significant time delay [25, 26]. Infection symptoms include fever, cough, rhinorrhea, chest pain, dyspnea, headache, anosmia or ageusia, myalgias, and gastrointestinal symptoms including vomiting and diarrhea.

EMS has to prenotify the target hospital not only about the soon-arriving stroke patient but also of a COVID-19 high-risk situation in case of suspicion of such a condition. Whenever tolerable, the patient will also get a surgical face mask. Regular ambulances, but also the recently developed mobile stroke units [27], have to be disinfected after each transport or treatment of patients. In case of unstable respiratory or circulatory conditions, extensive suggestions have been made regarding intensive care management of suspected COVID-19 patients including the use of high-efficiency particulate air filters that may simplify prehospital resuscitation situations [28].

Recommendations: the time is brain concept remains valid in prehospital stroke care, with urgent transport of acute stroke patients to the hospital, but with the caveat of being combined with appropriate safety measures around reducing SARS-CoV-2 infection/transmission.

Protected Pathways in the ER for Stroke Patients with COVID-19

The COVID-19 pandemic requires substantial adaptions of current stroke care protocols in the ER to maintain high-quality care of stroke patients whilst protecting healthcare team members and patients. An overflow of patients with infection in the ER not only bears the risk of spreading the infection among patients and healthcare providers but also results in a shortage of hospital beds, personnel, and other resources which are allocated to those with infection. Furthermore, stroke neurologists and staff members may be redeployed to other medical settings or affected by prophylactic quarantine or direct illness [29–31].

Thus, separate pathways for patients without suspected infection and for those with suspected or confirmed infection are necessary to maintain the standards of care for stroke patients. Such pathways require that each patient should be assessed for suspected or confirmed COVID-19 before entering the ER. In the screening area, health personnel must wear appropriate personal protection equipment (PPE), and patients should wear a surgical mask all the time.

If the infection control screen or the exposure or travel history is positive or if patients are aphasic or confused, and thus unable to reliably communicate, or there are no family members present to provide the necessary information, nasopharyngeal swabs should be taken from the nasopharynx and each nostril. In all patients without suspected infection, standard stroke pathways can be followed. Nevertheless, nasopharyngeal swabs are recommended depending on availability of tests. In areas with high rates of infection, all patients may be considered potentially being infected and undergo nasopharyngeal swabs.

Real-time quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) assays with a rapid turnaround time are important to minimize the time lag until SARS-CoV-2 test results are available in order to provide guidance as to which patients need quarantining procedures. Point-of-care antigen tests for rapid detection of SARS-CoV-2 are meanwhile becoming available for detecting a specific viral antigen collected from nasopharyngeal swab specimens. Their results are rapidly available within 15–30 min. However, antigen tests are less sensitive than nucleic acid tests, with a sensitivity of only 70–80%. Despite a high specificity of 97–98%, a high number of false-positive results may occur in a population with a low prevalence of COVID-19. Therefore, results from antigen tests require confirmation by RT-qPCR [32].

For all patients with suspected or confirmed infection, protected pathways should be activated. Even if protected pathways for stroke patients with suspected or confirmed COVID-19 are established, a shortage of trained personnel may affect the ability to assess and monitor neurologic status in these patients. In this situation, inpatient telemedicine has become an important tool to enable stroke team members to perform essential neurological monitoring of patients in dedicated COVID-19 areas, thereby reducing person-to-person contact and preserving scarce supplies of PPE. Evaluation of stroke patients in the ER as well as on daily inpatient rounds may be entirely conducted virtually using telemedicine equipment [33, 34]. Moreover, a telestroke network allows patients with low $ABCD_2$ scores to be treated in peripheral hospitals to avoid unnecessary transports to comprehensive stroke centers, especially in situations where the ERs there are overwhelmed by COVID-19 management activities [33, 34].

Protected pathways should meet the following requirements [31, 35]: dedicated CT and ultrasonography (US) rooms only for those stroke patients with suspected or confirmed infection, if >1 CT or US device is available in the hospital.

Patients with suspected infection can wait in dedicated areas, clinically monitored by the stroke team, and transferred to regular stroke units when the test results are negative. Thrombolytic therapy can also be administered there.

Only patients who are eligible for mechanic thrombectomy need to be transferred immediately to the interventional radiology (IR) suite, while the neuroradiology team should be alerted for adopting adequate PPE. A good interteam communication between the transferring and receiving team and appropriate use of PPE are essential for protecting both patients and team members from spreading the viral infection during invasive procedures. Furthermore, technicians are prompted to implement adequate decontamination protocols after the patient is leaving the room.

Aerosol-generating medical procedures, such as oropharyngeal suctioning, bag-valve-mask ventilation, noninvasive positive pressure ventilation, nasal high-flow therapy, nebulization, and placement of nasogastric tubes, should be deferred if possible in the hyperacute phase. If such procedures are needed, appropriate use of PPE is mandatory. Viral filters should be used for inline endotracheal tube suctioning and bag-valve-mask ventilation [35–37].

Intubation and extubation should be performed only in a controlled setting and where possible in negative pressure rooms. Although conscious sedation is preferred as first line for thrombectomy to protect anesthesiologists, a low threshold for intubation is recommended in order to avoid intubation in an emergency setting should the patient deteriorate [35–37]. Since most IR suites are positive pressure rooms, patients requiring general anesthesia should be intubated before entering the IR suite [37].

Stroke patients with confirmed infection should be transferred to dedicated wards or intensive care units (ICU) for COVID-19 patients. During the entire protected pathways, all stroke patients need to be kept under the responsibility of stroke physicians, although this may require a joint care model with respiratory or critical care physicians.

Recommendations: protected pathways for acute stroke patients with suspected or confirmed infection are mandatory to maintain high-quality standards of care. Requirements for stroke patients with suspected or confirmed infection include dedicated CT and US rooms, avoidance of aerosol-generating medical procedures, and transfer to dedicated wards or ICU for COVID-19 patients. Inpatient telemedicine enables neurological monitoring of patients in dedicated COVID-19 areas and reduces person-to-person contact.

Stroke Imaging in COVID-19

Confirmed or suspected COVID-19 patients with acute stroke should receive standard of care imaging and be evaluated for intravenous thrombolysis and/or intra-arterial mechanical thrombectomy (MT). All patients, but especially those with suspected COVID-19, should wear a surgical mass during transfer to imaging suites with supplemental oxygen applied underneath the mask through nasal prongs or similar devices. All healthcare personnel physically in contact with the patient should wear appropriate PPE including full sleeved gown, surgical mask, eye protection, and gloves.

