How to manage traumatic brain injury without invasive monitoring?

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Purpose of review
Severe traumatic brain injury (TBI) is an extremely serious health problem, especially in low–middle income countries (LMICs). The prevalence of severe TBI continues to increase in LMICs. Major limitations in the chain of care for TBI patients are common in LMICs including suboptimal or nonexistent prehospital care, overburdened emergency services, lack of trained human resources and limited availability of ICUs. Basic neuromonitoring, such as intracranial pressure, are unavailable or underutilized and advanced techniques are not available.

Recent findings
Attention to fundamental principles of TBI care in LMICs, including early categorization, prevention and treatment of secondary insults, use of low-cost technology for evaluation of intracranial bleeding and neuromonitoring, and emphasis on education of human resources and multidisciplinary work, are particularly important in LMICs. Institutional collaborations between high-income and LMICs have developed evidence focused on available resources. Accordingly, an expert group have proposed consensus recommendations for centers without availability of invasive brain monitoring.

Summary
Severe TBI is very prevalent in LMIC and neuromonitoring is often not available in these environments. When intracranial pressure monitors are not available, careful attention to changes on clinical examination, serial imaging and noninvasive monitoring techniques can help recognize intracranial hypertension and effectively guide treatment decisions.

Keywords
low resources, low–middle income countries, management, neurotrauma, severe traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a major health problem worldwide, but it disproportionately affects low-income and middle-income countries (LMICs) (https://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html) [1,2]. LMICs have certain characteristics: absence of industrialization, low per capita income, high unemployment rates, social inequality, bad distribution of wealth, poor educational level with limited development of human capacities, political instability and health systems with severe deficiencies (https://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html). Many of these conditions (poor road infrastructure, insufficient safety education, misinformation, inadequate prevention policies, social violence and poor compliance with existing laws) may explain why the prevalence of TBI continues to increase in LMICs [1–3]. A recent analysis showed that more than two-thirds of the world's population has limited access to appropriate surgical and anesthetic care [4]. In these countries, the incidence of neurotrauma ranges from 800 to 939 cases for every 100 000 people [4,5]. Road injuries remain the leading cause of death in the 10–24 and 25–49 age groups, especially in countries with a low sociodemographic index [6▪,7▪]. Approximately, 69 million people sustain a TBI each year, principally in LMICs of Africa, Latin America and South-East Asia [4]. LMICs have nearly three-fold increase in both cases and mortality [5,8].

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KEY POINTS

- Severe TBI is a serious, highly prevalent problem that grows day by day, especially in regions with low or no resources.
- In these regions, the limitations in the care chain are varied, numerous and complex. Each region should adapt its therapeutic guidelines to its reality and available resources.
- Achieving physiological homeostasis is key to avoiding secondary and tertiary insults.
- Given the lack of advanced neuromonitoring, it is necessary to understand and perform a precise clinical examination supported by the serial evaluation of neuroimaging (computed tomography scan) to guide decision-making.
- The refinement of noninvasive neuromonitoring techniques in conjunction with multidisciplinary education programs is essential.

On the contrary, due to barriers like absence of registries and limited research funding, availability of data to analyze the impact of TBI in low resources settings is limited [9]. A common finding in epidemiological studies from LMICs is the increased mortality in rural areas compared with urban settings due to constraints in access to resources for appropriate emergency, surgical, ICU and rehabilitation services [10–13]. LMICs typically lack policies, laws and controls to ensure that a minimum standard of care for the treatment of severe TBI. This occurs throughout the entire chain of care. Prehospital care is highly variable, and sometimes, inexistent. Resources vary across hospitals, with limited or no computed tomography (CT) imaging, neurosurgery or available ICU beds. In LMICs the availability of ICU beds is low, being reported as 0.1–1.6 beds per 100 000 people in some African and South Asian countries to a mean of one to five beds per 100 000 people in countries of Latin American and the Caribbean Region [14,15]. Neurotrauma specific training programs are absent [16]. Common limitations in the delivery of care across LMICs are listed in Fig. 1.

