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Neuroemergencies in South America: How to Fill in the Gaps?

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Abstract

South America is a subcontinent with 393 million inhabitants with widely distinct countries and diverse ethnicities, cultures, political and societal organizations. The epidemiological transition that accompanied the technological and demographic evolution is happening in South America and leading to a rise in the incidence of neurodegenerative and cardiovascular diseases that now coexist with the still high burden of infectious diseases. South America is also quite heterogeneous regarding the existence of systems of care for the various neurological emergencies, with some countries having well-organized systems for some diseases, while others have no plan of action for the care of patients with acute neurological symptoms. In this article, we discuss the existing systems of care in different countries of South America for the treatment of neurological emergencies, mainly stroke, status epilepticus, and traumatic brain injury. We also will address existing gaps between the current systems and recommendations from the literature to improve the management of such emergencies, as well as strategies on how to solve these disparities.

Keywords: Neurocritical care, Outcome, Health policy, South America, Critical care, Neurological emergency

Introduction

South America covers 12% of the world's land surface and has ~6% of the world population [1]. In high-income countries, degenerative and cardiovascular diseases have become the leading causes of death surpassing pandemics of infection [2, 3]. The same transition now takes place in low- and middle-income countries in South America, where *both* degenerative and infectious diseases are endemic [4, 5].

Unfortunately, South America is quite heterogeneous regarding the existence of systems of care for the various neurological emergencies (Fig. 1) [6–9]. In this article, we will discuss the existing systems of care in different countries of South America for the treatment of neurological emergencies, mainly stroke, status epilepticus (SE), and traumatic brain injury (TBI). We also will address these systems adequacy to current guidelines and propose strategies to improve compliance. The information presented here stems from the meeting that took place at The Galapagos Neurocritical Care Summit in San Cristobal, Galapagos Islands, Ecuador November, 2016, sponsored by the Universidad San Francisco de Quito, Ecuador, and endorsed by the Neurocritical Care Society (NCS).

Epidemiology

Stroke

Stroke is the first or second cause of death in most South American countries, with 10% of all strokes affecting patients < 45 years old [10–12].

The reported annual incidence of first-ever stroke varies from 73.6 to 183 per 100,000 per year [10, 13, 14].

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See "Appendix" for a full listing of investigators.

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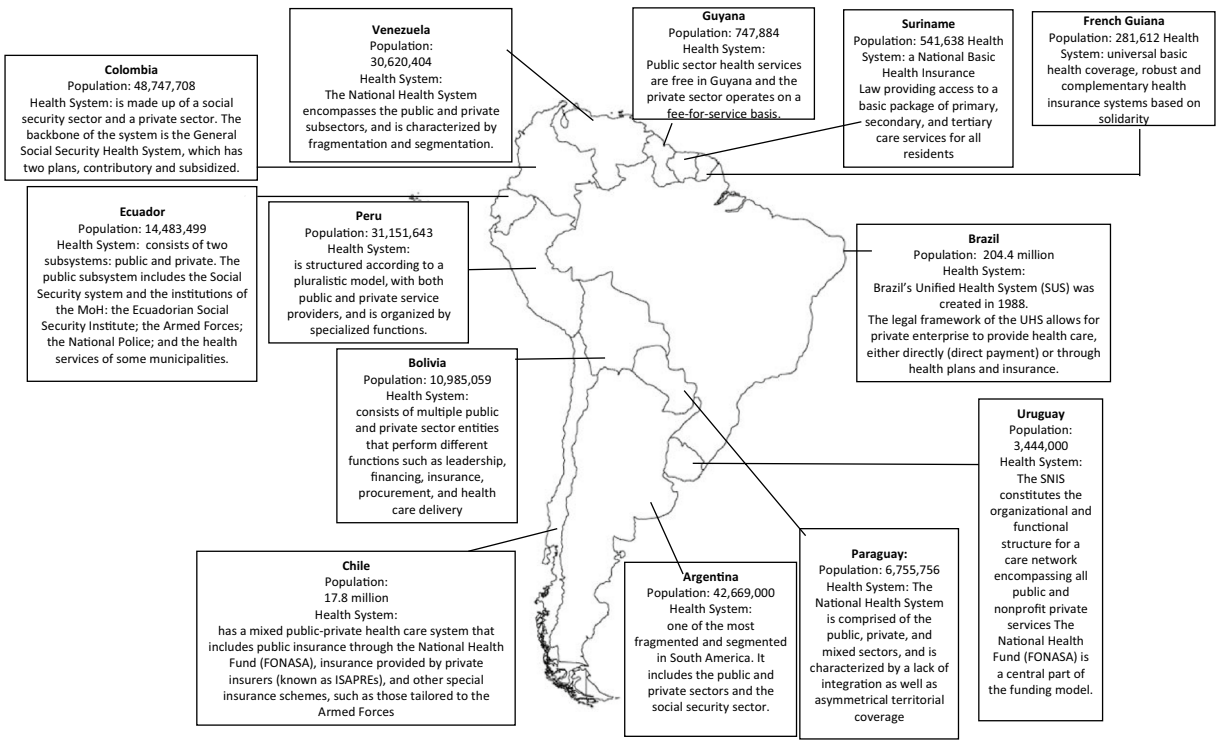