Neurological and Neurovascular Imaging

In general, most centers are maintaining a consistent approach to imaging for ischemic stroke patients in the setting of COVID-19. Centers which have historically relied on CT/CTA/CTP continue to use these modalities on a routine basis, and centers relying on MRI/MRA/MRP are doing the same. Centers with multiple CT or MRI scanners have started to adopt a COVID-19 imaging suite that accommodates all patients with COVID-19. This is being done to avoid noninfected patients from being infected in CT scanners.

Regarding the imaging of COVID-19 patients, there is no reason to suspect that the imaging manifestations of acute ischemic stroke are any different to the general population. There is some suspicion that the diffuse endothelial injury caused by COVID-19 and associated prothrombotic state could lead to larger clot burdens, but this has yet to be confirmed [38].

In view of the highly infectious nature of COVID-19, dedicated CT rooms should be used for patients with suspected or confirmed COVID-19. The room should be thoroughly cleaned after each patient, with the number of staff in contact with the patient minimized.

Role of Chest CT Imaging

The main difference in the management of these patients is the debate regarding whether or not to include chest CT imaging in the imaging workup of ischemic stroke, especially in those with suspected large vessel occlusion (LVO) who may require general endotracheal anesthesia. There is wide variation in protocols across institutions. In one recent survey of 25 units across Germany, for example, 11 units required chest CT; 3 in any patient and 8 when COVID-19 was suspected based on body temperature [39]. In a similar study in the Netherlands, patients who underwent chest CT showed that the identification of COVID-19 was good with a sensitivity of 86%, specificity of 75%, and negative and positive predictive values of 94 and 55%, respectively [40]. Overall, it is reasonable to include chest CT as a screening mechanism for this patient population, in particular to protect other patients and providers, especially where a patient requires aerosolizing procedures. It would therefore be reasonable to perform a low-resolution chest CT while performing CT and CT angiogram of the brain prior to thrombolysis or thrombectomy to detect evidence of COVID-19 even though the patient may not have fever or respiratory symptoms.

Ultrasonography

US is well suited for patients who are isolated, treated on ICU, or intubated. Similar to a variety of multidisciplinary US applications in COVID-19 patients such as duplex US for screening venous thromboembolism, transthoracic echocardiography for structural and functional evaluation of the heart, and lung US for diagnosis and monitoring of pneumonia, there are numerous potentials for US evaluation in stroke patients. These include transcranial Doppler for detection of cerebral artery occlusion, confirmation of vessel recanalization, and evaluation of residual stenosis; US imaging for monitoring midline dislocation of the third ventricle to facilitate identification of patients who could benefit from decompressive craniectomy; and extracranial US evaluation of the carotid and vertebral arteries. An excellent review of disinfection procedures for ultrasound equipment in the setting of stroke and COVID-19 [41] has been published recently.

Recommendations: urgent neuroimaging should continue to be provided, including advanced imaging techniques, as the patient may arrive late. Strict infection control is needed. Dedicated scan rooms should be used for patients with suspected or confirmed COVID-19, and the room should be thoroughly cleaned after each patient, with the number of staff in contact with the patient minimized. CT thorax may be performed at the time of CT/CTA brain. US is a useful modality.

Intravenous Thrombolysis

Triaging acute stroke patients eligible for intravenous thrombolysis (IVT) has evolved from the conventional 4.5 (or 3)-h time window from the last well-known criterion to that according to viable brain tissue on advanced imaging findings, typically in those patients with an unknown onset time [42–44]. COVID-19 reportedly increases the risk of thromboembolism, particularly venous [45, 46]; young-onset major stroke might not be so rare in patients with COVID-19 [47]. These findings suggest that relatively fresh venous/cardiac thrombi cause stroke in such patients, and thrombolysis would be accordingly effective, despite the underlying inflammatory component being associated with an unfavorable stroke outcome in general.

Some centers have reported increased door to needle times during the COVID-19 pandemic attributed to the institution of infection control measures and the inrotation of inexperienced staff [48–50], while some have noted no change [51, 52]. Efforts should continue to use advanced imaging modalities in patients with suspected COVID-19 and administer revascularization therapies to eligible patients even in late time windows, as acute stroke patients may be delayed arriving to the hospital, while managing the need to screen for COVID-19 and instituting infection control measures.

It would be best to perform quick screening tests for COVID-19 using the currently developing easily inspecting antibody kit or RT-qPCR kit immediately after a patient's arrival in ER. This is to ensure that such patients are truly COVID-19 negative and to allow smooth passage of care with IVT. The spread and availability of viral screening will vary within and between facilities and countries.

For patients with confirmed COVID-19 and in those without proven COVID-19 negativity during the initial minutes after ER arrival, "safety is brain" should be emphasized more than "time is brain": that is, efforts should be made to balance avoidance of risk of infectious exposure to stroke team members with reducing time to initiation of reperfusion therapy. Appropriate PPE should be used by every staff who has direct patient care responsibility, with surgical masks applied to patients. Noncontrast CT, contrast CT, or MRI should be chosen according to a patient's condition (time after stroke onset or recognition, calmness tolerable for several-minute examination, renal function, and others) and conditions of imaging equipment specific to each institute. Check points for imaging rooms include ease of equipment disinfection, ventilation performance, and certainty of body search for magnetic materials. Since acute renal injury is reported to increase in patients with COVID-19 [53], care should be taken to avoid this adverse reaction if contrast is required for CT perfusion/angiography. The use of protected pathways discussed in the earlier section that commence in the ER and continue through the hyperacute phase of care would help minimize treatment delays. Training of inexperienced staff would also be helpful in reducing treatment delays. At present, special toxicity of thrombolytic agents (alteplase and tenecteplase) including hemorrhagic transformation for patients with COVID-19 has not been reported.

Recommendations: IVT should continue to be provided for all eligible stroke patients, irrespective of their COVID-19 status. The use of protected pathways that commence in the ER and continue through the hyperacute phase of care would help minimize treatment delays.

Thrombectomy for Treatment of Acute Stroke in the COVID-19 Pandemic

Selection of Patients for MT for LVO in COVID-19

Despite the challenges imposed by COVID-19, the Stroke Council of the American Heart Association (AHA)/American Stroke Association (ASA) has reiterated the need to maintain promulgated criteria for selection of patients for MT [54]. Studies have shown delays in door-to-MT time in some centers again attributed to the institution of infection control measures [55–57], but not in others [51]. Khosravani and others [30] recommend use of a protected "code stroke" (PCS) to maintain the service time and reduce treatment delays. Figure 1 shows a modification of PCS for use in ERs to select and prepare "at-risk" patients for MT in LVO stroke. COVID-19 patients with ischemic stroke tend to be younger and have more severe stroke, more large artery occlusions, and higher mortality than those without COVID-19 [58, 59]. There is no reported increased risk of hemorrhagic transformation after MT in COVID-19 patients. However, efficacy for MT for recanalization of LVO may be reduced due to multiple arterial occlusions, high clot burden, and clot fragmentation [60].

