Neurological Critical Care: The Evolution of Cerebrovascular Critical Care

KEY WORDS: acute ischemic stroke; cerebrovascular disease; critical care medicine; history; intracerebral hemorrhage; neurocritical care; subarachnoid hemorrhage

Cherylee W. J. Chang, MD, FCCM, FACP, FNCS[1]

Jose Javier Provencio, MD, FCCM, FNCS[2]

Shreyansh Shah, MD[1]

In 1970, when 29 physicians first met in Los Angeles, California, to found the Society of Critical Care Medicine (SCCM), there was little to offer for the acute management of a patient suffering from an acute cerebrovascular condition except supportive care. Stroke patients were not often found in the ICU. Poliomyelitis, and its associated neuromuscular respiratory failure, created a natural intersection of neurology with critical care; such was not the case for stroke patients. Early textbooks describe that the primary decision in the emergency department was to ascertain whether a patient could swallow. If so, the patient was discharged with the advice that nothing could be done for the stroke. If unable to swallow, a nasogastric tube was inserted and then the patient was discharged with the same advice. In the 50 intervening years, many advances in stroke care have been made. Now, acute cerebrovascular patients are not infrequent admissions to an ICU for neurologic monitoring, observation, and aggressive therapy (**Fig. 1**).

HISTORY

Over 50 years ago, stroke, previously called "apoplexy" which means "struck down with violence" or "to strike suddenly," was a clinical diagnosis that was confirmed by autopsy as a disease of the CNS of vascular origin (1). In the 1960s, approximately 25% of stroke patients died within 24 hours and nearly half died within 2 to 3 weeks. Of those that survived the acute stroke, nearly half were dead within 4 to 5 years (2).

In 1970, the World Health Organization (WHO) convened a group in Monaco for 4 days to address the topic of stroke, which was the third leading cause of death (behind infectious/parasitic disease and ischemic heart disease) in 40 of 57 countries represented by the WHO, including the United States, and the top 10 causes of death in 54 countries (3, 4). Nearly 50 years later, globally, stroke is the second leading cause of death behind ischemic heart disease with 6.2 million deaths in 2017 attributed to cerebrovascular disease and a prevalence of 79% ischemic, 17% hemorrhagic, and 9% subarachnoid hemorrhage (SAH) (5, 6). In the United States, stroke has fallen to the fifth leading cause of death but remains the leading cause of serious long-term disability (5).

Mortality is higher following hemorrhagic stroke than ischemic stroke, and this gap is widening. Advances in acute treatment for acute ischemic stroke (AIS), such as revascularization and management, has led to decrease in the AIS mortality rate from 29 per 100 person-years to 11 per 100 person-years, but mortality

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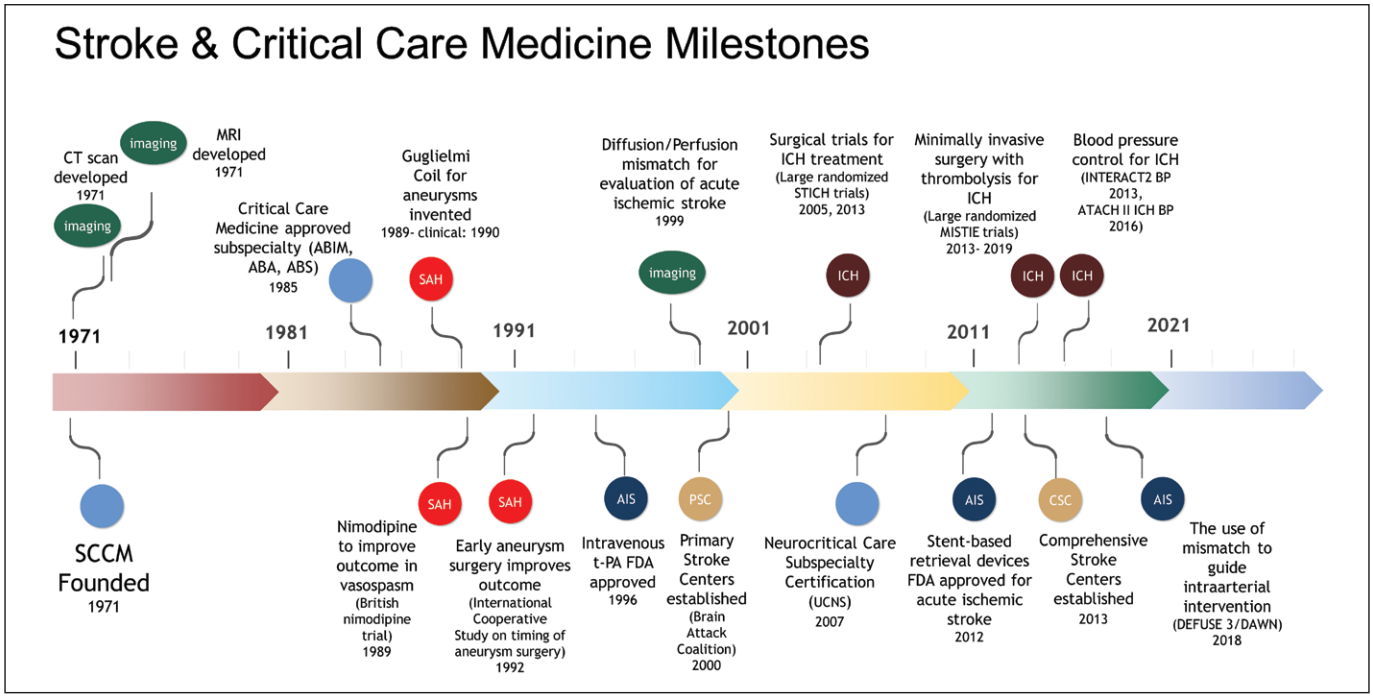

Figure 1. Notable events in the evolution of cerebrovascular critical care. ABA = American Board of Anesthesiology, ABIM = American Board of Internal Medicine, ABS = American Board of Surgery, AIS = acute ischemic stroke, ATACH = Antihypertensive Treatment of Acute Cerebral Hemorrhage, BP = blood pressure, CSC = Comprehensive Stroke Center, DAWN = Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention, DEFUSE 3= Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3, FDA = U.S. Food and Drug Administration, ICH = intracerebral hemorrhage, INTERACT2 = Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial, MISTIE = Minimally Invasive Surgery plus Alteplase in Intracerebral Hemorrhage Evacuation, PSC = primary stroke center, SAH = subarachnoid hemorrhage, SCCM = Society of Critical Care Medicine, STICH = Surgical Trial in Intracerebral Hemorrhage, t-PA = tissue plasminogen activator, UCNS=United Council for Neurologic Subspecialties.

is essentially unchanged following intracerebral hemorrhage (ICH) (from 25 to 30 per 100 person-years) (7).

In the intervening years, advances in imaging and treatment have changed it from a condition where the stroke victim was triaged as the last to be seen in the emergency department, to a "stroke code" where urgency is sought not only in the emergency department, but in the prehospital arena with a high priority for critical care admission and management.

It is important to mention an important obstacle to the improvement of care that has bedeviled neurologically injured patients for more than 50 years is nihilism. Since neurologic damage associated with cerebrovascular disease: 1) was thought to be complete prior to admission to the hospital and 2) this damage affects aspects of the human condition that healthcare workers value, there has been a trend of clinician pessimism that permeates decisions. This has led to less aggressive treatment and early withdrawal of life-saving measures that impact the ability to understand the true outcome cerebrovascular diseases and the benefit of treatments. The development of thrombolytic therapy for AIS has begun to change the attitudes of practitioners toward more aggressive care.