Fig. 1 South American countries with populations and health systems [1, 9]

Prevalence of stroke ranges from 140 to 1600 per 100,000 habitants [15–17].

Ischemic stroke (IS) accounts for 80.4–87.3% of all strokes [10, 13, 18]. In South America, Chagas disease (American trypanosomiasis) is responsible for about 50,000 annual deaths from cardiomyopathy [11, 19] and is an independent risk factor for all stroke subtypes, especially in the young [20–23]. Chagas cardiomyopathy results in cardiac dilatation, cardiac wall motion abnormalities, and, in some patients, formation of apical aneurysm. More than 20% of patients with Chagas disease who have had a stroke can have recurrent events; therefore, effective secondary prevention strategies are of utmost importance. Other infectious diseases such as malaria, gnathostomiasis, arboviruses hemorrhagic fevers, and neurocysticercosis also play a role. Nevertheless, most strokes in South America can be attributed to classic modifiable cardiovascular risk factors [11, 24].

Status Epilepticus

There are few data on the epidemiology of SE in South America as a whole. The overall incidence appears to be between 9.9 and 41 per 100,000/year, affecting mainly children and elderly patients [8, 25]. Roughly 50% of patients with epilepsy in Latin America and the Caribbean do not receive any type of treatment for the disease [26, 27]. The short-term mortality of patients admitted with SE ranges from 16 to 31.4% [8, 26]. Epilepsy is the primary cause of ~5800 deaths annually in Latin America [28].

Infectious diseases are frequent etiologies of SE [29]. In a series in São Paulo, Brazil, the most frequent etiology of SE was inappropriate use of antiepileptic medications in patients with a history of epilepsy. In those without, the main etiologies were central nervous system infections, stroke, and metabolic disorders [30]. In Central and South America, the main etiologies of SE were TBI, idiopathic epilepsy, and neurocysticercosis [8]. In fact, central nervous system infections are the main etiology of seizures and acquired epilepsy in low- and middle-income countries. Neurocysticercosis is the most common cause of epilepsy of adulthood in Latin America, with a prevalence twice that of high-income countries. Epileptic seizures occur in more than 90% of patients in several series and may occur at any stage of parasite evolution. Acute seizures are also common in viral encephalitis including arboviroses, meningitis, and malaria and in most cases are associated with increased mortality and morbidity, and subsequent epilepsy. Tubercular meningitis is still a very common chronic central nervous system infection in low- and middle-income countries. Seizures occur in over half

of the cases and are usually focal and frequently associated with vasculitis and infarcts.

Traumatic Brain Injury

The epidemiology of TBI in South America is not well documented [31]. However, death by accidents, including TBI, is the most frequent cause of death among men in the 15–59-year age-group in Latin America and the Caribbean [32]. Moreover, the incidence of TBI in Latin America in adults is around 1.8 times higher than in developed countries. The main documented causes of TBI in South America include auto accidents and violence [31, 33].

A multicenter study evaluating severe TBI in South America showed important differences in the capacity for pre-hospital evaluation, availability of intensive care unit (ICU) beds, and the use of intracranial pressure monitors depending on the locality. There were also important inequalities within the same country, depending on whether the health service was public or private. Patients enrolled in services with greater availability of resources had a better long-term functional outcome [34].

Mortality from severe TBI in low- and middle-income countries in Latin America remains high, but the rate of favorable outcome in survivors is similar to those of high-income countries. The main factors associated with outcome are race and medical institution outweighing other important clinical factors such as hypotension and pupillary reactivity [34].

