Updates in Neurocritical Care

Lead Guest Editor: Dimitrios Karakitsos
Guest Editors: Christos Lazaridis and Laith Altaweel
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Caring for acutely and critically ill neurological and neurosurgical patients comprises the focus of the specialty of neurocritical care. It should be recognized that in reality, the care of such patients requires the expertise and involvement of a number of specialists including intensivists, neurologists, neurosurgeons, anesthesiologists, and specialized nurses. Although it is not only about “saving brain,” admittedly successful neurocritical care is care that salvages injured brain tissue and enhances the prospects of neurologic recovery. Hereby, we briefly mention recent clinical updates in neurocritical care; several of them are further and thoroughly discussed in the manuscript collection of this volume. The areas to be selectively highlighted in this short piece include the following: (a) management of large vessel occlusion (LVO) ischemic stroke, (b) global strategies for brain monitoring and protection after cardiac arrest and during extracorporeal cardiorespiratory support, (c) the approach towards monitoring and managing severe traumatic brain injury, and (d) minimally invasive neurosurgical approaches for intracerebral and ventricular hemorrhages.

Until recently, intravenous tPA was the only evidence-based treatment for acute ischemic stroke. More recently however, a number of high-quality multinational randomized controlled trials (RCTs) have proven that for selected patients presenting with LVO up to 24 hours from symptom onset, endovascular recanalization improves functional neurologic outcome, when compared to medical therapy. Six RCTs have independently demonstrated clinical benefit of stent-retriever thrombectomy when performed within 6 hours from stroke onset (REVASCAT, SWIFT PRIME, EXTEND-IA, ESCAPE, THRACE, and MR CLEAN). THRACE and MR CLEAN independently demonstrated benefit based solely on noncontrast CT and demonstration of LVO; consequently, these are the recommended imaging eligibility criteria. Two other trials have provided evidence for extending the window even further based on additional perfusion imaging and demonstration of a favorable ratio between salvageable brain and infarcted core (DEFUSE 3: 6–16 hours; DAWN: 6–24 hours) [1]. Based on the aforementioned literature, there is a clear imperative evaluating patients presenting with an NIHSS >5 for LVO, and depending on timing size of ischemic infarct core, and penumbra. Challenges that remain relate to the availability of experts and organization of care towards centers that can offer expedited, specialized clinical and radiographic assessment followed by prompt intervention for eligible patients. Additional questions for future research include extending the time window further, or abandoning all together “time from onset” as an eligibility criterion and replacing it with imaging eligibility criteria.

Outcomes of patients who survive cardiac arrest are critically dependent on the degree of global brain injury sustained. The earlier days of enthusiastic endorsement of therapeutic hypothermia with the goal of 32–34°C, based on the 2002 RCTs by Bernard et al. and the HACA study group, have been tempered by the more recent, and larger, Nielsen et al.’s study [2–4]. The latter study found that 33 versus 36°C were equivalent targets in terms of mortality and neurologic outcomes for patients with out-of-hospital cardiac arrest. A detailed comparison of these studies is out of scope, but it
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is worth noting that the Nielsen study had a remarkably high rate of expedient bystander application of CPR (an unrealistic situation in most parts outside of Scandinavia) and that what Nielsen et al. compared were two different strategies of targeted temperature management (TTM) rather than what the earlier RCTs tested, mild hypothermia versus no temperature control. As a result, there is an ongoing debate on what the most appropriate target may be within the 32–36°C, and if there are patient characteristics or monitoring modalities (or biomarkers) that could provide patient-specific targets. Nevertheless, what should be uncontroversial is that TTM is the indicated brain protective strategy for 24–48 hours after cardiac arrest and that temperatures above 36–37°C are to be prevented with maintenance of normothermia thereafter. Global anoxic-ischemic brain injury in addition to more focal ischemic and hemorrhagic strokes has been observed, in nontrivial rates, in patients subjected to extracorporeal membrane oxygenation (ECMO). In view of the increasing use of ECMO modalities for the management of various causes of respiratory and/or cardiac failure, it is important that we consider methods to prevent, monitor, and potentially ameliorate brain injury in this setting. Unfortunately, current tools for noninvasive monitoring of cerebral blood flow (CBF), brain oxygenation, and energy dynamics are not advanced enough to be informative in optimizing patient-specific brain physiology. More study is clearly required while use of transcranial Doppler (TCD) and near-infrared spectroscopy (NIRS) has been reported with interest. Interestingly, the ability to monitor the status of CBF autoregulation after cardiac arrest and during ECMO may shed light to pathophysiologic mechanisms.

The value of invasive, multimodality monitoring is another passionately debated topic when it comes to managing patients with severe traumatic brain injury. It seems that there are two camps of thought; one sees great potential in obtaining compartmental pressures, tissue oxygenation, and metabolic data with a goal of tailoring interventions to the individual patient and according to physiologic principles of oxygen delivery, demand, and utilization. The second camp maintains skepticism towards the aforementioned approach arguing on the basis of a lack of hard data for improved patient outcomes in the face of potential adverse effects, resource utilization, and cost. This debate has not been helped by recent RCTs addressing specific interventions against refractory intracranial hypertension. The Eurotherm 32-35 trial established that hypothermia should not be used early (i.e., before other stage 2 treatments such as osmotherapy) in patients with diffuse TBI, despite beneficial effects on intracranial pressure (ICP) control [5]. The clinical outcomes of patients in the intervention arm of this study were worse than those of control patients. More recently, the RESCUEicp trial sought to establish the role of decompressive craniectomy (DC) for treating refractory ICP [6]. This trial took about 10 years to complete, involving 52 centers in 20 countries to recruit 408 patients. While there was a substantial mortality benefit with surgical decompression (for every 100 patients treated surgically versus medically there were 22 more survivors), it came at the expense of increased rates of moderate and severe disability when compared to the medical management cohort. Such results require careful, engaged, and transparent conversations with families during shared decision-making to avoid cognitive biases that may derive goals of care towards either an overly pessimistic or nihilistic stance or, on the contrary, be influenced by unrealistic optimistic biases. Finally, a promising step was made in favor of the monitoring camp by the completion of the BOOST phase II trial demonstrating that adding brain tissue oxygenation (PbtO2) monitoring to standard ICP/CPP resulted to less cerebral hypoxia [7]. The forthcoming phase III trial will determine whether PbtO2-targeted therapy will improve long-term neurologic outcomes.

Ischemic stroke, traumatic brain injury, neuro-monitoring, and global cerebral protection are among the conditions that the field can claim some developments and successes. The same cannot be said for nontraumatic, non-coagulopathy-related intracerebral and/or intraventricular hemorrhages (ICH/IVH). These types of hemorrhages remain the most debilitating type of stroke with no specific treatments that can alter their course for the better. The promise of finding the optimal blood pressure target remains elusive with more aggressive control to possibly confer modest benefits in terms of hematoma expansion but no proof that it improves patient outcomes. Surgery trials have also failed in this regard with the possible exception of superficial lobar hemorrhage cases. Hope has been placed on minimally invasive approaches where a less morbid way of evacuating intraparenchymal or clearing intraventricular blood may eventually confer either clinical outcome benefits or secondary benefits such as faster resolution of hydrocephalus or a decreased need for shunt placement. The relevant studies are the recently completed CLEAR IVH III and the ongoing MISTIE-III and ENRICH trials. CLEAR-III tested patients with ICH <30 cc and large IVH causing hydrocephalus for improved clinical outcomes when given low-dose rtPA via an external ventricular drain versus placebo. Despite a reduction in mortality, no functional outcome benefit was seen in the intervention arm [8]. MISTIE-III seeks to demonstrate that minimally invasive surgery (MIS) plus rtPA for intraparenchymal hematoma evacuation, and for three days, improves functional outcome by a 12% increase in the modified Rankin Scale (mRS) score 0–3 compared to medically treated subjects assessed at 180 days; it is underway involving 90 centers in the US, Europe, Israel, China, and Australia ([ClinicalTrials.gov Identifier: NCT01827046]). Finally, ENRICH is a multicenter, randomized, adaptive clinical trial comparing standard medical management to early surgical hematoma evacuation (less than 24 hours) using minimally invasive parafascicular surgery (MIPS) in the treatment of intracerebral hemorrhage ([ClinicalTrials.gov Identifier: NCT02880878]).

The science and clinical medicine of “saving brain” are still at an early stage. Notwithstanding, there have recently been significant developments for a number of conditions. We have highlighted a few of these without an intention to be exhaustive; the manuscripts in this special issue on
updates in neurocritical care cover some of these and other relevant topics in depth.

Christos Lazaridis  
Laith Altaweel  
Dimitrios Karakitsos

References


Research Article

Improved Outcomes following the Establishment of a Neurocritical Care Unit in Saudi Arabia

Ibrahim Soliman (1), Waleed Tharwat Aletreby (1), Fahad Faqihi, Nasir Nasim Mahmood, Omar E. Ramadan, Ahmad Fouad Mady, Babar Kahlon, Abdulrahman Alharthy, Peter Brindley, and Dimitrios Karakitsos

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Background. Dedicated neurocritical care units have dramatically improved the management and outcome following brain injury worldwide. Aim. This is the first study in the Middle East to evaluate the clinical impact of a neurocritical care unit (NCCU) launched within the diverse clinical setting of a polyvalent intensive care unit (ICU). Design and Methods. A retrospective before and after cohort study comparing the outcomes of neurologically injured patients. Group one met criteria for NCCU admission but were admitted to the general ICU as the NCCU was not yet operational (group 1). Group two were subsequently admitted thereafter to the NCCU once it had opened (group 2). The primary outcome was all-cause ICU and hospital mortality. Secondary outcomes were ICU length of stay (LOS), predictors of ICU and hospital discharge, ICU discharge Glasgow Coma Scale (GCS), frequency of tracheostomies, ICP monitoring, and operative interventions. Results. Admission to NCCU was a significant predictor of increased hospital discharge with an odds ratio of 2.3 (95% CI: 1.3–4.1; p = 0.005). Group 2 (n = 208 patients) compared to Group 1 (n = 364 patients) had a significantly lower ICU LOS (15 versus 21.4 days). Group 2 also had lower ICU and hospital mortality rates (5.3% versus 10.2% and 9.1% versus 19.5%, respectively; all p < 0.05). Group 2 patients had higher discharge GCS and underwent fewer tracheostomies but more interventional procedures (all p < 0.05). Conclusion. Admission to NCCU, within a polyvalent Middle Eastern ICU, was associated with significantly decreased mortality and increased hospital discharge.

1. Introduction

Neurocritical care (NCC) is an expanding subspecialty within critical care medicine while NCC board certification has been offered since 2007 [1, 2]. NCC units (NCCUs) have become more widespread and have typically evolved from larger multidisciplinary intensive care units (ICUs) into freestanding units. The goal of the NCCU is to optimize care for brain- and spine-injured patients, who can be vulnerable to physiological and biochemical perturbations [3, 4]. Accordingly, a dedicated NCCU—which includes specialized team, protocols, monitoring, imaging, and expertise—may result in less secondary injury and better outcomes [5–7].

There is growing evidence regarding the benefits associated with NCCU-based care for brain-injured patients. These include shorter hospital length of stay and/or better neurological and functional outcomes for all comers [8–12]. Better outcomes have also been reported for specific disease states: cerebral hemorrhage (ICH) [13], acute ischemic strokes [14], subarachnoid hemorrhage (SAH), and traumatic spinal
cord and brain injuries [15]. A dedicated NCCU might also be associated with more appropriate resource utilization [14], better adherence to protocols [16], better chart documentation [11], and readmission rates [17]. If so then objective data are important as it could provide justification and leverage for institutions eager to start their own NCCU [18]. Thus far, the vast majority of the NCCU studies have come from North America and Europe, whereas there are scarce data from other nations. This is the first study in the Middle East that evaluated the impact of a newly launched NCCU on the outcome of neurologically injured patients, within the largest polyvalent ICU department in the Middle East.

2. Patients and Methods

This study was part of a NCCU performance audit and was approved by the Total Quality Management (TQM) of King Saud Medical City (KSMC). KSMC is the largest ministry of health tertiary referral hospital in Riyadh, Kingdom of Saudi Arabia. The polyvalent KSMC ICU department is the largest in the Middle East (130 operational beds). It is a closed ICU operated 24/7 by consultant intensivists, with an in-house critical care fellow or resident at all times, bar ing a patient: physician ratio of 12:1 and patient: nurse ratio of 1:1. In this retrospective cohort study, we compared two time periods: a period of one year prior to the NCCU launching (January 1st to December 31st, 2016) versus a period of nine months after the NCCU was fully operational (January 1st to September 30th, 2017). Patients from the former time period were designated as Group 1, while patients from the latter period were designated Group 2. The latter group included in all neurologically injured patients admitted to the NCCU. In contrast, Group 1 included all neurologically injured patients admitted to the general ICU (since NCCU was not operating at that time) but who fulfilled NCCU admission criteria. These NCCU admission criteria, also served as the study’s inclusion criteria, were as follows:

1. Need for intracranial pressure (ICP) monitoring
2. Need for advanced neuromonitoring
3. Need for frequent clinical monitoring due to concerns of neurologic deterioration (including spinal injury)
4. Subarachnoid hemorrhage patients in the vasospasm time window (day 1-14 post-SAH)
5. Complex neurosurgery cases immediately after procedure (as determined by the surgeon)
6. Acute stroke after thrombolytic therapy as well as neuroradiological and/or surgical interventions.

Exclusion criteria applied to both groups were as follows: age ≤18 years old, patients admitted for brain death declaration or in need of solely palliative care, and patients with Do Not Resuscitate (DNR) order. We also excluded patients isolated for infectious conditions (i.e., bacterial meningitis, viral infections, tuberculosis etc.) from Group 1, as the NCCU has no isolation rooms at present, and Group 2 included no such patients. The primary outcome was all-cause mortality and hospital all-cause mortality. Secondary outcomes were ICU length of stay (LOS), identify predictors of ICU and hospital discharge, ICU discharge Glasgow Coma Scale (GCS), as well as the frequency of tracheostomies, ICP monitoring, and operative neurosurgical interventions such as ventriculostomies, craniotomies for hematoma evacuation or removal of contusion, and last tier decompressive craniectomy in TBI and malignant stroke [19, 20]. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ICU Ethics Committee.

3. Statistical Analysis

Demographic and clinical data were collected retrospectively for all patients from the departmental electronic database and included age, gender, acute physiology, and chronic health evaluation (APACHE) four score and admission diagnosis. Also, we retrieved data of operative interventions in the ICU, ICU LOS, discharge GCS and airway status as well as ICU and hospital outcome. All discrete variables were reported as number (%) and compared with the chi-square test. Continuous variables were reported as mean ± SD and compared with the t-test, accounting for unequal sample sizes (Welch’s t-test) [21]. All tests were two-sided and considered to be statistically significant when p value was <0.05.

In a logistic regression analysis to identify predictors of ICU and hospital discharge [22], we used ICU or hospital discharge as a binary outcome measure and admission to NCCU as a predictor adjusted for age, gender, ICU LOS, and APACHE 4 score, whether the patient had experienced trauma or not, and whether an operative intervention occurred or not. The prediction models used enter method with enter p value of <0.1 and tested for goodness of fit with Hosmer–Lemeshow test, the calibration of each model was evaluated by the area under the curve (AUC) of receiver operator characteristics (ROC) curve, accepted as good if the AUC ≥0.7. All statistical tests were carried out by SPSS© version 21 for Windows (SPSS Inc. Chicago, Illinois, USA).

4. Results

In 2016, a total of 2442 patients were admitted to the polyvalent ICU. Of those, 364 patients fulfilled inclusion criteria for NCCU admission. Since no NCCU yet existed, they were admitted in the polyvalent ICU and represented Group 1 in our study. In 2017, 1765 patients were admitted to the ICU in 9 months, with 208 patients admitted to the NCCU and therefore designated as Group 2. The comparative demographics of Groups 1 and 2 are presented in Table 1.

ICU mortality in Group 2 (5.3%) was significantly lower than Group 1 (10.2%) (p = 0.034), likewise, hospital mortality was significantly lower in Group 2 compared to Group 1 (9.1% versus 19.5%, p = 0.001), (Table 2). The most common causes of death in Group 1 in the ICU were acute respiratory distress syndrome (ARDS) 43%, followed by brain herniation 30%, and then sepsis and septic shock 27%, whereas Group 2 ICU mortality was mostly due to ARDS 45%, sepsis and septic shock 36%, and brain herniation 19%. Withdrawal of care, however, was statistically similar in both
groups although lower in Group 2 (13% in Group 1 and 8% in Group 2, \(p < 0.09\)). Sepsis and septic shock was the most common cause of hospital mortality in both groups (56% in Group 1 and 55% in Group 2). Since the majority of patients in both groups were trauma patients with high severity scores, 62% of Group 1 patients were mechanically ventilated as compared to 61% in Group 2 (\(p = 0.9\); 61.5% of Group 1 patients required hemodynamic support (\(>0.05\) mcg/kg/min noradrenaline) to maintain the BP targets of perfusion of the acutely injured brain and spinal cord, while 70.2% of Group 2 patients required hemodynamic support (\(p = 0.04\)); the rate of renal failure requiring hemodialysis at least once was not different between groups (31% in Group 1 versus 27% in Group 2, \(p = 0.4\)). Analysis of secondary outcomes revealed decreased ICU LOS in Group 2 compared to Group 1 (\(p < 0.001\); Table 2). Group 2 patients exhibited a higher ICU discharge GCS, underwent fewer tracheostomies but had more ICP monitoring and operative neurosurgical interventions compared to Group 1 patients (all \(p < 0.05\)).

Two multivariate logistic regression models were fitted to evaluate independent predictors of ICU and/or hospital discharge among NCCU patients (evaluated for age, APACHE 4 score, gender, NCCU admission, presence of trauma, LOS, and operative intervention; Table 3). The models revealed that NCCU admission was not significantly correlated to ICU discharge (OR = 1.5; 95% CI: 0.71–3.3; \(p = 0.285\)) but was a significant predictor for hospital discharge with an OR of 2.3 (95% CI: 1.3–4.1; \(p = 0.005\)). Other significant predictors in both models were age and ICU LOS.

Both models were well fitted as \(p\) values of the Hosmer–Lemeshow test were 0.28 and 0.67 in the multivariate logistic regression analysis, respectively. Both models were also well calibrated (evaluated the degree of correspondence between the estimated probabilities of mortality produced by a model and the actual mortality) as evident by the AUC of the logistic regression model for ICU discharge of 0.78 (95% CI: 0.71–0.84) and that of the hospital discharge model of 0.74 (95% CI: 0.68–0.8) (Figure 1).

### Table 1: Study demographics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 364)</th>
<th>Group 2 (n = 208)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean (\pm) SD)</td>
<td>39.5 (\pm) 18.1</td>
<td>40.3 (\pm) 17.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Males ((n) (%))</td>
<td>301 (82.7%)</td>
<td>165 (79.3%)</td>
<td>0.3</td>
</tr>
<tr>
<td>APACHE 4 (mean (\pm) SD)</td>
<td>67.9 (\pm) 22.2</td>
<td>70.9 (\pm) 22.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma ((n) (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Polytetra</td>
<td>257/364 (70.6%)</td>
<td>145/208 (69.7%)</td>
<td>0.9</td>
</tr>
<tr>
<td>With TBI</td>
<td>129/257 (50.2%)</td>
<td>74/145 (51%)</td>
<td>0.96</td>
</tr>
<tr>
<td>With spinal cord injury</td>
<td>104/129 (80.6%)</td>
<td>59/74 (79.7%)</td>
<td>0.97</td>
</tr>
<tr>
<td>With spinal cord injury</td>
<td>25/129 (19.4%)</td>
<td>15/74 (20.3%)</td>
<td>0.97</td>
</tr>
<tr>
<td>(ii) Isolated head injury</td>
<td>128/257 (49.8%)</td>
<td>71/145 (49%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Brain contusion</td>
<td>32/128 (25%)</td>
<td>23/71 (32.4%)</td>
<td>0.3</td>
</tr>
<tr>
<td>EDH</td>
<td>11/128 (8.6%)</td>
<td>7/71 (9.9%)</td>
<td>0.96</td>
</tr>
<tr>
<td>SDH</td>
<td>6/128 (4.7%)</td>
<td>4/71 (5.6%)</td>
<td>0.95</td>
</tr>
<tr>
<td>SAH</td>
<td>15/128 (11.7%)</td>
<td>11/71 (15.5%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diffuse brain injury</td>
<td>64/128 (50%)</td>
<td>34/71 (47.9%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Nontraumatic ((n) (%))</td>
<td>107/364 (29.4%)</td>
<td>63/208 (30.3%)</td>
<td>0.89</td>
</tr>
<tr>
<td>ICH</td>
<td>17/107 (15.9%)</td>
<td>11/63 (17.5%)</td>
<td>0.95</td>
</tr>
<tr>
<td>SDH</td>
<td>4/107 (3.7%)</td>
<td>2/63 (3.2%)</td>
<td>0.8</td>
</tr>
<tr>
<td>SAH</td>
<td>3/107 (2.8%)</td>
<td>2/63 (3.2%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>44/107 (41.1%)</td>
<td>19/63 (30.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>8/107 (7.5%)</td>
<td>7/63 (11.1%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Others</td>
<td>31/107 (29%)</td>
<td>22/63 (34.9%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

NCCU = neurocritical care unit; SD = standard deviation; \(n\) = number; APACHE = acute physiology and chronic health evaluation; EDH = extradural hemorrhage; SDH = subdural hemorrhage; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; * other neurological diagnoses included status epilepticus, encephalopathy, Guillain–Barré syndrome, and transverse myelitis.

### Table 2: Primary and secondary outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality ((n) (%))</td>
<td>37 (10.2%)</td>
<td>11 (5.3%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Hospital mortality ((n) (%))</td>
<td>71 (19.5%)</td>
<td>19 (9.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU LOS (days; mean (\pm) SD)</td>
<td>21.4 (\pm) 18.5</td>
<td>15 (\pm) 12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge GCS (mean (\pm) SD)</td>
<td>11.5 (\pm) 2.6</td>
<td>12.5 (\pm) 2.5</td>
<td>0.025</td>
</tr>
<tr>
<td>Tracheostomy ((n) (%))</td>
<td>52 (14.3%)</td>
<td>28 (13.5%)</td>
<td>0.006</td>
</tr>
<tr>
<td>ICP monitoring, ((n) (%))</td>
<td>87 (24%)</td>
<td>112 (33.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurosurgical interventions ((n) (%))</td>
<td>34 (9.3%)</td>
<td>41 (19.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NCCU = neurocritical care unit; ICU = intensive care unit; LOS = length of stay; GCS = Glasgow Coma Scale; ICP = intracranial pressure.
In this retrospective before and after cohort study, we have shown that establishment of a dedicated NCCU was associated with an increase in meaningful clinical outcomes for neurologically injured patients.

The mortality rate (5.3%) in the NCCU was significantly lower compared to the general ICU (10.2%; \(p = 0.034\)). This mirrors work by Jeong et al. [8]. Other larger studies have reported overall higher rates of NCCU mortality, such as 18% by Broessner et al. [23] \((n = 1000)\). Our hospital mortality rate was significantly reduced from 19.5% in general ICU to 9.1% \((p = 0.001)\) in NCCU. This is also in accordance with findings of Varelas et al. [24], although other studies reported insignificant difference [25]. Adding to the significance of the reduced ICU and hospital mortality rates is the fact that, throughout the study period, there were no changes in our ICU’s discharge policy or DNR policy. Furthermore, the general management of critically ill patients was consistent throughout the study period; however, the addition of new standards of management in the form of NCCU specific protocols to maintain better brain and spinal cord perfusion during acute injury guided by more ICP/CPP monitoring (evident by the significantly different rates of hemodynamic support requirement) may explain the difference in outcome objectively as adherence to guidelines was translated to more monitoring which guided us to maintain more perfusion of CNS by using more hemodynamic support in Group 2.

ICU LOS was significantly shorter for patients hospitalized in the NCCU compared to the general ICU \((p < 0.001)\), although there were no changes in the setting or discharge policies of our institute nor was a step-down unit.

<table>
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<th>Table 3: Predictors for ICU/hospital discharge.</th>
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<td>Predictors</td>
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<td><strong>ICU discharge</strong></td>
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<td>APACHE 4 score</td>
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<td>ICU LOS (days)</td>
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<td>Invasive procedures (%)</td>
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<td><strong>Hospital discharge</strong></td>
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<td>Presence of trauma</td>
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OR = odds ratio; CI = confidence interval; ICU = intensive care unit; NCCU = neurocritical care unit; APACHE = acute physiology and chronic health evaluation; LOS = length of stay.