RISK FACTORS AND PREVENTION

Ischemic Stroke

Fifty years ago, given the lack of treatment and high rate of mortality, initially, prevention was the natural priority, although there was limited understanding of preventable risk factors. Advances in cardiovascular epidemiological research had a key transformative impact. In 1970, based on the landmark Framingham study, hypertension was identified as "the most common and potent precursor of atherothrombotic brain infarction" and recognized that early detection and blood pressure control was a key factor in stroke prevention (8, 9). Data from existing studies of the association of stroke and serum cholesterol or smoking were conflicting (10). At the time, smoking remained popular with approximately 43% of men and 31% of

women, an estimated 48.8 million cigarette smokers in the United States. (11). As a point of reference, in 2018, the year with the most up-to-date statistics, the prevalence of smoking has dropped to 13.7% (12).

Other advances included the 1978 Framingham Heart study that demonstrated that diabetes increased stroke risk and that nonvalvular atrial fibrillation was clearly associated with a 5.6-fold increase in the risk of stroke (13). The advanced electrophysiology ablation of atrial fibrillation, interventional cardiac procedures, and development of the direct-acting oral anticoagulants (DOACs) provides additional pharmacological strategies other than warfarin to prevent cardioembolic stroke (14).

Intracerebral Hemorrhage

In 1971, there was already a trend toward a decrease in the overall prevalence of ischemic and hemorrhagic stroke (15). The use of thiazide diuretics beginning in late 1950s and a multicenter Veterans Administration Cooperative study (phase 1 and 2) between 1964 and 1971 showed for the first time that treating diastolic hypertension (ranging between 90 and 129 mm Hg) reduced cardiovascular events such as stroke and heart failure and improved mortality (16, 17). Hypertension treatment to prevent ICH remains the mainstay of therapy.

Risk factors for spontaneous ICH in 2021 expand beyond hypertension and vascular abnormalities such as vascular malformations and dural arteriovenous fistulas known in 1971. In 2021, other risk factors include the more frequent use of illicit sympathomimetics such as cocaine and methamphetamine, and, in our aging population, cerebral amyloid angiopathy (CAA). Newer antithrombotic agents, the DOACs that inhibit thrombin (e.g., dabigatran) or factor Xa (e.g., apixaban, rivaroxaban, edoxaban) have been developed as safer, more effective agents than warfarin for preventing thromboembolic complications in nonvalvular atrial fibrillation. However, when associated with ICH, they pose a hazard since detectable levels or the degree of antithrombotic effect is not easily measured in patients with acute injury or hemorrhage. Ecarin clotting time and thrombin time have been used as markers for dabigatran. Other techniques such as thromboelastography and rotational thromboelastometry are being explored to evaluate hemostasis. Reversal agents have been Food and Drug Administration (FDA)-approved for both the direct thrombin inhibitor and more recently for Factor Xa inhibitors, which remain expensive, on the order of $30,000 to $60,000 (United States) per event, depending on the patient's weight (18). New guidelines have been developed to address the reversal of antiplatelet and antithrombotic agents (19). The reversal of these newer agents is an important area of research and understanding for the critical care provider when addressing intracerebral and other life-threatening hemorrhages.

Subarachnoid Hemorrhage

Compared with AIS and ICH, aneurysmal SAH occurs at a relatively young age with poorer outcome. Studies over the last 50 years have confirmed immutable risk factors include hereditary preponderance, female sex, and older age, but also drawn attention to modifiable risk factors such as hypertension, smoking, and excessive alcohol intake have the potential to decrease an individual's risk for hemorrhage (20, 21).

ADVANCES IN NEURODIAGNOSTIC IMAGING

When addressing the issue of treatment, a key barrier to effective treatment has been accurate diagnosis. Prior to advanced imaging, it was unclear what proportion of strokes were ischemic and hemorrhagic. In the United States in 2020, 87% of strokes are ischemic, 10% are hemorrhagic, and 3% SAH (5). However, in 1970, of 207,166 deaths reported, cerebral thrombosis reportedly accounted for 57,845 (28%) deaths, cerebral embolism 884 (< 1%), cerebral hemorrhage 41,379 (20%), and "all other cerebrovascular disease" 107,068 (52%) (4). Half of all strokes were not categorized. There are a number of reasons for lack of accurate categorization, but accurate diagnosis likely represented a significant proportion of patients.

For the younger generation of physicians, it is almost inconceivable that a day existed without rapid neurodiagnostic imaging to elucidate an etiology for an acute neurologic deficit. However, in 1971, the diagnosis of stroke relied on a detailed history and a thorough neurologic examination to "localize the lesion." At the time, before the advent of the CT scan, both pneumoencephalography and cerebral angiogram were the commonly used modalities to assess intracranial pathology. For example, a headache accompanied by an acute focal neurologic deficit or coma was most likely classified as an ICH. To determine if a space-occupying mass such as a tumor or hemorrhage was

the cause for focal neurologic deficits, a pneumoencephalography was performed. American neurosurgeon, Dandy developed the pneumoencephalogram in 1918 to diagnose brain tumors by injection of air into the ventricles with subsequent radiography to evaluate for midline shift or deformation of the ventricles (22). Plain roentgenograms were performed to look for "shift" of calcified structures such as the pineal gland or choroid plexus. Calcified vascular malformations or tumors might be detected in this manner.

Cerebral angiography was devised in 1927 as a means to use radiocontrast agents to evaluate cerebral blood vessels for alterations of blood flow (e.g., ischemic stroke, vasculitis) and distortion of blood vessel location from a space-occupying mass (e.g., tumor or hemorrhage) or edema. The ensuing years were marked by developing less irritating, painful, epileptogenic, and carcinogenic contrast materials (23). However, cerebral angiography still carried a significant morbidity and mortality, especially with the commonly used direct carotid puncture performed near the bifurcation in stroke patients with carotid atherosclerotic disease. Due to this risk, cerebral angiography was reserved primarily if a SAH was suspected.

Evolving computer technology in the 1970s and 1980s fueled the development of digital subtraction angiography (DSA) evaluation of cervical and cerebral vasculature. This technique removes overlapping tissues by registering a mask image taken before contrast material is injected. Subtraction images show the filled vessels and require less contrast. DSA provides high-quality images and currently is the gold standard to detect and confirm the successful obliteration of cerebral aneurysms (24, 25).

Other tests were used less commonly. Lumbar puncture then, and now, can be helpful to evaluate for SAH. In the setting of trauma and focal neurologic deficits, previously, exploratory burr holes were performed to look for intracranial, extra-axial hemorrhage. Cerebral scintigraphy, depending on the radiopharmaceutical tracer used, can evaluate blood flow or brain perfusion. Based on factors including disruption of the blood-brain barrier, increased or decreased vascularity, timing of scan to injection, and the appearance of the abnormality, scintigraphy can detect vascular venous malformations, tumors, infarcts, and intracerebral or extra-axial hemorrhage. Radioisotopic scintigraphy, however, has a poor ability to discriminate between different pathologic entities. Fifty years later, its neurologic use is mostly relegated to radionuclide studies to confirm the absence of cerebral blood flow for brain death (26).