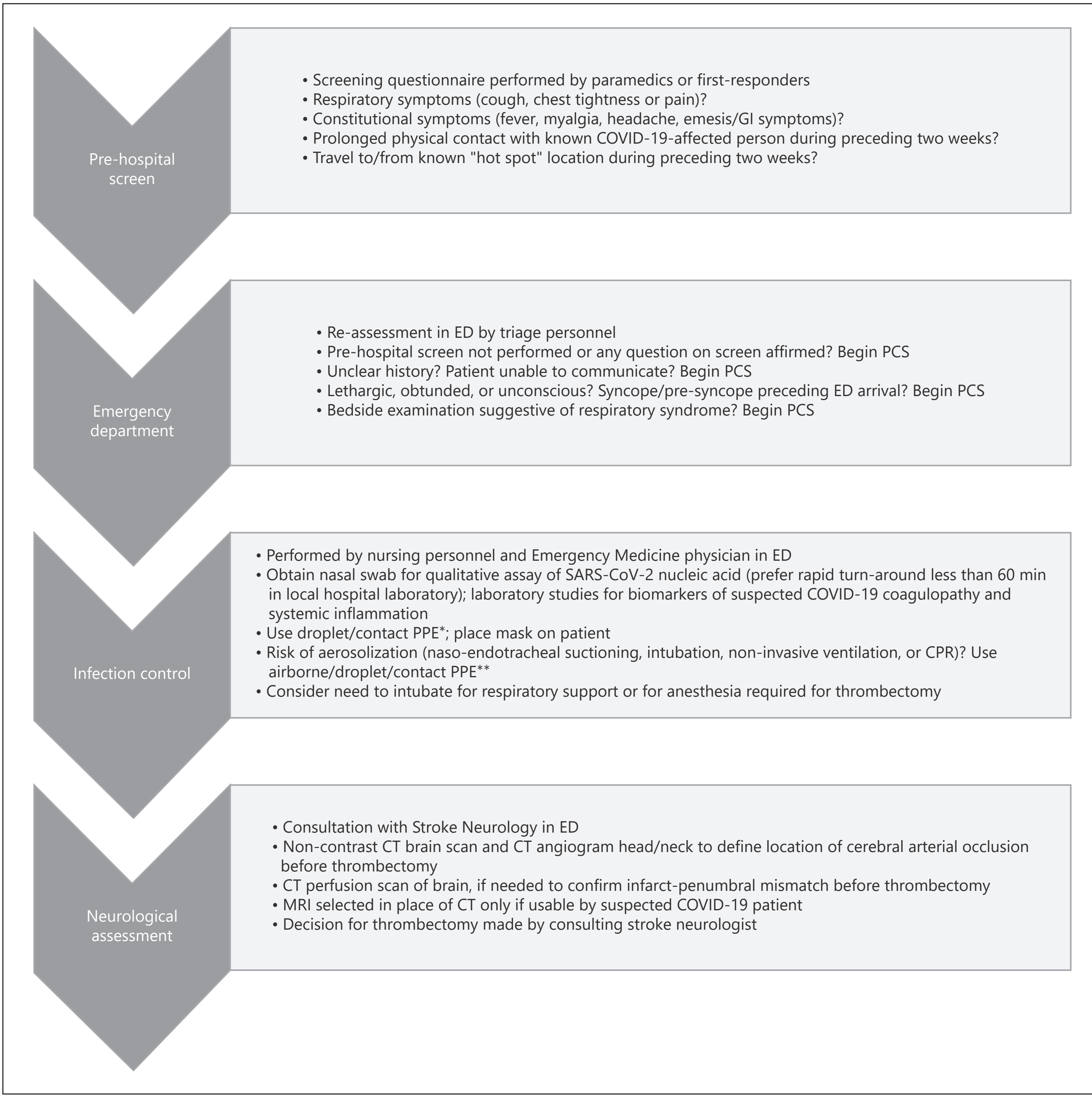

Fig. 1. Pathway identifying suspected COVID-19 patients for thrombectomy to treat stroke caused by LVO: note that assessment begins in the prehospital setting and continues into the Emergency Department, culminating with consultation provided by Stroke Neurology. LVO, large vessel occlusion; PPE, personal protective equipment; PAPR, powered air-purifying respirator; PCS, protected code stroke (see Khosravani et al. [30]); *droplet/contact PPE (fully sleeved gown, face mask, eye protection, and gloves); **airborne/droplet/contact PPE (droplet/contact PPE with use of N95 mask and face shield or PAPR device).

Accumulated Experience with MT for Treatment of Acute Stroke in COVID-19

There have been a number of publications of the results of MT in patients with COVID-19, after the initial case report by Al Saiegh et al. [61] describing the performance of MT for recanalization of an occluded proximal left middle cerebral artery in a 62-year-old woman with acute onset of right hemiparesis and aphasia. The patient had successful reperfusion but was readmitted from a rehabilitation facility 10 days later after developing intracerebral hemorrhage in the left hemisphere. During the second hospitalization, infection with SARS-CoV-2 was confirmed by routine screening by nasal swab undertaken as the patient was prepared for tracheostomy.

Oxley et al. [47] reported a case series of 5 patients, aged 33–49 years, with limited vascular risk factors who presented with characteristic LVO syndromes and clinical features of COVID-19 in only 3. The report highlighted the danger of ignoring medical emergencies during the pandemic, as 2 patients hesitated calling for ambulance transport from fear of contracting COVID-19. One patient was managed by anticoagulation for right internal carotid artery occlusion; the remaining 4 were treated by MT. One of the thrombectomy patients underwent cerebral thrombolysis by infusion of recombinant tissue-plasminogen activator (rtPA) before thrombectomy, but ultimately required hemicraniectomy to control malignant cerebral edema.

Escalard et al. [62] published a case series of 10 patients who underwent thrombectomy for treatment of acute LVO in COVID-19. Cerebral reperfusion by thrombectomy was initiated within 6 h of stroke onset for all patients; 5 underwent rtPA infusion before thrombectomy. Successful reperfusion was achieved in 9 patients, although "COVID-19 coagulopathy" caused difficulty in clearance of accumulated intraluminal thrombus and provoked recurrent arterial occlusion after thrombectomy. None of the 10 patients had dramatic early neurological improvement after reperfusion. The overall inhospital, all-case morality rate was 60% among the 10 victims of LVO associated with COVID-19, compared to 11% among uninfected patients.

In a more recent case series of 20 patients with COVID-19 and acute ischemic stroke [63], mean age was 63 ± 10·7 years (range: 37–78), and all had at least one vascular risk factor and 11 (55%) had LVO. Stroke mechanism was attributed to large artery atherosclerosis in 5 and atrial fibrillation in 2. While 4 received IVT, 5 underwent MT. Overall, 10% had recurrent stroke during the same hospitalization.