STRATEGIES FOR TRAUMATIC BRAIN INJURY CARE IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES

Serial neurological examination

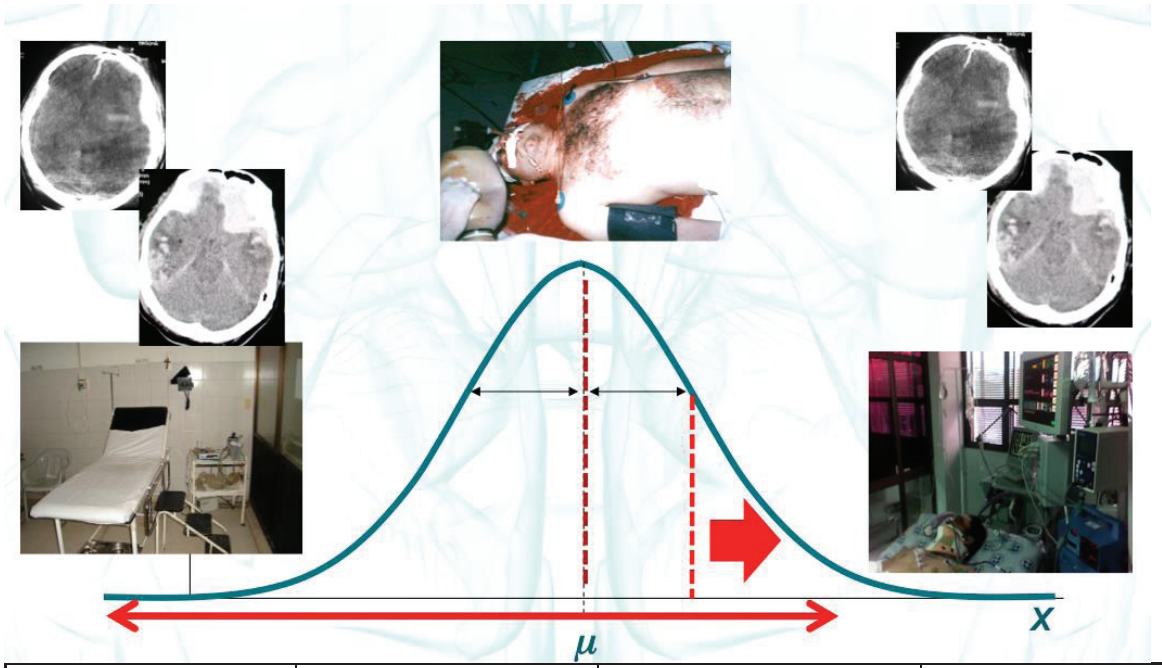
The neurological examination remains the central pillar in the evaluation and monitoring of severe TBI. The Glasgow Coma Scale (GCS) has been the preferred tool for the clinical evaluation [17]. It is easy to perform with minimal training [17,18]. It is used to categorize severe TBI (GCS $\leq$ 8). GCS is inversely associated with in-hospital mortality in patients with TBI [17,18]. The motor component of the GCS is particularly useful [17–19]. Yet, the GCS has limitations [17], and consequently the Full Outline of Unresponsiveness (FOUR) score has been proposed as an alternative [20–22]. The FOUR score has undergone extensive validation with good inter-rater reliability [20–22]. In comparison with GCS, it includes assessment of brainstem reflexes and breathing pattern and does not include point adjudication for verbal response; thus, it is not affected by tracheal intubation [20]. The FOUR score has been shown to predict outcomes in severe TBI [20–22].

Coma scales are useful, but, they are not sufficient. An optimal neurological examination should include evaluation of the pupils (shape, size, symmetry, reactivity), gaze (central versus deviated, conjugate versus deconjugate), motor asymmetries (new focal lesions or herniation), muscle tone and adventitious movements (suggestive of seizures or drug toxicity) [23]. Education to perform an optimal clinical examination is crucial. Understanding that the exam can be affected by sedation, analgesia and major metabolic derangements is necessary. This problem does not have an easy solution. The option of sedation holidays may not be safe to pursue in patients with intracranial hypertension (ICHt) [24]. Of note, assessment of brainstem responses remains usually reliable in sedated patients [25,26].

Brain imaging

Brain imaging is essential to detect hemorrhage and mass effect in patients with TBI [18,19]. CT scan is typically preferred due to its wide availability, rapid acquisition, low cost and ease of use particularly in mechanically ventilated patients. It can show the type, localization and severity of the injury (brain contusions, brain edema, intracerebral hemorrhage, subarachnoid hemorrhage, subdural or epidural hematomas, brain tissue shift, skull fractures), and provides early prognostic information [18,19]. CT scan can guide surgical decisions and it helps to identify patients at risk for ICHt [18,19].