A less well-known diagnostic procedure used in 1970 was ophthalmodynamometry, where the ophthalmic artery and its branches on the optic disc were evaluated with an ophthalmoscope while gradually increasing the ocular pressure with either direct pressure or graduated suction applied directly to the eye (27). The observer would evaluate for appearance and then disappearance of the pulsations of the central retinal arteries and had been proposed as a method for measuring intracranial pressure (ICP) but never found widespread favor (28). In 2021, although ophthalmodynamometry is not used, a related bedside diagnostic examination based on ultrasound technology has shown promise for the diagnosis of increased ICP. Using B-mode sonography, recent work shows that optic nerve sheath diameter as detected by point of care ultrasound offers a noninvasive method that can be used to detect intracranial hypertension (29).

The indications for carotid endarterectomy previously relied on symptomatology associated with a localized unilateral carotid bruit or transient ischemic attack patients with a contraindication to anticoagulation. However, Doppler ultrasound, a noninvasive modality, was developed and first used to detect carotid stenosis in 1968 (30) by detecting pressure and flow changes in the distal vessels. The modality was greatly enhanced by the development of the duplex scanner in the 1970s. The carotid duplex combines real-time 2D B-mode imaging and pulsed-Doppler flow detection to characterize the flow patterns and velocity changes of normal and diseased vessels and has since been widely validated and used by vascular laboratories to detect significant carotid extracranial disease without the risk of embolic phenomenon and vascular and renal injury of a more invasive technique (31).

In addition to the carotid duplex, transcranial Doppler (TCD) evaluation of the intracranial vasculature has been promising. Using high frequency ultrasound to insonate the intracranial vessels, one can discern intracranial stenosis, evaluate cerebral vasospasm after SAH, and detect cerebral emboli during cardiac or vascular surgery, after the administration of agitated saline, or from a diseased proximal vessel. All of these conditions can be detected using other diagnostic tools, but the low cost, bedside availability, and lack of exposure to radiation make TCD a useful tool (32).

CT changed the world of diagnostic imaging. Similar to the SCCM, the CT scan celebrates its 50-year anniversary in 2021. In 1967, Sir Godrey Hounsfield and Allan Cormack, winners of the 1979 Nobel prize in medicine or physiology for their work, used pattern recognition, x-rays taken from various angles and rotation, and a computer to analyze readings to invent the CT scanner at Electrical and Musical Industries (EMIs) Central Research Laboratories. The first patient brain CT scan was performed in 1971 in Wimbledon, United Kingdom (33). As a bit of trivia, the music and electronics company, EMI, used monies from the sales of their successful recording artists, "The Beatles," to fund the project that developed the CT scan. In the ensuing 50 years, CT scans have become portable, faster (30 min in 1971 to a few seconds in 2021), with better resolution and less radiation exposure. More recently, the advent of sophisticated computer algorithms allows a high-resolution, noninvasive visualization of blood vessels (CT angiogram) with contrast dye. In the same time frame that a diagnostic CT scan is performed, the visualization of the aneurysm has allowed planning for surgical/endovascular intervention (34). In comparison with the gold standard DSA, it is less sensitive to detect a small residual aneurysm, but if seen on CT angiography, it is a reliable indicator that one is present (25). Additionally, CT angiography with perfusion software discerns a mismatch between hypoperfused brain tissue at risk for infarct from an irreversibly damaged infarcted core (35). This concept of mismatch, which can be detected by MRI or CT scan, has revolutionized stroke care by opening the limited time-window from onset of stroke symptoms, to a tissue-based window for the brain that may still be salvaged by reperfusion (36).

MRI also celebrates its 50th anniversary with Raymond Damadian's (37) report in 1971 (and patent approval in 1974) of the differences in tissue proton relaxation between normal tissues and cancer tissue. It is an interesting historical controversy that Paul Lauterbur and Sir Peter Mansfield, but not Damadian, shared the 2003 Nobel Prize for Physiology of Medicine for their work leading to MRI (38). In the ensuing decades, based on work by Damadian, Lauterbur, Mansfield, and Richard Ernest (winner of the 1991 Nobel Prize in chemistry), rapid advances were made including the building of a human-sized superconducting magnet with the use of magnetic field gradients and development of various techniques including pulsed-sequences, and spin-warp and echo-planar imaging that resulted in high-resolution images that provide the contrasts and anatomic detail unique to MRI. Qualitative diffusion-weighted imaging (DWI) with associated quantitative apparent diffusion coefficient parameters have allowed AISs to be detected by MRI when not yet visible by CT imaging (39, 40). Additionally, similar to CT perfusion, MRI comparison of perfusion-weighted mismatch from the DWI changes, that is, area of poor perfusion compared with the area likely destined for infarct, can help select patients who would benefit best for reperfusion strategies (41).

For ICH and SAH, the susceptibility-weighted imaging (SWI) and gradient echo (GRE) imaging techniques of visualizing hemosiderin make MRI extremely sensitive to detecting both acute and previous hemorrhage. Most recently, cerebral microbleeds, small (2 to 10 mm) circular or elliptical hypodense lesions on SWI or GRE imaging, with "blooming artifact" on a T2 weighted MRI image, have been identified as a biomarker for cerebral small vessel disease, due to hypertension and CAA, and have been used to evaluate the risk for rehemorrhage (42).

ACUTE INTERVENTION AND MANAGEMENT

Acute Ischemic Stroke

Revascularizing an area of ischemia was the primary focus for acute treatment. Early research in animal models showed that thrombolytic agents reduced the volume of cerebral infarction poststroke and improve neurologic deficits (43), however, there were a number of challenges in translating this to the human clinical setting. Early clinical trials of thrombolytic treatment of AIS using streptokinase showed increased mortality and increased risk of hemorrhagic transformation (44). The landmark National Institute of Neurologic Disorders and Stroke (NINDS) recombinant tissue plasminogen activator trial published in 1995 revolutionized the management of AIS and established the use of a thrombolytic agent, recombinant tissue plasminogen activator (t-PA), as the first effective drug treatment for AIS (45). Although there was an increased rate of symptomatic intracranial hemorrhage, there was no significant difference in mortality at 3 months compared with placebo, and t-PA treated patients were 30% more likely to have minimal or no disability at 3 months. This led to the FDA approval for IV t-PA for the treatment of AIS within 3 hours after

stroke onset. It is estimated that the number needed to treat to improve outcome shifts depending on the time from onset was 3.6 for patients treated between 0 and 90 minutes, 4.3 between 91 and 180 minutes, 5.9 between 181 and 270 minutes, and 19.3 with treatment between 271 and 360 minutes (46). Later, pooled analysis from randomized control trials of IV t-PA showed that the benefit of t-PA treatment persists up to 4.5 hours in a time-dependent fashion (47–49).

IV t-PA is now the standard of care for appropriate patients. Initial FDA contraindications to t-PA use were based on the exclusion criteria used in the NINDS and European Cooperative Acute Stroke Study trials but have now been modified and limited to those that directly impact the risk for bleeding. Most recently, studies show that a subset of patients who would have been considered outside the time window for t-PA, for example, those with "wake up strokes," can benefit from treatment with t-PA when screened with a rapid, limited sequence MRI for DWI findings but absence of corresponding changes on the fluid-attenuated inversion recovery imaging (50).

Tenecteplase is a promising stroke thrombolytic agent that offers the advantage of one-time 5-second IV bolus dose and a higher rate of recanalization with a similar safety profile as t-PA (51). Using advanced CT or MRI to screen for occlusion and hypoperfused tissue at risk for infarct, tenecteplase is being studied to expand the time-window to 24 hours from symptoms onset (52).