Recommendations: stroke patients should be screened for LVO notwithstanding their infection status, especially in the young. MT should not be withheld from those with LVO. The use of protected pathways discussed in the earlier section that commence in the ER and continue through the hyperacute phase of care would help minimize treatment delays.

Neurocritical Care during the COVID-19 Pandemic

Faced with new challenges in the absence of solid evidence, many critical care and neurological societies issued recommendations and statements to support and restructure neurocritical care during the COVID-19 pandemic in addition to conduction of surveys among neurocritical care providers [64–67].

Triage

During the COVID-19 pandemic, there is an obligation to save as many lives as possible. Discussion of quality of life and goals of care remain important components of the management of patients requiring neurocritical care [65].

Triage in situations of scarce intensive care resources requires a specialized team of intensivists, nurses, pharmacists, other medical staff with neurocritical care expertise, including some not directly involved in patient care, and including clinical ethicists to ensure consistent and transparent decisions based on an individual patient's situation and wishes that are independent of race, sex, ethnicity, socioeconomic, and social status. Risk stratification should be applied across all patients requiring intensive care and without relying exclusively on disease-specific prognostic scales [64, 65]. Triage should be performed at presentation to the ER [65].

Infection Control

Critically ill patients with stroke and COVID-19 should be cared for in a designated isolation unit. Patients with suspected COVID-19 should be kept in a designated unit or in a defined triage room with closed doors until the return of the test result.

For healthcare workers performing aerosol-generating procedures (e.g., endotracheal intubation, manual bag-valve-mask ventilation, and resuscitation) or in aerosol-generating situations (e.g., seizure, cough, and agitation) on patients with suspected or confirmed COVID-19, usage of fitted respirator masks (N95 respirators, FFP2, or equivalent) in addition to other PPE (i.e., gloves, gown, face shield, or safety goggles) is recommended [66].

Aerosol-generating procedures on ICU patients with COVID-19 should be performed in a negative pressure room [68]. For endotracheal intubation of patients with COVID-19, video-guided laryngoscopy is recommended over direct laryngoscopy, where available, undertaken by those most experienced with the procedure [66].

Diagnosing Irreversible Loss of Brain Function

Testing for SARS-CoV-2 prior to brain death examination is recommended, if results are available within 48 h [69]. If the SARS-CoV-2-PCR is negative, the usual policy of determination of irreversible loss of brain function should be utilized.

Decisions must be guided by the principle of balancing the minimization of harm to healthcare colleagues with the benefit of establishing a diagnosis for the patient and family [69]. If the SARS-CoV-2 infection cannot be excluded, appropriate PPE should be used with aerosol-generating procedures. Ancillary diagnostic tools to replace apnea testing are recommended for SARS-CoV-2-positive patients [68].

Recommendations: neurocritical care should continue to be provided for patients who may benefit from intensive care. Infection control measures must be strictly enforced. Aerosol-generating procedures on ICU patients with COVID-19 should be performed in a negative pressure room. Video-guided laryngoscopy is preferred over direct laryngoscopy for endotracheal intubation of patients with COVID-19.

Stroke Unit Care

Given the apparent higher CFR and infectious nature of stroke patients with COVID-19, the overall management of patients on a stroke care unit is now different [70, 71]. The outcomes from stroke are related to the severity of COVID-19 on a background of established prognostic factors.

Several prognostic variables in patients with COVID-19 include older age, higher Sequential Organ Failure Assessment (SOFA) score, acute respiratory distress syndrome, acute renal failure, leukopenia, and elevation in hepatic enzymes, C-reactive protein, ferritin, creatinine phosphokinase, and fibrin D-dimers [24]. The SOFA score, which assesses levels of oxygen saturation, coagulation, hepatic enzymes, and cardiovascular, neurological, and renal function and markers of sepsis [72], appears to provide the overall prognosis before treatment.

Negative pressure carrier isolators have been used to encapsulate (isolate) patients within a nonporous vinyl material during neurovascular imaging, allowing contaminated air to escape from the isolator [73]. The appropriate use of PPE by all team members is the cornerstone of PCS. Head covering is optional in most protocols. Precautions should be upgraded to include airborne precautions including a secure fitting of N95 respirator masks when there is any aerosol-generating procedure [30].

It should be noted that nebulization of medicines, continuous positive airway pressure, and high nasal flow therapies should be avoided given the associated increased risk of aerosolization [74]. Where possible, early placement of nasogastric tubes should be avoided as this also appears to increase the risk of aerosolization [75].

While stroke unit care should continue to be provided for stroke patients without COVID-19, recommendations have also been made to limit the number of staff on ward rounds, increase the use of electronic rather than face-to-face communications, apply rigorous safe distancing, handwashing, and use of telemedicine/robots, and minimize patient and staff movements/transfers. The AHA/ASA guidelines now include a template for a new/revised stroke care pathway for COVID-19 patients [29].

Recommendations: stroke unit care for COVID-19-negative patient should continue as before with strict infection control measures. Care of stroke patients with COVID-19 requires negative pressure imaging, avoidance of nebulization of medicine and nasogastric intubation, use of PPE by all team members, and lower use of face-to-face communication.

Stroke Care in Isolation Areas

COVID-19 isolation areas are defined as those used specifically for the care of asymptomatic or mildly symptomatic COVID-19 patients who require close monitoring due to potential for rapid development of pulmonary and neurological complications. The frequencies of ischemic stroke in COVID-19 patients are estimated at 5% and intracerebral hemorrhage and cerebral venous thrombosis in about 1%. Most patients are aged over 60 years in the context of vascular risk factors [24, 70, 76].

Patients with vascular risk factors are at high risk of developing stroke from COVID-19. Primary and secondary stroke prevention measures in these patients should be undertaken aggressively, including the use of blood pressure-lowering medications, antiplatelets, anticoagulants, antidiabetic medications, and lipid-lowering agents, according to indication in appropriate patients irrespective of symptoms from COVID-19.

Early identification of stroke symptoms in isolation areas is important. Nursing staff in isolation areas must be trained for early recognition and reporting. Patient education regarding stroke symptoms and the Fast Arm Speech Time criteria may be useful. Most internal medicine or infectious disease physicians can diagnose stroke, but neurological consultation should be sought urgently. In the absence of a neurologist, teleneurology consultation can be used for confirmation of stroke in these patients [77]. Nursing and other staff in isolation areas should be trained for PCS especially when dealing with a suspected stroke patient.

Stroke type/subtypes can be confirmed by imaging (CT scan or MRI), as usual practice, according to availability for rapid and safe use (e.g., use at the end of the day) where isolation can be maintained through the use of dedicated scanners, negative pressure equipment, and application of PPE for patients and radiology staff. Scanners must be cleaned thoroughly after imaging of a COVID-19 patient.