**Figure 1**: ROC curve of logistic regression models. (a) ICU discharge; (b) hospital discharge.
or new rehabilitation services established throughout the study period. This also duplicates what others have reported [26, 27]. Notably, we did have a relatively high ICU LOS, which we believe can be largely attributed to the lack of a step-down unit in our institution. Notably, Kurtz et al. [10] reported a longer stay in NCCU, but this may reflect the binary model analysis used in his study, namely, patients were separated in two groups, those admitted less than or more than 10 days.

We found NCCU patients to have a better GCS at discharge. Importantly, many studies [8, 25] evaluate the Glasgow Outcome Scale (GOS) or modified Rankin Scale. Unfortunately, we lacked proper GOS data before the launching of NCCU. We accept this as a study limitation that was remedied by our new NCCU electronic medical records archive. Regardless, GCS at ICU discharge was significantly higher in the NCCU Group 2 compared to Group 1 \( (p = 0.025) \). Also, the rate of tracheostomies was significantly lower in the NCCU Group 2 compared to Group 1 \( (p = 0.006) \). While speculative, this could be partially attributed to the increased GCS, to better overall outcome, or to an evolving strategy towards less tracheostomies. In contrast, Kurtz et al. [10] reported that more NCCU patients (35%) were receiving tracheostomy. However, we are unsure about their airway management strategy and intend to pursue this important question now that we have an established NCCU database. Despite the discrepant tracheostomy rates, our data are otherwise in agreement with Kurtz et al. [10] NCCU patients underwent closer neuro-monitoring for secondary brain injuries clinically and through ICP insertions (parenchymal or ventricular) according to unit-specific protocols and guidelines for monitoring of different types of neurologic emergencies; hence, those protocols were applied after intensive educational and training activities for bedside nurses and physicians aiming for prevention and early detection and management of secondary injuries mainly intracranial hypertension [8, 10, 22, 23]. The management included more neurosurgical interventions as craniotomies and decompressive craniectomies for refractory intracranial hypertension cases. However, the aforementioned finding does raise the question of whether more neurointerventions could be attributed to more intense neuromonitoring.

Multivariate models, when adjusted for age, gender, APACHE 4 score, LOS, trauma, and postoperative status, revealed that while NCCU admission was not an independent predictor of ICU discharge \( (OR = 1.5; \ 95\%\ CI: 0.71–3.3;\ \ p = 0.285) \), it was a significant predictor of hospital discharge \( (OR = 2.3; \ 95\%\ CI \ of \ OR: 1.3–4.1; \ p = 0.005) \). This is in accordance with other studies from other jurisdictions. Diringer and Edwards [13] reported that hospitalization outside of NCCU is associated with increased odds of in-hospital death \( (OR 3.4; \ 95\%\ CI: 1.65–7.6) \). Similarly, Suarez et al. [17] showed that the presence of NCCU team is an independent predictor of decreased mortality \( (OR 0.7; \ 95\%\ CI: 0.5–1) \).

5.1. Limitations. This study has several limitations including its retrospective single-center design and the inherent weaknesses of any before and after analysis, as well as the aforementioned absence of GOS data or other neurological outcome measures such as modified Rankin Scale (mRS), as well as data of discharge disposition. With that said, we are excited to have shown such a positive impact associated with the establishment of a NCCU within a polyvalent ICU setting. Notably, our multivariate logistic regression analysis was tailored to evaluate general prognostic factors but did not include factors specific for particular neurological conditions such as ICH volume/score, SAH grade, and ischemic stroke type/size.

Finally, the age and gender distribution—although similar in both groups—revealed a preponderance of males with a mean age of about 40 years, that is consistent with previous studies on road traffic accident victims in Saudi Arabia [28] who constitute the majority of our patients, a finding that is although typical of the milieu in Saudi Arabia may affect the generalizability of our findings. Further larger prospective multicenter studies are clearly required to confirm and establish the generalizability of our findings.

6. Conclusion

Creation of a dedicated NCCU was associated with a significant reduction in ICU and hospital mortality rates, as well as ICU LOS. Admission to NCCU was an independent predictor of discharge from the hospital. NCCU-discharged brain-injured patients exhibited higher GCS and required more frequently invasive neuromonitoring and other interventional procedures with the notable exemption of performed tracheostomies.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors’ Contributions

Ibrahim Soliman helped to form the conceptual framework for this article and to conduct the literature search, participated in interpretation of data, and shared responsibility for the tables. Waleed Tharwat Aletreby helped to form the conceptual framework for this article, to conduct the literature search, and performed the statistical analysis. Fahad Faqhi, Nasir Nasim Mahmood, Omar E. Ramadan, and Ahmad Fouad Mady participated in the literature search, data collection, and interpretation. Babar Kahlon, Abdulrahman Alharthy, and Peter Brindley helped in quality control and statistical analysis. Dimitrios Karakitsos conducted critical revision of the manuscript and supervised the study. All authors contributed to the drafting, revising, and approval of the final manuscript.

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References


Review Article

Reversal Strategies for Intracranial Hemorrhage Related to Direct Oral Anticoagulant Medications

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1. Introduction

Intracerebral hemorrhage (ICH) is a nontraumatic brain parenchymal hemorrhage, a stroke subtype, that may extend into the ventricular system or into the subarachnoid space [1]. Other types of intracranial hemorrhages are epidural, subdural, and subarachnoid hemorrhage, most commonly caused by trauma.

The annual incidence of ICH is 16 to 33 cases per 100,000 general population [2]. In 2010, there were an estimated 5.3 million cases globally, with more than 3.0 million deaths [3]. Despite the relatively low incidence, ICH is responsible for the majority of the stroke mortality, with case-fatality rate ranging from 35% at 7 days to 59% at one year, with half of the fatalities occurring in the first 48 hours of onset [4]. ICH survivors are usually left with severe disability, and only about 40% of them achieve partial functional independence about a year later [1, 5].

Though hypertension and cerebral amyloid angiopathy contribute to the vast majority of ICH incidence, in recent times, the anticoagulant therapy has been recognized as a small but significant avoidable cause of ICH. Amongst the anticoagulant medications, vitamin K antagonists (VKAs), such as warfarin, as well as other VKAs, have been traditionally considered the principle offenders. Historically in 1938, 3,3′-methylenebis-(4-hydroxycoumarin), a congener of warfarin, was first discovered in spoiled sweet clover ingested by Wisconsin cows. Warfarin was then used as a rodenticide, with later use in human cases, including President Eisenhower as an anticoagulant in the 1950s [6]. However, recently warfarin has been superseded by the newer medications, collectively called direct oral anticoagulants (DOACs), approved for nonvalvular atrial fibrillation because of its efficacy and improved side effect profile regarding intracerebral bleeding.

DOACs fall into 2 categories—factor IIa (thrombin) inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban). Direct thrombin inhibitor, hirudin, was first isolated from leech saliva, whereas factor Xa inhibitor, TIX-5, was first discovered from tick
The first medication of the DOAC group to be approved by the United States Food and Drug Administration (FDA) was dabigatran etexilate (Pradaxa) (Boehringer Ingelheim Pharmaceuticals, Inc.) in October 2010, and this is a direct thrombin inhibitor. This was quickly followed by rivaroxaban (Xarelto) FDA approval in July 2011 (Janssen Pharmaceuticals, Inc.) and then by apixaban (Eliquis) in December 2012 (Bristol-Myers Squibb Company and Pfizer Inc.). Relatively recently, edoxaban (Savaysa) by Daiichi Sankyo, Japan, has been FDA-approved in January 2015. Another DOAC called betrixaban (Bevyxxa, Portola Pharmaceuticals, Inc. California, USA) got FDA approval in June 2017 [8] (Figure 1). The DOACs which are either Xa inhibitors or direct thrombin inhibitors are oral agents. Unlike dabigatran, a direct thrombin inhibitor, at present, there is no reversal agent for the Xa inhibitors.

This new category of drugs, that is, DOACs, provides many advantages over VKAs. With warfarin, the disadvantages are as follows: wide array of pharmacokinetic variability, the multiple drug-drug interactions, and the need for restrictions on diet and alcohol consumption, and consequently the need for frequent blood monitoring of INR, a normalized ratio of prothrombin time, which measures the narrow therapeutic window of warfarin’s efficacy. It has been found that warfarin stays within the therapeutic range rarely above 65% of the duration of the therapy [9].

DOACs have been found to have about 50% lower chances of ICH than warfarin, with a lower incidence of hemorrhage in all other major bleeding sites with the only exception being the gastrointestinal (GI) tract. Their convenient fixed dosing, rapid onset of action, short half-lives, more predictable pharmacokinetics, and relative lack of drug and food interactions make them an attractive alternative to warfarin and other VKAs. Most current guidelines in USA, Canada, and Europe now prefer DOACs over the VKAs for stroke prevention in nonvalvular atrial fibrillation (AF) and venous thromboembolic (VTE) treatment and prophylaxis in patients without active cancer. Current DOACs (except edoxaban and betrixaban) are also approved for thromboprophylaxis after elective hip or knee surgery [10]. With all these advantages, not surprisingly, the use of DOACs has increased, particularly in the United States and Canada [11]. With increasing number of DOAC prescriptions, certain concerns have also been raised about their use, namely, higher drug costs, lack of a specific reversal agent, lack of available laboratory monitoring of the level of anticoagulation provided, and their use in patients with renal dysfunction. Therefore, physicians are now encountering increasing number of patients with hemorrhages, including
the life-threatening ICH, associated with the use of DOACs (Table 1) [12].

1.1. Intracranial Hemorrhage (ICH) with the Use of DOACs. Incidence of major bleeding with the use of DOACs is about 3-4% of the patients per year [16]. ICHs comprise about 13% of all major bleeds in all DOAC-treated patients, with annual rates ranging from 8 to 16%, whereas gastrointestinal (GI) hemorrhage constitutes above 50% of all major bleeding events [17]. The unusually high prevalence of GI hemorrhage with DOACs is thought to be due to relative lack of GI absorption leading to increased local drug level, with subsequent mucosal hemorrhage.

More than 900 ICH cases are associated with factor Xa inhibitors each month in the United States. Importantly, even this rate of hemorrhagic complications associated with the use of DOACs is either equivalent or significantly lower than that of warfarin. Major bleeding events, however, do increase the risk of mortality. Of all the types of bleeding complications from DOACs, the ICH leads to most cases of mortality accounting for up to 45% of all the bleeding-related deaths. Amongst all DOAC-related major bleeding events, ICHs accounted for about 11% and was associated with a 4-fold increased risk of mortality, as compared to other extracranial major bleeds [18].

The hemorrhagic complications due to anticoagulant medications lead to significant additional health-care costs. These patients need to be admitted to hospital, mostly to the intensive care units, with a need to be attended by additional physician specialists, with a median number of up to 4 specialist consult encounters per admission. Among all hospital admissions related to major hemorrhagic events, independent of the site of bleed, the average patient length of stay was about 10 days, with the mean total health-care cost per patient of about $60,000. Total all-cause health-care cost during the first 12 months of follow-up for patients with atrial fibrillation, with major bleeding, was almost double the amount compared to patients without major bleeding (about $64,000 versus about $38,000) [19]. Unfortunately, patients who experience a major hemorrhagic complication on the DOACs or warfarin use are also at a higher risk of developing subsequent thromboembolic events. The rate of venous thromboembolic events may range from 7 to 12% within 30 days of a DOAC-associated major hemorrhagic complication [20]. This study did not look into the occurrence of thromboembolic complication whether the patient was on or off anticoagulation in the postbleed period.

1.2. Optimal DOAC Selection. Use of DOACs is contraindicated for patients with mechanical heart valves, and it is

| Table 1: Properties of different direct oral anticoagulants (DOACs) [8, 13–15]. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Mechanism of action**        | Dabigatran      | Rivaroxaban     | Apixaban        | Edoxaban        | Betrixaban      |
| Time to peak serum level       | Direct thrombin inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor |
| 1 hour, 2 hours with food      | 2–4 hours       | 3–4 hours       | 1–2 hours       | 3–4 hours       |
| Elimination half-life (hours)  | 12–17 (young), 14–17 h (in elderly) | 5–9 (young), 11–13 (in elderly) | 12 (8–15) | 10–14 | 19–27 |
| 80% renal                      | 70% liver, 30% renal | 66%–100% higher with food | 30% renal | 50% renal | 11% renal, 89% fecal |
| Bioavailability                | 3%–7%           |                 |                 |                 |                 |
| Dose/frequency                 | 150 mg bid (110 mg bid, if age > 80 years) | 20 mg once daily | 5 mg bid | 60 mg once daily | Not licensed |
| VTE therapy and prophylaxis    | 150 mg bid (after 5 d of LMWH) | 15 mg bid × 21 d, then 20 mg once daily | 10 mg bid × 7 d, then 5 mg bid | 60 mg bid (after 5 d of LMWH) | 160 mg on day 1, then 80 mg daily |
| VTE prophylaxis post elective  | 150 mg once daily | 10 mg once daily | 2.5 mg bid | Not licensed | Not licensed |
| hip/knee surgery                | Yes             | Yes             | Yes             | Yes             | Yes             |
| P-gp resecretion               | No              | No              | Yes             | Minimal         | No              |
| CYP3A4 metabolism              | Renal function, CBC periodically, at least annually | Renal function, CBC periodically, at least annually | Renal function, CBC periodically, at least annually | Renal function, CBC periodically, at least annually | Renal function, CBC periodically, at least annually |
| Follow-up monitoring           | Dilute thrombin time (dTT), ecarin clotting time (ECT) | Specific, calibrated anti-FXa assays | Specific, calibrated anti-FXa assays | Specific, calibrated anti-FXa assays | Specific, calibrated anti-FXa assays |
| Quantitative assay             | Anti-FXa assay = anti-factor Xa assay, bid = twice daily, CBC = complete blood count, CYP3A4 = cytochrome P450 3A4, d = day, DOACs = direct oral anticoagulants, FXa = factor Xa, INR = international normalized ratio, LMWH = low-molecular weight heparin, mg = milligram, NVAF = nonvalvular atrial fibrillation, P-gp = P glycoprotein, PTT = partial thromboplastin time, and VTE = venous thromboembolism.
2. Intracranial Hemorrhage Management

The emergency treatment of ICH starts with the basic care of the acutely ill patient, with an aim for stabilizing the hemodynamic condition, assessing the level of neurologic injury, and providing specific therapeutic measures and interventions if possible, along with the supportive medical management.

2.1. Initial Evaluation and Clinical Stabilization.
Spontaneous intracranial hemorrhage, being a medical emergency, needs to be managed aggressively. Basic steps are recommended to be followed as per the guidelines from the American Heart Association and the Neurocritical Care Society [26, 27].

(i) A summarized version of the recommendations includes immediate evaluation and stabilization of the airway, breathing, and circulation, with a focused neurologic and clinical exam for lesion location and its severity evaluation and the use of CT (computerized tomography) scan to help with this. Meticulous management of hemodynamic stability can be achieved by appropriate blood pressure medications and adequate intravenous (i.v.) fluid resuscitation, including blood product transfusion, if indicated. Concurrent optimization of blood pressure management, reversal of coagulopathy and prompt surgical intervention when indicated, is essential in decreasing morbidity and mortality. This is usually followed by intensive care management and monitoring for prevention of any untoward complications (Figure 2).

2.2. Poor Prognostic Factors

(i) Presence of coma, neck stiffness, focal neurologic deficits with seizures, diastolic blood pressure e > 110 mmHg, and vomiting on presentation suggests a presence of ICH. Poor prognostic predictors in this situation are decreased level of consciousness, larger hematoma volume on presentation, and presence of intraventricular hemorrhage (IVH) [28].

Patients with ICH volume of above 60 mL (millilitres) with Glasgow Coma Scale (GCS) below 8 have a likely poor outcome (predicted 30-day mortality rate above 90%) versus patients with hematoma volume below 30 mL and GCS above 9, who have mortality rate below 20% in the same period. IVH presence is an independent poor predictor of outcome. An increase in IVH volume by more than 2 mL in the first 24 hours is associated with an odds ratio (OR) for poor outcome of 4.2 (95% CI 1.06–16.63, \(p = 0.0405\)) [29].

2.3. Hematoma Location.
Typical hypertensive ICH locations are basal ganglia, thalamus, deep cerebellar nuclei, internal capsule, midbrain, and pons. Lobar hemorrhages are usually associated with cerebral amyloid angiopathy, arteriovenous malformations, brain tumors, or other structural lesions. Lobar hemorrhages are typically associated with a worse outcome as compared to the usual hypertensive ICH locations [26, 27].
Indications of DOACs
(i) Stroke prevention in NVAF
(ii) VTE prophylaxis and treatment
(iii) VTE prophylaxis post elective hip/knee (not for edoxaban)

Contraindications for DOACs
(i) Mechanical heart valve patients
(ii) Severe renal dysfunction
(iii) Extremes of body weight
(iv) Concern for compliance
(v) History of GI hemorrhage

Specific reversal agents for DOACs
Dabigatran
(i) Idarucizumab (dose 5 g; 2.5 g i.v. bolus × 2)
(ii) If idarucizumab not available—then 4-factor PCC (25–50 units/kg i.v.)
(iii) aPCC (25–50 units/kg i.v.)
(iv) Continuous dialysis: if overdose suspected/ inadequate control despite PCC/a PCC use

Specific interventions for ICH
Hematoma expansion: rapid and adequate BP control
Seizure: treat clinical seizures, but no prophylaxis needed

Imaging
1. CT/other imaging
   (i) If ICH—for location, volume, IVH presence, mass effect/herniation, “Spot sign,” and etiology

History and laboratory parameters:
1. Symptom onset, prior drugs, coagulopathy, prior surgery
2. CBC, BMP, PTT, INR, glucose, troponin, drug screen

Basic measures
1. ABC
   (i) Airway protection (intubate if GCS < 8)
   (ii) Maintenance of normal oxygenation & (Sao₂ > 94%; PaO₂ 35–45 mmHg)
   (iii) Hemodynamic resuscitation
2. Monitoring
   (i) Vital signs and objective neurologic assessment

Specific reversal agents for DOACs
Factor Xa inhibitors
(i) 4-factor PCC (25–50 units/kg i.v.)
(ii) 3-factor PCC (if 4-factor PCC not available)
(iii) aPCC (25–50 units/kg i.v.)
(iv) Once FDA approved, may use the following
   (v) Andexanet-α (bolus 400 to 800 mg → infusion i.v. @ 4 to 8 mg/minute)
   (vi) Ciraparantag—100 to 200 mg i.v. bolus
2.4. Hematoma Expansion. All the ICH patients are at risk of early hematoma expansion (HE) that may lead to further neurological deterioration. HE has been noticed in up to 40% of patients within first 24–48 hours. Most of these patients have HE within first 6 hours of the onset, with about 26% of ICH patients demonstrating substantial hematoma volume increase (>33% rise above baseline hematoma volume) within 4 hours of symptom onset. Additional 12% patients had HE within 20 hours on repeat CT scan [30, 31]. Predictors of hematoma expansion include history of warfarin/DOAC use with associated coagulopathy, shorter time from ICH onset to CT, and presence of “spot sign” on CT angiogram. Latter is due to contrast extravasation within the hematoma on postcontrast CT head. If it is detected in the arterial phase of CT angiogram, then it has higher chances of absolute HE and therefore a worse outcome [31, 32].

2.5. Clinical Severity Assessment. Regular use of clinical severity assessment scales helps to evaluate objectively the ICH patients, in a standardized, observer-independent manner. Of the several clinical grading scales, the ICH score is probably the most popular. It uses consciousness level (as measured by GCS or Glasgow coma scale), age, ICH volume, IVH presence, and ICH location (supratentorial/infratentorial) to generate a score between 0 and 6; the higher the score, the more the mortality rate. However, these clinical grading scales should never be used in isolation, for deciding the acute initial management of ICH patients.

2.6. Medical Management of ICH. Acute management and monitoring of ICH patients should preferably be done in dedicated neuroscience critical care units or dedicated stroke units, to positively impact the outcome and mortality rates. Essential monitoring of neurologic and hemodynamic parameters with the use of intracranial pressure-monitoring devices, multimodal neuromonitoring should be provided, as needed.

Several clinical trials (INTERACT 2 and ATACH 2) have established the safety of early intensive blood pressure reduction. Rapid intensive blood pressure lowering has been shown to decrease the chances of hematoma expansion, particularly with larger hematomas/positive spot sign on contrast-CT, though with systolic BP level below 130 mmHg, there may be complications, especially related to renal function [32, 33]. It is equally important to maintain tight control over several important clinical and physiological parameters, such as prevention of venous thromboembolism (VTE), infections, and seizure control and prophylaxis. Maintenance of normothermia (goal core body temperature < 37.5°C) and normoglycemia (serum glucose between 140 and 180 mg/dcilitre) is also recommended for critically ill patients.

Close monitoring for possible intracranial hypertension, and aggressive management of the same, if detected, is critical. Its management involves simple measures such as head-of-bed elevation, neck positioning in midline, avoidance of unnecessary noxious stimuli, with adequate analgesia and sedation, and maintenance of normal temperature and ventilation to complex interventions such as hyperosmolar therapy, ventriculostomy placement, medically induced coma with use of barbiturates or therapeutic hypothermia, and decompressive craniectomy (Figure 2) [26, 27].

2.7. Reversal of Anticoagulant Medications. The use of antiplatelet medications is also associated with increased incidence of the hemorrhagic complications, including ICH. Use of platelet transfusion to reverse the antiplatelet activity is controversial, with lot of variation in the daily practice between the institutions. Based on the limited evidence about the use of platelet transfusion to reverse the effect of irreversible antiplatelet medications (such as aspirin), there is no benefit in platelet transfusion in patients with aspirin resistance (as can be found by platelet function assays), in those with normal platelet function, and in those who are not undergoing neurosurgical procedure. If there is a need for neurosurgical procedure and when platelet function assay is not available, then transfusion may be reasonable [26].

For patients on warfarin with INR above 1.5, the current guidelines recommend the use of 4-factor PCC (prothrombin complex concentrate) that effectively reverses the warfarin within 30 minutes of its use [34]. The PCC is a donated blood byproduct that contains virally inactivated concentrated plasma coagulation factors.

For patients on DOAC use, there was no specific reversal agent available until the approval of idarucizumab in October 2015, for dabigatran reversal. Subsequently, there has been fast-tracking for FDA approval of another 2 candidate medications for reversal of factor Xa inhibitors, andexanet-α and ciraparantag, and the latter can also reverse the anticoagulant effects of unfractionated heparin and low-molecular weight heparin, in addition to that of the factor Xa inhibitors (Table 2).

2.8. Idarucizumab. Idarucizumab (Praxbind) is a fully humanized Fab fragment of monoclonal antibody against dabigatran, with 350-fold higher binding affinity for dabigatran than for thrombin. It is cleared renal, and it rapidly and completely reverses the anticoagulant action of dabigatran, with no prothrombotic activity of its own. It can be used multiple times if needed, without loss of activity. It has not shown any evidence of significant immunogenicity. It does not affect other anticoagulants and does not activate clotting despite its structural resemblance to thrombin. It has been approved for dabigatran reversal in emergent surgery, urgent procedures, or life-threatening and/or uncontrolled bleeding including ICH.

The recommended dose is 5g (given as 2 consecutive infusions of 2.5 g vials within 15 minutes interval). The anticoagulant effect of dabigatran may reappear after 12–24 hours after idarucizumab use due to dabigatran redistribution from the tissues into the plasma, and idarucizumab may have to be repeated to maintain the normal coagulation profile. Similarly, it may be administered again if
excessively high dabigatran concentration is present, as in cases of overdose [37, 45].

Idarucizumab is not affected by renal or hepatic dysfunction and is reported to have delirium, headache, and constipation as common side effects. Onset of activity is within minutes of idarucizumab administration, and hemostasis is restored in a median of 11.4 hours, with duration of effect lasting at least 24 hours. Its metabolites are excreted in urine within the first few hours. Dabigatran can be restarted within 24 hours after idarucizumab use, if indicated [44]. The REVERSE-AD study (reversal effects of idarucizumab on active dabigatran; Clinicaltrials.gov NCT02104947) studied 504 patients on dabigatran needing urgent reversal due to major bleeding event or due to the need for emergent surgery or procedure. This was reversed with the use of idarucizumab (5 g). After its administration, at 4 hours, the median maximum reversal was 100% for the diluted thrombin time (dTT), ECT (ecarin clotting time), and aPTT. In the procedural group, 93% of patients had normal peri-procedural hemostasis. It also normalized conagulation tests to the same extent in ICH cases, as it did in other major bleeding event cases [14, 37, 39, 46].