Despite the use of IV t-PA, the occlusion of a large artery such as the internal carotid, proximal middle cerebral, or the basilar artery, has a low recanalization rate (53, 54). This has served as the impetus to develop a more effective therapy using intra-arterial techniques. The Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial, with intra-arterial urokinase, showed an increased rate of recanalization and improved functional outcome (53). Similar success in recanalization was noted with intra-arterial t-PA in the Interventional Management of Stroke (IMS II) trial (55). However, it was recognized that mechanical retrieval of a thrombus possibly in conjunction with IV t-PA might be more effective than intra-arterial pharmaceutical therapy alone. The Merci Retrieval System was the first device to be approved for intra-arterial clot extraction by FDA in 2004 following single-arm studies showing efficacy for recanalization and safety (56). Second-generation mechanical thrombectomy devices used a clot aspiration device approved by the FDA in 2007 (57).

A newer generation of thrombectomy retrieval devices with a stent-based design that entraps the clot within its tines was approved by the FDA in 2012. These stent retrievers have the advantage of higher recanalization rates and shorter procedure times with a significantly increased likelihood of favorable functional outcomes without increased adverse impacts when compared with medical therapy alone in a number of randomized control trials performed between 2010 and 2016 (58, 59). With stent retrieval, the number needed to treat to reduce functional disability at 90 days is 5.1. As a result, these newer generation mechanical thrombectomy devices are guideline-recommended and the mainstream modality for endovascular therapy for ischemic strokes caused by large vessel occlusion (LVO) (58).

The most recent advance in the treatment of AIS is the use of advanced imaging to evaluate appropriate patients with LVO for mechanical thrombectomy. The Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3 (DEFUSE 3) trials screened patients with clinical signs of an LVO with noninvasive vessel imaging such as CT angiography or MR angiography to identify an area of core infarct/perfusion deficit mismatch and selected patients for clot-retrieval based on these findings (60, 61). The results of these trials have led to the replacement of the concept of a "time-based" window of treatment to a personalized "tissue-based" window and show the number needed to treat to decrease functional disability of 2.0 (**Figs. 2** and **3**).

An intensivist must also be aware of the surgical options in managing the critically ill stroke patient. For the AIS patient, malignant cerebral edema and mass effect that may require a life-saving decompressive hemicraniectomy (DCH) and presents a critical decision-making timepoint for the clinician and legally authorized representative and family.

Mortality as high as 80% has been reported with malignant brain swelling prior to the widespread use of DCH (62). DCH is the definitive therapy of malignant cerebral edema that develops after ischemic stroke (63). Based on multiple studies, mortality is improved,

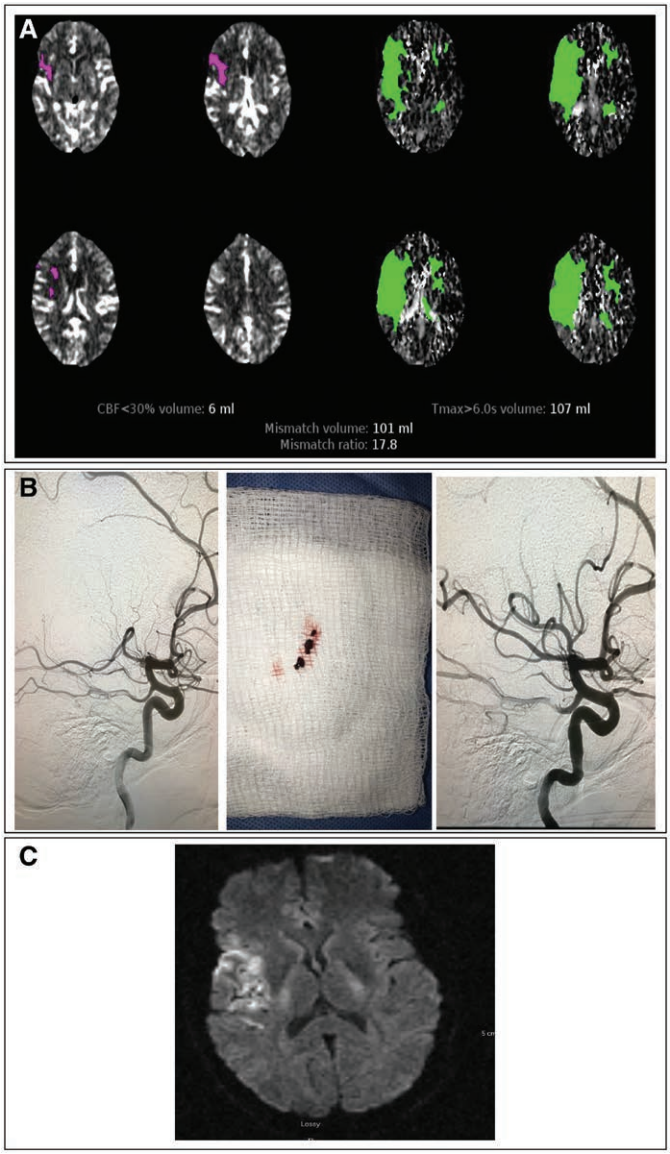

Figure 2. An acute ischemic stroke amenable to intervention. **A**, CT perfusion scanning shows an optimal mismatch pattern to treat with thrombectomy: Cerebral blood flow less than 30% volume indicates areas of core volume of infarct. Time-to-maximum of the residue function greater than 6.0 s volume indicates slow perfusion and area at risk for infarction. The ischemia penumbra, or area at risk for infarct, is depicted by the mismatch volume and ratio. (The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3 [DEFUSE 3] trial treated when the core volume was < 70 mL, mismatch ratio > 1.8, and mismatch volume ≥ 15 mL). This patient presented with a right gaze preference, left homonymous hemianopsia, and left hemiplegia and hemihypesthesia with hemineglect; National Institutes of Health Stroke Scale (NIHSS) 17. **B**, *Left* to *right*—Cerebral angiogram with middle cerebral artery cutoff (Thrombolysis in Cerebral Infarction [TICI] 0 flow); clot removed with stent retrieval; and cerebral angiogram showing reconstitution TICI 3 flow. **C**, MRI completed after retrieval showing area of infarct on diffusion-weighted imaging. NIHSS 0 at discharge 1 d later.