Initial stroke management includes blood pressure control, blood sugar control and temperature management, aspiration pneumonia precautions, and venous thromboembolism prophylaxis, all starting in isolation areas. Stroke workup including use of carotid US, Holter monitoring, and echocardiography can be done by using portable equipment in isolation areas. All investigations and stroke management in isolation areas must be provided with full protection of nursing staff, laboratory staff, therapists, and doctors through use of PPE. Early rehabilitation should be started in the isolation area according to the availability of therapists and rehabilitation physicians. Duration of isolation is an important issue: stroke patients must be isolated until confirmation of negative COVID-19 status, which may take 2–4 weeks. All acute stroke patients must be evaluated for need of thrombolysis and thrombectomy in isolation areas before transfer to an acute stroke unit without unnecessary delay [35].

Recommendations: isolated COVID-19 patients are at high risk of developing stroke. All primary and secondary stroke prevention guidelines must be implemented. Physicians and nursing staff should be trained for early identification of stroke and quick teleneurological confirmation. Acute stroke care could be provided in isolation areas. Patient candidate for thrombolysis and thrombectomy should be transferred to stroke units.

Investigations and Secondary Prevention, including Surgery/Stenting/IR

Strokes, mainly ischemic, are being reported as a complication of COVID-19, consistent with the spectrum of thrombosis-related complications, including venous thromboembolism and arterial thrombotic complications [16, 78]. The pathophysiology is likely to be multifactorial, but sepsis-induced coagulopathy, vascular endothelial dysfunction, and microthrombosis are the likely proposed mechanisms [55, 79–81]. Additionally, there are reports of COVID-19 patients developing intracerebral hemorrhage [82], subarachnoid hemorrhage, or cerebral venous thrombosis [83].

Among patients with previous stroke, a pooled analysis of 4 studies reported a ~2.5-fold increase in odds of severe COVID-19 [84]. Nevertheless, it is of outmost importance to prevent recurrent stroke, and these patients should be treated with antihypertensives, lipid-lowering agents, antiplatelets, and anticoagulants for secondary prevention. Investigations to identify causes of stroke, for example, AF, cardiomyopathy and other structural and functional cardiac disease, carotid disease, and systemic causes, should be performed as per guideline recommendations. Indeed, cardiac arrhythmias including AF are more common in COVID-19, and ECG monitoring is recommended. Cardiac dysfunction is also evident, and imaging, such as echocardiography, should be performed.

The use of ACE-I and ARBs is common among stroke patients, and there is no evidence that they affect the risk of COVID-19 [85, 86]; indeed recent evidence suggests benefit of continuing them. Similarly, there is no evidence that other antihypertensives, such as calcium-channel blockers, lipid-lowering drugs, antiplatelets, and oral anticoagulants, affect the risk of COVID-19 [85]. Therefore, the use of these drugs for secondary prevention of stroke should continue to be recommended for stroke patients during the COVID-19 pandemic.

Each surgeon/interventionist should carefully consider whether to postpone or cancel elective cerebrovascular interventions, including craniotomy and endovascular treatment. Such emergency procedures in COVID-19 patients should be performed under negative pressure with PPE in accordance with each institution's policy. If possible, it is desirable to perform 2 COVID-19 tests separated by 24 h before the surgery, with the patient quarantined between the tests. For unavoidable (or emergency) surgery in patients positive for COVID-19, or in those whose status is undetermined, the proceduralist and all other personnel in the surgical suite should use powered air-purifying respirators, which filter the breathing air in addition to face shields and other standard PPE [87–89].

Recommendations: prothrombotic states and cardioembolic sources should be specifically looked for in stroke patients with COVID-19. Secondary prevention treatments should be administered. However, interventional procedures may need to be deferred for COVID-19 patients till they are cleared of infection; else strict infection control and negative pressure procedure rooms are advised.

Medical Management of COVID-19 Patients with Stroke

Management of patients should follow guidelines recommended by professional organizations regardless of COVID-19 status. However, some specific COVID-19 considerations should be given to acute stroke protocols for the use of IVT and MT because of the increased risk of a hypercoagulable state. As hypercoagulability occurs in many COVID-19 patients, therapeutic anticoagulation in those with acute stroke and COVID-19 should be considered, particularly if the underlying mechanism is unclear. If an ischemic stroke patient is not given rtPA or anticoagulation and is not considered to have high risk of bleeding, then the use of aspirin, statin (with an LDL goal <70 mg/dL), and VTE prophylaxis is clinically appropriate. In this section, details are given for the medical management for COVID-19 patients with ischemic stroke and intracerebral hemorrhage.

Hypertension

COVID-19 patients frequently present with associated cardiometabolic diseases (i.e., hypertension and diabetes mellitus). Early management of hypertension is mandatory to reduce the risk of intracerebral hemorrhage in the context of thrombolytic therapy [90] and recurrent secondary ischemic events. A blood pressure goal of <185/<110 mm Hg is generally considered appropriate prior to the use of rtPA. Despite the debate over the use of ACE-I/ARB in COVID-19 patients, 2 large retrospective studies found no association between these agents and COVID-19 positivity or severity [91, 92]. Another large study of COVID-19 inpatients found an inverse association between ACE-I/ARB use and all-cause mortality [93].

Anticoagulation

A systemic prothrombotic and hypercoagulable state is reflected in elevated D-dimer and thrombosis at multiple sites including stroke in COVID-19 patients [94]. Treatment with anticoagulants including low-molecular weight heparin (LMWH) has therefore been proposed in those with severe COVID-19 disease to reduce thrombotic events in the lung (alveolar), as well as VTE [95], which occurs in approximately 25% of critical care COVID-19 patients. In a recent study, Paranjpe et al. [96] documented improved survival among anticoagulated patients in comparison with those not receiving anticoagulants, especially for the critically ill requiring mechanical ventilation. The group receiving anticoagulants had a higher risk of bleeding events (3%) in comparison with those not receiving anticoagulants (1.9%). Similarly, Tang et al. [97], in Wuhan, China, documented decreased mortality of patients with severe COVID-19 treated with parenteral anticoagulants in comparison with those not receiving anticoagulants. Although the overall mortality at 28 days for the 99 patients treated with anticoagulants (94 with LMWH and 5 with unfractionated heparin [UFH]) and the 350 patients not treated with anticoagulants was similar (30 and 29.7%, respectively), those with severe COVID-19 (with associated thrombocytopenia, elevated prothrombin time, and D-dimer) had significantly better survival after use of parenteral anticoagulation, mostly LMWH. In a recent study including 1,403 inhospital patients, enoxaparin was associated with lower inhospital mortality in the group of 799 treated patients (odds ratio 0.53, 95% CI: 0.40–0.70) [98]. However, caution should be exercised in stroke COVID-19 patients, as anticoagulation is not routinely recommended in AIS [90], in whom the use of anticoagulation in the acute phase carries a risk of symptomatic hemorrhagic transformation or intracerebral hemorrhage.