In general, guidelines for the treatment of TBI are based on data from developed countries [35]. However, there is no evidence that those results are generalizable to low- and middle-income countries. Therefore, the World Health Organization has developed guidelines for cost-effective, feasible, and sustainable treatments for trauma care services that can be applied to any location worldwide [36].

Public Awareness

In severe TBI, witnesses usually feel compelled to call emergency systems when facing a patient with systemic or orthopedic traumas. However, patients with stroke and SE (especially when nonconvulsive) may have more subtle or negative symptoms, making it difficult to identify as another medical emergency [37–39].

For example, in Brazil, 22% of subjects interviewed in three major cities did not recognize a single warning sign of stroke [40]. A survey in Colombia showed that 65.3% did not recognize stroke symptoms and signs; 54% were not aware of stroke risk factors; and only 11.7% would seek urgent medical help when facing stroke symptoms [41]. This lack of recognition plays a role in considerable delays in hospital admission of stroke patients in Lima (Peru), Montevideo (Uruguay), and Joinville (Brazil) [42–45]. In Argentina, 75% of the patients admitted with stroke symptoms to a hospital from November 2012 to July 2013 arrived at the emergency department after 4.5 h of stroke symptoms onset [46].

Even healthcare professionals have quite heterogeneous and often insufficient knowledge on the subject [8]. A survey conducted in São Paulo showed that physicians are more exposed to educational contents about epilepsy than other healthcare professionals. In this study, 58% of dietitians, 47% of physical educators, 31% of psychologists, 27% of physiotherapists, and 14% of nurses reported not having received any information about epilepsy during their professional training, as compared to 3% of physicians [47]. In Brazil, there is a direct correlation between educational level and knowledge about attitudes when facing a patient with a seizure [48]. Investing in appropriate national recognition campaigns is therefore an important step for the community to recognize neurological emergencies.

Emergency Medical Services

Few publications have addressed national strategies against stroke in South America. In Brazil, the implementation of a National Stroke Project was very important to improve stroke care in the country. The project developed acute stroke centers and trained pre-hospital personnel. The pre-hospital emergency medical system (SAMU, Serviço de Atendimento Móvel de Urgência) was actively involved. In a pilot study in Porto Alegre (Brazil), SAMU and five stroke centers were trained on acute stroke interventions. After the project, the proportion of stroke patients treated with intravenous thrombolysis (rt-PA) increased from 1.7 to 5.3% [49]. The use of smartphone apps is a new strategy that can assist patients and families in recognizing symptoms and activating emergency services. In stroke, some experiences have been reported and are being implemented with good results in South America [50].

Strategies to improve pre-hospital care include awareness campaigns, a centralized emergency number, emergency medical services training in neurological emergencies, the existence of clinical networks, priority transfers straight to appropriate centers, and collaboration between hospitals [51–53]. Triaging patients among the different stroke centers is vital to optimize allocation of resources and transport times, especially if thrombectomy is available. Several scales can help identify patients with a large vessel occlusion with greater sensitivity than specificity [54–57].

Simple recommendations for the pre-hospital approach of the patient with seizures exist and include drugs of choice, instructions on when to repeat dosing, and the need for tests such as capillary blood glucose prior to medication [39].

For patients with TBI, there are also specific guidelines suggesting recommended levels of oxygen saturation, blood pressure, and the use of specific scales for evaluating the level of consciousness such as the Glasgow Coma Scale, including the timing of the assessment [35]. A study evaluating the outcomes of TBI of 550 patients in nine centers in South America showed that 50% of the patients were admitted within 3 h of the accident, with most patients coming directly from the scene of the event [34].

The adaptations necessary to the training of each emergency system within specific countries in South America depend on the economic and social reality of the country, the existence of a centralized pre-hospital medical service, as well as on the need to integrate public and private services, a common dichotomy in most South American countries.

In-hospital Evaluation

To optimize the treatment in patients with acute neurological emergencies, it is essential to have a minimum infrastructure of equipment and processes. In stroke, for example, important process measures are: door-to-neuroimaging time < 45 min, door-to-intravenous tPA time < 60 min, appropriate evaluation, and rapid treatment of large vessel occlusions [58–60]. Additionally, care under specialized stroke units with dedicated multidisciplinary teams is highly recommended [61, 62].