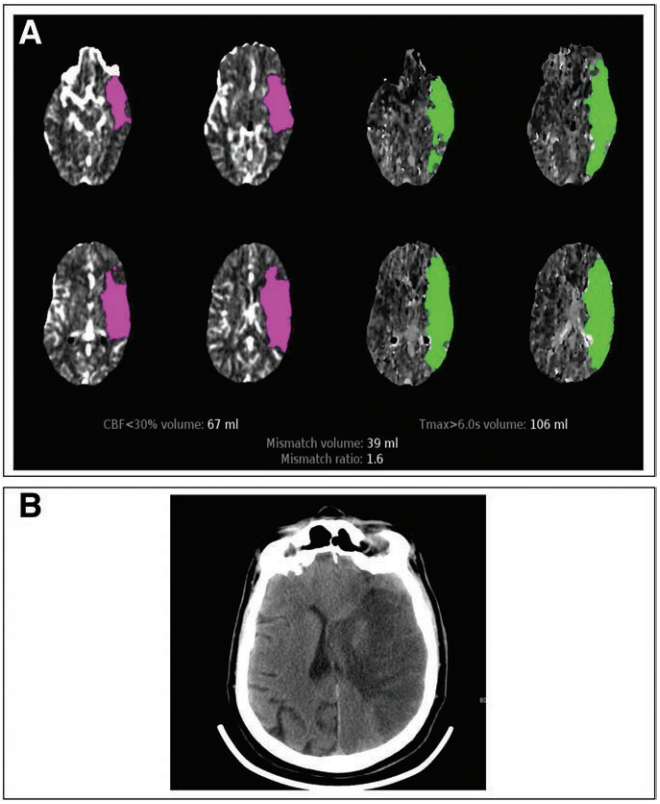

Figure 3. An acute ischemic stroke not amenable to intervention. **A**, CT perfusion imaging shows nearly matching deficits with large core infarct. The Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) study used the area of core infarction defined as cerebral blood flow (CBF) greater than 30% volume of greater than 21 cc for ages younger than 80 or 31–51 cc for ages older than 80, National Institutes of Health Stroke Scale [NIHSS] less than 10; or less than 20. This patient presented with global aphasia, left gaze preference, right homonymous hemianopsia, and right hemiplegia and hemihypesthesia; NIHSS 25. **B**, Follow-up CT scan shows large left middle cerebral artery infarct consistent with area seen on CBF less than 30%. The patient was discharged to a skilled nursing facility with an NIHSS of 23.

however, it increases the likelihood of leaving a patient alive with significant disabilities (64). It is essential that the critical care team work closely with the patient's legally authorized representative such that the ramifications and long-term outcomes are clarified and consistent with the patient's wishes before DCH is offered.

Intracerebral Hemorrhage

The main acute treatment for ICH remains blood pressure control as it was 50 years ago. The advances in this area have included studies to determine optimal blood

pressure goals and the development of new and faster titratable agents. Based on these studies, critical care management of the patient with ICH includes close blood pressure monitoring, although the optimal treatment target is still in question (65). Current ICH guidelines recommend a systolic blood pressure (SBP) target of less than 140 mm Hg based on studies including the Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT-2) (66, 67). This trial of nearly 2,800 patients with ICH showed no difference in death or moderate or severe disability, but functional outcomes were better with SBP targeted for 7 days to less than 140 mm Hg compared with less than 180 mm Hg. Serious adverse outcomes were similar between groups. A recent retrospective analysis of 384 patients from the placebo arms of spontaneous ICH international trials demonstrated a 16% increase in the risk of unfavorable outcome for each 10 mm Hg increase in SBP and 11% for each 10 mm Hg increase in diastolic blood pressure. The association was strongest when SBP exceeded 190 mm Hg and remained significant at the majority of thresholds down to 140 mm Hg. These data support the current guideline target of SBP less than 140 mm Hg (68). Of note, the Antihypertensive Treatment of Acute Cerebral Hemorrhage-II (ATACH-2) multicenter trial of 1,280 ICH hypertensive patients with the same systolic targets as ATACH-2 had a goal to achieve target within 4.5 hours of hematoma onset for at least 24 hours, with the first-line use of nicardipine, a titratable dihydropyridine (69). Unlike the INTERACT-2 trial, ATACH-2 stopped due to futility, showed no difference in outcomes, and instead showed an increase in renal adverse events within 7 days of the intensive arm, and subsequent analysis also showed higher rates of neurologic deterioration and cardiac-related adverse events with tighter control (70). Key considerations may be speed, degree, and variability of blood pressure control. Although in our futuristic world, the concept of more and faster might seem better, this may not be the case since the INTERACT-2 trial also showed that a SBP less than 130 mm Hg was associated with a worse prognosis (65, 71). More recent studies show that greater hyperacute blood pressure variability management may worsen outcome (72); therefore, smooth, conservative control may be optimal.

Patients with infratentorial, that is, cerebellar, hemorrhage, or infarct, are at risk for mass effect from the hemorrhage or edema that may cause acute hydrocephalus, brainstem compression, and sudden neurologic deterioration. Decompression of the posterior fossa in these patients is life saving and decrease disability. This is most likely to be beneficial if performed before severe brainstem compression/dysfunction with cranial neuropathies and severe hydrocephalus from fourth ventricular compression develops.

In contrast, the optimal surgical management for a patient with a supratentorial ICH with or without intraventricular hemorrhage (IVH) is an area rich for exploration. After conventional craniotomy of hematoma evacuation with and without IVH yielded negative results in the Surgical Treatment for Intracerebral Hemorrhage (STICH) trials (73, 74), numerous studies using new minimally invasive technology have been undertaken (75). In the Minimally Invasive Surgery plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE) trials, minimally invasive surgery (MIS) with thrombolysis using t-PA did not improve functional recovery, although the study showed that smaller postsurgical ICH volume did improve the likelihood of a good functional outcome (76, 77). A meta-analysis compared MIS, that included endoscopic surgery or stereotactic thrombolysis, with conventional treatment that included medical treatment and conventional craniotomy. Patients who received MIS when performed within 24 hours were 2.8 times more likely to result in functional independence and two times more likely when performed within 48 hours (78). Even more novel techniques have been trialed. The Safety of Lysis With Ultrasound in the Treatment of Intracerebral Hemorrhage and Intraventricular Hemorrhage (SLEUTH) trial included using t-PA in conjunction with an ultrasound-emitting microcatheter that is stereotactically delivered into the bed of the ICH alongside a ventricular catheter (79). A device approved for stereotactic removal of IVH has been used with a newly devised Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration (SCUBA) technique where dry hematoma aspiration is followed by infusion of saline into the cavity saline-facilitated ICH removal as a proof of concept that has the advantage to visualize and cauterize bleeding vessels and visualize residual clot burden (80). Clearly, practice changes and new guideline recommendations may occur in the near future.

IVH associated with ICH typically worsens outcome. Studies have been undertaken to rapidly clear IVH including strategies such as placement of

intraventricular drains and irrigation with a thrombolytic such as t-PA. Although these methods have been shown to clear IVH, they have not yet shown improved functional outcomes (81).

Subarachnoid Hemorrhage

Early treatment of severe SAH targets the two most important causes of early deterioration: acute obstructive hydrocephalus and rebleeding of the aneurysm. Strategies to prevent rebleeding, primary remain securing the aneurysm, and blood pressure control. Downstream critical care management that are more unique to SAH include prevention of delayed ischemic deficits and the recognition and management of cerebral salt wasting.

A significant driver of reduced mortality following SAH is the aggressive treatment of acute obstructive hydrocephalus. A major advance in the area of obstructive hydrocephalus, which historically was not possible due to limitations in materials, was the development of silastic external ventricular tubes in 1969 that replaced rubber and metal tubes (82) and the adoption of CT scanning as an identification tool.

The risk of rebleeding and the utility of securing aneurysms was hotly debated in the early 1970s. A randomized trial of conservative versus operative treatment (comprising clipping, wrapping and injecting muscle, or adipose into the aneurysm) published in 1966 solidified the need to operate on patients with SAH (83). The timing of surgery was also a topic of contention. It was customary to allow patients with severe symptoms to wait up to 14 days before securing the aneurysm (84).

There was almost no data about the optimum therapy for patients in the ICU. A number of late syndromes such as cerebral salt wasting and delayed deterioration (vasospasm) were described, but there was no consensus on treatment. Common practice was to try to limit stress by keeping patients in the dark and in bed for prolonged periods of time with the hopes of preventing sympathetically induced blood pressure increases that could result in rebleeding. In addition, patients were often not given nutrition and kept purposefully hypovolemic due to the perceived risk of increased ICP. Needless to say, mortality and morbidity were high (83).