In AIS patients who undergo fibrinolytic therapy with alteplase, it is reasonable to consider the use of prophylactic LMWH after 24 h in high-risk patients, such as those with AIS of confirmed/suspected cardioembolic origin and in those with concomitant VTE, high D-dimer, or prolonged immobilization. It is unclear whether prophylactic LMWH has an advantage over UFH.

Similarly, in patients with AIS starting aspirin, addition of prophylactic LMWH may be considered in low bleeding risk patients with severe COVID-19 disease (ICU admission, acute respiratory distress syndrome, and mechanical ventilation). Bleeding risk assessment should always be performed before starting LMWH treatment, in order to identify major risk factors for bleeding such as severe thrombocytopenia (<100,000/mmc), hemorrhagic transformation of AIS, and active bleeding.

There are limited data to guide the possible duration of anticoagulation beyond the acute phase, although the presence of AF and those at high risk of VTE recurrence may merit long-term anticoagulation. There is debate whether direct-acting oral anticoagulants (DOACs) may be a good alternative to dose-adjusted warfarin if long-term prescribing is needed, and prescribing needs to be in keeping with guidelines for DOAC prescribing, or if warfarin is used, to aim for a TTR >70%.

For patients with acute intracerebral hemorrhage or VTE, it is prudent to avoid full anticoagulation until stability of the hemorrhage is achieved. However, if the brain hemorrhage is stable but, for example, pulmonary embolism leads to hemodynamic instability (e.g., severe right heart strain, systemic hypotension, and refractory hypoxemia due to poor perfusion despite adequate ventilation), intra-arterial thrombolysis and full-dose anticoagulation should be considered. If anticoagulation is inevitable, then UFH infusion may be safer than longer-acting LMWH in the event of hemorrhagic complications.

Recommendations: early management of hypertension is necessary in stroke COVID-19 patients. Patients on ACE inhibitors should not be discontinued from their therapy because of SARS-CoV-2 infection. LMWH could be started in COVID-19 patients with suspected cardioembolic stroke or those with low bleeding risk and severe COVID-19 disease. UHF, rather than LMWH, may be preferred if full anticoagulation is required.

Inpatient Rehabilitation

Stroke rehabilitation services in COVID-19 patients must be provided with all protective precautions. At least 45 min of each relevant stroke rehabilitation therapy can be offered for a minimum of 5 days per week to those who have the ability to participate and where functional goals can be achieved. If more rehabilitation is needed at a later stage, the intensity can be tailored to the person's needs at that time [99]. Speech and language therapy for people with stroke should be led and supervised by a specialist speech and language therapist working collaboratively with other appropriately trained people – for example, speech and language therapy assistants, carers and friends, and members of the voluntary sector [99]. Swallowing therapy should be offered at least 3 times a week to those with dysphagia after stroke who are able to participate, for as long as they continue to make functional gains. Swallowing therapy could include compensatory strategies, exercises, and postural advice [99].

Neuropsychiatric disorders, such as depression, delirium, and cognitive impairment, are common in stroke survivors. Delirium is prevalent in acute stroke, affecting around one-quarter of patients [100], and presents particular challenges for staff and patients in the COVID-19 era. Patients may be agitated and distressed and unable to comply with infection control measures such as wearing a mask and social distancing and may reach out and touch staff and other patients. In addition, delirium may be worsened or prolonged by impaired communication caused by physical distancing of staff, use of face masks, and lack of availability of relatives owing to visiting restrictions. These factors may also worsen the long-term cognitive prognosis and increase the risk of dementia. Staff should be aware of the adverse consequences of delirium and should endeavor to mitigate the impact of isolation by providing a calm quiet environment and orientation aids and facilitating visits from family whilst observing appropriate infection control guidance. Use of vizors rather than face masks may aid communication.

In addition to stroke, the COVID-19 pandemic embodies many overwhelming stresses. A few of the obvious ones are loss of employment; deaths of family members, friends, or colleagues; and financial insecurity. The COVID-19 pandemic also requires quarantine and isolation, which may precipitate new psychiatric symptoms in people without mental illness or aggravate existing conditions [101]. Health workers treating stroke patients during the COVID-19 pandemic should be aware of symptoms of depression, anxiety, insomnia, and/or distress developing in their patients and carers.

Clinicians, clergy, and friends may be able to help through telephone, email, or internet-facilitated video contact. Mental health service providers, including psychiatrists, clinical psychologists, and social workers, should be available in every facility taking care of stroke patients with and without COVID-19. Telemedicine is considered to be an especially good fit for psychiatric treatment and has been found to be effective, while reducing cost and improving access to care [102]. There are no absolute contraindications; however, it is recommended that patients be assessed for suitability for videoconferencing and that emergency protocols be developed for situations such as heightened risk for suicide or aggression toward others [103]. Provision of targeted psychological interventions for stroke patients affected by COVID-19, particularly supports for those at high risk of psychological morbidity, can help diminish or prevent future psychiatric morbidity [104].

In the stroke ICU, it is recommended to use either single-use disposable equipment or dedicated equipment (e.g., stethoscopes, blood pressure cuffs, and thermometers). If equipment needs to be shared among patients, it should be cleaned and disinfected between each patient use (e.g., ethyl alcohol 70%). All healthcare workers in stroke ICU must use PPE. Components of PPE should include glove, gown/apron, mask, respirators, goggles, face shields, and shoes. Compared with usual rehabilitation, telerehabilitation, particularly in the COVID-19 era, offers several advantages, including easier access, mentoring for disabled stroke patients, and the ability of patients to self-record on their pain, mood, and activity. Different models of telerehabilitation include telephone calls, videoconferencing, educational videos, web-based chats, and virtual reality systems.

Recommendations: rehabilitation should continue with strict infection measures in place. Telerehabilitation has a role. Health workers should be aware of symptoms of depression, anxiety, insomnia, and/or distress developing in their patients and caregivers.

Stroke Outpatient Care – Clinic Visits, Rehabilitation, Home Visits, Family Support, and COVID-19

The care of patients after stroke hospitalizations can critically affect the likelihood of short-term rehospitalization, risk of stroke recurrence, and functional recovery. Although events occurring during the hospitalization are important, for those transitioning to home, follow-up with a primary care physician is associated with a 16% lower 30-day readmission rate (HR 0.84, 95% CI: 0.72–0.98) compared to no follow-up during this period [105, 106]. In addition, appropriate use of secondary preventive medications is associated with a lower risk of recurrent stroke, major vascular events, and death [107]. Stroke patients having an appointment with a primary care provider are more likely to continue secondary preventive medications 1 year after stroke [108]. More than two-thirds of stroke patients receive rehabilitative services after the acute hospitalization; multidisciplinary poststroke rehabilitation is associated with lower complication rates and improved functional recovery [109].