Few case reports have demonstrated that idarucizumab may be used to reverse the dabigatran if the patient has an acute ischemic stroke while on dabigatran. This small review reported 21 patients who had mild to moderate ischemic stroke while on dabigatran, with the use of idarucizumab to reverse the formers’ effect. This was followed by administration of tissue plasminogen activator (tPA) in 18 patients. An unfavorable outcome was present in 3/19 patients (16%), with one fatality from symptomatic postthrombolysis intracranial hemorrhage and worsening of ischemic stroke in other 2 patients. Systemic bleeding, venous thrombosis, or allergic reactions was not noticed. The suggested thresholds for i.v. thrombolytic therapy that can be performed safely in dabigatran-treated patients are TT (below 38 seconds) or aPTT (below 37 seconds) [42, 47, 48].

A concern has been raised regarding significant delay in cessation of bleeding by idarucizumab in dabigatran-associated intracranial hemorrhage. It is unclear if the blood-brain barrier has a role in ease of access to the bleeding site by idarucizumab. Adding blood component therapy (e.g., PCC and/or activated PCC) along with idarucizumab may be helpful till we have more robust clinical data [49].

2.9. Andexanet Alpha. Andexanet-alpha (PRT064445) is a catalytically inactive recombinant form of factor Xa that is derived from Chinese hamster ovarian cells. This Xa mimic molecule serves as a "decoy" for the Xa anticoagulants by acting as a competitive inhibitor for the native factor Xa. In essence, andexanet-alpha diverts anticoagulants away from its intended target, the factor Xa. Though andexanet-alpha was designed to work against rivaroxaban, apixaban and edoxaban by binding to the above drugs in 1:1 ratio, it also binds various forms of heparin, including unfractionated heparin, low-molecular weight heparin, as well as, fondaparinux. The latter action is by competitive binding to the antithrombin-heparin complex. It therefore reverses the indirect factor Xa inhibitors, direct factor Xa inhibitors, and also the heparin and low-molecular weight heparin via its effect on the antithrombin-heparin complex. It therefore reverses the indirect factor Xa and anti-factor IIa (thrombin) activity of the heparins due to its noncovalent interaction with the antithrombin-heparin complex. Being similar to factor Xa, it also binds to the tissue factor pathway inhibitor (TFPI), reducing TFPI activity, but unlike native factor Xa-TFPI complex, the andexanet-TFPI complex fails to inhibit the factor V/IIa-tissue factor complex. Consequently, andexanet-alpha administration in a patient on
factor Xa inhibitors may develop a transient procoagulant state by this mechanism. The clinical significance of this interaction, however, remains to be clarified.

Andexanet has an initial half-life of approximately 15 minutes, with terminal half-life of approximately 6 hours after intravenous infusion. It is supplied in vials of 100 mg of lyophilized drug that remain stable for 2 years with refrigeration. The antidote needs to be reconstituted with sterile water for intravenous infusion. Reconstituted drug is stable for at least 8 hours at room temperature. A low-dose regimen typically needs 9 vials, and a high-dose regimen needs a total of 18 vials. Typically, it is administered as an initial bolus (400 or 800 mg), and then the remainder of the drug is infused over next 2 hours (at 4 mg to 8 mg/minute) [12].

In ANNEXA-4 study (ability of andexanet-α to reverse the anticoagulant activity study; Clinicaltrials.gov-NCT02329327), 47 patients were medicated with either rivaroxaban or apixaban for the treatment of atrial fibrillation or VTE; subsequently, they were treated with andexanet-α for high anti-factor Xa activity. 66% patients were found to have excellent hemostasis, with anti-factor Xa activity reduction for several hours following its use. 18% patients developed thromboses (5 strokes and 8 VTEs) within 30 days after andexanet treatment. All of them, except one, were not receiving therapeutic anticoagulation at the time of the adverse event [40]. Andexanet-α is not yet FDA-approved for use.

2.10. Ciraparantag. Ciraparantag (PER977) is a synthetic small molecule antidote that has a charge-dependent binding to the heparins, as well as, a hydrogen bond-mediated interaction with DOACs, thus, preventing both old and new anticoagulant classes of medications from binding to their endogenous targets. It potentially can work as a universal anticoagulant antidote, providing activity against direct thrombin inhibitors, factor Xa inhibitors, heparins (including low-molecular weight heparin), and fondaparinux. Metabolites of ciraparantag are rapidly eliminated through the kidneys. Unfortunately, routine coagulation tests cannot monitor the reversal effect of ciraparantag. Although the “whole blood-clotting time” can be used to monitor its effect, this test has limited availability.

Ciraparantag was able to reverse the effect of therapeutic enoxaparin (at doses of 200 mg and 100 mg within 5 and 20 minutes, respectively, following the enoxaparin dose. This was a phase I/II study of 40 healthy volunteers [41]. In another phase I/II study of 80 healthy volunteers receiving edoxaban, ciraparantag demonstrated dose-dependent reversal of whole blood-clotting time to within 10% of the baseline [43].

Though a single bolus is sufficient to reverse the effects of enoxaparin or edoxaban, ciraparantag can be repeated if needed. The side effects include transient perioral and facial flushing, abnormalities in taste sensation, and headache. This will be supplied in vials of 300 mg that is stable for 2 years at room temperature [12]. Ciraparantag is not yet FDA-approved.

Another novel anticoagulant antidote under development is FXaI16L, a mutant factor Xa that has leucine substituting for isoleucine at position 16. It has a potential use as a universal bypassing agent for multiple anticoagulants. It circulates in a zymogen-like (inactive) state in plasma, without binding to any anticoagulant and is resistant to active-site inhibitors. It is activated when it comes across activated factor V (factor Va) on damaged cellular surfaces, leading to selective restoration of hemostasis at the bleeding site. FXaI16L has demonstrated reversal of rivaroxaban in a mouse model and the reversal of rivaroxaban and dabigatran in human plasma in vitro [50]. Results of further studies on this potential drug are eagerly awaited.

2.11. Nonspecific Reversal Agents. DOACs can be reversed at least in part by the use of activated charcoal, provided that the last dose was ingested within 2 hours. Hemodialysis can be used for dabigatran-related hemorrhagic states, particularly in cases of overdose, due to its renal-dependent clearance.

3. Prothrombin Complex Concentrate (PCC)

3.1. Activated PCC. Activated PCC (FEIBA or factor eight inhibitor bypassing activity) contains the regular 4-factor PCC, but unlike the PCC, factor VII is in the activated state, with the usual dose being 50 units/kilogram. This medication has shown to effectively control the ICH expansion in a small prospective trial of 127 ICH cases, with 6 patients on DOACs [52].

The current guidelines recommend the use of FEIBA (activated PCC) for reversal of factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). The usual dose found to be effective is 50 units/kilogram for restoring normal bleeding time and reestablishing thrombin generation. Currently, the guidelines recommend PCC as the treatment of choice for patients taking DOACs presenting with ICH. This applies for both factor Xa inhibitors and for dabigatran if idarucizumab is not available [51].

3.2. Recombinant Factor VIIα (rFVIIa). Though the utility of rFVIIa in control of hematoma expansion in a mouse model has been proven, but due to lack of strong human data and elevated thrombotic risk, the use of rFVIIa is not recommended currently with DOACs related ICH, unless other
measures have failed. The usual dose used is 90 micrograms/kilogram body weight.

3.3. Practical Considerations during Reversal of DOACs. DOAC reversal may not be necessary if the last dose was taken at least 48 hours prior to the hemorrhagic event, but likely if associated severe renal or hepatic dysfunction exists. With limited information regarding dosing, rapid quantitative serum levels of DOAC may be helpful. DOAC levels exceeding 30 nanograms/mL require reversal of the DOACs. Direct thrombin inhibitor (dabigatran) can be reversed by the antibody, Idarucizumab, (two boluses of 2.5 grams each within 15 minutes) or by administering a 4-factor PCC (50 units/kilogram dose) if this specific antidote is unavailable.

3.4. Reinitiation of the DOACs after ICH. Though the annual risk of any major bleed from oral anticoagulant (OAC) use is 2-3%, with OAC-related ICH risk of 0.3–0.5%, the annual risk for thromboembolic complications is much higher in the absence of OAC therapy, in patients where it is indicated. The annual arterial thromboembolic complication risk for patients with mechanical heart valves is 12% to 22%, atrial fibrillation with CHA2DS2-VASc score of above 3 is 6% to 18%. To help with the clinical decision-making, there have been several scoring systems devised, but they may provide an inadequate ability to differentiate between a major bleeding event and clinically relevant nonmajor hemorrhage predictability [53]. Two major factors that guide the clinical decision-making about the reinitiation of the DOACs after ICH are indications for DOAC use and the predicted risk of VTE/stroke versus the risk of hemorrhage associated with it. Factors that favor restarting OAC therapy are location of ICH (deep ICH), presence of mechanical heart valve, secondary prevention of acute ischemic stroke, high risk of stroke or VTE, and a corrected cause of potential bleeding (e.g., a clipped aneurysm or repaired vascular malformation). Factors that demonstrate higher risk of hemorrhagic complications include lobar ICH and imaging suggestive of cerebral amyloid angiopathy (multiple microbleeds on gradient-echo magnetic resonance imaging) [28].

The next important decision would be the timing of reinitiation of the OAC therapy. In patients with mechanical heart valve or stable gastrointestinal bleed, the OAC therapy is restarted earlier, as compared to patients with ICH or low risk of stroke/VTE. On the other hand, in patients with lobar ICH, it may not be safe to restart OAC therapy at all. For deep ICH and high risk of cerebral ischemia (e.g., mechanical heart valve/atrial fibrillation with high CHA2DS2-VASc Score), the OAC treatment should be restarted within 1-2 weeks and even later (after 4 weeks) if the risk of hemorrhage is higher. It is important to note that DOACs reach therapeutic anticoagulation level within a few hours, unlike VKAs that need a few days to do so.

4. Conclusion

Spontaneous ICH remains an important cause of mortality amongst the patients with stroke. Its mortality rate has unfortunately not improved in the last several years. Oral anticoagulant medications account for a small but increasingly common cause of this dreaded complication. DOACs are likely to further contribute to this neurological emergency due to their rising popularity. Most of the hemorrhagic complications from DOACs can be managed without any specific reversal agents. Presence of the rare ICH in a patient on DOAC, however, warrants immediate reversal of anticoagulation, and, therefore, all the hospitals should have a management protocol in place for hemorrhagic complications due to DOACs. Comprehensive information about DOACs, their specific reversal agents, and recommended dosing, along with information on supportive measures, need to be made available to all the staff who are involved in the management of such patients, especially those with ICH.

DOAC use is likely to become more prevalent with the improved understanding of growing indications and increased availability and development of the specific reversal agents. However, this needs to be supplemented by prepared emergency response system for these rare hemorrhage-related events from DOAC complications with a management protocol based on a multidisciplinary team approach. A collaborative, efficient, and effective strategy, that has the flexibility of adapting to the ongoing developments in diagnostic tests for DOACs, as well as, invention of better and broader spectrum antidote agents, must be developed and implemented for the best patient care.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


Review Article

Update in the Early Management and Reperfusion Strategies of Patients with Acute Ischemic Stroke

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Acute ischemic stroke (AIS) remains a leading cause of death and long-term disability. The paradigms on prehospital care, reperfusion therapies, and postreperfusion management of patients with AIS continue to evolve. After the publication of pivotal clinical trials, endovascular thrombectomy has become part of the standard of care in selected cases of AIS since 2015. New stroke guidelines have been recently published, and the time window for mechanical thrombectomy has now been extended up to 24 hours. This review aims to provide a focused up-to-date review for the early management of adult patients with AIS and introduce the new upcoming areas of ongoing research.

1. Introduction

Stroke ranks number five among all causes of death in the United States (US) and is also a leading cause of serious long-term disability. On average, every 40 seconds, someone in the United States has a stroke and, every 4 minutes, someone dies of stroke. Stroke costs at least $70 billion each year in the US. World-wide, stroke is the second leading cause of death. Of all strokes, 87% are ischemic [1]. Given the massive social and economic burden that ischemic stroke represents, prevention and acute management of this disease is of paramount importance.

In acute stroke, ischemia is rarely complete at presentation. Residual perfusion, which depends on collateral vessels and local perfusion pressures, creates a region, called the penumbra, in which residual perfusion attempts to supply sufficient oxygen to maintain a close to normal tissue concentration of ATP with some degree of energy failure [2]. In contrast to areas of benign oligemia, the penumbra is an ischemic, but malfunctioning, living brain tissue that will die unless the blood supply is restored [3]. Acute stroke management, including reperfusion therapies, is aimed at restoring adequate blood supply to these areas at risk of infarction.

Until recently, intravenous alteplase administered within 3–4.5 hours after symptom onset was the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke. However, after the publication of five pivotal clinical trials [4–8], endovascular thrombectomy is accepted as the standard of care for patients with large vessel occlusion (LVO) in the anterior circulation [9]. Although the initial trials indicated that endovascular thrombectomy did not confer benefit when reperfusion was not accomplished within 6-7 hours, two recent trials, DAWN [10] and DEFUSE 3 [11], have demonstrated that the window for
Endovascular thrombectomy can, in some patients, be extended up to 16–24 hours from last known normal using perfusion imaging. New stroke guidelines have been published to incorporate these findings and the potential time window for mechanical thrombectomy has now been extended up to 24 hours [9]. Figure 1 depicts one of the most common endovascular techniques using a stent retriever to treat acute ischemic stroke secondary to an LVO presenting at 12 hours. The aim of this manuscript is to provide a focused up-to-date review for the early management of adult patients with acute arterial ischemic stroke and introduce the new upcoming areas of ongoing research.

2. Prehospital Care

The use of Emergency Medical Services has been associated with earlier hospital arrival and more rapid treatment [12]. The primary goals of EMS in acute stroke are rapid evaluation, triage, and transport to a stroke-ready hospital. Current guidelines prioritize supplemental oxygen to maintain adequate oxygen saturations (SpO₂ > 94%), determination of glucose level, and treatment if <60 mg/dL to rule out a potential stroke mimic. EMS may also establish large bore IV access and obtain blood samples for laboratory testing en route. Although these recommendations represent an ideal scenario, it is critical that these interventions do not delay transport of the patient to the hospital [9]. The most important reason for missing recanalization therapy is time delay in the prehospital phase [13].

Obtaining information prior to hospital arrival can assist in the prehospital diagnosis of stroke or stroke mimic using stroke assessment systems, assess comorbidities, medications, and recent trauma or surgeries that could contraindicate the use of IV tPA. However, the most important piece of information necessary for potential reperfusion therapy is the time the patient was last known normal. The patient should then be promptly triaged and transported to the nearest facility with reperfusion therapy capabilities [9]. Also, prehospital providers should notify the hospital about pending stroke patient arrival, as this has been associated with significant reduction in stroke time targets and tPA administration [9, 14].

Current guidelines recommend patient transportation to the nearest hospital with tPA capacity [9]. This, however, may be detrimental for patients with LVO because of the time delay associated with established “drip and ship” models [15]. IV tPA results in a low recanalization rate of patients with LVO occlusion [16]. A study by Mokin et al. [17] demonstrated that one out of three patients with LVO with initial favorable imaging profile became ineligible for endovascular thrombectomy during interhospital transfer based on ASPECTS criteria. In this study, except for NIHSS severity, no other baseline factors could identify which patients were at risk for ASPECTS deterioration during interhospital transfer. In the SWIFT PRIME trial, when comparing the outcomes in patients treated under the current drip and ship paradigm versus primary endovascular center presentation, outcomes were significantly worse for those patients who were transferred to the center with endovascular thrombectomy capabilities after receiving IV tPA at the outside hospital [6]. In the current era of endovascular therapy, current prehospital stroke evaluation should include stroke severity and not only stroke recognition. Triaging severe

Figure 1: (a) Schematic representation of one of the most common endovascular techniques using a stent retriever to treat an acute left middle cerebral artery stroke secondary to an LVO presenting at 12 hours. (b) Identification of infarct core and potentially salvageable tissue using automated software (RAPID). (c, d) Angiogram demonstrating L MCA occlusion (black arrow) and stent retriever deployment (white arrow).
cases directly to endovascular therapy-capable center may provide the best opportunity to optimize endovascular thrombectomy [18]. To address this matter, several approaches for the early recognition of LVO have been developed. These include prehospital stroke scales to be used by prehospital personnel in the field such as the 3ISS (3-Item Stroke Scale) [19], LAMS (Los Angeles Motor Scale) [20], RACE (Rapid Arterial Occlusion Evaluation Scale) [21], CPSSS (Cincinnati Prehospital Stroke Severity Scale) [22], and PASS (Prehospital Acute Stroke Severity) [23], as well as Mobile Stroke Units (MSU), and telemedicine. Current guidelines integrate these findings and recommend (Class IIb) that when several facilities with tPA capabilities exist within a specific region, the benefit of bypassing the nearest facility to transfer the patient to one that offers a higher level of stroke care located within a reasonable distance, including mechanical thrombectomy, may be considered [9]. RACECAT (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients with Suspected Large Vessel Occlusion) is an ongoing prospective, multicenter, cluster randomized controlled trial occurring in Spain. In this study, two strategies in acute stroke patients with suspected acute LVO identified by EMS at first assessment in the field will be compared: transfer to the closest local stroke center versus direct transfer to an endovascular stroke center. In order to maximize the sensitivity and specificity of LVO diagnosis, EMS will utilize the RACE: scale (Rapid Arterial Occlusion Evaluation) as a prehospital screening tool to identify acute stroke patients with suspicion and will contact a stroke neurologist on call using a prehospital telestroke system within the ambulance, who will confirm inclusion criteria for LVO and will allocate the subjects to a specific intervention according to a preestablished temporal sequence. Figure 2 depicts a potential alternative to current prehospital stroke paradigms that will need to be elucidated in the near future.

An alternative approach to improve the triage and treatment process has occurred through the implementation of Mobile Stroke Units (MSU) with imaging capabilities in large urban areas. The BEST-MSU (Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit) trial was launched to compare stroke management using a MSU versus standard management. So far, the run-in phase of this study has provided essential information to help in the final design of their study. They have also shown that their average door-to-needle time (25 minutes) on the MSU is comparable with the fastest ED door-to-needle times reported in the literature [24]. Another study by the Cleveland Clinic compared the evaluation and treatment of patients on a Mobile Stroke Unit, using telemedicine for physician presence, against a control group of patients brought to the emergency department through ambulance. The time from door to CT completion (13 minutes (IQR, 9–21 minutes) versus 18 minutes (IQR, 12–26 minutes)) and from door to IV tPA (32 minutes (IQR, 24–47 minutes) versus 58 minutes (IQR, 53–68 minutes)) was significantly shorter in the MSU compared with the control group. This study showed the feasibility in performing prehospital stroke assessment and IV tPA therapy using a MSU with telemedicine capabilities [25]. Some studies have suggested that MSU systems can be cost-effective, especially when reducing the number of staff within the unit by using telemedicine [26, 27]. The efficiency of these systems, however, is related to population density, which may limit its benefits in rural areas [26].

Parallel with the development of reperfusion therapies, several measures are underway to optimize the prehospital stroke rescue chain. Measures for improvement include continuous public awareness campaigns; education of emergency medical service personnel; the use of standardized, validated scales for recognition of stroke symptoms and for triaging to the appropriate institution; advance notification to the receiving hospital; mobile CT-equipped ambulances directed by an onboard stroke neurologist or telemedicine consultation; and blood biomarkers [28–30]. Prompt assessment and adequate triaging of patients with acute ischemic stroke is crucial for timely delivery of reperfusion therapies and optimize outcome.

3. Intravenous Thrombolitics

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) trials showed the benefit of using intravenous (IV) tissue plasminogen activator (tPA) over placebo within 3 hours of symptom onset [31]. Based on these results, in 1996, the Food and Drug Administration (FDA) approved the use of IV tPA (or alteplase) for patients with AIS presenting within 3 hours of symptom onset. Table I lists the inclusion and exclusion criteria for the use of IV tPA within 3 h of symptom onset. In 2008, ECASS (European Cooperative Acute Stroke Study) III showed benefit of IV tPA over placebo among those treated within 3 to 4.5 hours of symptom onset [32, 33]. Although the FDA has not modified the use of IV tPA beyond the 3 hours window, the recent stroke guidelines from the American Heart Association (AHA) recommend using IV tPA up to 4.5 h from onset of symptoms in eligible patients: patients ≤80 years of age, without a history of both diabetes mellitus and stroke, with NIHSS score ≤25, not taking oral anti-coagulation, and without radiologic evidence of ischemic injury involving more than one-third of the MCA territory [9, 34]. Delay in treatment reduces the opportunity of receiving reperfusion therapies and worsens neurological
A meta-analysis that included 3670 patients, described the therapeutic benefit and clinical risk of IV tPA in relation to time. In this analysis, the odds of a favorable 3-month outcome increased as onset to start of treatment decreased ($P < 0.0269$). Adjusted odds of a favorable 3-month outcome were 2.55 (95% CI 1.44–4.52) for 0–90min, 1.64 (1.12–2.40) for 91–180min, 1.34 (1.06–1.68) for 181–270min, and 1.22 (0.92–1.61) for 271–360min in favor of the alteplase group. Based on these results, five patients need to be treated 0–90min, nine patients 91–180min, or 15 patients 181–270min after symptom onset for one of them to have an excellent outcome (mRS score 0–1) attributable to treatment. No benefit of alteplase treatment was seen after around 270 min, and beyond 4.5 h the risk of using IV tPA might outweigh the benefit [36]. Of note, most of the patients included in this meta-analysis did not have an LVO.

Other clinical trials have explored using low-dose tPA (0.6 mg/kg) as compared to the standard dose (0.9 mg/kg). Although they demonstrated less risk of intracerebral hemorrhage with low-dose tPA, they did not show noninferiority of low-dose tPA to the standard dose with respect to death and disability at 90 days [37]. More recently, the WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-up Stroke) trial has shown that the administration of intravenous alteplase thrombolysis decreases functional disability at 3 months in patients with mild to moderate severity strokes of unknown time of onset, when patients were selected on the basis of simple MRI criteria showing a lesion on diffusion-weighted imaging but without a corresponding hyperintensity on fluid-attenuated inversion recovery (FLAIR) [38].

Despite recommendations to reduce the door-to-needle time to <60 min, fewer than one-third of patients treated with IV tPA received tPA within 60 minutes, and less than 5% of all stroke patients receive tPA at all [35, 39]. In addition to the narrow time window, IV tPA has numerous limitations. IV tPA has a low potential to recanalize occluded vessels with a large (>8mm) thrombus [40], resulting in a poor recanalization rate (13% to 50%) in large vessel occlusion stroke and a low rate of benefit in the patients having the most disabling strokes [16]. To overcome these limitations, alternative therapies have been studied. Some of these alternatives that have been tested in clinical trials include (1) the use of systemic tenecteplase [41, 42], or desmolteplase [43, 44] or (2) the augmentation of systemic IV tPA recanalization with ultrasound. Tenecteplase (TNK) is a genetically engineered variant of tPA that has a longer half-life and is more fibrin specific than tPA. TNK has properties which make it a faster and more complete thrombolytic agent and, at the same time, with less bleeding complications and early recurrences [45].

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**Table 1:** Inclusion and exclusion criteria for the treatment of acute ischemic stroke with IV tPA within 3 hours from symptom onset.