A revolution of advances has changed the way SAH patients are treated. Two trends greatly influenced this: 1) the initiation of randomized trials in the field took the place of tradition-based therapies and 2) the advent of neurocritical care as a specialty led to incorporation of best practices from other disciplines in critical care. Despite any single "game-changing" advance in care, the mortality from SAH has decreased over the last 50 years (85, 86). This is likely due to a culmination of advances that have been made in all aspects of care including acute management, management of complications of SAH, and how we assess outcomes for patients who survive.

With respect to preventing rehemorrhage, after the initial aneurysm timing study of the late 1960s, two additional studies supported the early securement of aneurysms. Whereas it was typical to wait up to 14 days before attempting intervention to secure an aneurysm in the 1970s, in the 2020s, it is typical to secure aneurysms within 24 hours of admission (87) before the window of potential delayed ischemic deficits peaks.

The invention and approval of the Guglielmi coil in 1995, which allowed securement of aneurysm without an open craniotomy, fundamentally changed the approach to the management of aneurysms (88). Some aneurysms, such as those that developed at the terminus of the basilar artery, were only approachable surgically with great risk of death or disability. With endovascular coils, the risk became similar to the risk attributed to "easier" to treat aneurysms. In addition, the combination of stents and coils overcame the risk of coils migrating out of aneurysms by crafting artificial walls to the aneurysm that allowed the coils to remain in place. The most recent advance has been in the use of diverting stents that are deployed over the opening of difficult to coil or clip aneurysms excludes the aneurysm from the circulation and leading to aneurysm thrombosis (89).

The development of coiling and stenting techniques have revolutionized the securement of aneurysms; however, a remaining challenge is to identify which patients to clip and which to coil. There is still significant center to center disparity between these two treatments, as large as a 70% difference between what percentage of aneurysms some centers clip versus others (90). There is still a need for a large randomized trial to determine the best treatment strategy for the majority of aneurysms but the divide by practitioners who predominantly coil aneurysms and neurosurgeons who have not been trained in endovascular approaches leads to lack of equipoise for a study.

CRITICAL CARE AND CEREBROVASCULAR DISEASE

Optimal outcome for the stroke patient is reliant on careful management of systemic complications following the stroke. The neurologically trained critical care team is best equipped to monitor and manage secondary injury from hypoperfusion, hypoxemia, hyperthermia, as well as the neurologic complications including symptomatic hemorrhagic transformation, rehemorrhage, undetected seizures, and cerebral edema.

For AIS, in one estimate, 24% of all patients admitted with AIS potentially need critical care intervention (91). Identifying these patients ahead of neurologic worsening and complications is ideal but not simple. The triage criteria for an ICH or SAH patient is clearer. Those needing invasive monitoring or surgical and/or endovascular intervention or those at high risk for decompensation with a large ICH or IVH or posterior fossa lesions with a high risk for obstructive hydrocephalus clearly need ICU admission.

Following AIS, those with LVO or strokes in multiple vascular territories are at a high risk of developing brain swelling. There are a number of clinical and imaging findings that can help identify susceptible patient populations with high sensitivity and specificity (92). Frequent clinical assessment using clinical scales that yield easy to understand objective scores with high inter-rater reliability like Glasgow Coma Scale (GCS), Full Outline of Unresponsiveness score, or National Institutes of Health Stroke Scale may facilitate early identification and appropriate clinical responses (93). Findings of mass effect due to cerebral edema on CT brain like loss of identifiable sulci, compression of the ventricular system, and midline shift are helpful to differentiate decrease in consciousness caused by other confounding factors such as sedatives or fever from compression related encephalopathy. Another promising bedside tool being developed to identify worsening cerebral edema is automated quantitative pupillometry (94).

Years ago, hyperosmolar agents are shown to be effective in reducing cerebral edema. In the ensuing years, the most significant change was that urea, popular in the 1960s was supplanted by mannitol in the early 1970s due to urea's difficulty with preparation and chemical stability, but mostly due to its side effects of coagulopathy, hemoglobinuria, electrographic changes, tissue necrosis with extravasation, and rebound intracranial hypertension (95). Hypertonic saline and mannitol are the most commonly used hyperosmolar agents. Due to lack of equipoise, there continues to be no strong evidence to show that they improve neurologic outcomes. The use of prophylactic hyperosmolar therapy in patients at high risk of cerebral edema is not supported by evidence. Although hypertonic saline has certain physiologic advantages over mannitol including more rapid onset of action and more robust and durable ICP reduction, there is insufficient evidence to suggest that one hyperosmolar therapy agent is superior to the other. There is still a need for high-quality research to better inform clinicians about the optimal practical use of these therapies. Guidelines currently recommend the use of either hypertonic saline or mannitol for initial management of intracranial hypertension or cerebral edema in patients with ischemic stroke with the recognition that there is insufficient evidence that they improve neurologic outcome. An evolving area is the recognition that severe hyperchloremia (> 115 mEQ/L) appears to be associated with acute kidney injury and renal function should be monitored closely in these patients (96).

The neurocritical care management following ICH has been focused on the targeting of blood pressures and reversal of antithrombotic agents. However, there are emerging surgical options for hematoma and IVH evacuation discussed below, which require appropriate and timely neurosurgical consultation.

Specific to the neurocritical care management of SAH patients, the evolution over 50 years have stemmed from debunking common practices and strongly held beliefs. Until the mid-1980s, patients were kept relatively volume depleted in an effort to prevent cerebral edema. Studies done by the fledgling field of neurocritical care showed that not only did patients do better if they were volume expanded early, but the occurrence of malignant cerebral edema in SAH patients decreased as well (97). With the development of noninvasive volume assessment, the reliance on volume management based on central venous catheters and pulmonary artery occlusion catheters fell out of fashion as it did in most critical care specialties. Likewise, the routine use of blood transfusions, albumin, and hetastarch solutions have also not weathered the test of time.

Secondary cerebral injury (called delayed cerebral ischemia [DCI] by most) following SAH is a complication that has most influenced the need for specialists in neurocritical care. Described in the early 1900s, the advent of the cerebral angiogram associated cerebral vascular spasm gave the syndrome its colloquial name of cerebral vasospasm. In the 1980s, trials of volume expansion (after days of forced volume depletion) led to improved outcomes (98). This effect was difficult to replicate once early volume resuscitation for SAH patients became standard. These early trials led to more than 40 years of randomized clinical trials of medications and interventions aimed at reversing vascular spasm. This modern approach, although unsuccessful at improving patient outcome, showed the benefit of randomized clinical trials to change tradition-based therapies.

The belief that delayed cerebral injury is due to vasospasm leading to ischemia has significantly stifled innovation in SAH treatment. An early trial of a calcium channel blocker, nimodipine, supported this belief initially (but is now thought to be a neuroprotectant more than a vasodilator) (99, 100). Additionally, others have hypothesized that the blinded administration of nimodipine, a dihydropyridine that lowers blood pressure, resulted in fluid administration to an otherwise volume-depleted patient and the volume expansion thereby improved neurologic outcome seen in the published studies. A number of clinical trials have shown that vasodilation of arterial beds as a treatment do not improve outcomes. This coupled with studies using advanced imaging that show that patients with DCI do not have predominant ischemia as their pathology show that the mechanism of brain damage is likely not solely ischemic. Recently inflammation and spreading cortical depressions have been implicated in direct nonischemic brain injury, but large-scale clinical trials aimed at these pathologies have been delayed significantly while efforts were focused on vasodilatory treatments (101, 102). There still is no effective treatment for DCI, the common names DCI and vasospasm are still in common usage, and standard of care in DCI patients still centers on strategies to improve perfusion. More recently, however, clinical trials have involved pharmacotherapeutics with anti-inflammatory properties such as statins, endothelin receptor antagonists, and selective phosphodiesterase III inhibitors (103).