Provision of these services in patients who have had stroke associated with COVID-19 may be particularly challenging. Some of these patients may have coagulopathies that might necessitate anticoagulation [47, 78, 110]. As there are no data for the use of DOACs in this setting, the majority of these patients will likely be treated with warfarin and require ongoing monitoring. During the initial stages of the pandemic, many primary care settings at least temporarily closed or moved to telehealth options, limiting access to many or becoming impossible for those without appropriate internet connectivity. Telephone consultations may be a useful alternative, but it should be noted that even this may be problematic if a patient has a cognitive or a hearing impairment. Because approximately one-quarter of patients have dementia within 1 year

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Fig. 2. Social distancing is the new order in the OPD waiting areas with a restricted number of patient attendants. OPD, outpatient department.
Fig. 3. Adopting distancing in the physician practice environment.

after stroke [111] and mild poststroke cognitive impairments are common, telemedicine may not be feasible or requires substantial support from caregivers.

In countries or other areas in which teleneurology is not practical or possible, "social distancing" in the hospital's outpatient department waiting area as well as in physician-patient interactions is required for care delivery while reducing the chances of further disease transmission (Fig. 1-3). Home health workers may be prohibited from entering patient homes without appropriate PPE, which may have limited availability in some areas. Similarly, rehabilitation providers and other professional caregivers may not be able to provide these services in the home. Inpatient rehabilitative facilities may not accept patients with stroke associated with COVID-19 until they have repeatedly negative tests for the virus because of the real concern of transmission of the infection to other vulnerable patients in these settings. As a result, family and other "nonprofessional" caregivers need to be prepared and trained to take more responsibilities and be actively involved in the care of stroke patients. For example, they should ensure that medications are taken as prescribed and that dietary, exercise, and rest recommendations are followed. They can help with feeding, hygiene, personal care, daily tasks, and social activities. They can reinforce skills learned in formal rehabilitation settings and can help with communication in patients with speech and language impairments [112].

It is particularly important to try to mitigate the impact of isolation and restricted social activities resulting from the COVID-19 pandemic in patients with poststroke cognitive impairment or mood disorders because this may worsen outcomes. Particular efforts should therefore be made in this vulnerable group to facilitate visits from selected friends and family members (observing infection control procedures) including in care homes. Cognitively impaired patients may not be able to use internet-based stroke or other self-help resources to support their longer-term management and will require face-to-face contact from relatives or health and social care staff. Developing systems to address the needs of the post-COVID-19 stroke patient requires a coordinated approach that will vary depending on a country's hand region's healthcare system, available technologies, and resources.

Recommendations: telemedicine should be employed where possible. If clinic visits are needed, distancing and infection control measures are needed. Caregivers need to be prepared and trained to take more responsibilities and be actively involved in the care of stroke patients.

Social Support

Patients with COVID-19 – especially those with multiple organ dysfunction – have been found to be at increased risk of experiencing an acute stroke. If stroke patients are suspected or confirmed to have COVID-19, the healthcare workers treating them must wear protective clothing, masks, and facial shields, which may heighten the patient's sense of isolation. If remote interviews are available, telemedicine should be also used where possible to minimize the risk of infection among the healthcare staff. Regardless of their infection status, stroke patients who reside in rural or mountainous areas, on remote islands, or districts without nearby medical facilities may experience their first response through a remote interview.

As the COVID-19 pandemic intensifies, overwhelming the healthcare system and the medical community, doctors must consider the overall balance and be aware of how it affects them [113]. Physicians need to consider how their decisions affect their patients and others, COVID-19 patients, and the local community. In addition, coworkers, nurses, social workers, and related healthcare professionals with advanced medical care are similarly affected by this crisis and need to adapt quickly [64].

Stroke patients may be alone and feel lonely due to restrictions on their freedom to interact with family and friends and to leave their homes, even if they are not infected. Stroke support is thus necessary for stroke patients and their families. The patients should be shown how they can interact safely with family members and friends, and a variety of stroke support activities are needed. Many activities for home-bound individuals are available online, but some have lost their personal touch. In addition, many older people are unfamiliar with computers, which may worsen their isolation and their stroke-related disability and increase their cognitive decline and likelihood of becoming bedridden. Thus, online systems providing social support to stroke patients and their family should be very user friendly and geared forward to patients of all ages, including the elderly.

For the prevention of strokes, professionals such as public health nurses and registered dietitians who provide community support for stroke prevention should be provided to educate both stroke patients or healthy persons without stroke about healthy lifestyle habits such as maintaining a healthy diet, quitting smoking, restricting alcohol intake, adequately hydrating, avoiding excessive negative messaging, getting adequate sleep, and keeping physically active [114]. The isolation and physical restrictions of stroke patients and others may lead to inactivity and an increased risk of venous thromboembolism, in addition to comorbidities. Physical activity should be strongly encouraged for stroke patients (e.g., in a home setting or walking outside) and will improve their well-being. Maintaining social networks physically and the use of virtual methods for socializing (e.g., online classes, text messaging, and visual application) should be encouraged. As community support, it is necessary to create an environment where online systems that are new or difficult for the elderly can be easily used.

Recommendations: stroke support is needed, especially for those who are isolated or home-bound. A healthy lifestyle, physical activity, and maintaining social networks, even virtually, should be encouraged.

Continued Professional Development

In the times of COVID-19, clinical training and education of medial students, residents, and fellows was halted around the world. Similarly, continued medical education for all physicians was disrupted. Medical education and professional development have never been more important than now as the extraordinary times of COVID-19 pandemic will continue to challenge the profession not only to reinforce current knowledge but also to acquire new insights of this novel disease and how it affects patients. Neurologists function in many roles – clinicians, scientists, educators, and leaders. Neurologists are used to teamwork and multidisciplinary interactions. Vascular neurologists together with their stroke teams have been early adopters of virtual care and virtual research and education. Student, residency, and fellowship programs have rapidly undergone structural changes to adapt to the COVID-19 pandemic. Flexibility, frequent communication, and teamwork are the key factors for the successful transition in this crisis.

The American Academy of Neurology (AAN) has issued a statement with specific recommendations and adaptations to patient care and medical education [64]. A need for continuous adaptation to the rapidly changing pandemic circumstances and neurological consequences is recognized with the consideration of national and regional standards and variations. Neurologists manage competing clinical and educational assignments during the COVID-19 pandemic. The education of trainees and medical needs of our patients continue during the pandemic. Although some services experienced low volumes of patients, acute admissions increased for some conditions such as status epilepticus, Guillain-Barre, and encephalopathy [64]. Neurologists are also called to help on nonneurological services during the surge. Professional medical education however would need to include flexible and rapidly adaptable knowledge-based and evidence-based information for the crisis situations.