### Inclusion criteria

(i) Diagnosis of ischemic stroke causing measurable neurological deficit 
(ii) Onset of symptoms <3 h before treatment begins 
(iii) Age ≥ 18 yrs

### Exclusion criteria

(i) Significant head trauma or prior stroke in the previous 3 months 
(ii) Symptoms suggest SAH 
(iii) Arterial puncture at noncompressible site in previous 7 d 
(iv) History of previous intracranial hemorrhage 
(v) Intracranial neoplasm, AVM, or aneurysm 
(vi) Recent intracranial or intraspinal surgery 
(vii) Elevated blood pressure (systolic > 185 mmHg or diastolic > 110 mmHg) 
(viii) Active internal bleeding 
(ix) Acute bleeding diathesis, including but not limited to 
(x) Platelet count < 100000/mm$^3$ 
(xi) Heparin received within 48 h resulting in abnormally elevated aPTT above the upper limit of normal 
(xii) Current use of anticoagulant with INR > 1.7 or PT > 15 s 
(xiii) Currrent use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (e.g., aPTT, INR, platelet count, ECT, TT, or appropriate factor Xa activity assays) 
(xiv) Blood glucose concentration < 50 mg/dL (2.7 mmol/L) 
(xv) CT demonstrates multi-lobe infarction (hypodensity > 1/3 cerebral hemisphere)

### Relative exclusion criteria

(i) Recent experience suggests that under some circumstances, with careful consideration and weighing of risk to benefit, patients may receive fibrinolytic therapy despite ≥1 relative contraindications. Consider risk to benefit of intravenous tPA administration carefully if any of these relative contraindications is present. 
(ii) Only minor or rapidly improving stroke symptoms (clearing spontaneously) 
(iii) Pregnancy 
(iv) Seizure at onset with postictal residual neurological impairments 
(v) Major surgery or serious trauma within previous 14 d 
(vi) Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d) 
(v) Recent acute myocardial infarction (within previous 3 months)

Note. Adapted from the AHA study [105].
TNK can be given as a one-time bolus without need for an infusion [46]. In the Tenecteplase versus Alteplase for Acute Ischemic Stroke (TAAIS) trial, 75 patients, who arrived <6 h after the onset of ischemic stroke, were randomly assigned to receive either tPA (0.9 mg/kg) or TNK (0.1 mg/kg or 0.25 mg/kg). Patients treated with TNK had greater reperfusion rates and better clinical outcomes at 24 h than tPA patients, while no significant differences in intracranial bleeding or other serious adverse events were noted between the groups. EXTEND-IA TNK is a multicenter, randomized trial where patients eligible for thrombectomy were randomized to either IV alteplase (0.9 mg/kg, maximum 90 mg) or tenecteplase (0.25 mg/kg, maximum 25 mg) up to 4.5 hours from onset prior to thrombectomy. The primary outcome measure was reperfusion on the initial catheter angiogram, assessed as modified treatment in cerebral infarction (mTICI) 2b/3 or the absence of retrievable thrombus. Patients who received TNK achieved higher rates of recanalization than patients who received tPA (22% versus 10%, resp.) with no differences in intracranial hemorrhage (1% in both groups). Although some of these therapies have shown promising results, IV tPA is still recommended as the standard of care. Because of its high fibrin specificity, non-activation by β-amyloid, long half-life, and absence of neurotoxicity, desmoteplase is an attractive alternative to tPA for systemic thrombolytic treatment of AIS [47, 48]. Recently DIAS (desmoteplase in acute stroke) assessed the safety and efficacy of desmoteplase given between 3 h and 9 h after symptom onset in patients with occlusion or high-grade stenosis in major cerebral arteries. Treatment with desmoteplase did not improve functional outcomes as measured by modified Rankin Scale of 0–2 at 90 days. Thus, desmoteplase use in the treatment of AIS remains investigational.

Glycoprotein IIb/IIIa antagonists prevent platelet aggregation, thereby preventing reocclusion and facilitating thrombus breakdown [49]. In the cardiac literature, in phase IIb studies, these agents have demonstrated improved coronary revascularization in the setting of acute MI, but no significant improvement in the phase III studies [50–52]. Safety of Tirofiban in Acute Ischemic Stroke (SaTIS) was a phase II placebo-controlled study of monotherapy with intravenous tirofiban in patients presenting up to 22 hours after stroke onset. There was no neurological/functional benefit found compared with placebo at 5 months except for lower mortality shown in the treatment group [50, 53]. The subsequent Abciximab in Emergency Treatment of Stroke Trial (AbESTT-I/II) was a phase III study of GP IIb/IIIa inhibitor monotherapy which was terminated prematurely because of an unfavorable risk-benefit profile in the treatment arm. There was no benefit in neurological recovery in any of the cohorts (within 5-hour onset, between 5 and 6 hours and wake-up strokes) in the abciximab group compared to placebo. Notably, there was a significant increase in symptomatic intracranial hemorrhage [50, 54, 55]. Efficacy and safety of combined intravenous tPA and epifibatide compared with intravenous tPA alone were investigated in the phase II Combined Approach to Lysis Utilizing Epifibatide and Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke-Enhanced Regimen stroke trial (CLEAR-ER) study. The combined treatment group had a lower rate of symptomatic intracranial hemorrhage (2%) and showed a trend towards better functional outcome, with 49.5% achieving mRS 0-1 versus 36% in the standard tPA group [56].

Argatroban is a direct thrombin inhibitor which has demonstrated safety in the Argatroban Anticoagulation in Patients with Acute Ischemic Stroke (ARGIS-I) trial [57]. The use of argatroban as an adjuvant to intravenous tPA was investigated in the Argatroban TPA Stroke (ARTTS) study and demonstrated 63% complete recanalization rate at 24 hours [50, 57–63]. In Phase II ARTTS-2 (Randomized Controlled Trial of Argatroban with tPA for Acute Stroke), Barreto et al. conducted a randomized exploratory study to assess safety and the probability of a favorable outcome with adjunctive argatroban and tPA in acute ischemic stroke patients. Patients were treated with standard-dose tPA versus tPA and argatroban (100 μg/kg bolus) followed by infusion of either 1 (low dose) or 3 μg/kg per minute (high dose) for 48 hours. They found that in patients treated with tPA, adjunctive argatroban was not associated with increased risk of symptomatic intracerebral hemorrhage. However, there was no difference in outcomes based on 90-day mRS [64]. Onset to Stroke Treatment Time (MOST) Stroke Trial is a recently funded StrokeNET multicenter multiarm phase 3 clinical trial that will evaluate the benefit of combining either argatroban or epifibatide with tPA compared to tPA alone in patients with acute stroke.

4. Thrombectomy

Initial trials intended to demonstrate the efficacy of endovascular intervention as a potential therapy for acute ischemic stroke were unsuccessful. It was not until recently that its efficacy has been proven.

In 2013, three multicenter prospective randomized controlled trials (RCTs) failed to show a benefit from endovascular intervention for acute ischemic stroke: IMS (Interventional Management of Stroke) III [65], MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) [66], and SYNTHESIS Expansion (Intra-arterial versus Systemic Thrombolysis for Acute Ischemic Stroke) [67]. These trials raised concerns about the efficacy of endovascular therapy in large vessel occlusion. However, there were also concerns in the design and conduct of these studies. First, only one of the three trials, MR RESCUE, routinely identified large vessel occlusion with either CTA or MRA. Second, mainly first-generation MT devices were used. Third, patients in the interventional arm of SYNTHESIS Expansion did not receive IV-tPA and were treated in a delayed fashion compared to the medical arm [68]. Considering these limitations, new trials were designed that included the use of second generation stent retriever devices (Solitaire, ev3/Covidien, Trevo, Stryker) that demonstrated significant superior rates of recanalization when compared to the first-generation devices. In 2014, MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) results were presented which demonstrated
significant benefit from endovascular stroke therapy [4]. Following these favorable results, other ongoing trials were stopped early and assessed for efficacy: ESCAPE [5], SWIFT PRIME [6], EXTEND-IA [7], and REVASCAT [8].

MR CLEAN randomized acute stroke patients presenting within 6 hours of stroke onset to standard medical management alone (n = 267) or standard medical management followed by MT (n = 233). Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that (1) was confirmed on vessel imaging and (2) could be treated intraarterially within 6 hours after symptom onset. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intra-arterial treatment. There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score (mRS), 0 to 2) at 90 days in favor of the intervention (32.6% versus 19.1%) [4].

In ESCAPE, 165 patients underwent intervention and 150 were enrolled in the controlled group. 120 in the intervention group and 118 in the control group received IV tPA. In this trial, patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on computed tomography (CT) and CT angiography were excluded. In the intervention group, the median time from head CT to first reperfusion was 84 minutes. The rate of functional independence (90-day mRS of 0 to 2) increased with the intervention (53.0%, versus 29.3% in the control group; P < 0.001). Intervention was also associated with reduced mortality (10.4%, versus 19.0% in the control group; P = 0.04) [5].

In SWIFT PRIME, 196 patients (98 patients in each group) underwent randomization into a control group receiving t-PA alone or tPA plus endovascular thrombectomy within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic core lesions. Thrombectomy with the stent retriever plus intravenous tPA reduced disability at 90 days over the entire range of scores on the modified Rankin Scale (P < 0.001). The rate of functional independence (modified Rankin Scale score, 0 to 2) was greater in the intervention group than in the control group (60% versus 35%, P < 0.001) [6].

EXTEND-IA included 70 patients who had received IV tPA within 4.5 hours who were randomized into a control group of receiving IV tPA alone (n = 35) or to undergo endovascular thrombectomy within 6 hours after the onset of stroke. As in the aforementioned studies, noninvasive vascular imaging was used to identify large vessel occlusion in the anterior circulation. Patients also underwent CT perfusion imaging, which was processed with the use of fully automated software (RAPID) to identify potentially salvageable brain tissue. At 24 hours, the percentage who achieved reperfusion was greater in the mechanical thrombectomy group than that in the IV tPA alone group (median, 100% versus 37%; P < 0.001). Also, endovascular therapy improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0 to 2 on the mRS, 71% versus 40%; P = 0.01) [7].

REVASCAT randomized 206 patients to receive either medical therapy (including IV tPA when eligible) and mechanical thrombectomy (thrombectomy group) or medical therapy alone (control group). All patients had confirmed proximal anterior circulation occlusion that could be treated within 8 hours of symptom onset and had absence of a large infarct on neuroimaging. Initially, exclusion criteria on imaging were evident of a large ischemic core, indicated by an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of less than 7 on computed tomography (CT) or a score of less than 6 on diffusion-weighted magnetic resonance imaging (MRI). After the enrollment of 160 patients, the inclusion criteria were modified to include patients up to the age of 85 years with an ASPECTS score of more than 8. In this study, thrombectomy reduced the severity of disability over the range of the mRS (adjusted odds ratio for improvement of 1 point, 1.7; 95% confidence interval (CI), 1.05 to 2.8) and led to higher rates of functional independence (mRS 0–2) at 90 days (43.7% versus 28.2%; adjusted odds ratio, 2.1; 95% CI, 1.1 to 4.0) [8].

The PISTE (Pragmatic Ischaemic Thrombectomy Evaluation) was a pragmatic multicenter French clinical trial published in 2017. In this study, 65 patients with anterior circulation LVO who had received IV tPA within 4.5 from stroke onset were randomized 1:1 into groups of patients who received IV tPA alone (control group) and patients who received additional mechanical thrombectomy with a target interval time for IV tPA start to arterial puncture of <90 min. In this study, patients who were candidates for thrombectomy if noninvasive vascular imaging (CTA or MRI) showed occlusion of the intracranial ICA, M1 segment of the MCA, or a single M2 MCA branch. Intervention was to be initiated as quick as possible, and a maximum of 90 min from start of IV tPA to start of the MT procedure was permitted. The primary outcome was the proportion of patients achieving independence defined by a mRS score of 0–2 at day 90. In the intention-to-treat analysis, there was no significant difference in disability-free survival at day 90 with MT (absolute difference 11%, adjusted OR 2.12, 95% CI 0.65 to 6.94; P = 0.20). Secondary analyses showed significantly greater likelihood of full neurological recovery (mRS 0–1) at day 90 (OR 7.6, 95% CI 1.6 to 37.2; P = 0.010) [69].

The HERMES collaboration was formed to pool patient data from the first five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA). This meta-analysis concluded that endovascular thrombectomy reduced disability from anterior circulation stroke with LVO, and benefits could be seen in most patients, irrespective of patient characteristics including age or geographical locations [70]. The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2.6. More importantly, in pre-specified subgroup analysis, HERMES revealed that there was a significant benefit in groups that were not eligible for tPA and in a small group of patients who had a large core infarct measured by pretreatment ASPECT scores. These findings represent the foundation of upcoming trials that will evaluate the effect of endovascular therapy in those.
populations. Table 2 demonstrates a comparison of these trials.

While these pivotal endovascular trials were in process, an emerging literature suggested that the evolution of ischemic penumbra into the ischemic core and the rate of progression of irreversible injury were highly variable among individuals. This variability is likely mediated by the adequacy of collateral blood flow and the metabolic milieu of stroke patients. Thus, by measuring the individuality of penumbra evolution, the time the window for endovascular therapy could potentially be expanded in selected individuals. DEFUSE 2 demonstrated that outcomes following endovascular thrombectomy differ between patient subgroups based on an MRI profile that suggested that salvageable tissue was present (target mismatch). This study included patients in whom endovascular therapy was anticipated to begin within 12 hours of symptom onset. Patients with target mismatch had greater odds of good functional and radiographic outcomes following reperfusion therapy when compared with patients without target mismatch [71]. In DEFUSE 2, the growth rate of early DWI lesions in these patients was highly variable. A slower rate of DWI growth was associated with a greater penumbral salvage and improved functional outcome following revascularization. These findings suggested that assessing acute infarct growth rates could help identify patients who are most likely to benefit from revascularization [72].

Table 2: Comparison of randomized clinical trials of endovascular thrombectomy in acute ischemic stroke.

<table>
<thead>
<tr>
<th>RCT</th>
<th>Time window for intervention</th>
<th>Number of patients</th>
<th>Median NIHSS</th>
<th>Median ASPECTS</th>
<th>IV tPA (0−2 at 90 days)</th>
<th>TICI score 2b/3 (%)</th>
<th>mRS 0−2 at 90 days (%)</th>
<th>sICH (%)</th>
<th>Death rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>&lt;6 h from onset</td>
<td>I: 233, C: 267</td>
<td>I: 17, C: 18</td>
<td>I: 9, C: 9</td>
<td>I: 87.1, C: 90.6</td>
<td>73</td>
<td>I: 33, C: 19</td>
<td>I: 7.7, C: 6.4</td>
<td>I: 21, C: 22</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>&lt;12 h from onset</td>
<td>I: 165, C: 150</td>
<td>I: 16, C: 17</td>
<td>I: 9, C: 9</td>
<td>I: 72.7, C: 78.7</td>
<td>71</td>
<td>I: 33, C: 29</td>
<td>I: 3.6, C: 2.7</td>
<td>I: 10, C: 19</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>&lt;6 h from onset</td>
<td>I: 98, C: 98</td>
<td>I: 17, C: 17</td>
<td>I: 9, C: 9</td>
<td>I: 100, C: 100</td>
<td>88</td>
<td>I: 60, C: 36</td>
<td>I: 0, C: 3.1</td>
<td>I: 9, C: 12</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>&lt;6 h from onset</td>
<td>I: 35, C: 35</td>
<td>I: 17, C: 13</td>
<td>I: NR, C: NR</td>
<td>I: 100, C: 100</td>
<td>86</td>
<td>I: 71, C: 40</td>
<td>I: 0, C: 5.7</td>
<td>I: 9, C: 20</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>&lt;8 h from onset</td>
<td>I: 103, C: 103</td>
<td>I: 17, C: 17</td>
<td>I: 7, C: 8</td>
<td>I: 68, C: 77.7</td>
<td>66</td>
<td>I: 44, C: 28</td>
<td>I: 1.9, C: 1.9</td>
<td>I: 18, C: 16</td>
</tr>
<tr>
<td>PISTE</td>
<td>&lt;6 h from onset</td>
<td>I: 33, C: 32</td>
<td>I: 18, C: 14</td>
<td>I: 9, C: 9</td>
<td>I: 100, C: 100</td>
<td>87</td>
<td>I: 57, C: 35</td>
<td>I: 0, C: 0</td>
<td>I: 21, C: 13</td>
</tr>
<tr>
<td>DAWN</td>
<td>6–24 h from onset</td>
<td>I: 107, C: 99</td>
<td>I: 17, C: 17</td>
<td>I: NR, C: NR</td>
<td>I: 4.7, C: 13.1</td>
<td>84</td>
<td>I: 49, C: 13</td>
<td>I: 6, C: 3</td>
<td>I: 19, C: 18</td>
</tr>
<tr>
<td>DEFUSE 3</td>
<td>6–16 h from onset</td>
<td>I: 92, C: 90</td>
<td>I: 16, C: 16</td>
<td>I: 8, C: 8</td>
<td>I: 11, C: 9</td>
<td>76</td>
<td>I: 45, C: 17</td>
<td>I: 7, C: 4</td>
<td>I: 14, C: 26</td>
</tr>
</tbody>
</table>

RCT: randomized clinical trial; I: intervention group; C: control group; MR CLEAN: Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; ESCAPE: Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; SWIFT PRIME: Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; EXTEND-IA: Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; REVASCAT: Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation LVO Presenting within Eight Hours of Symptom Onset; PISTE: Pragmatic Ischaemic Stroke Thrombectomy Evaluation; DAWN: DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; IV tPA: intravenous recombinant tissue plasminogen activator; TICI: thrombolysis in cerebral infarction; d: day; mRS: modified Rankin Scale; sICH: symptomatic intracranial hemorrhage; NR: not reported.

The DAWN multicenter randomized trial sought to determine the efficacy of endovascular thrombectomy using the TREVO stent retriever in acute stroke 6–24 hours after symptoms onset. Patients who had evidence of LVO in the anterior circulation on noninvasive vascular imaging (CTA or MRA), who had last been known well 6–24 hours earlier, and who had a determined mismatch between the radiological core infarct measured by an absolute 30% decrease on CBF or DWI and the clinical deficit according to age (<80 years or ≥80 years) were included in the study. Most of the population included patients who did not receive IV tPA because of late presentation. Patients were stratified into three groups: Group A, ≥ 80 years of age, NIHSS ≥ 10, and infarct volume < 21 ml; Group B, < 80 years, NIHSS ≥ 10, and infarct volume < 31 ml; and Group C, < 80 years of age, NIHSS ≥ 20, infarct volume 31 to < 51 ml. Infarct volume was processed using RAPID. In each of the three strata, patients were then randomized 1:1 into a thrombectomy plus standard medical care (thrombectomy group, n = 107) or to standard medical care (control group, n = 107). The trial was stopped early because results of a prespecified interim analysis indicated a high probability of benefit with thrombectomy. The utility-weighted mRS at 90 days was 5.5 in the thrombectomy group versus 3.4 in the control group.
The rate of functional independence (mRS 0–2) at 90 days was 49% in the thrombectomy group versus 13% in the control group. Symptomatic intracranial hemorrhage (6% in the thrombectomy group and 3% in the control group, \( P = 0.50 \)) and 90-day mortality (19% versus 18%, \( P = 1.00 \)) did not differ significantly between the two groups [10]. The number needed to treat to achieve functional independence at 90 days was 2.8.

DEFUSE 3 is the most recent randomized trial assessing thrombectomy in patients beyond 6 hours from last known well. This multicenter study sought to assess the efficacy of mechanical endovascular thrombectomy using second generation stent retrievers and/or aspiration techniques in patients with AIS presenting 6 to 16 hours after they were last known to be well. This trial included patients with proximal anterior circulation LVO, an initial infarct size of less than 70 ml measured by DWI or absolute CBF reduction <30% of normal tissue, and a ratio volume of ischemic tissue on perfusion imaging (defined as \( T_{\text{max}} > 6 \text{ secs} \)) to infarct volume of \( \geq 1.8 \). The study was halted early due to efficacy. 182 patients were randomized, 92 patients into the endovascular therapy group and 90 into the medical therapy group. Endovascular therapy plus standard medical therapy was associated with a more favorable distribution of 90-day mRS scores when compared to medical therapy alone (OR, 2.77; \( P < 0.001 \)). Endovascular therapy was also associated with a greater percentage of patients with functional independence (mRS 0–2) at 90 days (45% versus 17%, \( P < 0.001 \)) [11].

When selecting patients for mechanical thrombectomy in patients with AIS onset in <6 hours, current guidelines do not recommend additional neuroimaging beyond CT and CTA or MRI and MRA [9]. This is based on the fact that THRACE and MR CLEAN required only noncontrast CT and demonstration of LVO, and both demonstrated benefit in the treated group [4, 73]. Therefore, criteria based on additional imaging could exclude patients who might benefit from treatment. However, in patients with AIS within 6 to 24 hrs from onset and anterior LVO, additional advanced imaging (CT perfusion, DW-MRI, or MRI perfusion) is recommended to assist in selecting patients for MT based on DAWN and DEFUSE 3 criteria [9].

These studies represent a new imaging-based approach for the selection of patients who are most likely to benefit from endovascular thrombectomy. As described by Hacke [74], the usual 6-hour time window for stroke treatment was replaced with a "tissue (viability) window." These trials represented the bases to the current 2018 AHA guidelines [9].

5. Anesthesia for Endovascular Thrombectomy

The best approach to patient sedation, analgesia, and/or anesthesia during endovascular thrombectomy (EVT) has been controversial. This is because most, but not all, observational studies have suggested outcomes that are more favorable when conscious sedation (CS) is used instead of general anesthesia (GA) [73, 75, 76]. The key questions that follow these observations are whether the apparent adverse effect of GA was due to (1) selection bias and/or (2) a process variable (e.g., workflow) or a physiological variable (e.g., blood pressure) related to GA. The answer appears to be "probably yes" to all of these potential explanations.

In terms of selection bias, the great majority of observational studies have reported patients who were selected for GA had greater stroke severity at presentation (e.g., greater NIHSS). Other biases present in many observational studies include (1) a disproportionate assignment of posterior circulation strokes to GA; (2) inclusion of patients who required intubation prior to thrombectomy to GA; (3) inclusion of patients who failed sedation to GA; (4) a greater frequency of proximal (or tandem) occlusions to GA; and (5) a comparison of noncontemporaneous populations (GA patients early in the experience and CS patients later in the experience). Some meta-analyses have attempted to adjust for NIHSS [77], including a recent meta-analysis by Campbell et al. which suggests that GA for EVT was associated with a worse outcome when compared with patients who were not treated under GA. Although these meta-analyses have adjusted for certain baseline variables, other forms of bias remain yet to be explored. Thus, meta-analyses have not entirely provided insight into these questions.

Institutional workflow practices likely contribute to the apparent association between GA and delays in the start of treatment in some observational studies. In the ESCAPE trial, in which only 9% of EVT patients received GA, (1) time between CT scan and arterial puncture was 22 minutes more with GA (RR = 1.43 (95% CI = 1.05–1.93)); and (2) time between arterial puncture and reperfusion was slightly (~5 minutes), but not significantly, greater with GA (RR = 1.15 (95% CI = 0.77–1.70)) [78]. In contrast, in the SWIFT PRIME trial, in which 36% of EVT patients received GA, neither the time between CT scan and arterial puncture (median 52 minutes) nor the time between arterial puncture and reperfusion (median 32 minutes) was greater with GA; RRs of 0.96 (95% CI = 0.81–1.13), and 0.91 (95% CI = 0.74–1.13), respectively [79]. Thus, it is likely that if, how, and when the anesthesia team is included in the workflow and preparation of the patient prior to EVT is the basis for differences among observational studies regarding treatment delays associated with GA. In particular, when the anesthesia team participates only when a “rescue” is required, GA will appear to be unfavorable both in terms of workflow and outcome. It is also likely that differences among centers in the location of the neurointerventional suite (near versus far from the operating rooms) and availability of the Anesthesia team for emergent procedures can explain some of the apparent delays associated with GA. Nevertheless, if GA is selected, the process of induction of GA and endotracheal intubation unavoidably adds some delay in the onset of treatment. As will be discussed, randomized trials indicate that delay is small, on the order of 10 minutes.

A key determinant of EVT effectiveness is the adequacy of collateral perfusion to the penumbra prior to establishing reperfusion [80, 81]. The most likely reason is that good collaterals result in greater cerebral blood flow (CBF) to the ischemic penumbra [82, 83]. At least in part, collateral flow to
the penumbra depends on systemic blood pressure [84]. Because collateral perfusion is so important, it follows that decreases in systemic blood pressure prior to reperfusion may be injurious. This has been observed in two recent observational studies. First, in a subset of 60 GA patients from the MR CLEAN trial, decreases in intraprocedure mean arterial pressure (MAP) were associated with less favorable outcome (mRS) (per 10 mmHg decrease from baseline MAP (which was 100 mmHg) OR = 0.60 (95% CI = 0.43–0.90); P = 0.03) [85]. In a different study by Whalin et al., all patients underwent EVT with CS (dexmedetomidine) [86]. Patients presented with a MAP ≥ 107 mmHg and functional outcome was associated with all indices of decreased MAP prior to reperfusion. Almost identical to the MR CLEAN results, in patients receiving CS, a decrease in MAP below 100 mmHg decreased the likelihood of good outcome (per 10 mmHg decrease OR = 0.78 (95% CI = 0.62–0.99); P = 0.043). Thus, with both CS and GA, any substantive decrease in blood prior to reperfusion may be harmful. Outcome differences between CS and GA in some observational studies may be explained, at least in part, because of blood pressure differences between CS and GA [87, 88].