When CT is not available, new technologies like the near infrared spectroscopy for noninvasive hemoglobin detection or hematoma diagnosis and transcranial sonographic monitoring for detection of hematoma expansion have been proposed [27,28]. Current studies are in development to define their impact in LMICs.



Prehospital Stage	Emergency Room	Intensive Care Unit	Rehabilitation Phase
• Means of transport not equipped or not available (air, ground, water, etc) • Untrained human resources • Long response times • Poor or absent communication systems • Insufficient laws and controls • Absence of coordination systems	• Overwhelmed services • Inability to perform active therapies (mechanical ventilation) • Absence of necessary number of human resources and equipment • Absence of trained personnel • Absence of coordination and continuity in the service chain • Work overload	• Lack multidisciplinary work • Beds unavailable or in insufficient number • Underutilization of available monitoring • Absence of advanced technology • Suboptimal nurse/patient ratios • Excessive workload (burnout) • Absence of specialized units	• Culture and religion (limits this and other stages of care) • Absence of specialized centers • Lack of comprehensive care and multidisciplinary work • Not available everywhere and for the entire population

FIGURE 1. Limitations of chain of care of severe traumatic brain injury in low-income and middle-income countries. Near to 80% of severe traumatic brain injury patients arrive on daily basis to centers with low or medium level of resources for care. Less than 20% of the worldwide patients have access to advanced neuromonitoring systems. Development of strategies to improve quality of care even in areas of low level of resources it is a priority from the global health perspective.

CT-based scales have been proposed to categorize the TBI. The Marshall scale was designed to predict mortality by classifying three imaging findings: high or mixed density masses, compression of the basilar cisterns and midline shift [29]. Using these parameters, the scale classifies cases into categories that correspond to early prognosis [29].

Serial CT scans can aid in the recognition of disease progression (brain swelling or delayed growth of hemorrhagic contusions or extra-axial

blood collections) and in the evaluation of the response to therapeutic interventions. An expert consensus recommends performing a CT scan on admission and if this occurs within 4 h of the trauma, repeating it at 12 h [30,31,32▪▪]. Subsequently the recommendation is to repeat CT at 24 and 72 h or when necessary according to clinical judgment [30,31,32▪▪].

Noninvasive evaluation of intracranial pressure

The question whether ICHt can be reliably diagnosed and effectively treated without intracranial pressure (ICP) monitoring, remains one of the most heated debates in neurotrauma. Unavailability of invasive ICP monitoring is a very common situation in LMICs.

A randomized-controlled trial known as BEST-TRIP conducted in six ICUs in Bolivia and Ecuador compared adult patients with severe TBI ($n = 324$) assigned to a management protocol guided by invasive ICP monitoring against a management protocol based on serial physical examination and neuroimaging [33]. Mortality, functional outcome, ICU length of stay and serious adverse events were similar in both groups [33]. In the monitoring arm, almost 80% of patients had elevated ICP at some point during the relatively short monitoring (average between 3 and 4 days). Brain-specific treatments (osmolar therapy) were used more frequently in the group without ICP monitoring. Yet, barbiturates were used more commonly in the ICP monitoring group [33]. Although the methodology of this trial was criticized and its external validity in centers with experience using ICP monitoring is questionable, it nonetheless provides evidence for a treatment protocol guided by serial examination and radiological scans when invasive ICP monitoring is not available [34]. That said, when ICP monitoring is available, it should be employed for the monitoring of patients with severe TBI deemed to have high risk of ICHt.

A recent study developed a diagnostic rule based on clinical and tomographic data to predict ICHt (Table 1) [35]. When ICHt was defined as ICP more than 22 mmHg, the sensitivity and specificity of this diagnostic rule was 93.9 and 42.3%, respectively, reaching 100% sensitivity when ICHt was defined as ICP more than 30 mmHg [35]. Yet, systematic review and meta-analysis that evaluated the noninvasive diagnosis of ICHt in critically ill patients, concluded that the absence of clinical signs and symptoms is not enough to rule out ICHt [36]. The only radiological signs on CT scan found to reliably predictive of ICHt were compression of the basal cisterns and midline shift more than 10 mm of the septum pellucidum [36]. The predictive performance of transcranial Doppler (pulsatility index) was poor [36]. While measurement of the optic nerve sheath diameter showed encouraging results, cutoff values for diagnosis of ICHt varied across studies and sensitivity was suboptimal [36].

