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## Management of severe traumatic brain injury in regions with limited resources

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### ABSTRACT

**Importance:** Severe traumatic brain injury (sTBI) is a critical health problem in regions of limited resources (RLRs). Younger populations are among the most impacted. The objective of this review is to analyze recent consensus-based algorithms, protocols and guidelines proposed for the care of patients with TBI in RLRs.

**Observations:** The principal mechanisms for sTBI in RLRs are road traffic injuries (RTIs) and violence. Limitations of care include suboptimal or non-existent pre-hospital care, overburdened emergency services, lack of trained human resources, and surgical and intensive care. Low-cost neuromonitoring systems are currently in testing, and formal neurotrauma registries are forming to evaluate both long-term outcomes and best practices at every level of care from hospital transport to the emergency department (ED), to the operating room and intensive care unit (ICU).

**Conclusions and Relevance:** The burden of sTBI is highest in RLRs. As working-age adults are the predominantly affected age-group, an increase in disability-adjusted life years (DALYs) generates a loss of economic growth in regions where economic growth is needed most. Four multi-institutional collaborations between high-income countries (HICs) and LMICs have developed evidence and consensus-based documents focused on capacity building for sTBI care as a means of addressing this substantial burden of disease.

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## Introduction

Regions with limited resources (RLRs) generally have high unemployment rates, social inequality and unfair distribution of wealth, low educational level and weak health-care systems. Many of these conditions lead to poor health infrastructure and poor compliance with existing laws, and they help explain why the prevalence of severe traumatic brain injury (sTBI) continues to increase in low- and middle-income countries (LMICs), where RLRs remain more common than their high-income country (HIC) counterparts (1,2). According to a recent analysis of global neurosurgery academic groups, more than two-thirds of the world's population has gaps in the provision of appropriate surgical and anesthetic care(3). There are an estimated 13.8 million potential neurosurgical cases every year worldwide, with more than 80% occurring in LMICs(4). It has also been calculated that nearly 45% of the total neurosurgical cases are related to traumatic brain injury (TBI) care, including burr holes, craniotomies, and craniectomies(4).

The Global Burden of Disease Study 2019 reports that road injuries remain the leading cause of death in the 10–24 and 25–49 age groups(5), especially in countries with a low socio-demographic index (SDI), measured by a combination of personal income, educational attainment, and total fertility rate and considered a strong indicator of a country's development

and poverty level(6). Recent modeling suggests that nearly 69 million people sustain a TBI each year, of which the highest incidences map to RLRs in Africa, Latin America, and South-East Asia(3). While HICs have nearly 18 million cases, LMICs have around 50 million cases, a nearly 3-fold increase in both cases and mortality (4,7).

This data matters because in RLRs, pre-hospital care of sTBI is highly variable, and in some cases, inexistent. Resources vary substantially across hospitals, with limited or no CT imaging capacity, neurosurgery services or intensive care units (ICU). With the disproportionately high burden of neurotrauma disease in LMICs, neurotrauma is a highly technical and complex subspecialty in these geographic areas where it is most needed. It is not uncommon to see formal fellowship training programs in endovascular or spine neurosurgery in LMICs, with an absence of neurotrauma specific training (8,9). In these countries, the national burden of neurotrauma has an incidence of 800 to 939 cases for every 100,000 people. This, in contrast to the incidence of aneurysms and cervical stenosis in these countries as 3.4 to 6.9 cases for every 100,000 and 2.3 to 3.4 cases for every 100,000, respectively (3,10,11).

The objective of this review was to review recent algorithms, protocols, and guidelines for improving the care of patients with sTBI in specific RLR contexts.

## Methods

We carried out a systematic search using specific search terms in PubMed, EMBASE, ProQuest, and LILACS as described in the supplementary file. We also performed free-text searches for keywords like, “traumatic brain injury” AND “consensus” OR “guidelines” OR “protocols” AND “low-and middle-income countries” in Google Scholar. We also used these search terms to scan international websites of groups working in this discipline, like the Global Health Research Group in Neurotrauma at the University of Cambridge (NIHR-UK), the Benchmark Evidence from South American Trials at the University of Washington (NIH-USA), the Program in Global Surgery and Social Change in the Department of Global Health and Social Medicine at Harvard Medical School (USA) and others. Finally, we reviewed the references of articles selected through our search strategy to identify additional pertinent citations. In this review, we included all relevant articles describing the development of algorithms, protocols, or guidelines for the management of patients with sTBI designed for application in RLRs.