With this background, the findings of three single-center randomized clinical trials (RCTs) of CS versus GA for EVT can be placed in context: SIESTA [89], ANSTROKE [90], and GOLIATH [91]. As summarized in Figure 3, all the three trials found GA to not be associated with less favorable 3-month functional outcomes. All three trials had similar intraprocedure blood pressure goals: SIESTA (systolic pressure = 140–160 mmHg); ANSTROKE (systolic pressure = 140–180 mmHg); and GOLIATH systolic pressure ≥ 140 mmHg and MAP ≥ 70 mmHg. Most patients, including those receiving CS, required vaso pressors to maintain arterial pressure, but with much greater frequency and dosage in patients receiving GA. Nevertheless, in both ANSTROKE and GOLIATH, the minimum value for intra-EVT MAP and the percentage of patients who had >20% decrease in intra-EVT MAP were greater in GA patients. Thus, it is much more difficult to maintain blood pressure at pre-EVT values with GA than with CS.

As summarized in Table 3, in all three RCTs, GA appeared to increase the time between evaluation and arterial puncture by about 10 minutes—an interval consistent with the time required to induce GA and intubate the patient. Good reperfusion was slightly, but not significantly, greater with GA. In SIESTA and ANSTROKE, 14% and 16% of the sedation patients required conversion to GA during EVT, respectively, primarily because of troublesome patient movement. In contrast, in GOLIATH, only 6% of the sedation patients required conversion to GA. Why CS was more successful in GOLIATH than in the other two trials is not obvious. In ANSTROKE, there was a higher incidence of pneumonia in the GA group, while in the CS group, angiographic quality was worse. In SIESTA, the GA group also demonstrated a higher incidence of pneumonia (13.7% versus 3.9%, P = 0.03), along with hypothermia (32.9% versus
of evidence.

vascular thrombectomy remain controversial due to the lack of many of the postprocedural approaches following endovascular thrombectomy. In large vessel occlusion stroke, IV tPA results in a recanalization rate that varies between 13% and 45% [16]. On the other hand, mechanical thrombectomy in recent trials has shown successful revascularization (thrombolysis in cerebral infarction score ≥2b) in more than 70% of cases [70]. With this in mind, efforts to increase perfusion with permissive hypertension up to 24–48 hours are commonly practiced in patients who receive IV tPA only [95]. This enables adaptation of the collaterals to accommodate increase blood flow in a durable fashion. In contrast, persistent elevated blood pressures in the setting of near or total reperfusion and existing ischemic injury may be harmful [94]. A recent retrospectively analysis of patients who underwent endovascular thrombectomy reported that greater values of systolic blood pressure (SBP) in the first 24 postprocedural are independently associated with greater severity of hemorrhages within 48 hours and worse functional outcomes. Notably, hemorrhage was observed at lower mean values of peak SBP in patients who had successful revascularization compared to those who did not [95]. In hemorrhagic transformation, persistent elevated blood pressures in the setting of near or total reperfusion and existing ischemic injury may be harmful [94].

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The most dreaded complication of thrombolysis is ICH. It typically presents with nausea, vomiting, headache, worsening neurologic deficit, and, in severe cases, with altered level of alertness. In the original NINDS tPA trial, the rate of symptomatic ICH (sICH), defined as the presence of hemorrhage on CT of the head and a decline in neurologic status, was present in 6.4% of those receiving r-tPA and 0.6% in those receiving placebo [31]. Of those patients who suffered sICH in the r-tPA group, approximately 50% died at 3 months. 4.4% of patients had asymptomatic ICH. Major systemic hemorrhages were rare, while minor extracranial hemorrhage occurred in 23% of patients treated with IV-tPA (only 3% in placebo). Risk factors for developing sICH after systemic thrombolysis were hypoattenuation on head CT, achieved successful reperfusion, it is reasonable to maintain the blood pressure ≤180/105 mmHg [9]. Recanalization rates with IV tPA differ with those with endovascular thrombectomy. In large vessel occlusion stroke, IV tPA results in a recanalization rate that varies between 13% and 45% [16].

### Table 3: Workflow and reperfusion in randomized trials of conscious sedation (CS) versus general anesthesia (GA) for endovascular thrombectomy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trial</th>
<th>CS</th>
<th>GA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between door, a CT, b and MRI to arterial puncture (min)</td>
<td>SIESTA a</td>
<td>66 ± 20</td>
<td>76 ± 29</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>ANSTROKE b</td>
<td>91 (55–123)</td>
<td>92 (68–121)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>GOLIATH c</td>
<td>54 (40–75)</td>
<td>61 (48–73)</td>
<td>0.13</td>
</tr>
<tr>
<td>Time between arrival in interventional suite to arterial puncture (min)</td>
<td>ANSTROKE c</td>
<td>25 (15–36)</td>
<td>34 (18–47)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>GOLIATH c</td>
<td>15 (12–20)</td>
<td>24 (20–27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI 2b/3 reperfusion</td>
<td>SIESTA a</td>
<td>62/77 = 81%</td>
<td>65/73 = 89%</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>ANSTROKE b</td>
<td>40/45 = 89%</td>
<td>41/45 = 91%</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>GOLIATH c</td>
<td>38/63 = 60%</td>
<td>50/65 = 77%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are reported as either mean ± SD, median (interquartile range), or percentage.

9.1%, *P* < 0.001) and delayed extubation (49.3% versus 6.5%, *P* < 0.001). Despite these findings, none of these studies support the sole use of one technique over the other.

Because these are single-center RCTs, it is not known whether the findings are generalizable. Nevertheless, SIESTA, ANSTROKE, and GOLIATH demonstrate that when (1) GA is integrated into the standard workflow of EVT patients and (2) blood pressure is actively and intensively managed (especially in GA patients), GA does not result in less favorable outcomes than CS. Accordingly, the best evidence indicates that neurointerventional teams can decide to use GA when conditions require it, with less concern that the patient will necessarily be adversely affected. The keys to success with both CS and GA continue to be timely initiation of therapy and support of the penumbra (i.e., blood pressure support) prior to reperfusion. At this time, there is no human data that any specific anesthetic agent or technique is superior to another [92]. An individualized approach, based on patient condition, comorbidities, and expected intraprocedure challenges, appears to be reasonable.

### 6. Postreperfusion Therapy Management

Although guidelines for management of the stroke patient following IV tPA have been established for several years, many of the postprocedural approaches following endovascular thrombectomy remain controversial due to the lack of evidence.

Regardless of the type of reperfusion therapy used, stroke patients should receive intensive neurologic, hemodynamic, respiratory, and metabolic monitoring in a designated stroke or intensive care unit. Stroke patients who received organized care in a stroke unit were more likely to survive, regain independence, and return home when compared to patients who received care in a less organized service or general wards [93].

Hemodynamic support to sustain ischemic penumbral tissue in patients with unsuccessful or partially successful recanalization after reperfusion therapy is essential. However, it is also important to limit the risk of postreperfusion injury and risk of intracerebral hemorrhage (ICH) [94]. Current guidelines recommend that for patients receiving IV tPA and/or mechanical thrombectomy and who have achieved successful reperfusion, it is reasonable to maintain the blood pressure ≤180/105 mmHg [9].
elevated serum glucose and history of diabetes, hypertension, increased stroke severity, and protocol violations with treatment outside of the time window [96–99].

Management of sICH after IV tPA usually starts with discontinuation of the tPA infusion followed by immediate noncontrast head CT. A full coagulation panel including fibrinogen and complete blood count are usually ordered. Unfortunately, most patients usually have completed their IV tPA infusion by the time a hemorrhage is detected on CT. There is no proven reversal agent for IV tPA. However, the suggested reversal options include cryoprecipitate (includes factor VIII), tranexamic acid, or aminocaproic acid on a case by case basis.

Another uncommon complication of IV-tPA is angioedema, which occurs in 1–3% of patients. It typically occurs 30–120 minutes after IV tPA infusion. It is thought to be mediated by a similar pathway implicated in angiotensin-converting enzymes (ACEs) and tends to occur contralateral to the infarct. These patients are usually at a high risk of developing the same complication with ACE inhibitors [100]. Treatment involves the administration of diphenhydramine and H2-blockers, followed by IV methylprednisolone or nebulized or subcutaneous epinephrine. In cases of recognition of angioedema IV, tPA should be discontinued, and patients may require endotracheal intubation or even emergent tracheostomy.

Recently, Guidelines from the Society of Neurointerventional Surgery were published to provide guidance in the postprocedural management of a patient undergoing endovascular thrombectomy [94]. According to these guidelines, ICP monitoring has no defined role in LVO since malignant cerebral edema can cause severe clinical deterioration through herniation syndromes despite normal ICP values. Therefore, continuous ICP monitoring does not substitute for clinical and imaging follow-up [101]. Interventions for malignant cerebral edema demonstrated by imaging can include ICP monitoring, head of bed positioning, hyperosmolar agents, hyperventilation, and decompressive craniectomy. Hyperosmolar agents may benefit patients who present cerebral edema following a large volume stroke. Hyperventilation has a short-lived effect (~1–3 h), and it should be used as a bridging therapy prior to surgical management. Prophylactic hyperventilation however is not recommended. Decompressive craniectomy should be considered in patients who are <60 years of age with large volume strokes who decompensate or who are at imminent risk of decompensating [102]. In patients > 60 years of age, with large volume strokes who decompensate or who are at imminent risk of decompensating, decompressive craniectomy may be considered. However, the mortality benefit may not be followed by functional recovery [103]. EVD placement and sub-occipital craniectomy in patients with cerebellar stroke who deteriorate or at imminent risk of decompensating despite medical management may be considered [94].

Finally, given the association with better neurological outcomes, effort should be made to place stroke patients in aggressive rehabilitation facilities [104], and a 90-day follow-up is a reasonable and appropriate standard follow-up in this population [94].

7. Conclusion
Substantive advances have been made in the acute management of acute ischemic stroke. Recent trials demonstrating the benefit of endovascular therapy have brought a new era in the treatment of stroke. Now that endovascular thrombectomy has been established as part of the standard of care, further research is needed to continue to optimize existing strategies at prehospital and posthospital care and develop newer methods that incorporate adjunctive emerging reperfusion therapies.

Conflicts of Interest
Colin P. Derdeyn owns stock options in pulse therapeutics and received honorarium from Bayer. Santiago Ortega-Gutierrez is a medtronic and styker neurovascular consultant.

References


Refactory status epilepticus is defined as persistent seizures despite appropriate use of two intravenous medications, one of which is a benzodiazepine. It can be seen in up to 40% of cases of status epilepticus with an acute symptomatic etiology as the most likely cause. New-onset refractory status epilepticus (NORSE) is a recently coined term for refractory status epilepticus where no apparent cause is found after initial testing. A large proportion of NORSE cases are eventually found to have an autoimmune etiology needing immunomodulatory treatment. Management of refractory status epilepticus involves treatment of an underlying etiology in addition to intravenous anesthetics and antiepileptic drugs. Alternative treatment options including diet therapies, electroconvulsive therapy, and surgical resection in case of a focal lesion should be considered. Short-term and long-term outcomes tend to be poor with significant morbidity and mortality with only one-third of patients reaching baseline neurological status.

1. Introduction

Status epilepticus (SE) is a neurologic emergency associated with significant morbidity and mortality. It is seen across all ages, and around 200,000 cases are seen in the United States annually [1].

Status epilepticus is defined as persistent or recurrent seizures due to a failure of seizure termination mechanisms. In bilateral tonic-clonic seizures, it has been well accepted that 5 minutes of seizure activity constitutes status and has been shown that long-term consequences begin at 30 minutes of status. Similar data are lacking for focal status epilepticus. However, recently, the International League Against Epilepsy (ILAE) has proposed 10 minutes' duration as a time point for which focal status epilepticus can be defined (termed "point t1") and 60 minutes for which long-term consequences may occur in focal status (termed "point t2") [2]. These are arbitrary terms which lack substantial evidence in the case of focal SE.

Refractory status epilepticus (RSE) occurs when seizures persist despite administration of one first-line medication (IV benzodiazepine) and one second-line medication (IV antiepileptic drug) [3]. Super-refractory status epilepticus (SRSE) is defined as SE that persists despite 24-hour treatment with IV anesthetic and recurs when weaning the patient off the anesthetic [4]. New-onset refractory status epilepticus (NORSE) is defined as new-onset RSE where no discernible cause is identifiable in otherwise healthy individuals [5, 6].

SE is classified based on semiology and clinical manifestations. Trinka et al. proposed semiology as axis 1 of classification of SE. These are broadly differentiated into those with and without prominent motor symptoms. Those with prominent motor symptoms are further divided into convulsive (generalized and focal to generalized), myoclonic, or focal. SE without prominent motor symptoms is termed “nonconvulsive status epilepticus” either with or without coma. The distribution of convulsive and nonconvulsive SE varies widely across different studies [2].

The scope of this review is to primarily provide updates in management of refractory status epilepticus. With this aim, we focused on adult RSE cases. We also tried to exclude the common etiology of anoxic brain injury as it has significantly different managements and outcomes. Given that some status epilepticus research does not clearly differentiate between SE, RSE, and SRSE, some of the matter here will also apply for SE and SRSE.
2. Epidemiology

The incidence of status epilepticus ranges from approximately 5 to 40 per 100,000 based on several population-based studies across the US, Europe, and Asia with a recent meta-analysis reporting an annual incidence of 12.6 per 100,000 [7–9]. There is no significant difference in the incidence of SE in males and females. However, the annual incidence in elderly of 27.1 per 100,000 is approximately four times that of nongeriatric adults. There is no difference in the incidence in developing and developed countries. The more severe and prolonged types of SE are refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE). RSE occurs in 29 to 43% of SE cases, and SRSE in seen in 12 to 26% of SE cases and 13 to 42% of RSE cases.

3. Etiology

Of SE episodes, 29 to 43% will develop into RSE in retrospective studies [3, 12, 15–20]. One large prospective study and one small prospective study show incidence at the lower spectrum of the above range at 33% and 31%, respectively [10, 21]. The etiology of RSE can broadly be categorized into those with existing epilepsy and those with no known history of epilepsy. New-onset refractory status epilepticus (NORSE) could be of unknown cause (idiopathic or cryptogenic being other commonly used terms) or secondary to an inflammatory etiology [5].

An accepted etiological classification of RSE is not available. However, ILAE does broadly break down the etiology of SE into known and unknown as mentioned in Table 1. Known can be further differentiated into acute, remote, and progressive and as part of electroclinical syndromes. Some studies have used this classification as shown in Table 2. An acute symptomatic etiology is the predominant cause accounting for 41 to 77% of the cases. In two studies, the acute symptomatic etiology reached statistical significance as the most common cause of RSE as compared to nonrefractory status epilepticus (NRSE) [3, 10]. One study showed that the remote symptomatic etiology was more likely with NRSE as compared to RSE [21].

A more exhaustive list of SE etiologies is also provided by ILAE (Table 1) [2]. These etiologies are also applicable for RSE. Some other studies have described etiologies in this format (Table 3). When specific etiologies are considered, CNS infections, especially encephalitis, are a frequent cause. Neurocysticercosis is the leading cause of epilepsy in developing countries and worldwide. However, it is likely an uncommon etiology of SE occurring in less than 10% of cases [22]. Interestingly, in one study, anoxic brain injury was the reason in 50% of cases, but no CNS infections were found. Two studies showed encephalitis as a statistically significant most common etiology at 22% and 31%, respectively [3, 12]. Other commonly noted etiologies include unknown, immunological, and cerebrovascular (including hemorrhages). Most studies do not break down cases into those with new onset versus seizure versus established epilepsy. Regardless, missing AEDs is not an insignificant reason for RSE accounting for up to 16% of cases. One study found substance abuse as more likely to be associated with NRSE than RSE [3]. Specific studies mentioned in Tables 2 and 3 excluded anoxic brain injury as an etiology [11, 23]. Etiology is usually singular, but a significant minority can have multiple etiologies. As per an international audit, 13% of patients had two or more etiologies [24]. One study showed nonconvulsive status epilepticus (NCSE) or focal motor seizures at onset as independent risk factors for RSE [19]. Specifically, NORSE has a different distribution of etiologies with the most common being unknown, while a significant number (37%) tend to be secondary to paraneoplastic or autoimmune pathologies [5].

4. Investigations

4.1. Overview. The management of SE is challenging, and establishing an etiology is integral to the treatment of SE. In most cases, the etiology is known, with the usual culprits being previous seizures, intracranial lesions, and infections. However, in cases of refractory and super-refractory status epilepticus, it is often difficult to ascertain a cause.

The initial investigation should be done within minutes of patient arrival and should be inclusive of but not limited to venous blood for analyzing electrolytes, liver function tests, glucose, complete blood count, AED levels (in case of known history of epilepsy), and other drug levels or toxicological screens (e.g., in young patients with new-onset seizures). This should be followed up with computerized tomography of the head as soon as the patient is stable to look for any structural lesion(s) or any acute intracranial lesions like hemorrhages and hematomas that might need emergent intervention. In patients with fever and sudden-onset altered mental status, there should be a low threshold to perform a lumbar puncture to rule out common infections especially herpes encephalitis. An emergent EEG should be considered in cases of prolonged seizures and if the patient is not back to baseline soon to look for NCSE. Consider testing for metabolic and mitochondrial diseases in

<table>
<thead>
<tr>
<th>Table 1: Etiologies of status epilepticus.</th>
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<tbody>
<tr>
<td><strong>Broadly defined etiologies of status epilepticus</strong></td>
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<tr>
<td><strong>Known</strong></td>
</tr>
<tr>
<td>(i) Acute</td>
</tr>
<tr>
<td>(ii) Remote</td>
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<tr>
<td>(iii) Progressive</td>
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<tr>
<td>(iv) In defined electroclinical syndromes</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Specific etiologies of status epilepticus</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
</tr>
<tr>
<td>CNS infections</td>
</tr>
<tr>
<td>Neurodegenerative diseases</td>
</tr>
<tr>
<td>Intracranial tumors</td>
</tr>
<tr>
<td>Cortical dysplasias</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Alcohol related</td>
</tr>
<tr>
<td>Intoxication</td>
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<tr>
<td>Withdrawal of or low levels of AEDs</td>
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<tr>
<td>Cerebral hypoxia or anoxia</td>
</tr>
<tr>
<td>Metabolic disturbances</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
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<tr>
<td>Mitochondrial diseases</td>
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</table>
a young adult with known myoclonus, intellectual disability, and other unexplained neurological and systemic symptoms and signs. Proposed workup in identifying the etiology of RSE if a discernible cause is not apparent with initial testing is described in detail in Table 4 [25]. More detailed discussion on EEG, autoimmune testing, and neuroimaging is provided below.

4.2. EEG. Electroencephalography (EEG) is used to detect and later manage SE. EEG criteria for the diagnosis of SE include frequent repetitive electrographic seizures and repetitive generalized or focal epileptiform discharges of greater than 3 Hz. Repetitive or periodic epileptiform discharges less than 3 Hz can be considered ictal if associated with an improved clinical response with repeated short treatment with a benzodiazepine. Without a clear response, such EEG patterns fall along the ictal-interictal continuum without clear indication or consensus for continued treatment [26].

Patients who are treated after convulsive SE and who go on to have persistent coma for two hours or more develop NCSE in 13 to 48% of cases reviewed [27, 28]. Patients with an underlying brain pathology are more likely to develop NCSE after convulsive SE, while patients with AEDs or alcohol withdrawal are less likely to develop NCSE. Patients who are critically ill with a depressed level of consciousness were found to have NCSE in 8% of cases despite no prior seizures [29]. In about half of the cases, seizures are captured within the first hour of EEG recording [30], and in the comatose, it can take 24 to 48 hours to capture seizures [31].

Continuous EEG (cEEG) is also required to help achieve treatment goals of seizure freedom versus the burst suppression pattern after IVAD administration is initiated [32]. In some instances, the reactivity of EEG to drug administration such as the development of frontal alpha after administration of ketamine has been proposed to be a possible indicator of success [33]. Automated and quantitative EEG (qEEG) software can be employed to aid in the detection of seizures and assessing burst suppression ratios using the color density spectral array and amplitude-integrated EEG. Although qEEG improves the reader time for the EEGer, sensitivity for seizure detection is decreased especially in short seizures with low amplitudes and slow frequencies [34, 35]. False-positive rates can also be high and average about one per hour when qEEG is used alone [34].

4.3. Autoimmune Investigations. Recently, an autoimmune etiology of status epilepticus is increasingly recognized. However, it remains an uncommon cause. Contrarily, it is becoming clear that, in certain circumstances, the autoimmune etiology should be suspected early. Early identification of immune-mediated disorder may lead to immune modulatory intervention early in the disease and improve the outcome. One of the vital presentations of autoimmune encephalitis is new-onset refractory status epilepticus or NORS, which represents up to 40% of refractory convulsive status epilepticus [36]. Other syndromes, perhaps representing a similar spectrum of disorders, described primarily in children include febrile infection-related epilepsy syndrome (FRES) or devastating epileptic encephalopathy in school-aged children (DESC). The following scenarios should heighten the suspicion of autoimmune etiology in patients with status epilepticus: (1) status epilepticus as presentation of new-onset seizures; (2) progression to refractory or super-refractory status epilepticus; (3) relatively recent but explosive onset of seizures; (4) the absence of established epilepsy history; (5) the presence of other neurological problems such as memory loss, autonomic or hypothalamic dysfunction, and ataxia or movement disorder; (6) new psychiatric symptoms or behavioral changes; (7) known history of cancer; and (8) lymphocytic pleocytosis on CSF examination [37].

Commonly associated autoantibodies to refractory status epilepticus are mentioned in Table 5 [38, 39]. Hashimoto encephalopathy and Rasmussen encephalitis are more distinct syndromes and often present with refractory status epilepticus. Hashimoto encephalopathy is associated with very high titers of anti-thyroid peroxidase (a-TPO) antibody and autoimmune thyroiditis, while Rasmussen encephalitis is thought to be a T-cell-mediated disorder, although various antibodies are found in this disorder [40]. Hashimoto encephalopathy responds well to corticosteroids in the majority and is also identified as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) [41]. On the other hand, Rasmussen encephalitis does not respond well to medical management (except some response to IVIg) and often requires surgical intervention in the form of hemispherectomy to halt the progression of the disease and control status epilepticus.