The quality of stroke care and number of stroke centers are largely variable in South America. Areas of excellence are intermingled with regions of extreme poverty depending upon socioeconomic level [63]. For example, half of the patients with stroke in rural Bolivia are not evaluated by physicians [17]. In a series in São Paulo in a private care hospital, 15% of patients were treated with recanalization therapies [64]. Conversely, in Fortaleza (Brazil), a city with 4 million people, only 1.1% of the patients with IS were treated with rt-PA between 2009 and 2010 [65]. In Argentina between 2004 and 2006, only 1% were treated with rt-PA, and no more than 5.7% were admitted to stroke units [46]. In population-based studies in Iquique, Chile, 29% of patients with first-ever stroke were not even hospitalized [13]. A retrospectively review of patients admitted with IS from a sample of seven public hospitals in Santiago (Chile) showed low adherence to evidence-based performance measures as well as a low frequency of rt-PA use [66, 67].

Examples of successful stroke networks in South America should be the basis for building new networks in different countries. Despite the sociocultural differences between South American countries, many economic similarities exist, allowing experiences to be shared [49].

Endovascular treatment was proven effective in comprehensive stroke centers with experience in treating patients with large vessel occlusion in developed nations. Generalizability to low- and middle-income countries is therefore not straightforward. In South America, an attempt to implement endovascular therapy carries some specific challenges. First, as described, there is very poor stroke awareness in the population and delays in recognition of stroke. Secondly, quality of care is extremely heterogeneous due to large economic inequalities [68–72]. Finally, the population concentrates in urban areas, but there are large areas that are clinically underserved. In Brazil, a randomized clinical trial of mechanical thrombectomy (the RESILIENT trial) is being conducted in order to evaluate the efficacy of thrombectomy when coupled with the ancillary care delivered by major public stroke centers of the country [73].

Similarly, some important requirements should be available in the hospital care of patients with SE. The initial response should be based on the Emergency Neurological Life Support (ENLS), and post-initial response, based on NCS/ESICM guidelines of SE management [74–76]. Patients should be transferred to a tertiary hospital if seizures continue, if seizures have stopped and the patient did not return to the pre-status neurological baseline, and if the underlying condition causing SE requires management that is not available at the spoke site (i.e., neurosurgical intervention such as placement of an intracranial pressure [ICP] monitor) [76, 77]. Evaluation for the etiology of SE, including investigation of infectious causes, is essential. Rapid identification and treatment of conditions like bacterial and some viral meningoencephalitis can dramatically change clinical prognosis and the risk of long-term neurological deficits.

In TBI, organized systems of care are of utmost importance. Hospitals that treat a larger volume deliver better outcomes. Prompt availability of neurosurgery teams is paramount in tertiary hospitals. Monitoring of patients with severe TBI in ICU may require high complexity; so specific centers must be developed [35, 78]. The BEST TRIP randomized trial conducted in Latin America showed that outcomes were similar between patients with TBI managed using ICP monitoring and those managed using a protocol based on imaging and clinical examination [79]. This result has led to a suggestion of a protocol approach to TBI management in the absence of ICP monitoring was published [80].

A summary of the minimum requirements for treatment of stroke, TBI, and SE in a primary/secondary or tertiary hospital is given in Table 1.

Neurocritical Care

Specialized units are known to improve clinical outcomes in patients with acute neurological diseases [81, 82]. The possibility of strict neurological monitoring,

Table 1 Suggested minimum requirements for the treatment of stroke, traumatic brain injury, and status epilepticus

	Stroke	Status epilepticus	Traumatic brain injury
Pre-hospital	Protocols available for stroke identification Triage scales Neurological evaluation Pre-notification Transport to a stroke center	Basic skills training of EMS: protect airway in the field, place intravenous access, recognize clinical presentation of convulsive status epilepticus EMS medications IV fluids (normal saline or DW 5–10% in case of hypoglycemia) Benzodiazepine (options include IV lorazepam, IM midazolam, rectal diazepam, or IV clonazepam)	Protocols available for pre-hospital assessment and treatment of traumatic head injury Protocols on spine immobilization Transport to a designated trauma center
Primary care hospital	Neuroimaging 24 × 7 Intravenous thrombolysis Neurological evaluation physically or by telemedicine Continuous measurement of performance indicators	Initial response based on ENLS Patients may be managed at community hospitals spoke if status epilepticus is aborted after the administration of emergent and urgent treatment Head CT obtained 24/7 may be read via telemedicine Routine EEG: may be read via telemedicine, consider simplified montage and head bands/caps Lumbar puncture if CNS infection suspected Urgent Control Therapy: IV antiepileptic drug (options include phenytoin, fosphenytoin, valproic acid, with phenobarbital being an alternative). IV levetiracetam or lacosamide in case of known liver failure or porphyria	Initial response based on ENLS 24/7 availability of head and body CT, including CT angiography Availability of mannitol and IV phenytoin or levetiracetam Availability of blood bank and blood product transfusion Availability of an intensive care unit with trauma capabilities
Tertiary hospital	Intravenous Thrombolysis Endovascular procedures Neurosurgery Stroke or neurocritical care unit	Additional IV antiepileptic drug: ideally levetiracetam or lacosamide as the interaction between phenytoin and valproic acid make them bad choices to use together in a patient. This additional IV AED should be added to the already given AEDs Continuous antiepileptic drug: ideally midazolam (to be titrated up to 2.9 mg/kg/hr only if needed) Spot EEG available 24/7, read over telemedicine link by expert at home Continuous EEG monitoring: Available during business hours 7 days a week Neurosurgical support: 24/7	24/7 availability of a neurosurgeon and trauma surgeon Availability of mannitol and hypertonic saline, as well as antiepileptic drugs Availability of a neurocritical care unit