Inclusion criteria: algorithms, protocols, or guidelines for the management of sTBI in RLRs developed by inter-institutional and interdisciplinary teams in addition to collaborations between HIC and LMIC practitioners.

## Results

The search identified 1903 publications, of which six fulfilled the inclusion criteria (12–17). Three additional publications were found, which did not fulfill all inclusion criteria, but were found to be useful, of which one focused on neuromonitoring in emerging economies (not specific for patients with sTBI)(18), another with a definite recommendation for performing a decompressive craniectomy in patients with sTBI in low-resource settings(19), and lastly, one which provided comprehensive policy recommendations for head and spine injury care in LMICs(20).

A comparative analysis of the six publications which met all inclusion criteria is presented in Table 1, including the scope, developing team and algorithms, and protocols or guideline recommendations.

Overall, these six documents present the evolution of recommendations for the management of sTBI in RLRs. The Neurosurgical Australasian Society developed the first of these recommendations(12). The guidelines were initially published in 1992 and updated in 2000 and most recently in 2009 for the management of acute neurotrauma in rural and remote locations in the Pacific island region. The society developed the guidelines using data from clinical and surgical case series performed in the 80s and early 90s when neurosurgeons’ access to essential neurosurgical equipment was limited to instruments like the Hudson brace to perform burr-holes to facilitate necessary decompression in rural settings. The guidelines relied upon possibilities of communication by the primary health-care facility and the remote neurosurgery service in order to define additional measures like hyperventilation

or hyperosmolar therapy with mannitol (standard therapies at that time). The guidelines present useful schemes for anatomical localization of neurosurgical procedures, including specific protocols for medical interventions and recommendations for pediatric and spine trauma cases.

In 2014, two guidelines were developed for LMICs. One was a multi-institutional collaboration between several medical associations from India and the United States (13). This consensus-based document offers a public health system perspective, presenting recommendations for prevention, facilities, infrastructure, and pre-hospital, in-hospital and rehabilitation care. General recommendations for airway management, ventilation, blood pressure management, CT scanning and ICP monitoring are presented, describing specific medical therapies and providing general algorithms.

In the same year, the Colombian Clinical Practice Guidelines for the Management of Severe Traumatic Brain Injury in Adult Patients was published as a technical document by the Colombian Ministry of Health(15). This was a multi-institutional, evidence-based, and consensus-based exercise supported by international methodological advisors like the Cochrane Collaboration. Following a strict GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, ten structured PICO (population, intervention, comparison, and outcome) type questions were answered using different clinical studies with low to a high quality of evidence. The questions designed to evaluate heterogeneity of practice among different TBI care providers are shown in Table 2. Recommendations were developed for each question, along with specific algorithms to offer guidance specific to RLRs. An example of the algorithm for referral of patients with TBI from low resources facilities to high resources facilities is presented in Figure 1.

In 2020, the updated version of the 2012 Benchmark Evidence from South American Trials: BEST-TRIP study protocol, for the management of patients with sTBI without ICP monitoring and based on clinical examination and CT imaging was published with a new acronym called “Protocol for the Treatment of Severe Traumatic Brain Injury Based on Imaging and Clinical Examination for Use When Intracranial Pressure Monitoring Is Not Employed (CREVICE)”(10). The protocol, based on an expert consensus approach, includes three levels of interventions and additional recommendations for patient monitoring, general measures, goals for cerebral perfusion and oxygenation treatment and for escalation or tapering therapies. This protocol also includes heat maps for withdrawing sedation therapy in ICU for patients with sTBI in the first 24 to 72 or more hours of hospital stay. The major and minor criteria for defining high ICP in the absence of ICP monitoring of the CREVICE protocol are presented in Figure 2.