Examination of CSF is helpful but shows nonspecific inflammatory changes with mild pleocytosis and elevation of

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Table 2: Etiology of RSE in selected studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Known (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acute</td>
<td>Remote</td>
</tr>
<tr>
<td>Delaj et al. (RSE versus NRSE) [21]</td>
<td>RSE = 301</td>
<td>58.5</td>
<td>12.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RSE = 268</td>
<td>51.6</td>
<td>15.2</td>
</tr>
<tr>
<td>Holtkamp et al. [3]</td>
<td>36</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.2</td>
</tr>
<tr>
<td>Giovannini et al. [10]</td>
<td>26</td>
<td>77&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
</tr>
<tr>
<td>Kantanen et al. [16]</td>
<td>75</td>
<td>41</td>
<td>51</td>
</tr>
</tbody>
</table>

<sup>a</sup>NRSE was significantly more likely to have a remote etiology as compared to RSE; <sup>b</sup>RSE was significantly more likely to have an acute etiology as compared to NRSE; Delaj et al. differentiated RSE and SRSE cases in their cohort (RSE = refractory status epilepticus and NRSE = nonrefractory status epilepticus).
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Unknown</th>
<th>Cerebrovascular disease</th>
<th>CNS infections</th>
<th>Intracranial tumor</th>
<th>Head trauma</th>
<th>Substance related AEDs</th>
<th>Metabolic disturbances</th>
<th>Hypoxic/anoxic brain injury</th>
<th>Metastatic brain tumor</th>
<th>Autoimmune/ immunological conditions</th>
<th>Sepsis/ systemic infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferlisi et al.</td>
<td>478</td>
<td>20</td>
<td>13</td>
<td>13</td>
<td>3</td>
<td>7</td>
<td>23</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>5</td>
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<tr>
<td>Holtkamp et al.</td>
<td>36</td>
<td>0</td>
<td>30</td>
<td>22*</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>8</td>
<td>0</td>
<td>0*</td>
<td>11</td>
<td>11</td>
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<tr>
<td>Vooturi et al.</td>
<td>45</td>
<td>11</td>
<td>18</td>
<td>31*</td>
<td>9</td>
<td>4</td>
<td>44*</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>7</td>
<td>16</td>
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<tr>
<td>Giovannini et al.</td>
<td>26</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>50*</td>
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<tr>
<td>Hocker et al.</td>
<td>63</td>
<td>4.8</td>
<td>11</td>
<td></td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>16</td>
<td>3</td>
<td>19</td>
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<td>11</td>
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<tr>
<td>Gaspard et al.</td>
<td>130</td>
<td>0</td>
<td>52</td>
<td></td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>37</td>
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<tr>
<td>Kantanen et al. 1,3</td>
<td>75</td>
<td>4</td>
<td>12</td>
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<td>0</td>
<td>17</td>
<td>17</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Sutter et al.</td>
<td>111</td>
<td>9</td>
<td>13</td>
<td></td>
<td>7</td>
<td>14</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>13</td>
<td>23</td>
<td>4</td>
</tr>
</tbody>
</table>

1 Hypoxic/anoxic brain injury excluded; 2 NORSE cases only; 3 preexisting epilepsy in 32% of cases in Kantanen et al. and 10% of cases in Sutter et al.; * statistically significant etiology of RSE as compared to NRSE; # statistically less likely etiology of RSE as compared to SE; NORSE = new-onset refractory status epilepticus, RSE = refractory status epilepticus, and NRSE = nonrefractory status epilepticus.
However, it can be normal in up to 40–50% of patients. Other autoimmune inflammatory markers such as the presence of oligoclonal bands are typically absent. CSF abnormalities can also be transitory and may present in some samples but may not be present during same illness sampled at another time [5, 42]. Antibody testing in serum versus CSF is a difficult one to answer as no systematic review is available, and most studies are retrospective. In general, the presence of a specific antibody in CSF is given more weight in making a definite diagnosis. Likelihood of finding antibodies in CSF is higher compared to checking the serum titer in isolation in cases of anti-NMDA-R and anti-GABAB-R antibody syndromes [43, 44]. The antibody titer in the CSF compared to that of serum, especially higher than the IgG index, is considered a sign of intrathecal antibody synthesis and more likely to be associated with the autoimmune encephalitis.

### 4.4. Neuroimaging

Structural lesions can be responsible for seizures and status epilepticus; hence, structural neuroimaging can reveal abnormalities frequently. A CT scan can reveal either acute abnormalities or an old lesion in case of chronic epilepsy. The lesions that can be easily identified on cranial CT scan include intracranial hemorrhage, vascular malformation, brain tumor, stroke, abscess, or other infectious processes or even brain malformation (Figure 1). Brain MRI with a better definition of the brain structure is more sensitive in identifying structural lesions that might be responsible for epilepsy in the acute or chronic setting [45]. At times, the CT scan may show focal decreased attenuation with effacement of sulci and loss of gray-white differentiation in the area where the seizures originate (Figure 2).

On the other hand, specific, transient peri-ictal MRI abnormalities are reported following status epilepticus. Some of these are transitory, and it is necessary to repeat the MRI after the acute phase has passed. In these cases, MRI may show structural changes, such as edema, necrosis, or hemorrhage.
Table 5: Immunomodulating treatment.

**First-line immunotherapies**

PLEX
- Dosage: various numbers of plasma exchanges reported, typically 5 sessions of plasma exchange
- Advantages: no long-term immunosuppressive effect
- Disadvantages: requires large lumen intravascular indwelling catheter placement increasing chances for line sepsis and procedure-related complication and hemodynamic effect of PLEX can be detrimental in a patient with hypotension due to IVAD use

Corticosteroids
- Dosage: various dose regimens reported in literature. Most commonly used regimen is IV methylprednisolone 1g daily for 5 days followed by weekly single administration of 1g for 4–6 weeks or conversion to oral prednisone 80mg/day with a slow taper
- Advantages: easily available, relatively inexpensive, and familiarity with the drug
- Disadvantages: increases blood pressure, may increase vulnerability for infection, and may worsen hyperglycemia in patients with diabetes mellitus

IVlg
- Dosage: 0.4 g/kg daily for 3–5 days and can be repeated weekly/monthly for 1–3 months
- Advantages: no immunosuppressive effect
- Disadvantages: allergy; increased volume load may worsen congestive heart failure; increased risk of thrombotic events such as deep vein thrombosis and pulmonary embolism and risk of renal function impairment especially in the presence of renal artery stenosis may cause aseptic meningitis presenting as headache and allergy

**Second-line immunotherapies**

Cyclophosphamide
- Dosage: 750mg/m²
- Advantages: well-known drug with a long track record which can be used by administrating monthly
- Disadvantages: may not be immediately effective (suitable for maintenance therapy), may increase the risk of infections, has teratogenic potential, may increase the risk of future malignancy, and side effects include hemorrhagic cystitis, severe cardiotoxicity, alopecia, and nausea/vomiting

Rituximab
- Dosage: most commonly used dose is 375 mg/m² every week for 4 weeks
- Advantages: usually well tolerated
- Disadvantages: may not be immediately effective and may cause cytopenia, infusion reaction, potential for severe allergic reaction, renal failure, pregnancy, and hepatitis

Mycophenolate
- Dosage: 250 mg–2 g per day (no standard dosing for autoimmune encephalitis)
- Advantages: oral preparation for long-term use, usually well tolerated
- Disadvantages: may not be immediately effective (suitable for maintenance therapy), needs oral administration, may be difficult in the ICU setting, may cause significant gastrointestinal side effects and hyperglycemia, and highly protein bound so may interact with AEDs that are protein bound

Azathioprine
- Dosage: 1–3 mg/kg per day
- Advantage: oral preparation for long-term use, usually well tolerated, and can be used as a steroid-sparing agent
- Disadvantage: side effects such as elevated hepatic transaminases, leukopenia, pancreatitis, and immunosuppression

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Figure 1: Emergent CT scan of the head obtained in the setting of new-onset recurrent seizures or status epilepticus showing various abnormalities. (a) A CT without contrast showing an area of a rounded lesion (arrow) with perilesional edema proven to be a cerebral abscess. (b) A postcontrast CT scan showing a small round enhancing lesion (arrow) with perilesional edema later proven to be neurocysticercosis. (c) A postcontrast CT showing a large enhancing heterogeneous mass (arrow) pathologically proven to be glioblastoma cerebri. (d) A CT scan without contrast showing an area of calcifications (arrow) in arteriovenous malformation in a young man presenting with recurrent seizures.
cluster of seizures and are thought to be the direct result of recurrent seizures in a short time span. These changes are potentially caused by increased perfusion and metabolic activity due to ictal activity, postictal hypoperfusion, and transient ultrastructural pathologic alteration [46]. Commonly described findings include increased T2 fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) signals, a variable degree of reduction in the apparent diffusion coefficient (ADC), and enlargement of the hippocampus ipsilateral to the seizure onset (Figures 3 and 4). Other patterns described include gyral distribution, T2 prolongation, and restricted diffusion involving the area of seizure origin or propagation (Figures 4 and 5). Less commonly seen abnormalities include patchy focal enhancement due to blood-brain barrier breakdown and increased vessel caliber/flow indicative of increased perfusion around the seizure origin (Figures 4 and 5). More distant abnormalities are also described, such as restricted diffusion affecting the splenium [47], unilateral or bilateral increased signal on T2 FLAIR imaging affecting the ipsilateral posterior thalamus/pulvinar region, or the contralateral cerebellum representing cerebellar diaschisis [48, 49] (Figure 5). The involvement of the pulvinar tends to occur less frequently compared to the cortical involvement and is associated with longer duration of SE suggesting the spreading pattern of seizure discharges. The location of the DWI and T2W changes correlates with the ictal onset but cannot be utilized as definitive seizure onset area as it can be seen in the distant areas of seizure spread in.
the epileptic network, for example, ipsilateral pulvinar. In animal models of status epilepticus, the severity of decrease in ADC maps correlated with the extent of neuronal loss [50]. The areas of increased T2 FLAIR and DWI signals in the acute phase may progress to show atrophy of the affected structure on subsequent MRI, suggesting that the initial abnormalities were indicative of the neuronal loss (Figure 6) [51–54]. It is likely that MRI changes are more common in patients with focal seizures, and EEG patterns often include lateralized periodic epileptiform discharges or intermittent seizure patterns with rhythmic epileptiform discharges and may also have a preexisting cortical lesion [52, 55].

Neuroimaging findings in autoimmune status epilepticus are variable and can be normal. If abnormal, they tend to show an increased signal on T2W or FLAIR images involving medial temporal lobe structures unilaterally or bilaterally. It may also show multifocal lesions involving the temporal neocortex, medial frontal/parietal and orbitofrontal lobes, or hypothalamus. Occasionally, contrast enhancement is seen in the same area suggesting disruption of the blood-brain barrier. These changes usually lag clinical onset and are present few days during the illness and represent cytotoxic edema with an increased signal on DWI images. Over time, repeat MRIs have shown atrophy of some of these structures [54, 56, 57].

5. Treatment

5.1. Existing Paradigm. The primary aim of treating a patient with SE is the rapid termination of the SE and aggressive management of an underlying acute symptomatic etiology. Left untreated, it can progress to RSE and SRSE. In a general sense, the longer the duration of untreated SE, the harder it is to treat [58, 59]. The Veterans Affairs Cooperative Study, one of the most significant studies of SE, showed that SE treatment becomes less effective with increasing duration of SE [10]. Notably, nonconvulsive status epilepticus is harder to treat and is controlled by AEDs in only 15% of cases compared to convulsive status epilepticus, in which up to 55% of cases may respond to the first AED [10]. Moreover, the short-term mortality rate of RSE is between 16 and 39% which is about three times higher than that of NRSE [3, 18, 19, 60].

Figure 3: MRI changes associated with acute status epilepticus. A middle-aged man presenting with a previous history of epilepsy following a generalized tonic-clonic seizure. He failed to recover to baseline, and an urgent EEG was obtained that showed focal status epilepticus from the right temporal region (black arrow in (a)). MRI images obtained during the same admission showed an increased signal and swelling of the right hippocampus on axial (white arrow in (b)) and coronal (white arrow in (c)) FLAIR images.
The current guidelines for managing SE are not age-specific because the disease pathophysiology and the drug effects on neuronal receptors are the same in infants, children, and adults (though neonates may be the exception). They follow the sequential intravenous administration of three groups of drugs: (1) benzodiazepines aimed at rapid SE control; (2) classical AEDs targeted at early resistant forms and longer-term coverage; and (3) general anesthetics for SRSE.

Benzodiazepines (BZDs) act as positive allosteric modulators on gamma amino butyric acid (GABA) type A receptors [61]. A BZD in any form, either intravenous (IV), intramuscular (IM), or per rectal (PR), is recommended as the initial therapy of choice [62]. The commonly used BZDs are IM/IV midazolam and IV lorazepam or diazepam (PR in children). BZDs are more likely to work if used early, closer to seizure onset and decrease in effectiveness as seizure duration increases. This is because GABA receptors are internalized with time, and there is a paucity of receptors on the axonal membrane for the BZDs to work on [63]. One study showed that, during SE, endocytosis/internalization of GABA type A postsynaptic receptors is accompanied by an increase in the number of excitatory N-methyl-D-aspartate receptors (NMDARs) per somatic synapse on dentate granule cells. It is postulated that the decrease in GABA receptors with simultaneous upregulation of NMDARs may in part be the reason that BZDs fail to work in prolonged SE leading to RSE [64].

Early administration of benzodiazepines has been associated with better outcomes when studied in the prehospital setting in the randomized, controlled Prehospital Treatment of Status Epilepticus (PHTSE) trial. The trial showed that both diazepam and lorazepam were an effective prehospital treatment for seizures, as compared with placebo with early termination in 59.1% of patients receiving 4 mg IV lorazepam, 42.6% of those receiving 10 mg IV diazepam, and 21.1% of those receiving IV placebo [65]. Establishing intravenous access in patients who are having seizures in the prehospital environment can be challenging and time-consuming. The RAMPART trial compared IM midazolam (10 mg) to IV lorazepam (4 mg) in the prehospital status epilepticus setting. This study showed a lower rate of endotracheal intubation and recurrent seizures with IM midazolam administered through an autoinjector compared to IV lorazepam, thus proving that the IM route is safe and effective and can be considered as an alternative for prehospital treatment of convulsive seizures [66]. However, inadequate BZD dose by first responders continues to be a problem possibly leading to increased conversion to RSE, especially NCSE [67].

**Figure 4:** Various modalities of MR imaging showing changes associated with focal status epilepticus. A previously healthy middle-aged man presented with his first generalized tonic-clonic seizure followed by intermittent receptive dysphasia. Continuous EEG monitoring showed nonconvulsive status epilepticus originating from the left temporal leads (gray arrow in (a)). His MRI showed a focal area of abnormality involving the posterior superior aspect of the left temporal lobe. The DWI images showed a gyri form pattern of the increased signal (arrow in (b)), part of which showed decreased attenuation on an ADC map (arrow in (c)). The same area showed hypointensity on the T1W images with minimal pial surface enhancement (d, e) and increased signal with sulcal effacement on FLAIR images (arrow in (f)). The pathology showed neuronal necrosis, prominent reactive astrocytosis, microglial activation, and sparse mononuclear inflammation.
In a patient with SE, a second-line agent (IV AED) should be started at the onset as well, by giving a loading dose. The agents of choice are phenytoin (PHT)/fosphenytoin, valproic acid (VPA), levetiracetam (LEV), and lacosamide (LCM) [68]. There is no clear evidence that one drug is superior to another [69]. LEV has been studied extensively and has proven to be
useful in SE [70–73]. It has a good safety profile which has made it the first-line AED for many providers. However, one retrospective study reported that VPA was better than LEV and PHT in controlling SE [74]. There are also good data for the use of VPA in SE, and it has been studied in six randomized controlled trials (RCTs) showing good efficacy [75–80]. The relative efficacy of VPA, LEV, and the other second-line treatments for SE (phenytoin and phenobarbital) has been assessed in a systematic review with meta-analysis [81]. Efficacy of LEV (68.5%) and VPA (75.7%) were found to be comparable with that of phenobarbital (73.6%) and higher than that of PHT (50.2), suggesting that LEV and VPA may represent valid alternatives to phenobarbital and PHT as second-line treatments of SE. One direct and indirect comparison of meta-analysis of LEV versus PHT or VPA for convulsive SE showed no difference between any two AEDs [82]. LCM is a relatively newer agent, and several studies have found it to be effective, and one study showed it to be even better than VPA [83, 84].

Overall, there is no single best second-line IV AED, and a drug may be chosen based on the treating provider’s clinical experience and if the patient is already on one of these medications for chronic epilepsy. LEV and PHT (or fosphenytoin) tend to be the most common second-line IV AED.

5.2. Fourth-Generation AEDs. Although intravenous formulations are preferred for their fast onset of action, oral medications have been tried for RSE. Amongst the oral formulations, the ones which can be used in patients with SE are clobazam (CLB), perampanel (PER), topiramate (TPM), oxcarbazepine (OXC), and eslicarbazepine (ESL). CLB has been studied in patients with RSE as add-on therapy and found to be effective in terminating RSE [85, 86]. PER was marginally effective in a study by Rohracher et al. [87]. Similarly, TPM has been used as an add-on for RSE [88] but was not effective as monotherapy [89]. Kellinghaus et al. reported that OXC was effective in RSE after the failure of first- and second-line agents but required frequent electrolyte monitoring due to hyponatremia [90]. Brivaracetam was found to be effective in terminating SE in one study in Germany [91].

5.3. Other Medications Used as AEDs. RSE requires the administration of intravenous anesthetic drugs (IVADs) in the form of propofol (PRO), midazolam (MDL), or pentobarbital (PTB). Treatment of RSE has not been studied prospectively, and guidelines give a variety of options. In a systematic review comparing these three agents, PTB was efficacious and was associated with a lower frequency of short-term treatment failure, breakthrough seizures, and a change to a different IVAD. However, it was also associated with a higher frequency of hypotension which reflects the strong negative cardiovascular inotropic effect [92–94]. The administration of IVADs is typically associated with continuous EEG monitoring. Titration is done to achieve either seizure cessation or background suppression with the goal of EEG burst suppression patterns. In the same systematic review as above, compared with seizure suppression (30% of patients), titration of treatment to EEG background suppression (45% of patients) was associated with a significantly lower frequency of breakthrough seizures (4 versus 53%) and a higher frequency of hypotension (76 versus 29%). When aiming for burst suppression, the characteristic of the bursts is a better predictor of success in termination of RSE [95, 96]. While one theory suggests that burst suppression allows for the brain to rest, recover, and suppress the epileptiform activity, the disadvantage might be a worse outcome overall due to the need to use anesthetics and resulting prolonged intubation and hospitalization [11].

Ketamine’s success in the treatment of RSE has been established in several studies and ranges from 32 to 73% [33, 97–99]. The ketamine’s unique mechanism of action is through N-methyl-D-aspartate (NMDA) blockade, which in animal models has been demonstrated to be effective in prolonged SE when glutamatergic excitation is enhanced [100]. Additionally, ketamine tends to be more hemodynamically stable with protective properties in concomitant traumatic brain injury [101, 102].

Allopregnanolone is an endogenous neurosteroid with potent GABA modulation which demonstrated anti-convulsant properties in animal models [103]. In humans, brexanolone (SAGE 547) is an injectable allopregnanolone formulation used in the treatment of refractory status epilepticus in human patients [104]. Larger trials have demonstrated tolerability of brexanolone without demonstrable efficacy [105].

5.4. Immunosuppression. Treatment of RSE with immune etiology should follow the usual route with adequate dosing of abortive therapy with benzodiazepines followed by appropriately AEDs and IVADs. However, if an autoimmune cause is suspected especially if supported by the presence of autoantibody, prompt treatment with immunomodulating treatment is warranted. Early use of immunomodulating therapy may be associated with favorable outcomes. Considering progressive atrophy of the brain structures involved in status epilepticus on follow-up MRI, early aggressive therapy seems more appropriate. Though there may be increasing willingness to try immunotherapy early, there is no consensus or good quality data to suggest that one particular medication or therapy is better than others. Various immunotherapies are suggested and summarized in Table 5 (adapted from Zaccara et al.) [36, 37, 106].

One can start with IVIg or high-dose pulse corticosteroid therapy when an autoimmune etiology is suspected in case of RSE [107–110]. Initial laboratory evaluation to look for serum and CSF autoantibodies should be completed before initiation of immunomodulating therapies. If first-line treatment fails, one can consider either additional doses of the first-line treatment or PLEX [106, 111]. However, if IVIg is used initially, deploying PLEX is likely to negate its effects as it is likely to wash out immunoglobulins given prior. There is experience with various second-line therapies for the treatment of autoimmune encephalitis with

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neurological manifestations including seizures. However, in individual case series, there are very few patients with status epilepticus. Hence, the usefulness of the information for acute treatment of status epilepticus is limited. There are no systemic studies of using long-term immunotherapy for individuals who have autoimmune encephalitis with epilepsy. There is ample variability across the different case series with varying approaches and agents. At this point, the timing of the use of second-line immunomodulating agents in the management of SRSE is unclear. Their role in long-term management is more established, although the selection of an agent is on a case-by-case basis [44, 112–114]. Second-line agents are likely to take a longer time to produce the desired immunological response and are suited for chronic management of the underlying immunological dysfunction. This approach has limited application in the treatment of the acute setting of SRSE. On a different note, Rasmussen encephalitis, a childhood syndrome of refractory partial status epilepticus with presumed autoimmune etiology, is often treated with immunotherapy (chronic steroids, IVIg, or other immunosuppressive agents) or with hemispherectomy [115, 116].

5.5. Alternative Treatment. There is likely a significant publication bias for the following infrequently used treatment modalities.

There are 6 case reports described in the literature of vagus nerve stimulator (VNS) which is being used successfully in the treatment of SE. These included two children and six adults. It was effective in both generalized and focal SE. There was wide variability when the VNS was used ranging from 11 days to 14 months. However, all cases used a rapid increase in the VNS current and duty cycle. Efficacy varied between more than 50% improvement and seizure freedom. It was tolerated very well [117–122].

There have been 14 case reports and one recent case series of 8 patients with ECT use in the treatment of SE [123, 124]. Conventional thinking suggests that seizure induction during ECT is necessary for the cessation of SE; however, various cases have demonstrated that subconvulsive stimuli might be effective or even seizure induction might fail. From the published reports, there seems to be a success rate of approximately 70% for initial SE cessation. In the case series by Ahmed et al., ECT was initiated 7 to 39 days after onset of SE, and the patients underwent between 3 and 7 sessions guided by clinical judgment [123].

There are three documented case reports of the use of deep brain stimulation (DBS) in the treatment of SE. One patient with Rasmussen encephalitis of the left hemisphere origin and resulting epilepsy partialis continua intractable to immunotherapy was successfully treated with left caudal zona incerta (CZi) DBS [125]. Two other cases had bilateral DBS with leads placed in the centromedian nucleus (CMN): both of whom had the cessation of SE, but one patient who had cardiac arrest had poor clinical outcome [126, 127].

The ketogenic diet has been used in the treatment of refractory epilepsy in children for decades. While there is more experience of using diet therapy for treatment of SE in children [128, 129], it has recently been used in adults [130–138]. Ketogenic and modified Atkins diets lead to ketosis which controls seizures for unclear reasons. Ketosis likely also has some anti-inflammatory properties. Fat to carbohydrate and protein ratio of 4:1 or 3:1 is used. Across published case reports and series of 26 adult patients, diet therapy was started between days 2 and 60 of SE. It can take up to 16 days for ketosis to achieve, and the response can take up to 31 days since the onset of therapy but is less likely to occur after 14 days. Overall, the outcome is good with the resolution of SE in most cases that achieve ketosis although functional outcome can be variable [139]. In the largest recent prospective study of 15 patients, acidosis and hyperlipidemia seem to be the most common side effects leading to discontinuation of therapy in 3 patients. In the same study, few patients had switched to the modified Atkins diet by the time of long-term follow-up of 6 months [133].

Hypothermia not only produces electrocerebral silence [140] but may also be useful in treating RSE [141]. Experimental evidence further supports hypothermia’s significant anticonvulsant properties [142–144]. Hypothermic rats demonstrated reduced epileptic brain damage related to SE when compared to normothermic and hyperthermic groups. Cooling, particularly in conjunction with diazepam, diminished the amplitude and frequency of epileptic discharges that translated into an anticonvulsant effect in rats tested [144]. The anticonvulsant mechanism by which hypothermia works is not fully understood. Hypothermia reduces excitatory transmissions, decreases the global cerebral metabolic rate of glucose and oxygen, reduces ATP breakdown, and stimulates glycolysis by intracellular alkalization enhancing energy production [143, 145]. Despite the ample data supporting hypothermia as both an effective neuroprotective agent and a powerful anticonvulsant, it remains unclear whether its use will translate into improved outcomes for patients with RSE [146].

5.6. Surgery. Surgical interventions for the treatment of RSE include acute resective surgery and disconnection procedures such as multiple subpial transection or corpus callosotomy [147]. Outcome data in acute status epilepsy are based on case reports and small series and present some publication bias. However, when pooled in a literature review, 56% of both adult and pediatric patients who underwent surgery for treatment of RSE were seizure free, and 31.4% had improvement in seizure frequency [148]. In pediatric patients, malformation of cortical development is the most common etiology (58.3%) of RSE, for which surgery has been commonly employed; in adults, the etiology varied and had variable outcomes [148]. Success was observed when surgery was done early (within one week) or later (greater than one month) [149, 150]. Unilateral lesion on MRI and congruency with EEG appear to correlate with a better outcome based on case reports and larger series, and patients with an inflammatory etiology do not do as well with acute status epilepsy which highlights the importance of a preoperative workup before the decision to consider a palliative surgical option [148].
Various steps and options proposed for management of RSE are depicted in Figure 7.

6. Prognostic Factors and Outcomes

Many studies have looked at prognostic factors of SE overall and did not specifically obtain data for RSE or SRSE, so these studies will have an admixture of relatively better prognosis for SE and worse prognosis for SRSE.