AEDs antiepileptic drugs, *CNS* central nervous system, *CT* computerized tomography, *EEG* electroencephalogram, *EMS* emergency medical services, *ENLS* emergency neurological life support, *IM* intramuscular, *IV* intravenous

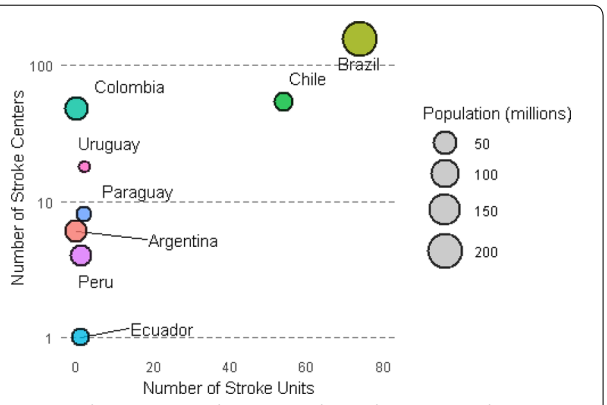

Fig. 2 Stroke centers, stroke units, and population in South American countries [12]. *No data available for Venezuela, Guyana, Suriname, and French Guiana

hemodynamic management with a focus on the brain, less frequent use of sedation, and professionals trained in neurological diseases are factors that may explain the better outcomes [82–84].

Many challenges must be faced for the proper functioning of these units in places with few resources. Bed availability, for example, can be a major problem. Another challenge is lack of formal specializations and fellowships in most countries [85, 86]. There is little epidemiological information regarding the existence of neurological critical care units (NCCUs) and their capabilities in South America. A recent survey showed a heterogeneous capability of ICUs in Latin America for the treatment of subarachnoid hemorrhage. Only 12.5% of ICU's had nurses with neurological training; 67% of the units described using a published guideline for directing treatment; 25% did not have 24-h computed tomography scan availability; and only 52% had access to transcranial Doppler monitoring [87]. Data on the number of stroke centers and stroke units are available for most countries in South America and can be used as a surrogate for the existence of units to treat at least one of the most common neurological emergencies requiring neurocritical care (Fig. 2).

The development of clinical guidelines adapted to local realities can very much contribute to the advancement of the structure of the treatment pathways of neurological emergencies in South America throughout the continuum of care. Regional infectious diseases such as neurocysticercosis and clinical complications of arboviruses such as Zika, dengue, and chikungunya should all have specific protocols for treatment and follow-up.

It is of utmost importance that low-income countries develop their own research in neurological intensive therapy, since data from developed countries cannot be completely extrapolated to low-income settings. Protocols and checklists may assist in monitoring services, especially when the professionals working in the NCCU do not have formal neurocritical care training. Recently, the NCS has made recommendations on standards of

Table 2 Strategic recommendations to improve care of patients with neurocritically ill disorders in South America