Neurologists depend on face-to-face engagement with their patients and families and their trainees. The COVID-19 pandemic has dramatically changed clinical practices and education programs to rely more on telemedicine and virtual care. But, it comes at significant cost and new learning experiences. This is an opportunity "to launch ourselves in this important direction" as it is likely "there will be no going back to the old model of long-distance patient travels for routine clinical encounters" [115].

Continued professional development during COVID-19 and beyond is going to be challenging, but there is a need to be prepared to continue virtual care, virtual education, and virtual research for the many observational and clinical studies. Information and new knowledge and continued professional development is possible through collaboration with professional organizations around the world. There is a need to assure the continued high-quality neurology training programs, CMEs, and extend training programs to other complementary disciplines such as epidemiology and public health, infectious disease, and health informatics. Some of these educational activities have already transitioned online or virtual, and the important issues of autonomy, role modeling, wellness, and skills in professionalism and humanism in neurology have been recognized as important topics to reinforce [116].

Numerous educational programs on COVID-19-related neurology issues are currently available at the websites of professional organizations (e.g., AAN, AHA/ASA, and AAMC) and published in the professional journals (*Neurology*, *Circulation*, *JAMA*, *NEJM*, and others). Going forward, rapid and accurate communication and information exchange will be a key component of our professional development. Learning from each other in new and extraordinary stressful situations such as in the COVID-19 pandemic will be a critical part of our future professional development.

Recommendations: continuous professional education and development should continue, including using online platforms.

Stroke Research

Because of the COVID-19 pandemic, human and material resources are now being allocated to fight it, with less means available for the care and research of the non-COVID-19 patients. For decades, we have been fighting to achieve prompt and adequate care of acute stroke patients. Since the beginning of COVID-19, however, anecdotal reports have shown a diminished number of stroke patients referred to emergency care [117]. This is likely due to the fact that patients, especially those with mild symptoms, may refrain from seeking hospital treatment for fear of COVID-19. This may adversely affect subject recruitment into studies involving these populations. Although the proportion of patients attending thrombolysis and thrombectomy may not have decreased, scarce data are available from peer-reviewed publications [118].

In the USA, the stroke national databank permits in real time to quantify and analyze local and national variations in the demand for acute stroke care [29]. We suggest that a similar instrument is needed in Europe and other continents in order to provide accurate and timely data, helping to establish research priorities. It may also support decisions such as media campaigns to reverse the tendency of patients not to come to a hospital after stroke symptoms. For ongoing clinical trials, there are difficulties in recruiting new patients and performing follow-up assessments. One strategy would be to use tele/video consultations. Academia and industry teleconferences should also be encouraged to maintain academic enthusiasm among stroke researchers.

The post-COVID-19 economic burden will have a negative impact on research grants available for stroke, since governments may focus more on infectious diseases rather than stroke. Pharmaceutical companies will face financial restrictions that may also adversely impact on stroke research. One strategy would be to "go with the flow of the COVID-19 tide." There are research topics such as stroke pathophysiology in the context of hypercoagulability related to critical illness or embolisms due to concomitant virus-related cardiac diseases. These COVID-19-related topics may enjoy advantages in obtaining research grants [119]. Finally, we should remember that our role is to remind everyone that stroke is and will still be a leading cause of death and disability regardless of COVID-19.

Recommendations: research subject recruitment and retention may be maintained by televideo consultations. Stroke research should continue.

Conclusions

The COVID-19 pandemic has placed a tremendous strain in healthcare and stroke services. New models of care had to be developed to cope with the highly infectious nature of the disease. While traditional stroke treatments are still being given to patients having both stroke and COVID-19, it is still unclear what the best treatments are. Research has been hampered, but clinicians need to use the best available evidence to guide them in the management of their patients. We hope the recommendations provided by the panel of experts who have authored this study will be of help to those involved in healthcare to develop treatment strategies and protocols even as we keep learning about COVID-19.

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Conflict of Interest Statement

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M.G.H. and N.V. conceptualized the study, compiled and edited the contributions, wrote the manuscript, and performed critical review. All other authors wrote the manuscript and performed critical review. Abstract: Jay P. Mohr and Craig Anderson. Introduction: N Venketasubramanian and Michael G Hennerici. (1) Biology of COVID-19 – Luther C. Pettigrew and Roman Haberl. (2) Mechanisms of stroke in COVID-19 – Graeme J. Hankey, Hakan Ay, Oscar H. Del Brutto, Gabriel R. de Freitas, Carlos S. Kase, David S. Liebeskind, Luther C. Pettigrew, and N. Venketasubramanian. (3) Prehospital care – Tsong-Hai Lee, Klaus Fassbender, and Panagiotis Papanagiotou. (4) Emergency room care – Luther C. Pettigrew, Klaus Fassbender, and Ulf Schminke. (5) Imaging – Waleed Brinjikji, Selma Aybek, Wolf-Dieter Heiss, David Liebeskind, Stephen Meairs, Panagiotis Papanagiotou, Guillermo Parrilla, and N. Venketasubramanian. (6) Thrombolysis – Kazunori Toyoda and Masatoshi Koga. (7) Thrombectomy – Luther C. Pettigrew, Waleed Brinjikji, Panagiotis Papanagiotou, and Guillermo Parrilla. (8) Neurocritical care – Katja E. Wartenberg and Masao Nagayama. (9) Stroke unit care – Pushpendra N. Renjen, Leonardo Pantoni, and Mohammad Wasay. (10) Stroke care in isolation areas – Mohammad Wasay, Roman B. Medvedev, and Leonardo Pantoni. (11) Investigations and secondary prevention, including surgery/stenting – Yukito Shinohara, Miki Fujimura, Satoshi Kuroda, Gregory Lip, and Tatjana Rundek. (12) Medical management – Daniele Pastori, Carlos S. Kase, Kiwon Lee, Gregory Lip, Leonardo Pantoni, Sarah T. Pendlebury, Tatjana Rundek, and Wai Kwong Tang. (13) Inpatient rehabilitation – Pushpendra Ranjen and Wai Kwong Tang. (14) Outpatient care – clinic visits, rehabilitation, home visits, and family support – Larry B. Goldstein and Man Mohan Mehndiratta. (15) Community/social support – Yoshihiro Kokubo. (16) Continued professional development – Tatjana Rundek and N. Venketasubramanian. (17) Stroke research – Jong S. Kim and Isabel Henriques. Conclusion: N. Venketasubramanian and Michael G. Hennerici.

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