An innovative approach for protocol development for the management of patients with sTBI in different levels of resource contexts was also published in 2020. This stratified process was named “Beyond One Option for Treatment of Traumatic Brain Injury: A Stratified

**Table 1.** Comparative analysis between the 5 publications presenting algorithms, protocols or guidelines for the management of sTBI patients in the context of RLRs. CT (computed tomography), ICU (intensive care unit, TBI (Traumatic Brain Injury), AGREE (appraisal of guidelines for research & evaluation instrument), PICO (population, intervention, comparison, outcome scheme for developing evidence based questions) .

| Publication   | Scope  | Developing Team  | Algorithms   | Protocols   | Guidelines  |
|---|--|--|--|---|---|
| The management of acute neurotrauma in rural and remote locations: A set of guidelines for the care of head and spinal injuries. 2009   | Rural Surgeons, General Surgeons and Rural Physicians  | Neurosurgeons, General Surgeons  | One for deteriorating head injury in county hospital.  | Prehospital Care, Primary Hospital Initial Management, Emergency Surgical Treatment, Coma Management, Pediatric Head Injury, Spinal Injury, Moderate Head Injury, Minor Head Injury, Special Issues, Nursing Management   | One general non structured guideline (according to the AGREE instrument) including all the protocols.   |
| Traumatic Brain Injury, Multi Organizational Consensus Recommendations for India. 1st Edition. 2014   | Health Care Providers  | Neurosurgeons, Rehabilitation Physicians, Emergency Physicians   | One for scope description, one for system of care description, one for TBI continuum of care, one for hospital categories, seven for in-hospital care, one for mild TBI, one for moderate TBI, one for severe TBI, one for ICP monitoring, and one for rehabilitation.   | Awareness and prevention, prehospital care, in-hospital care and rehabilitation.  | One general non structured guideline (according to the AGREE instrument) including all the protocols.   |
| Clinical Practice Guideline for Diagnosis and Treatment of Adult Patients with Severe Traumatic Brain Injury. Colombia; 1st Edition, 2014   | Prehospital healthcare personnel, General physicians, Emergency surgeons, Neurologists, Neurosurgeons, Intensive care doctors, Patients and Caregivers of patients | Neurosurgeons, Critical Care Physicians, Methodologists, Psychiatrists, Trauma Surgeons, Rehabilitation Physicians, Pediatric Neurologist, Emergency Physicians, General Physicians, Paramedics. | One for indications of a head CT, one for transfer indications between low complexity centers to high complexity centers, one for prehospital airway management, one for fluid resuscitation in prehospital care, one for hyperosmolar therapy in the emergency room, one for surgical indications of subdural hematomas, one for surgical indications of epidural hematomas, one for surgical indications for cerebral edema, one for ICU sedation, one for ICU thrombo-prophylaxis, one for ICU – ICP monitoring and one for ICU local hypothermia management. | No specific protocols. Evidence and consensus based recommendations for: indications of head CT, transfer indications between low level centers to high level centers, advantages of trauma centers vs. general hospitals, prehospital intubation, prehospital fluid resuscitation, emergency room hyperosmolar therapy, surgical indications for subdural, epidural bleedings and brain edema, ICU sedation, ICU thrombo-prophylaxis, ICP monitoring, and ICU local hypothermia. | Structured evidence based and consensus based Clinical Practice Guideline (according to the AGREE instrument), including answers to 11 PICO format questions. |
| Consensus-Based Management Protocol (CREVICE Protocol) for the Treatment of Severe Traumatic Brain Injury Based on Imaging and Clinical Examination for Use When Intracranial Pressure Monitoring Is Not Employed. 2020 | Neurosurgeons, Critical Care Physicians  | Neurosurgeons, Critical Care Physicians, Methodologists.   | One general algorithm for sTBI management based on imaging and clinical examination. One set of heat maps for sedation withdrawn.  | One general protocol for sTBI management, including 3 tier therapy approaches when ICP is not available.  | No guideline.   |

(Continued)