Table 1. Clinical tomographic rule for intracranial hypertension diagnosis

Major criteria	Minor criteria
Compressed basal cisterns	Motor GCS ≤ 4
Midline shift > 5 mm	Pupillary asymmetry
Nonevacuated mass lesion	Abnormal pupillay reactivity
	Marshall tomography classification type II

ICHt diagnosis is made when one major criterion or two or more minor criteria were present. GCS, Glasgow Coma Scale; ICHt, intracranial hypertension.

The maximum contraction velocity and the Neurological Pupil Index have been the more common measurements associated with ICHt using automated pupillometry [37]. Changes in pupillary reactivity detected by automated pupillometry may allow early recognition of midline shift and differentiate anisocoria related to brain tissue shift versus anisocoria a due to more benign causes [38▪].

Overall, noninvasive techniques for monitoring of ICHt deserve further investigation, but it is very questionable that they can be recommended for daily practice. None of them has been sufficiently validated in large, multicenter studies and their predictive performances have varied substantially across studies. In addition, these noninvasive techniques have some disadvantages, such as operator dependence (leading to high interobserver variability), lack of validated cutoffs, discontinuous monitoring and absence of validated protocols for their optimal timing and frequency.

INTENSIVE CARE MANAGEMENT

Severe TBI is a heterogeneous, evolutive and dynamic condition that demands complex multidisciplinary effort [18,19]. A priority in the management of severe TBI is to achieve physiological homeostasis directed to avoid, promptly detect and correct secondary and tertiary insults [18,19,39–41]. A practical strategy to achieve this target is trough physiology neuroprotection, a strategy that does not require any advanced technology and is consequently feasible in LMICs [40] (Fig. 2).

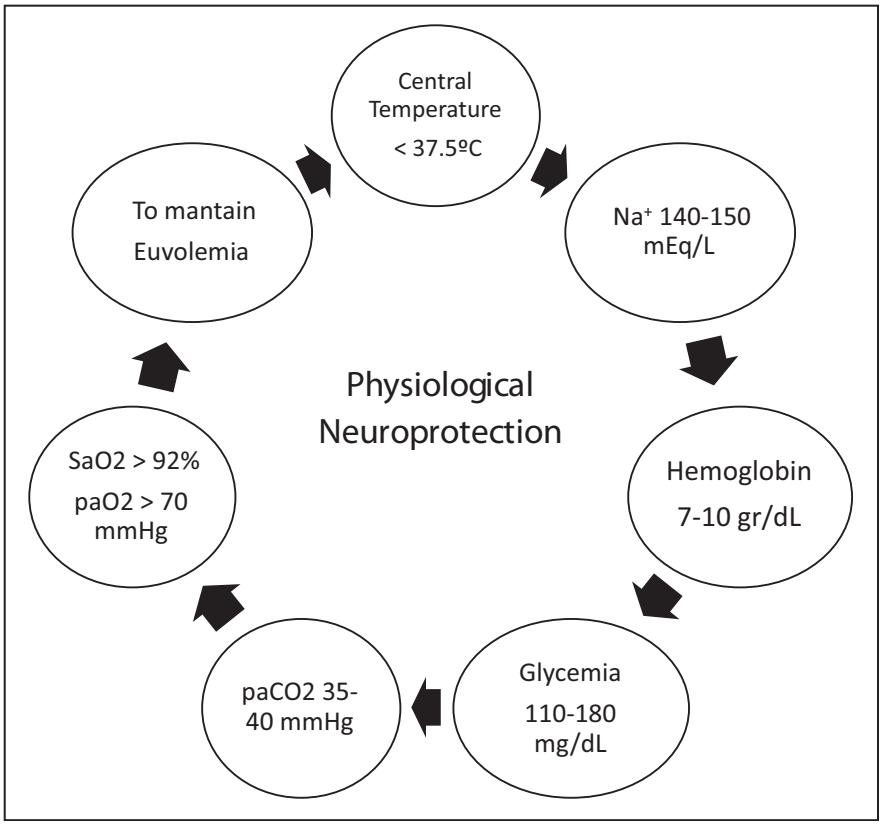


FIGURE 2. Physiological neuroprotection targets.