Epidemiology	• There is a need for more robust and widespread epidemiological studies to better characterize the incidence, prevalence, and etiologies of the most common disorders such as stroke, TBI, and SE. In addition, a better description of the availability of various components of the systems of care need to be made public.
Public Awareness	• Serious governmental efforts at educating the public on the basic concepts of the most common disorders and their risk factors must be undertaken. Such campaigns have to be divorced of political maneuvering and must focus on the areas of more need. Moreover, prevention campaigns ought to be instituted.
Pre-Hospital Care	• High-level governmental investment in pre-hospital management of patients with neurocritical care disorders is required. Whereas such program does not have to mimic exactly what happens in North American or European countries, some components of it should be available and adapted. For example, centralized telephone numbers for emergencies should be installed in every country and every region for the public to access. Because of the vastness and the difference in topography, each country or region will have to adapt methodologies or technologies that are best suited to each area.
In-patient care	• In-patient care should be directed at centralizing the care of the most severe patients for all disorders, including other medical emergencies. Patients with severe TBI, acute IS requiring thrombolysis or endovascular therapy, hemorrhagic strokes, and SE should be triaged at the pre-hospital level and emergency departments of local hospitals or medical centers and after initial stabilization transferred to comprehensive centers capable of handling these complex conditions. There should be one of these comprehensive or high-level hospital for every 1 million inhabitants. Care should be centralized to these specialized centers.
Rehabilitation	• Rehabilitation centers must be constructed to transfer patients from the comprehensive center to continue with their next phase of management. Such centers can be built within or adjacent to the comprehensive hospitals or stand alone depending of the economic plan laid out by each national or regional government. At a minimum such centers should have physical, occupational, and speech therapies, rehabilitation gymnasium, and aquatherapy capabilities.
Education of Healthcare Professionals	• Government officials should work in conjunction with institutions of higher education, both public and private, to ensure that educational opportunities are developed for individuals to become healthcare professionals who can fulfill all the required obligations that are needed to provide care for neurocritically-ill patients.

IS ischemic stroke, *SE* status epilepticus, *TBI* traumatic brain injury

NCCUs, designating units into levels depending on capabilities to handle complex patients. Such classification can be extremely useful in low-resource countries as well, helping structure systems of care and providing a framework to coordinate resources [88]. The ENLS has been translated into Spanish and is a critical tool for training professionals in intensive care [74].

Recommendations

South America is a vast and very diverse subcontinent. In addition, educational attainment, wealth distribution, and access to healthcare are unequal. However, we feel that there are specific areas to target to improve care of patients with neurocritically ill disorders, as summarized in Table 2.

Conclusions

Many challenges need to be overcome for the implementation of systems of care for the treatment of neuroemergencies in South America. The different socioeconomic and cultural realities do not allow a single solution to be used for all countries. However, experiences that have already worked in certain settings must be shared and implemented with the necessary adaptations [89]. The creation of structures capable of assisting patients with the various neurological emergencies in a centralized way is more effective than the development of systems for specific diseases. Several conditions that have time to evaluation as a determinant of outcome can be grouped in the design of lines of care. Finally, the collaborative work of healthcare professionals and managers is essential so that the epidemiological knowledge can be appropriately transformed into fair and effective public health policies.

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Authors' Contribution

GSS and JIS designed, directed this review and drafted the manuscript; NJM, JHM, SOG, JC and PV participated in the conceptual framing of the study and revision of the manuscript.

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Conflict of interest

Dr. Silva reports personal fees from Boehringer Ingelheim, personal fees from BARD, personal fees from Pfizer, Grants from Brazilian Ministry of Health, outside the submitted work. Dr. Maldonado has nothing to disclose. Dr. Mejia-Mantilla has nothing to disclose. Dr. Ortega receives Grants from Siemens, Society of vascular and Interventional Neurology. He is the site PI for 3 endovascular stroke trial at the University of Iowa including TESLA, SEGA and SELECT 2. Dr. Claassen reports Grants from Charles A. Dana Foundation , Grants from James S. McDonnell Foundation, from NIH: The Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial, Grants from NIH: I-SPOT, Grants from NIH: Established Status Epilepticus Treatment Trial (ESETT), Grants from Bard: Intrepid, Grants from NIH: Futility Study of Deferoxamine Mesylate in Intracerebral Hemorrhage (I-DEF), Grants from NIH / NLM: BIGDATA: Causal Inference in Large-Scale Time Series with Rare and Latent Events, Grants from NIH: Rhapsody (ZZ-3K3A-201), other from iCE Neurosystems, outside the submitted work. Dr. Varelas reports Grants from Marinus, outside the submitted work. Dr. Suarez reports non-financial support and other from Neurocritical Care Society (President of the Neurocritical Care Society), non-financial support and other from Stroke Journal (member of the Editorial Board of Stroke), non-financial support and other from BARD (Chair of the DSMB for the INTREPID Study), outside the submitted work.

Ethical Approval/Informed Consent

No ethical approval is required for this type of study.

Appendix

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