**Table 1.** (Continued).

| Publication  | Scope   | Developing Team  | Algorithms  | Protocols  | Guidelines   |
|--|---|--|---|--|--|
| Recommendations of the Colombian Consensus Committee for the Management of Traumatic Brain Injury in Prehospital, Emergency Department, Surgery, and Intensive Care (Beyond One Option for Treatment of Traumatic Brain Injury: A Stratified Protocol [BOOTStraP]). 2020 | Prehospital providers, general and emergency physicians, neurosurgeons, anesthesiologists, general and trauma surgeons, critical care physicians. | Paramedics, General Physicians, Emergency Physicians, Neurosurgeons, Critical Care Physicians, Methodologists. | Ten algorithms moving from less resourced to high resourced settings: basic emergency transport, advanced emergency transport, mild TBI in a low complexity emergency room, mild TBI in a medium complexity emergency room, management of a moderate-severe TBI in a low complexity emergency room, management of a moderate – severe TBI in a medium-high complexity emergency room, management of a TBI patient requiring emergency surgery in centers without neurosurgery, management of a TBI patient who requires surgery in a center with neurosurgery but without ICU, management of a moderate-severe TBI in an intermediate care unit, management of a moderate-severe TBI patient in an ICU. | Ten stratified protocols moving from less resourced to high resourced settings: basic emergency transport, advanced emergency transport, mild TBI in a low complexity emergency room, mild TBI in a medium complexity emergency room, management of a moderate-severe TBI in a low complexity emergency room, management of a moderate – severe TBI in a medium-high complexity emergency room, management of a TBI patient requiring emergency surgery in centers without neurosurgery, management of a TBI patient who requires surgery in a center with neurosurgery but without ICU, management of a moderate-severe TBI in an intermediate care unit, management of a moderate-severe TBI patient in an ICU | No guidelines  |
| <b>General care in the management of severe traumatic brain injury: Latin American Consensus. 2020</b>   | Critical Care Physicians, Neurosurgeons   | Critical Care Physicians, Neurosurgeons  | No algorithms.  | No protocols. General recommendations for best clinical practice in general care, physiologic homeostasis and nutritional aspects of sTBI patients in the ICU including: position of the head, use of cervical spine immobilization, mouth hygiene, management of artificial airways, eye protection, fluid therapy, optimization of blood pressure, management of body temperature, monitoring of glycemia, hemoglobin, plasma sodium, sedation and analgesia, prevention of gastrointestinal bleeding and early management of ventilation and oxygenation, plus nutritional management.  | Semi-structured guideline (according to the agree instrument). |

**Table 2.** List of questions for answering with GRADE methodology in the Clinical Practice Guidelines exercise of the Colombian Ministry of Health.

| Questions based on heterogeneity of practice between health providers taking care of sTBI patients in Colombia  |
|---|
| 1a – Which patients with TBI should have a computerized tomography (CT) of the head?  |
| 1b – Which patients with TBI should be transferred from low-level of care hospitals to centers with neurosurgery and neuroimaging services?   |
| 2 – In adult patients with severe TBI, does the treatment in an organized trauma care center, compared to treatment in a general non-specialized center reduce mortality?   |
| 3 – In adult patients with severe TBI, does prehospital orotracheal intubation, compared with orotracheal intubation in emergency departments, reduce neurological disability or mortality, evaluated at 6 months post-injury?  |
| 4 – In adult patients with severe TBI, does the use of 7.5% hypertonic solutions for resuscitation in prehospital setting, compared with the use of isotonic resuscitation solutions, reduce neurological disability or mortality, evaluated at 6 months post-injury? |
| 5 – In adult patients with severe TBI and intracranial hypertension, does the use of hypertonic saline at 7.5%, compared with mannitol, as a hyperosmolar initial therapy reduce mortality at discharge?  |
| 6a – In adult patients with severe TBI and acute subdural hematoma with surgical indication, does early drainage surgery (within 4 hours), compared with late surgery (after 4 hours), reduce mortality at discharge?   |
| 6b – In adult patients with severe TBI, and an epidural hematoma with surgical indication, does early drainage surgery (within 4 hours), compared with late surgery (after 4 hours), reduce mortality at discharge?   |
| 6c – In adult patients with severe TBI and surgical indication for cerebral edema, does early decompression craniectomy (within 24 hours), compared with late craniectomy (after 24 hours), reduce mortality at discharge?  |
| 7 – In adult patients with severe TBI being treated in an ICU, does sedation with propofol, compared to sedation using midazolam, reduce neurological disability or mortality, assessed at 3 months post-injury?  |
| 8 – In adult patients with severe TBI treated in an ICU, does thromboprophylaxis with low molecular weight heparin (LMWH), compared with thromboprophylaxis with un-fractionated heparin, reduce the presence of thrombotic events and mortality at discharge?        |
| 9 – In adult patients with severe TBI being treated in an ICU, does guided therapy with monitoring of intracranial pressure (ICP), compared with treatment without ICP monitoring, reduce mortality at discharge?   |
| 10 – In adult patients with severe TBI being treated in an ICU, does selective head cooling, compared to normothermia, decrease neurological disability and mortality at discharge?   |