Advances in general critical care have had a profound impact on the management of patients with cerebrovascular disease. Key among them is the respiratory care management to prevent nosocomial pneumonia to which patients with cerebrovascular disease are especially prone due to secondary dysphagia (104).

Over the last 50 years, the critical care community that cares for neurologically impaired individuals has had to evaluate new ventilator technologies and strategies and their impact on brain physiology. None has been more challenging than the use of positive end-expiratory pressure (PEEP) in patients with increased ICP and concomitant hypoxia. Because PEEP can increase intrathoracic pressure, it potentially inhibits two of the physiologic mechanisms the body uses to mitigate pressure: the low pressure in the thoracic cavity during nonventilated inspiration (ventilated expiration) that allows cerebrospinal fluid offloading to increase brain volume, and the low pressure caused during cardiac diastole for venous outflow from the cranial cavity. Animal studies and a recent study in patients with aneurysmal SAH have shown that a higher PEEP effects ICP in the setting of restrictive lung disease (high chest wall elastance) and a compliant lung that transmits an alveolar/pulmonary pressure to the intrathoracic space (105). There is still no consensus about how much PEEP is acceptable or how to weigh the relative merits of decreased ICP and oxygen saturated blood (106).

Another management area of general critical care that has had an important impact over the last 50 years is the development and refinement of strategies to modulate systemic blood pressure. In ischemic stroke, optimal blood pressure has not been identified but in hemorrhagic forms of stroke, as discussed above, early and aggressive SBP lowering has shown benefit (67, 68). In patients who have cerebral edema and increased ICP and whose cerebral autoregulation is impaired, mean arterial pressure augmentation to ensure adequate cerebral perfusion pressure has been shown to be beneficial (107).

There has also been an understanding that severe brain pathology can have a profound impact on nonbrain organs such as the heart in stress (Takotsubo aka cardiac myocytolysis aka myofibrillar degeneration) cardiomyopathy (108) and the lungs with neurogenic pulmonary edema. Both entities were described in the early 1900s; the specific coinage of Takotsubo ("octopus pot") cardiomyopathy or left ventricular apical ballooning on cardiac catheterization was described in

1991 (109, 110). Our understanding of the pathophysiology due to sympathetic effects and diencephalic changes and impact of these systemic diseases has increased, although specific therapies have not been found and treatment is mostly targeted at supportive care of ensuing hypotension and/or acute hypoxemic respiratory failure.

Cerebral salt wasting, frequently seen after SAH and traumatic brain injury, as an entity was hotly debated in 1971 with some advocating that all hyponatremia in SAH patients was the syndrome of inappropriate antidiuretic hormone (SIADH). Recognition that the release of brain natriuretic peptide release led to both hyponatremia and volume depletion led to a strategy of volume and salt repletion with hypertonic saline solutions. In a landmark study in the early 1980s, this strategy was shown to decrease the risk of stroke substantially over SIADH management with volume restriction (111).

Following focal cerebral ischemia, a putative cascade of events occurs that have been a focus for pharmacological neuroprotection in the last few decades. These include an increase in excitotoxicity with glutamate and calcium-mediated cell signaling, peri-infarct depolarizations, inflammation, and apoptosis (112). While work has progressed in reperfusion of ischemic stroke, in the last decades, scores of neuroprotective agents, effective in animal stroke models, have failed to show efficacy in human clinical trials (113). In the era of thrombectomy, there are ongoing efforts to find effective neuroprotectants (114). An example is nerinetide, an eicosapeptide that interferes with postsynaptic density protein 95 and is being explored in conjunction with reperfusion strategies (115).

Although no novel neuroprotectant has emerged to date, therapeutic temperature modulation (TTM) to maintain normothermia remains the only target that may confer cerebral neuroprotection. Hyperthermia is known to accelerate neuronal injury by increasing neuronal discharges, excitatory neurotransmitters, oxygen-free radical production, calcium-dependent protein phosphorylation, intercellular adhesion molecule-1, inflammatory response, DNA fragmentation, and apoptosis (116, 117). Unlike cardiac arrest outcomes with global hypoxic ischemic injury, which show improved outcome, hypothermia with focal ischemic injury, that is, acute stroke, has not shown efficacy. However, based on studies showing that patients with larger stroke and hyperthermia have poor outcomes, TTM to normothermia is a critical care goal that should be considered for all neurologically injured patients (118). With temperature management as the goal, the last few decades have seen the development of intravascular devices, esophageal balloons, and more advanced, computer-controlled topical devices.

Finally, over the last few decades, technology to measure intracranial blood flow and metabolism has been developed. Some technologies such as jugular venous bulb monitoring are no longer used. Emerging technologies, including noninvasive TCD, cerebral oxygenation saturation such as near-infrared spectroscopy and more invasive interstitial fluid brain oxygen tension monitoring, and cerebral tissue thermodilution blood flow monitoring are gaining support (119, 120). There is still no consensus about how these technologies, or their output, can be used to treat cerebrovascular disease, but studies in this area are ongoing. Finally, cerebral interstitial fluid microdialysis is a feasible technique to measure the metabolic state of areas of interest in the brain (121). This small catheter, placed in the parenchyma of the brain, samples the interstitial fluid so that it can be analyzed outside the body. Although the types of evaluation of this fluid that are possible are limitless, the current technology focuses on signs of metabolic stress. Until now, this technique has been solely experimental, but a few centers in the United States and Europe are beginning to incorporate it into clinical practice.

An older technology, electroencephalography is finding a place in the ICU as a continuous monitoring technology that can detect nonconvulsive seizures. Seizures, a cause for secondary injury, have been reported in 6–27% of ischemic stroke patients, 16–23% following ICH, and 10–19% following aneurysmal SAH. In a SAH population, 3–13% had nonconvulsive seizures, which makes a case for continuous recording (122).

The trend in neurocritical care in the 21st century has been to evaluate the use of multiple monitoring techniques together to hopefully get a better understanding of the true physiology of the injured brain (123). "Multimodal Brain Monitoring" has become a common term in the neurocritical care literature but has yet to show a specific benefit in patients with critical illness cerebrovascular disease.

STROKE SYSTEMS OF CARE-STROKE UNITS, NEUROCRITICAL CARE UNITS, STROKE CENTERS

It is not surprising, perhaps, that the subspecialty of neurocritical care has grown apace the advances in pharmaceuticals, imaging, and neurointerventional capabilities. In the 1970s, the development of organized inpatient stroke units helped counter the therapeutic nihilism surrounding stroke care in the medical community (124). These stroke units, not necessarily an ICU, but a ward dedicated to stroke patients, were developed to provide focused care of the stroke patient in the hospital by a multidisciplinary team including neurologists, specially trained nurses, and rehabilitation specialists. Patients receiving organized patient care in a stroke unit are more likely to be alive, independent, and living at home 1 year after stroke (125). Subsequent guidelines recommend that stroke patients should be cared for in areas with dedicated staff with specialty training in stroke (126).