The underlying etiology of RSE seems to be the most frequent and important prognostic factor. Stroke-induced RSE has a poor prognosis and high mortality [151]. In another study, postanoxic encephalopathy and brain tumors were independently associated with the increased rate of death [20]. A previous history of epilepsy was associated with poor outcome in one study but not in another [20, 152].

Lower levels of consciousness (coma or stupor) at the onset of SE are more likely to result in mortality. Also, GCSE and NCSE were independently associated with death [20]. Duration of RSE and duration of coma greater than ten days also have an unfavorable outcome [11, 152]. On the other hand, there have been reports of survival even after severely prolonged SE [153]. EEG findings of periodic epileptiform discharges are more frequently associated with RSE [19]. On the contrary, the absence of burst suppression and isoelectric EEG is associated with good outcome possibly due to the reduced burden of anesthetic medications and decreased duration of coma and hospitalization [11]. Low levels of albumin at onset are independently associated with RSE and death as per one study [154]. Reduction or withdrawal of AEDs is likely not going to result in RSE [3, 155]. Various prognostic factors from selected studies are noted in Table 6.

Short-term mortality in adults ranges from 9% in SE to 38% in RSE [20, 156, 157]. Status epilepticus severity score (STESS) was developed to assess short-term mortality and comprises variables of consciousness impairment, worst seizure type, age, and history of seizures. Stupor or coma, NCSE, and age greater than 64 years were considered poor outcome factors, while a history of previous seizures was considered a good outcome factor. A score of two or less is supposed to have a good short-term outcome [158], but a score greater than two has low specificity for poor outcome. Addition of modified Rankin scale to STESS and named mSTESS has been proposed. Based on one study, mSTESS has better positive predictive value (PPV) than STESS at scores greater than 3. An mSTESS has a PPV of 81.8% for short-term mortality as compared to 59.6% for the STESS [159].

In an extensive review of therapies in 596 convulsive RSE and SRSE cases, assessment of long-term outcomes showed that approximately 35% of cases reached baseline neurological status, 35% died, and 30% had variable neurological deficits. The duration at which outcome was assessed varied from months to years [107]. Since that review, multiple studies of RSE (convulsive and nonconvulsive) with cases numbering less than 100 have been published with a similar long-term outcome—recovery to baseline in 36%, neurological deficit in 23%, and death in 41% [23].

7. Conclusion

SE and its more severe forms RSE and SRSE continue to be a significant management challenge. NORSE tends to have autoimmune and paraneoplastic etiologies commonly, but clarity in testing and management protocols is lacking. Clinicians and patients would also benefit from a comprehensive meta-analysis of prognostic factors as currently different studies show variable results. Also, studies dedicated to
Table 6: Long-term outcome factors for RSE in selected studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Older age</th>
<th>STESS &gt; 2</th>
<th>History of epilepsy or status epilepticus</th>
<th>Longer duration</th>
<th>Sepsis/systemic infection</th>
<th>Baseline functioning</th>
<th>EEG findings (no BS or isoelectric EEG)</th>
<th>Seizure or status epilepticus type</th>
<th>Etiology category</th>
<th>Cardiac arrhythmia</th>
<th>Long duration of mechanical ventilation</th>
<th>Need for CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantanen et al. [23]</td>
<td>↓ NE</td>
<td>NE (epilepsy)</td>
<td>NE</td>
<td>NA</td>
<td>NE</td>
<td>NA</td>
<td>NE</td>
<td>NE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Madzar et al. [152]</td>
<td>↓ ↓</td>
<td>↓ (epilepsy)</td>
<td>↓¹</td>
<td>↓</td>
<td>NE</td>
<td>NA</td>
<td>NE</td>
<td>NE</td>
<td>NA</td>
<td>NE</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hocker et al.² [11]</td>
<td>NE NA</td>
<td>NE</td>
<td>↓³</td>
<td>↓⁴</td>
<td>NA</td>
<td>↑</td>
<td>NE</td>
<td>NA</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NA</td>
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<tr>
<td>Sutter et al. [20]</td>
<td>NE NA</td>
<td>NE</td>
<td>↓</td>
<td>NE</td>
<td>NA</td>
<td>NA</td>
<td>↓⁵</td>
<td>↓⁶</td>
<td>NA</td>
<td>NE</td>
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</tbody>
</table>

¹, worse outcome; ², better outcome; NE, no effect; NA, not assessed or not available; CPR, cardiopulmonary resuscitation; BS, burst suppression; ³, duration of RSE >10 days; ⁴, anoxic brain injury etiology excluded; ⁵, duration of coma >10 days; ⁶, effect seen with pneumonia; ⁷, effect seen with GCSE and NCSE; ⁸, effect seen only with hypoxic/anoxic brain injury and intracranial tumor.
management and outcome in special populations including elderly, pregnant females, and those with neurodegenerative diseases are lacking. There is also a need for large multicenter trials for early prediction models for SE and how different predictive factors should be weighted. Future studies should aim to tackle these issues.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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New Optic Nerve Sonography Quality Criteria in the Diagnostic Evaluation of Traumatic Brain Injury

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Background. New sonographic quality criteria to optimize optic nerve sheath diameter (ONSD) measurements were suggested. The latter were correlated to elevated intracranial pressure (ICP) in traumatic brain injury (TBI). Aim. We investigated whether ONSD measurements were correlated to simultaneous ICP measurements in severe TBI. Methods. Forty patients with severe TBI (Marshall Scale ≥II and GCS ≤8) participated in the study. All patients had an intraparenchymal ICP catheter inserted, while ONSD was measured bilaterally, upon admission and over the next 48 hours, based on the new sonographic criteria. A total of 400 ONSD measurements were performed, while mean ONSD values of both eyes were used in the analysis. Results. ONSD measurements were strongly correlated to ICP values (r = 0.74, p < 0.0001). Receiver operator curve (ROC) analysis revealed that the ONSD cutoff value for predicting elevated ICP was 6.4 mm when using the mean of both eyes (AUC = 0.88, 95% CI = 0.80 to 0.95; sensitivity = 85.3%, specificity = 82.6%). Linear regression analysis nested models revealed that sex (p = 0.006) and height (p = 0.04) were significant predictors of ONSD values. Conclusion. When applying the new sonographic quality criteria, ONSD is strongly correlated to ICP in severe TBI. Whether to use such criteria to monitor ONSD as a proxy for ICP trend in TBI remains to be further explored.

1. Introduction

Traumatic brain injury (TBI) is frequently complicated by elevated intracranial pressure (ICP). Secondary brain injury due to elevated ICP and decreased perfusion pressure to the brain is an important cause of morbidity and mortality in those patients. In order to treat this complication, elevated ICP must be diagnosed quickly and accurately [1–3]. Direct monitoring of ICP through insertion of an intracranial monitor is considered the gold standard in the diagnosis of intracranial hypertension [4]. Due to the invasive nature of these procedures and associated risks, intracranial monitoring is usually not employed until after elevated ICP is already suspected based on clinical picture and noninvasive testing such as computed tomography [5]. Additionally, invasive monitoring may not always be possible due to coagulopathy, thrombocytopenia, or lack of relevant procedural expertise and tools [6].
Ultrasound assessment of optic nerve sheath diameter (ONSD) has been assessed as a promising tool to aid in the diagnosis of elevated ICP both in TBI and various non-traumatic brain-injured patients [7, 8]. NZ_the optic nerve sheath (ONS) is contiguous with the dura matter surrounding the brain and contains cerebrospinal fluid, which allows transmission of pressure from the cranium [9]. In previous studies, acute increases in ICP have correlated strongly with increases in ONSD [8, 10, 11]. However, there is still some disagreement about the recommended threshold value above which a certain ONSD should indicate a pathological increase in ICP. Recommendations for these cutoff values have varied from 5.0 to 5.9 mm with sensitivities and specificities ranging from 70 to 100% and 30 to 100%, respectively, depending on the study and the optimal cutoff value identified [7, 8, 10]. NZ_here is also some dispute about what the normal range of ONSD is in healthy individuals, and how age, height, weight, sex, and ethnicity affect this [12–16]. Part of this variance may be due to the lack of rigorous standardization for obtaining quality images of ONSD. Currently, the most popular method studied in the literature for evaluating ONSD is the “black stripe” method and involves identifying the ONS as a black line behind the globe and measuring its diameter 3 mm behind the papilla [11, 17–20]. Recently, new sonographic quality criteria for optimizing ONSD measurements in critical care settings were suggested as a way to standardize measurements across different sonographers and scans and to improve image quality (Table 1; Figure 1) [21]. However, the new quality criteria have not been prospectively evaluated in the literature.

In this study, we compared ONSD measured by the application of the new quality criteria to invasive ICP evaluated simultaneously by intraparenchymal catheter in intensive care unit (ICU) patients with severe TBI. Hence, we aimed on identifying an optimal ONSD threshold value corresponding to elevated ICP.

### Table 1: Proposed sonographic quality criteria for optic nerve sheath diameter (ONSD) measurements (adapted from Sargsyan et al. [21]).

<table>
<thead>
<tr>
<th>Sonographic quality criteria for optimization of ONSD measurements</th>
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<tbody>
<tr>
<td>(i) ONSD measurement should not be made through the lens (even the edge of the lens may not be visible on the image).</td>
</tr>
<tr>
<td>(ii) Sonographic differentiation (contrast) between the nerve proper and the arachnoid (cerebrospinal fluid space) must be obvious; measuring a “dark stripe” behind the globe without nerve and arachnoid differentiation is not acceptable.</td>
</tr>
<tr>
<td>(iii) The outer border of the arachnoid must be identifiable for actual ONSD measurement; clear, well-focused images must thus allow confident measurement of the inner diameter of the dural sheath.</td>
</tr>
<tr>
<td>(iv) Ideal views of the optic nerve demonstrate the point of its penetration into the globe, that is, “dark meets dark” (nerve meets vitreous without interposition of thick echogenic layer of the posterior sclera).</td>
</tr>
<tr>
<td>(v) Good views offer opportunities for additional information potentially useful with growing experience, such as tortuosity of the nerve, hypoechochogenicity of the arachnoid, and its irregularity; this also allows seeing the optic disk area protrusion into the globe and flattening of the posterior globe in chronic ICP elevations (premorbid) that may mimic acute states in ICU.</td>
</tr>
<tr>
<td>(vi) Correct standardized measurements: since the most distensible portion of the sheath is at the 3–4 mm distance from the vitreoretinal interface, measurements are performed at this level in a direction perpendicular to the axis of the nerve.</td>
</tr>
<tr>
<td>(vii) It is highly recommended to measure ONSD bilaterally and in more than one image frame. This is an important quality assurance mechanism.</td>
</tr>
<tr>
<td>(viii) For ONSD trend monitoring, the previous record with images must be reviewed to ensure similar views and measurement technique. Prior images should be available at bedside (from the machine or in printout) for reference. ONSD measured in sagittal planes should not be compared with ONSD from axial planes.</td>
</tr>
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</table>

Figure 1: Employment of the “black stripe” method (white arrow) may underestimate the actual optic nerve sheath diameter (ONSD) measurement (x–x) based on the new sonographic quality criteria in patients with increased intracranial pressure.

Ultrasound assessment of optic nerve sheath diameter (ONSD) has been assessed as a promising tool to aid in the diagnosis of elevated ICP both in TBI and various non-traumatic brain-injured patients [7, 8]. The optic nerve sheath (ONS) is contiguous with the dura matter surrounding the brain and contains cerebrospinal fluid, which allows transmission of pressure from the cranium [9]. In

### 2. Patients and Methods

#### 2.1. Patients. This prospective study was performed from January to September 2017 at the Neurocritical Care Unit (NCCU) of the polyvalent ICU department (King Saud Medical City, Riyadh, KSA). It is an ongoing registered study (ISRCTN 33349) performed by our group to explore further the role of ONSD sonographic monitoring in brain-injured patients. In this report, we included only adult patients.
Patients with orbital trauma and/or known optic nerve pathology were excluded from the study. Severity of brain injury was graded according to a combination of Glasgow Coma Scale (GCS) and brain computed tomography scan derived Marshall Scale (1–VI) as previously described [22]. Power sample analysis determined that 400 ONSD measurements would provide approximately 90% statistical power (alpha = 0.05, one-sided) to compare the former to invasive ICP values. 

Upon hospital admission, all patients with severe TBI (GCS ≤ 8 and Marshal Scale ≥ II) underwent clinical evaluation by a multidisciplinary team of experts including neurosurgeons and neurointensivists. Patients were transferred to a specialized 16-bed neurocritical care unit within the premises of the polyvalent 120-bed ICU whether or not a neurosurgical intervention was performed depending on the clinical case scenario. All patients were closely monitored and placed under brain protective strategy in the ICU. Briefly, in all patients mean arterial blood pressure (MAP) was continuously monitored using an invasive arterial catheter to exclude hypotension (systolic blood pressure <110 mmHg). Heart rate was monitored to exclude bradycardia (heart rate <60 beats/minute), and pulse oximetry was initiated to exclude hypoxemia (arterial oxygen saturation <95%). Upon ICU admission, all patients were sedated and mechanically ventilated (volume-controlled continuous mandatory ventilation mode), and arterial carbon dioxide tension was maintained at 20–25 mmHg throughout the study period. Sedation vacation was performed on daily regular intervals to evaluate patients’ GCS and neurological status. Families’ consent was obtained in all cases for participation in the study. The latter conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional ethics committee.

2.2. Methods and Data Collection. Sonographic examinations were conducted using Philips HDI1XE (Philips Medical Systems; Bothell, WA, USA) equipped with a 10–20 MHz linear transducer. All patients were examined in the supine position as previously described [17–22], the exam takes less than a minute (images stored and analyzed later), and then the patient’s head immediately repositioned to 30 degrees head up position as per TBI protocol. The ONSD was measured according to the new quality criteria as detailed elsewhere (Table 1) [21]. The ONSD was recorded for both eyes in all cases, while the mean value of all measurements which were electronically stored and reviewed by expert sonographers was used in the statistical analysis. Initial sonographic scans were performed 15–20 minutes after a CT scan to determine severity of brain injury and eligibility for the study. Both eyes were scanned for each patient, and the mean of both readings was correlated to simultaneous ICP recordings. ONSD scans were repeated at 6, 12, 24, and 48 hours later for a total of 5 observations per patient per eye in the ICU, thus resulting in a total of 400 ONSD measurements. The latter were performed by a single expert operator who was blinded to the patient’s identity and to invasive ICP findings with the intention of minimizing bias. A Camino intraparenchymal catheter (Camino Laboratories, San Diego, CA, USA) was inserted by neurosurgeons in the frontal region of each patient. ICP measurements were continuously monitored and recorded simultaneously to ONSD measurements. Elevated ICP was defined as an ICP of 20 mmHg or greater [23].

2.3. Statistical Analysis. Summary data are expressed as mean ± standard deviation. Paired t-tests were used to compare the ONSD values between the left and right eyes of each patient. Initially, ONSD was correlated to ICP to establish linearity in a simple regression model. Subsequently, the impact of age, gender, weight, height, and ICP on ONSD was explored through a multiple regression nested (hierarchical) model. A multiple regression nested model simply means one model is a subset of another, where the independent variables are entered in the model at different levels, age and gender being the first level, followed by height and weight in the second, and ICP last. This model is known to produce unbiased estimates of the standard errors associated with the regression coefficients, and its goodness of fit is judged by the $r^2$ change as nested models are sequentially entered [24]. Additionally, receiver operating characteristic (ROC) curves were obtained to specify cutoff values of ONSD and ICP. Cutoff values were the threshold values that maximized the sum of specificity and sensitivity. A two-tailed significance level of 0.05 was regarded statistically significant. All data were stored on a spreadsheet (Excel 2011; Microsoft, Seattle, WA, USA), and analyses were performed using a commercially available statistical package (SPSS version 24; IBM Corporation, Armonk, NY, USA).

3. Results

Table 2 presents the baseline features of the study population. A total of 40 patients with severe TBI were analyzed in this study. All patients underwent a baseline clinical
evaluation and brain CT scan assessment. Patients exhibited a mean GCS of 4.5 ± 2.9 and a mean brain CT Marshall Scale of 4 ± 1.5 upon ICU admission. Concomitant injuries recorded upon admission included abdominal trauma (20%), thoracic trauma (40%), and other orthopedic injuries (65%). Thirty-four out of the 40 cases (85%) underwent various neurosurgical interventions (i.e., craniotomies, evacuation of subdural hematomas, and so on). In this cohort, males suffering from severe TBI were more than females and exhibited significantly higher ICP values (27.4, 95% CI 26.1 to 28.7 mmHg) compared to the latter (24.5, 95% CI 23.0 to 26.0 mmHg).

During the first 48 hours after admission, all patients underwent ONSD measurements as well as invasive ICP monitoring per study protocol as described previously. Both eyes were scanned for each patient, and the mean of both readings was correlated to simultaneous ICP recordings. One hundred seventy-seven (88%) of the 200 ONSD measurements for each eye were performed on patients with elevated ICP (>20 mmHg) who were managed according to the TBI protocol of our NCCU, while the remaining 23 (12%) were performed on patients with normal ICP recordings. The difference, although existent, in mean ONSD size between the left and right eyes was not significant (p = 0.35; 6.9 mm (95% CI 6.7 to 7.0 mm) versus 6.8 mm (95% CI 6.7 to 7.0 mm), respectively).

In simple linear regression model, ONSD measurements were strongly correlated to invasively monitored ICP values (r = 0.74, p < 0.0001; Figure 2). In the multiple regression nested model, ICP was a strong significant predictor of ONSD (standardized coefficient beta = 0.72, p < 0.001). In the same model, sex and height were significant predictors of ONSD, with p values of 0.006 and 0.04, respectively, whereas age (p = 0.32) and weight (p = 0.28) were not significant predictors in the model. The model was well fitted with r² change from 8% to 55% after the addition of all the nested models (Table 3).

The ROC curve analysis based on the diagnostic value of 20 mmHg or more for high ICP revealed that the optimal cutoff value of ONSD for predicting elevated ICP was 6.4 mm when using the mean of both eyes (area under the ROC curve = 0.88, 95% CI = 0.80 to 0.95; Figure 3). The sensitivity and the specificity of the cutoff value were 85.3% and 82.6%, respectively. Notwithstanding, when the ROC curve was repeated using a diagnostic value of 25 mmHg for high ICP, the optimal cutoff value of ONSD for predicting elevated ICP was 6.6 mm (AUC = 0.89, 95% CI = 0.84 to 0.94; Figure 4) baring a sensitivity of 87.2% and specificity of 80.2%, respectively, for the cutoff value.

In this cohort, five cases out of the 40 (12.5%) progressed towards cerebral circulatory arrest and were declared brain dead following pertinent clinical examination per hospital protocol. Four out of the 5 brain dead cases were harvested according to the regulations of the Saudi Center for Organ Transplantation (SCOT).

4. Discussion

Ultrasound evaluation of ONSD appears to be an increasingly popular noninvasive method of assessing ICP.
Sensitivity

In the nested regression analysis, not surprisingly, most of the changes in ICP readings in the left and right eyes although differences were evident and documented. Interestingly, the value we calculated for the optimal cutoff point to determine elevated ICP from sonographic ONSD measurement (6.4 mm) is higher than most previously published values. In our ROC analyses, the area under the curve is quite large at 0.88, indicating high accuracy, which is similar to previous studies [8]. When a higher cutoff value (25 mmHg) for increased ICP was used in ROC analyses, the corresponding cutoff value for ONSD predicting high ICP was also found to be higher (6.6 mm), resulting in higher sensitivity but lower specificity nevertheless (Figures 3 and 4).

In the nested regression analysis, not surprisingly, most of changes in ONSD can be predicted by simultaneous changes in ICP. Also, we found a small but significant association between ONSD, sex, and height. The relationship of ONSD to height is interesting as it has not been previously observed in the literature [12–16]. This would require further validation in a larger cohort; moreover, our study is ongoing and, therefore, we would be able to validate the correlations in the future by analyzing a larger patient sample.

The difference in ONSD between genders in our study is consistent with data recently published in a cohort of healthy men and women [16]. However, such difference is higher in our study likely due to the features of our cohort who consisted entirely of patients with severe TBI. In severe TBI, ICP is more likely to be elevated, which could potentially augment the already naturally occurring difference in size between men and women’s ONSD. Men are also more likely to suffer from a TBI, are more likely to be seriously injured, and have a grave prognosis [25] which may partially account for the significantly larger ONSD in these patients. In our study, males suffering from severe TBI were higher than females and exhibited significantly higher ICP values (27.4, 95% CI 26.1 to 28.7 mmHg) compared to the latter (24.5, 95% CI 23.0 to 26.0 mmHg). Further studies are required to analyze the effect of gender on ONSD measurements.

The present data suggest a reevaluation of previously defined thresholds for elevated ICP, either through new large prospective studies or remeasuring archived ONSD imaging utilizing the new criteria. These findings are important, as they indicate that previously published cutoff values for elevated ONSD generated using the black stripe method may not be applicable to images obtained using the new quality criteria. These higher cutoffs are similar to those seen when looking at ONSD as a predictor of elevated ICP in MRI studies [26].

The new quality criteria offer potential benefits such as standardization of ONSD measurements. The latter could translate to more accurate measurements between different sonographers, patients, or in the same patient over time. Hence, adopting new quality criteria opens the exciting possibility of monitoring ICP trend over time by ONSD measurements, a practice that has so far had disappointing results in the literature [22]. Notably, a large study showed that management based on measurement of ICP by intracranial catheter had no additional benefit compared to management based on clinical and imaging findings alone [27]. Despite lack of evidence of benefit, inaccessibility except in specialized centers, and risks of bleeding and infection, intracranial ICP monitoring is still the standard of care in patients with severe TBI [4]. More study is needed to determine whether ONSD can be safely used to diagnose ICP without the need of invasive monitoring or it will remain a noninvasive adjunct to help triage patients for intracranial catheter placement.

Despite the importance of our findings, there are several limitations to our study which could be mainly attributed to its inherent design and the small cohort of patients studied. Moreover, the results are likely only generalizable to the currently studied population. It has been previously shown that different ONSD cutoffs are useful for nontrauma and traumatic elevated ICP patients using the “black stripe” method [10], and we have no reason to believe this is
different using the new quality criteria. Factors such as the acuity of elevation of ICP, comorbid medical illness, and co-occurring orbitofacial trauma all likely affect ONSD [21]. Also, pretest probability of raised ICP in the patient population affects the optimal ONSD cutoff to use [8]. Despite the rigorous quality criteria followed, ONSD is still an operator-dependent task that requires precise measurement of a 3–6 mm structure to the nearest 0.1 mm. Inherence in a measurement technique of this type will be erroneous due to intraobserver and interobserver variation, which has been studied elsewhere [20, 28–30] as in the current report we utilized a single operator to minimize bias. We found that ONSD measurements made using the new quality criteria could provide useful information for detecting elevated ICP in severe TBI. More study is clearly required to evaluate the new criteria for ONSD measurements in other patient populations as well as to determine whether ONSD might be used for ICP trend monitoring in brain-injured patients. Hopefully, this ongoing study might be able to answer some of the aforementioned raised points in the upcoming years.

5. Conclusion

This is the first study applying new quality criteria for the sonographic evaluation of ONSD. When applying the new quality criteria in TBI patients, ONSD measurements are highly correlated to invasive ICP values; moreover, a larger cutoff value of ONSD is evident as compared to past data (“black stripe” method). Also, a previously undetected correlation between ONSD and anthropometric data may exist. ONSD measurements may be used to help identify which TBI patients need ICP-lowering treatment, particularly when intracranial monitoring is contraindicated or not available. Further study is needed to determine how these new criteria affect ONSD measurement in other patient populations, and whether they can be used in the future to monitor ONSD as a proxy for ICP trend in brain-injured ICU patients.

Disclosure

This manuscript was presented at the Critical Care Canada Forum, Toronto, Canada, on October 3, 2017, as eposter titled “New Optic Nerve Sonography Quality Criteria in the Diagnostic Evaluation of Traumatic Brain Injury.” Full details are available at the link https://cccf.multilearning.com/cccf/2017/eposter/198223/fahad.faqhi.new.optic.nerve.sonography.quality.criteria.in.the.diagnostic.html.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Ibrahim Soliman participated in designing the study and statistical analysis and drafted the manuscript. Garrett G. R. J. Johnson, Lawrence M. Gillman, Frederick A. Zeiler, and Waleed Tharwat Aletreby performed the statistical analysis and drafted the manuscript. Fahad Faqhi, Abdullah Balhamar, Nasir Nasim Mahmood, Shahzad Ahmad Mumtaz, and Abdulrahman Alhathary participated in data collection and quality control and drafted the manuscript. Christos Lazaridis participated in the study design and drafted the manuscript. Dimitrios Karakitsos performed the sonographic measurements and drafted the manuscript.