Protocol (BOOTStrAP).”(14) BOOTStrAP offers ten protocols to facilitate interactions from shallow resource scenarios to high-resource scenarios. The users of the protocols can choose the preferred treatment option according to the level of resources available and then move to another treatment option if resources increase or decrease. This is a common situation in daily practice for many RLR practitioners. The protocols specifically include recommendations for basic or advanced emergency transportation (pre-hospital level); low-, middle-, or high-resourced emergency rooms, defined by the availability of CT scanning capabilities; recommendations for managing patients in centers without neurosurgical services or with neurosurgical services but without ICU availability; and recommendations for centers with low-resource, intermediate postoperative units or centers with full ICU capabilities. All ten protocols are available open-access at [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7055642/bin/10-1055-s-0040-1701370\\_00284\\_s1.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7055642/bin/10-1055-s-0040-1701370_00284_s1.pdf)

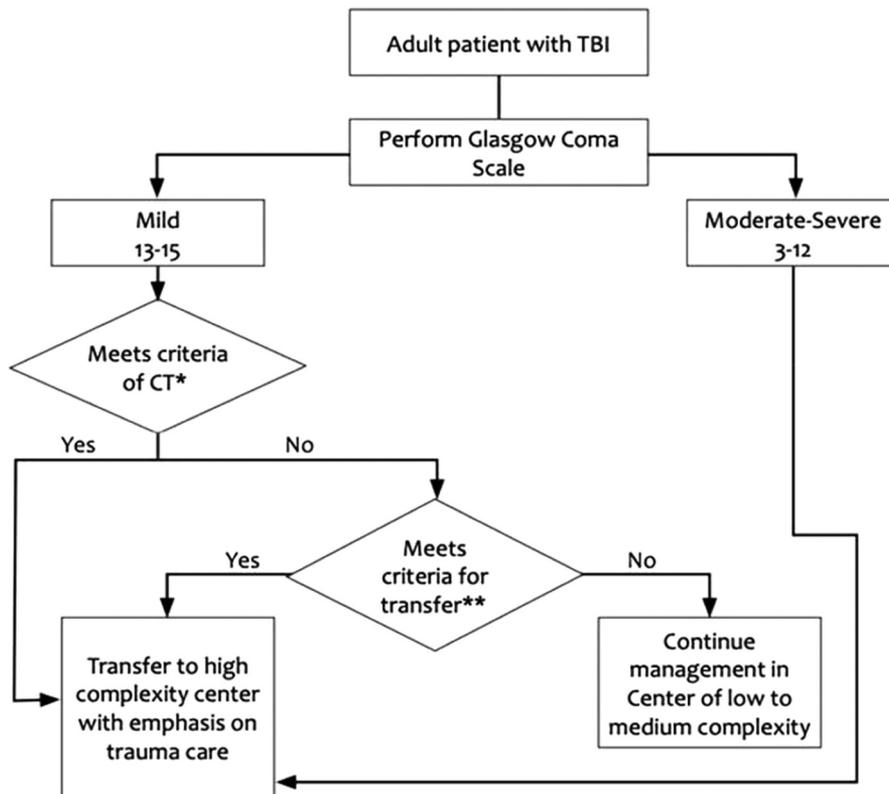
An example of an algorithm for the management of sTBI in emergency settings with a low level of resources is presented in Figure 3.

A group of Latin American critical care physicians and neurosurgeons, most of whom were involved in the development of the CREVICE protocol, developed another consensus guideline document in 2020, which focused on general care measures for patients with sTBI. The document provides updated recommendations on general UICU measures like head positioning, use of cervical collars, mouth hygiene, eye protection and management of artificial airways. Additional recommendations were generated for fluid resuscitation, blood pressure optimization, management of body temperature, and thresholds for hemoglobin, glycemia, sodium, and sedation levels(17).

There is a pressing need to define protocols and guidelines tailored regions with different degrees of resource limitations (21–24). Integrating the recommendations from these six documents opens a unique set of possibilities for developing a structured sTBI care pathway in RLRs.