In 2000, the members of the Brain Attack Coalition, a multidisciplinary group of representatives from professional organizations involved with delivering stroke care and stroke patients reviewed the literature with regard to improving the delivery of care to stroke patients in the new era of thrombolysis for AIS. They created the concept of primary stroke centers that included acute stroke teams, stroke units, written care protocol, integrated emergency response teams, and the essentials imaging and laboratory needs to deliver thrombolytic treatment quickly and safely (126).

Since 2001, studies performed in the United States and internationally have shown that AIS, ICH, and SAH patients managed in models of dedicated neurocritical care subspecialty expertise have decreased mortality, ICU, and/or hospital length of stay, and improved outcome as demonstrated by increasing the likelihood of discharge to home or to a rehabilitation facility (127–138). Standards for neurologic critical care units have been developed (139). The concept of a Comprehensive Stroke Center was developed to embrace advanced care including neurocritical care expertise to provide the full spectrum of care for the most seriously ill patients with cerebrovascular conditions (140).

Based on the opportunity and potential benefit of early intervention and advanced therapy, guidelines recommend rapid prehospital stroke screening and evaluation and the development of regional systems of stroke care and triage paradigms and protocols through collaborative efforts of emergency medical services leaders, and local, regional, and state agencies and local clinical experts (58, 141, 142). These efforts are focused on ensuring that stroke patients are transported quickly to the facility most appropriate for that patient's optimal care.

PROGNOSIS FOLLOWING CEREBROVASCULAR INJURY

Frequently an intensivist is asked regarding prognosis of a patient who is admitted to the ICU following a severe neurologic injury and equally of great interest and difficulty. At admission, typically predictive factors that are considered include grading scales based on clinical severity. These are compared with outcome measures that often use disability scores such as the modified Rankin Scale (mRS) or Glasgow Outcome Scale at various endpoints including discharge, 3 months, 6 months, or a year. For AIS, the grading scale most commonly used is the National Institutes of Health (NIH) stroke scale; for SAH, the Hunt and Hess scale or World Federation of Neurosurgical Societies; and for ICH, the ICH score. These scores typically include the clinical condition. For example, the ICH score includes factors such as the GCS score, hemorrhage location, size, presence of IVH, and patient age, which were shown to be independent predictors of outcome (143).

Unlike AIS that often leaves patients with significant motor deficits, SAH patients (particularly those that show signs of DCI) are burdened with cognitive and emotional deficits that outweigh their physical disability (144). Standard ischemic stroke outcome scales such as the mRS tend to underreport the cognitive disability of SAH. New studies are using neuropsychiatric evaluation to understand the domain-specific cognitive deficits more thoroughly. This will hopefully lead to better outcome assessment that will aid in testing treatment regimens.

Efforts to better define the crystal ball for these patients have included a recent gap analysis that reviewed multiple grading scales for various neurocritical are disease states including AIS, ICH, and SAH. The authors found that prognostic scoring models commonly failed to address and incorporate comorbidities and in-hospital events when evaluating patient outcome (145).

Given the lack of consistent prognostic tools and the potential plasticity of the brain during recovery, the current recommendation is to avoid early over-prognostication in the absence of adequate data that may result in a self-fulfilling prophecy. Prehospital comorbidities, in-hospital events, and clinical reassessment over time are important considerations for the clinician.

RESEARCH NETWORKS IN THE ADVANCEMENT OF CEREBROVASCULAR CRITICAL CARE

One of the major advances for acute neurologic treatment in the last 50 years was the establishment of research networks such as the NIH-funded, NINDS Neurological Emergencies Treatment Trials Network (NETT) in 2006. With a Clinical Coordination Center, a Statistical and Data Management Center, and a network of hubs each with two- to six-spoke centers, emergency neurologic treatments studies are able to run efficiently. In 2013, the NIH funded the StrokeNet, a stroke trials network consisting of 27 regional coordinating centers and 500 hospitals across the United States. StrokeNet trials focus on interventions for stroke prevention, treatment and recovery, and validation studies of biomarkers or outcome measures. These studies include sites in Canada, Germany, United Kingdom, Spain, and Japan. Related efforts such as the Network for Excellence in Neuroscience Clinical Trials, also funded by the NIH NINDS, established in 2011 with 25 clinical sites, have also been an important network to develop cooperative, pragmatic studies in the field.

More recently, the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN) were established in 2017. Under the SIREN umbrella with 11 award hubs with spoke centers, NETT studies take advantage of this emergency medicine-based network and have addressed or are addressing such topics as optimal temperature management targets after cardiac arrest, status epilepticus, traumatic brain injury, acute spinal cord injury, as well as AIS and ICH.

SUMMARY

In 1970, the total deaths from cerebrovascular disease in the United States was 81,068 for a rate of 93.5 (per 100,000) (4). Nearly 50 years later, in 2017, stroke contributed to 146,383 deaths but with half the death rate of 44.9 per 100,000 (146, 147). In the United States, stroke fell from the third to the fourth leading cause of death in 2008 and is now the fifth leading cause of death in the United States since 2013 (148). Conversely, globally, over the intervening years, stroke, previously the third leading cause of death, is now the second leading cause of death behind ischemic heart disease (6).

Major changes that occurred between 1971 and 2021 include a focus on the primary and secondary prevention of stroke with a recognition for the importance of blood pressure control, staying active, keeping a healthy weight, cholesterol management, eating a heart-healthy diet, avoiding smoking and smokeless tobacco, and good diabetes control; although this still remains a challenge for many populations (149). Better recognition of stroke by the general public and the emergency medical services has improved the speed in which patients can receive acute treatment with the concept that "Time-is-Brain" and education that 1.9 million brain cells, 14 billion synapses, and 7.5 miles (12 km) of myelinated fibers are lost each minute (150).

Major advances in acute stroke care have driven the need for critical care management of acute stroke patients. These include IV thrombolysis and advanced imaging that is expanding the number of patients who can benefit from acute stroke treatment.

Additionally, endovascular modalities for mechanical thrombectomy, coil embolization of aneurysms, microparticle embolization of arteriovenous malformations, surgical advances for large hemispheric stroke or hemorrhage, and, most of all, the increased understanding of the interplay and complexity of stroke care in the acute stroke patient and the critical care management of these patients have contributed to this decrease in stroke mortality.

Globally, ongoing challenges include access to healthcare, an aging population, and uncontrolled preventable risk factors. Additionally, there are disparities in access to advanced healthcare. The WHO has projected that the global stroke burden will continue to rise, nearly doubling from 38 million disability-life-years in the 1990s to 61 million life-years in 2020 (151).

As we follow our SCCM founders' lead to improve care into the future, we foresee the need to find more rapid, less technologically heavy modalities to identify an ischemic from a hemorrhagic stroke victim and find even more effective ways to reverse a stroke, evacuate a hemorrhage without damage, and secure an aneurysm. In the critical care arena, we need to better

understand the physiologic changes associated with acute brain injury to help prevent and/or treat secondary ischemia, inflammation and edema and to better understand and enhance prognosis, recovery, and outcome. Underpinning these efforts is the need for stroke prevention and improved access to care.

1 *Neurocritical Care, Department of Neurology, Duke University, Durham, NC.*

2 *Neurocritical Care, Department of Neurology, University of Virginia, Charlottesville, VA.*

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For information regarding this article, E-mail: cherylee.chang@duke.edu

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