References


Review Article

Cerebral Pathophysiology in Extracorporeal Membrane Oxygenation: Pitfalls in Daily Clinical Management

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Extracorporeal membrane oxygenation (ECMO) is a life-saving technique that is widely being used in centers throughout the world. However, there is a paucity of literature surrounding the mechanisms affecting cerebral physiology while on ECMO. Studies have shown alterations in cerebral blood flow characteristics and subsequently autoregulation. Furthermore, the mechanical aspects of the ECMO circuit itself may affect cerebral circulation. The nature of these physiological/pathophysiological changes can lead to profound neurological complications. This review aims at describing the changes to normal cerebral autoregulation during ECMO, illustrating the various neuromonitoring tools available to assess markers of cerebral autoregulation, and finally discussing potential neurological complications that are associated with ECMO.

1. Introduction

The purpose of ECMO is to provide adequate oxygenated blood to the tissues by bypassing either the pulmonary or cardiopulmonary system in severe respiratory failure and/or cardiac failure, respectively. The ECMO circuit essentially consists of 4 components: (1) an inflow cannula which drains blood from the venous system, (2) a pump which provides flow in the circuit, (3) an oxygenator, which is responsible for oxygenating the venous blood, and (4) an outflow cannula which delivers the warmed oxygenated blood back into the venous or arterial system [1, 2]. In venovenous- (VV-) ECMO, the outflow cannula is directed into the venous system (typically the femoral, internal jugular, or subclavian vein), whereas in venoarterial- (VA-) ECMO the outflow cannula is inserted into the arterial system (usually the femoral artery but the subclavian, axillary, and common carotid arteries can be used as well) [3].

The effects on cerebral circulation for a patient on ECMO are complex and not precisely understood. This review aims at delineating the possible mechanisms of impaired cerebral autoregulation, identifying the different modalities to measure cerebral blood flow characteristics, and reviewing the neurological complications associated with ECMO.

2. Cerebral Autoregulation

Cerebral autoregulation is the ability of cerebral arterioles to maintain steady cerebral blood flow (CBF) over a varying range of mean arterial pressures (MAP) [4]. This is termed as cerebral pressure autoregulation and can be classically described using the Lassen curve [5], where MAP on the x-axis is plotted against CBF on the y-axis (Figure 1). A steady CBF is achieved by vasodilation and vasoconstriction of cerebral arterioles which in turn are influenced by neurogenic, myogenic, and metabolic mechanisms responding to changes in MAP [6].
These are complex processes and are poorly understood in the setting of different pathophysiological states. Neurogenic regulation is thought to be influenced via sympathetic and cholinergic pathways [7]. Myogenic regulation is carried out by the smooth muscle cells in the cerebral vessels which are responsible for myogenic tone and subsequently cerebral vascular resistance [8]. Metabolic regulation is related to changes in perineuronal concentrations of CO$_2$, O$_2$, K$^+$, Ca$^{2+}$, H$^+$, and adenosine [9–13]. It should be kept in mind, however, that there is likely segmental and regional heterogeneity between the pial and parenchymal arteries and arterioles and their response to the above regulatory factors which can result in varying levels of CBF over the same range of CPP in different regions of the brain [8, 14–16].

In pathological conditions, cerebral autoregulation may become impaired. There may be focal impairment or global impairment depending on the pathological condition [17–19]. One of the most studied disease states resulting in impaired autoregulation is traumatic brain injury (TBI). Multiple studies have shown distorted autoregulation after varying degrees of TBI even within “normal” ranges of CPP and CBF [20–23]. The loss of cerebral autoregulation can result in ischemia or edema, and hemorrhage even with slight changes in CPP. This is likely secondary to a combination of impaired neurogenic, myogenic, metabolic, and pressure dependent mechanisms [24]. Similar aberrations in cerebral autoregulation have been found in ischemic stroke [18, 25–27], intracerebral hemorrhage [28–30], and subarachnoid hemorrhage [31–33].

3. Cerebral Blood Flow Regulation on ECMO

Perhaps the greatest parallel that can be drawn to provide insight into autoregulation during ECMO is from the cardiopulmonary bypass (CPB) literature. On-pump CPB resembles VA-ECMO to a certain extent from which we can extrapolate similar changes in cerebral and systemic hemodynamics leading to changes in cerebral blood flow and autoregulation. In certain studies, up to 24% of patients have showed signs of impaired autoregulation during CPB, with numbers higher during the rewarming phase from hypothermia [34]. Cerebral blood flow was found to be arterial-pressure passive, resulting in a linear correlation of CBF and MAP indicating impaired cerebral autoregulation. Predictors of impaired autoregulation included male gender, average cerebral blood flow velocity, time-averaged cerebral oximetry index (COx) during CPB, PaCO$_2$, and preoperative aspirin use according to one study which utilized near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) as tools to monitor cerebral autoregulation [35]; NIRS is a commonly used modality to monitor regional cerebral oxygen saturation during cardiac surgery, and its relationship with MAP can serve as an indicator of cerebral autoregulation. NIRS can provide information of cerebral oxygen supply and oxidative metabolic demand, from which a surrogate CBF can be derived [36–40]. TCD has been commonly used to measure CBF velocities from which CBF can be derived to give an estimation of CPP [41, 42]. In addition, TCD can also be used to detect microemboli [43]. The mean lower limit of autorregulation, after which a decrease in CPP results in a loss of CBF according to the Lassen curve, has been found to be 66 mmHg with values ranging from 40 to 90 mmHg in patients undergoing CPB [44]. Instead of targeting a specific number, it has been postulated that individualizing blood pressure management parameters using cerebral autoregulation monitoring can prevent neuronal injury [45].

Cerebral blood flow and autoregulation may be affected differently during ECMO. Initial animal studies suggested that CBF and oxygen metabolism did not change with the initiation of VA-ECMO [46]. However, at flow rates of less than 150 mL/kg/min, cerebral blood flow and oxygen delivery were found to decrease [47]. In addition, cerebral autoregulation was found to be impaired in newborn lambs on VA-ECMO at flow rates of 120–150 mL/kg/min [48]. These studies suggest that even though adequate cerebral blood flow can be maintained on VA-ECMO by adjusting flow rates, there are still aberrations in cerebral autoregulation. A possible explanation for these findings may be due to the pumps being used in the ECMO circuit. Previously used roller pumps have now been replaced by centrifugal pumps which provide continuous blood flow to the cerebral circulation. Pump flow is characterized by decreased systolic upstroke, lack of dichrotic notch, and continuous diastolic flow [49], and this loss of pulsatile flow may be responsible for the impairments seen in cerebral autoregulation. Indeed, low pulsatility indices have been demonstrated in patients undergoing ECMO along with decreased cerebral blood flow velocities [50, 51]. The pulsatility of CBF during partial bypass is likely related to preserved myocardial reserve while the regulation of CBF during prolonged bypass may be dependent on the presence of pulsatile flow [52].

Multiple pediatric studies have shown abnormal cerebral autoregulation in patients undergoing ECMO using non-invasive measures [53–55]. Most of these studies used the presence of a correlation between MAP and cerebral oxygen saturation using NIRS as a surrogate of cerebral autoregulation.
A recent study correlated impaired cerebral autoregulation with abnormal neuroimaging findings [56]. This was a study of 25 pediatric patients who underwent either VA- or VV-ECMO on whom cerebral autoregulation was monitored using MAP and NIRS, focusing on a pressure-passive state. Brain imaging consisted of head ultrasound, CT scan of the head, and MRI of the brain post-ECMO. The study showed a higher degree of cerebral autoregulation impairment during ECMO, measured using wavelet transform coherence [57]; this impairment was associated with severe neuroimaging abnormalities. Another study of 6 pediatric patients showed a higher concordance between MAP and oxyhemoglobin concentrations with decreasing ECMO flow rates, indicative of a loss of autoregulation [50]. These studies suggest that the cerebral circulation undergoes some degree of impairment of autoregulation while on ECMO in the pediatric population, which may affect long-term neurological outcomes. Data to assess similar changes in adults are lacking.

There are various factors that can affect CBF in patients on ECMO. Out-flow cannulation site in VA-ECMO may contribute to variations in CBF. In peripheral VA-ECMO, the femoral artery is usually the site for out-flow cannulation in adults. The return of oxygenated blood directed towards the descending aorta via the femoral artery results in retrograde flow which can result in limb ischemia. In addition, retrograde blood flow creates additional afterload to the left ventricle (LV) which may lead to LV distension, reduced coronary flow, pulmonary edema, and hypoxemia [58]. The high flow states in VA-ECMO which serve to optimize systemic perfusion can compromise LV recovery by increasing afterload and hence pulmonary edema. It can be postulated that CBF may also be affected. In pediatric patients, the out-flow cannulation site can be the carotid artery, which would also potentiate alterations in CBF. Prior studies have shown that carotid artery ligation may produce an acute drop in CBF velocity at the onset of VA-ECMO [49, 59–63]. In addition, internal jugular vein occlusion due to in-flow cannulation can cause cerebral venous hypertension resulting in decreased CBF velocities [64]. A common clinical problem encountered in patients undergoing ECMO is dual circulation or Harlequin syndrome. This mainly represents upper body desaturation due to the position of the out-flow cannula in the distal aortic arch in cases of poor pulmonary function. Given that left ventricular unloading is often incomplete, the blood supply to the coronaries, brachiocephalic, and left carotid may not be adequately oxygenated due to being proximal to the out-flow cannula, resulting in lower oxygen saturations measured in the right arm. The risk of upper body desaturation can be minimized if the out-flow cannulation site is made in the ascending aorta (via sternotomy), axillary artery, subclavian artery, or the carotid artery [65–68]. However, positioning the in-flow cannula in the superior vena cava, instead of the femoral vein, has also been shown to improve upper body oxygenation while keeping the out-flow cannulation site the same [69]. This can reduce the risk of Harlequin syndrome and provide adequate oxygen delivery to the cerebral circulation.

Ventilatory management in ECMO patients can also affect the cerebral circulation. "Ultraprotective" mechanical ventilation (tidal volume of less than 4 mL/kg of ideal body weight) has been a favored strategy in ECMO patients given the reduced rates of pulmonary edema and lung injury [70, 71]; however, it has not been shown to reduce the number of ventilator free days [72]. Higher plateau pressures have been associated with increased mortality [73]. Early higher positive end expiratory pressures (PEEP) has been independently associated with improved overall mortality in patients on ECMO [74]. The effects of these ventilatory strategies on cerebral circulation are not completely understood. Increased PEEP has been shown to increase ICP and decrease CPP in brain injury patients; however, this has not been shown to be clinically significant [75].

Many centers are now employing the addition of an intra-arterial balloon pump (IABP) in conjunction with VA-ECMO for patients in cardiogenic shock due to evidence that it improves outcomes [76]. One study showed adequate carotid blood flow and oxygenation during cardiac arrest with the dual VA-ECMO and IABP regimen [77]. The addition of an IABP can influence CBF depending on the degree of native LV function. One study showed that the addition of an IABP in peripheral VA-ECMO significantly decreased CBF in myocardial stunning. However, as the LV recovered, the CBF tended to increase with the IABP [78]. Further studies need to be conducted to ascertain the changes in CBF and if these changes are clinically significant.

\( \text{PaCO}_2 \) and pH are known to cause significant changes in CBF, and these parameters can rapidly change during ECMO [79]. In addition, peri-ECMO hemodynamic changes can affect the cerebral circulation. ECMO patients have severe derangements in their systemic hemodynamic status as baseline, and the addition of stress due to surgery, sedatives, paralytics, and vaspressors can induce a multitude of changes in the cerebral vasculature. If end-organ perfusion is not adequate, it can result in various systemic complications which may further affect CBF. It is difficult to ascertain exact individual etiologies and their effects on CBF during ECMO due to these reasons.

### 4. Neuromonitoring during ECMO

Neuromonitoring during ECMO is an important measure to obtain data on CBF features. A variety of noninvasive techniques have been suggested, each with their advantages and disadvantages, and these are employed across various institutions. The optimal neuromonitoring protocol has not been well established with current practices dependent on physician preference or device availability.

#### 4.1. Near-Infrared Spectroscopy (NIRS)

NIRS is a non-invasive modality that is able to obtain a continuous measurement of cerebral oxygenation saturation usually by placing a frontal scalp electrode. The near-infrared light penetrates up to 2–2.5 cm into the brain and detects the concentrations of oxygenated and deoxygenated hemoglobin in the cerebral circulation [80–82]. This is usually
expressed as a ratio of oxygenated hemoglobin to total hemoglobin termed regional cerebral oxygen saturation (rSO2). NIRS measures rSO2, which may be a reliable surrogate of CBF [83]. When rSO2 is plotted against a spectrum of MAPs, the cerebral oximetry index (COx) is generated which serves as a measure of cerebral autoregulatory vasoreactivity. When COx approaches 1, there is a strong correlation of MAP and rSO2 indicating a pressure-passive state of impaired autoregulatory vasoreactivity, and it has been validated in studies on adults [39, 84].

4.2. Transcranial Doppler. TCD has been used extensively in neurological and neurosurgical patients to monitor cerebral blood flow velocities. The device emits pulse wave ultrasounds that penetrate the brain and are reflected back after being scattered by moving red blood cells in the cerebral vasculature. The frequency is proportional to the blood flow velocity from which cerebral blood flow can be derived. The pulsatility index (PI) that is calculated as Doppler (systolic velocity–diastolic velocity)/mean velocity has been shown to be lower during ECMO initiation, and rising PI may be an indication of cerebral pathology [59, 62]. Furthermore, TCD can aid in detecting microemboli arising from the ECMO circuit in real time [85, 86]. The mean velocity index (Mx) is a derived variable that gives the strength of correlation between CBFV and CPP and has been described in the TBI literature [87]. Figures 2 and 3 are examples of TCD waveforms of patients on VV-ECMO and VA-ECMO, respectively (from our center).

4.3. Neuroimaging. Imaging of the brain during ECMO can be difficult; however, it is a helpful tool to aid in detecting neurological injury. In pediatric patients, head ultrasound can be used to detect acute neurological injury [88]. Computed tomography of the head, particularly if can be done portably, is a useful tool to rule out significant acute intracranial pathology. MRI of the brain cannot be used while on ECMO due to hardware incompatibility but is useful for evaluation of neurological injury post-ECMO. However, these imaging modalities give a snapshot of the brain architecture and do not give any information on dynamic cerebral hemodynamics.

4.4. Electroencephalogram. The electroencephalogram (EEG) monitors brain wave activity by placing electrodes on the scalp. When used continuously, it can provide important information regarding seizure activity; 50 to 80% of ECMO patients may have an abnormal EEG with electrographic seizures reported at 8–20% [89, 90]. However, cEEG is a scarce resource to have during the course of ECMO treatment; hence, many institutions may check periodic EEGs ranging from 20 min to 1 hour at a time.
4.5. Biomarkers. Various biomarkers of neuronal injury sampled from plasma have been used as markers of cerebral injury. Glial fibrillary acidic protein (GFAP), S100b, neuron specific enolase (NSE), intercellular adhesion molecule 5 (ICAM-5), brain-derived neurotrophic factor (BDNF), and monocyte chemoattractant protein 1/chemokine (c-c motif) ligand 2 (MCP-1/CCL-2) have been investigated in ECMO patients [91–94]. It is still not well established what the presence of these biomarkers signifies in terms of injury related to ECMO or from injury due to the initial diseased state. There is debate on the optimal cutoff values of these biomarkers as well as if serial assessment provides any meaningful information [95].

4.6. Other Neuromonitoring Techniques. Somatosensory evoked potentials (SSEP) provide information about cortical signals in the somatosensory cortex after a peripheral stimulus. This can be helpful to prognosticate cerebral injury if the cortical potentials are absent [96]. The optic nerve sheath diameter (ONSD) can be used at bedside to detect elevated ICP [97]. Diffuse correlation spectroscopy (DCS) is an emerging technique to noninvasively monitor regional CBF directly [98].

5. Neurological Complications on ECMO

Neurological injury causes significant morbidity and is a risk factor for mortality among critically ill patients undergoing ECMO. While the Extracorporeal Life Support Organization (ELSO) reports an overall survival rate of 55% with ECMO (http://www.elso.org), evidence of CNS infarction or hemorrhage confers a near fivefold increase in the odds for mortality, and poor survival rates of about 11% [99, 100]. Trends in prevalence of neurological complications from ECMO show that following an increase in prevalence rates between the early 1990s to early 2000s, there has been a significant decline in the prevalence of CNS injury in recent years [99]. Clinical seizures, ischemic strokes, and intracerebral hemorrhage are among the most common neurological complications reported.

5.1. Adults. Overall incidence of any clinical neurological event up to 19% has been reported with VA- and VV-ECMO [99, 101]. Reports from case series, population-based database, and the ELSO registry estimate a variable incidence rate for neurological complications among adults on ECMO: clinical seizures (1.8%–4%), cerebral infarction (2%–5.4%), and ICH (1.8%–19%) [99, 101–106]. Brain death is reported among 5%–21% of ECMO-treated adults [99, 100, 107–109]. A higher incidence of CNS complications is reported among patients on VA-ECMO when compared to VV-ECMO, based on data available from studies that separately analyzed patients based on ECMO-type [99, 101, 109–111]. An even higher prevalence of infarction and hemorrhage has been reported from postmortem neuropathological examinations of pediatric and
adult ECMO nonsurvivors, showing that neurologic injury may be clinically undetected in 23–50% of cases [112–114].

Age, female sex, pre-ECMO cardiac arrest, use of inotropes, and post-ECMO hypoglycemia are factors shown to be independently associated with CNS complications with VA-ECMO [99, 102]. Rapid PaCO2 decrease at ECMO initiation and renal failure at ICU admission were independent predictors of ICH among patients undergoing VV-ECMO in one study [101]. In the same study, interestingly, disorders of hemostasis and anticoagulant use were not associated with neurological complications, including ICH.

5.2. Pediatrics. Neurological outcomes among pediatric patients undergoing ECMO have also been extensively studied. In a retrospective review of over 5000 pediatric patients aged 1 month to 18 years receiving ECMO from the ELSO database, the overall rate of acute severe neurological complications with ECMO was 13%, while patients undergoing ECMO-CPR had a higher incidence (26%) [115]. Other studies from the ELSO registry have found the rate of clinical seizures of up to 9.4% and 5.9%, ischemic stroke rates up to 7.4% and 4%, and ICH rates up to 7% and 6%, respectively, among neonates and children [116]. Risk factors for CNS complications in pediatrics include use of vasopressors, inotropes, serum bicarbonate administration, sepsis, severity of acidosis, pulmonary failure, elevated creatinine, and myocardial stunning [115].

5.3. Neurological Complications in ECMO-CPR. The incidence rates of neurological complications with ECMO-CPR are as high as 22% and are higher than with ECMO for other indications; in-hospital mortality rates can be as high as 89% among patients with neurological injury [99, 117]. Hypoxia, cardiac disease, acidosis, and need for CPR while on ECMO, presence of renal failure, cerebral hypoperfusion, and post-resuscitation reperfusion injury are predictors of neurological injury after ECMO-CPR [108, 117, 118]. A cutoff value for arterial blood pH that can predict the occurrence of neurological complications has not been determined, and thus using blood pH as a sole predictor for decision-making in the context of neurological injury has been discouraged. It is possible that in many patients supported with ECMO-CPR, central nervous system (CNS) injury was sustained prior to ECMO deployment and as a consequence of cardiac arrest and shock.

5.4. Pathophysiology of Neurological Complications from ECMO. There is a lack of conclusive cause-effect relationship of CNS injury diagnosed during ECMO. The pathophysiology of neurological injury during ECMO is likely multifactorial and probably differs between VA-ECMO and VV-ECMO. While disorders from the ECMO circuit and oxygenator (hemolysis, thrombocytopenia, acquired Von Willebrand disease, and fibrinolysis) [119] are similar between VA- and VV-ECMO, pre-ECMO factors and the ECMO-induced metabolic changes could differ. Pre-ECMO illness severity and treatments (low blood pressure and low cerebral blood flow, acidosis, hypoxia, electrolyte disturbances, disorders of hemostasis secondary to hepatic failure from cardiogenic shock, to name a few), factors associated with ECMO implementation (reperfusion injury and embolic events from ECMO cannula), and post-ECMO events can contribute to CNS injury.

Loss of cerebral autoregulation during severe arterial hypertension or hypotension, hemorrhage secondary to anticoagulation, cerebral vasospasm, thromboembolism, and secondary brain injury from tissue edema surrounding an area of focal neurological injury are some mechanisms implicated in brain injury among ECMO patients [108–110, 114, 116, 120, 121]. A linear relationship between duration of ECMO and cerebral thromboembolic events was shown in one study [110]. Intracranial vascular hyperreactivity or hyporeactivity due to the loss of pulsatile blood flow during ECMO and in the presence of high dose vasoactive medications can cause tissue hypoperfusion and brain ischemia [50]. Long-lasting tissue hypoxia in the vascular distribution of the supraaortic blood vessels (Harlequin syndrome) [122] and suboptimal fluid and blood component management [121] further contribute to brain pathophysiology in an ECMO environment.

Factors specific to VV-ECMO include abrupt PaO2 and PaCO2 changes during initiation [123, 124]. Variations in arterial CO2 exert a profound influence on CBF. Around normal PaCO2, CBF changes by about 4% for each mmHg change in arterial PaCO2. Hypercapnia can cause cerebral vasodilation while hypocapnia causes constriction that can be marked. Cerebral vasodilation tends to increase cerebral blood volume and hence the intracranial pressure. Sudden changes in CO2 level (from hypercapnia to normocapnia or hypocapnia) during ECMO initiation can induce sudden decrement in CBF resulting in brain injury. A decrease in cerebral regional tissue oxygen saturation at VV-ECMO initiation linked to PaCO2 change has been demonstrated, which could be involved in pathogenesis of brain injury [125]. Avoiding rapid correction of hypercapnia by starting with a low sweep gas flow and gradually increasing with time is recommended to reduce the incidence of complications.

5.5. Healthcare Costs and Long-Term Neurological Outcomes. Neurological complications contribute significantly to the already-high healthcare costs associated with ECMO treatment. Hospitalization costs are more than US $100,000 higher among patients suffering from neurological complications of ECMO, than for patients without such complications [106]. Survival with good neurological outcomes has been estimated in the range of 13% to 65% among pediatric patients and up to 73% among adults undergoing ECMO and ECMO-CPR [126–128]. While there is scarcity of data on long-term neurological outcomes, one small study showed an unimpaired survival in nearly half of the adult survivors of ECMO during longer term (five years or more) neurological follow-up [129].

6. Practical Considerations

The management of ECMO can be challenging and complex. Most institutions have protocols to help guide optimal management; however, the neurological impact of ECMO is
often over looked. At our institution (Baylor St. Luke’s Medical Center, Houston, TX), we have instituted a neurosurveillance protocol termed the “Neuro-ECMO protocol.” This involves obtaining a CT head immediately after initiation of ECMO and a repeat scan 72 hours later. In addition, continuous electroencephalography is obtained and discontinued after 24 hours if there is no sign of seizures. Daily TCDs are also employed as well as NIRS, and daily neurological examinations are carried out by neurointensivists. We try to minimize sedation in order to obtain reliable neurological assessments when feasible. This can lead to the early detection of neurological complications. In addition, anticoagulation protocols mainly utilize heparin and take into account measuring partial thromboplastin times (PTT), measuring R time using thromboelastography (TEG), and obtaining anti-Xa and antithrombin 3 levels. PTT goals are usually set at 60 to 80 seconds if a patient has no risk factors. If two out of the three variables of PTT, R time and Anti Xa are therapeutic, the patient is considered to be adequately anticoagulated. Ventilator strategies aim for lung protective ventilation. A multidisciplinary approach is employed which involves cardiovascular anesthesiologists, cardiothoracic surgeons, cardiologists, perfusionists, and neurointensivists. We hope that the institution of such protocols and multidisciplinary teams can help improve the neurological impact associated with patients on ECMO.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References