Additional recommendations have been proposed from the public policy perspective. A document from the Program in Global Surgery and Social Change of the Harvard Medical School includes a six-component approach for building technical strategies in LMICs where neurotrauma is poorly organized as part of the healthcare system. The first component is related to recommendations for infrastructure (surgical facilities, facility readiness, and blood supply and referral systems) (20,25). The second set of recommendations is oriented toward workforce (surgical, anesthesia and obstetric providers, including other allied health providers). The third set is focused on service delivery (including aspects related to surgical volume, system coordination and quality and safety). The fourth set of recommendations is related to financing aspects (health financing and accounting, including budget allocation). The fifth and sixth sets of recommendations are related to information management (information systems, data streams and local research agendas), and governance (policy and political architecture to improve visibility and accountability). These aspects have been considered pivotal in order to establish organized neurotrauma care systems, especially in RLRs.

Protocols for the management of sTBI in RLRs can be refined using lessons learned from military protocols applied to civilian settings (26,27). Reliance on serial physical examinations (including basic neurological exams), optimizing the use of portable devices for intracranial bleeding detection(28), evaluation of intracranial hypertension with noninvasive portable devices (29,30), and early aggressive surgical management with specific decision-making ethics-based algorithms are good examples (31–33). Furthermore, neurotrauma registries have recently been developed to advance research in sTBI across RLRs (34–42). Analysis of data from these registries will be invaluable when evaluating the impact of future protocol modifications on the outcome of patients with sTBI.



|  |   |
|--|---|
| <p><b>*Criteria of CT</b></p> <ul style="list-style-type: none"> <li>• Skull fracture (clinical or radiological) including signs of fracture of the skull base (periorbital ecchymosis and ecchymosis headpiece, otoliquia, rinoliquia).</li> <li>• Traumatic seizure</li> <li>• Focal neurologic deficit</li> <li>• Persistent vomiting (greater than or equal to two episodes)</li> <li>• Fall of the Glasgow of at least 1 point</li> <li>• Previous Craniotomy</li> <li>• Mechanism of the trauma produced by runover in condition of pedestrian</li> <li>• History of coagulopathy or pharmacological anticoagulation</li> <li>• Patient with suspected poisoning</li> <li>• Fall from height greater than 1.5 meters</li> <li>• Retrograde Amnesia &gt; 30 minutes and/or anterograde</li> <li>• Age greater than or equal to 60 years</li> <li>• Severe headache</li> <li>• Blurred vision or diplopia</li> </ul> | <p><b>**Transfer criteria</b></p> <ul style="list-style-type: none"> <li>• Glasgow under 15 up to 2 hours after the injury</li> <li>• Severe headache</li> <li>• Persistent vomiting (greater than or equal to two episodes)</li> <li>• Skull fracture (clinical or radiological) including signs of fracture of the skull base (periorbital ecchymosis and ecchymosis headpiece, otoliquia, rinoliquia).</li> <li>• Age greater than or equal to 60 years</li> <li>• Blurred vision or diplopia</li> <li>• Traumatic seizure</li> <li>• Focal neurologic deficit</li> <li>• Previous Craniotomy</li> <li>• Fall from height greater than 1.5 meters</li> <li>• Retrograde Amnesia &gt; 30 minutes and/or anterograde</li> <li>• Suspicion of intoxication with alcohol and/or psychoactive substances</li> </ul> |
|--|---|

Figure 1.

**Conclusion**

The burden of sTBI is highest in RLRs, where it remains a significant cause of death, severe disability, and productivity loss. Several collaborations between HICs and LMICs have developed tailored algorithms, protocols and guidelines to improve the quality of sTBI care in RLRs. Neurotrauma registries in RLRs provide new valuable sources of information to study the impact of applying specific care protocols to practice. Innovation on

- Major Criteria
  - CT classification of Marshall III or worse
    - Compressed cisterns (Marshall DI III)
    - Midline shift > 5 mm (Marshall Di IV)
      - Non-evacuated mass lesion > 25 cc
- Minor Criteria
  - Glasgow Coma Scale motor score ≤ 4
  - Pupillary asymmetry
  - Abnormal pupillary reactivity
  - Marshall DI II

Figure 2.

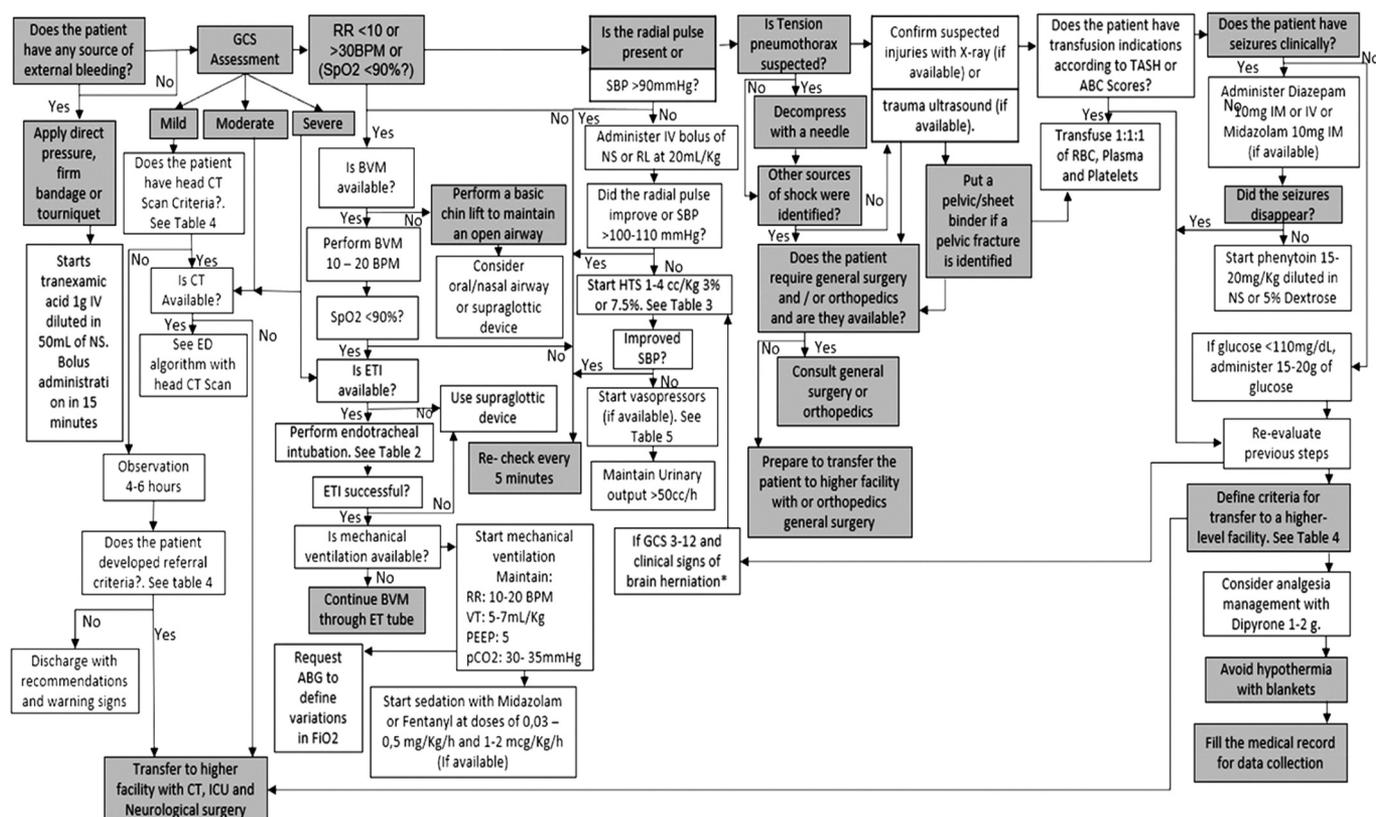


Figure 3.

portable and noninvasive technology for diagnosis and monitoring of sTBI promises to offer new possibilities to reduce the enormous personal and societal losses from sTBI in RLRs.

## Disclosure Statement

All authors contributed equally to the development and writing of this manuscript

Dr. Jibaja, Dr. Godoy, Dr. Rubiano, Mr. Griswold and Dr. Rabinstein declare no conflict of interest. None have received financial support or any fees to write this manuscript.

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