Early hemodynamic and respiratory stabilization

Hypoxemia and arterial hypotension are the secondary insults of greatest prognostic weight [18,42]. Ensure airway patency and adequate ventilation (normocapnia) and oxygenation ($SaO_2 > 92\%$ or $PaO_2 > 70$ mmHg) with orotracheal intubation and mechanical ventilation should be strict priorities [18,19]. Simultaneously, it is crucial to achieve and maintain SBP levels greater than 110 mmHg [43–45]. Hypotonic fluids should be avoided [46]. Isotonic fluids administration can be guided by bedside non-invasive dynamic tests such as variation in pulse pressure, legs elevation or echocardiography if available [46]. Vasopressors are sometimes necessary and norepinephrine is usually preferred [39,47]. It is always important to rule out ongoing bleeding and other causes of arterial hypotension in patients with refractory shock [48▪▪]. Systolic cardiac dysfunction is not uncommon. In such cases, inotropic drugs (dobutamine) may be employed [49,50].

Physiological homeostasis

Hyperthermia triggers neurotoxic cascades [19,40,51]. Avoiding and controlling fever is therefore advisable [19]. The injured brain has increased demands for glucose [52,53]. Hypoglycemia is deleterious [52,53]. Glycaemia levels between 110 and 180 mg/dl are optimal [52,53]. Microdialysis findings have shown that mitochondrial dysfunction may occur with glycaemia levels below 110 mg/dl [54]. Hyperglycemia may exacerbate inflammation and microthrombosis [53]. For glycemic control, regular insulin is the preferred agent [53]. Natremia should be maintained between 140 and 150 mEq/l [19,40,51]. Avoid acidosis (increases ICP) and alkalosis, factors that modify the transport and transfer of oxygen to cells [19,40,51]. It is desirable hemoglobin levels more than 7 gr/dl [55,56]. Risks and benefits should be carefully weighed before proceeding with transfusion [55,56]. Fresh blood is preferable to blood stored [55,56]. Infection control program and to avoid other adverse effects related to healthcare are mandatory.

Prevent injuries to the skin and eyes [19,48▪▪]. Mobilize and to start early enteral nutrition and physiotherapy [19,48▪▪]. Severe TBI is a risk condition for gastrointestinal bleeding and deep vein thrombosis so gastric protection and initial mechanical protection measures (elastic stockings, pneumatic compression) are necessary [57,58]. Once the risk of hemorrhagic lesion progression has subsided, pharmacological prophylaxis can be instituted with an acceptable margin of safety [58].

Seizures or nonconvulsive activity may increase ICP or trigger tissue hypoxia therefore they should be promptly treated [18,19]. Current guidelines suggest short, 1-week courses of phenytoin or levetiracetam in those individuals who present with seizures, prior anticonvulsant therapy or risk injuries such as: depressed skull fractures, penetrating traumas, cerebral contusions or extra-axial hematomas (epidural, subdural) [18].

MANAGEMENT OF INTRACRANIAL HYPERTENSION WITHOUT INTRACRANIAL PRESSURE MONITORING

The basic treatment measures for patients with TBI should be applied regardless of whether ICP monitoring is available. To minimize the risk of ICHt, head of the bed should be kept at 30° and in neutral position to avoid jugular vein compression [19,40,51]. Agitation and pain should be treated with sedoanalgesia, titrated to keep the patient comfortable, but trying as much as possible to avoid confounding the examination. When ICHt is suspected, stepwise treatment should be started building from one step to the next [19,40].

The first step is to determine whether surgery is indicated. Access to early neurosurgery (first 4–6 h) is an effective intervention to improve survival in LMICs [59–61]. Preventive surgery ('damage control approach') has been proposed to minimize the chances of secondary injuries from brain edema, ICHt and compromised tissue perfusion [62–65].

When neurosurgeons are not available, basic neurosurgical procedures could even be performed by general or trauma surgery, orthopedics specialists or even well trained general physicians [66].

Osmotherapy with hypertonic saline solutions (3,5%; 7.5%, 20%) or mannitol may be used as a bridge to surgery or as primary medical treatment [18,19,51]. In patients without ICP monitoring, osmotic agents can be administered based on clinical–radiological changes or using a scheduled regimen [30,31,32▪▪,33].

A detailed discussion of the relative benefits and disadvantages of these two approaches exceeds his scope of this review, but in simple terms, scheduled doses may be preferable because clinical changes may not be recognized until it is too late and radiological studies can only be done sporadically [30,31,32▪▪,33]. Yet scheduled doses may lead to overtreatment and higher risk of iatrogenic adverse effects. Deepening of sedation and analgesia, neuromuscular paralysis or moderate hyperventilation ($PaCO_2 = 30–35$ mmHg) [30,31,32▪▪,33,67] can be attempted in the absence of clinical–radiological improvement. If all those interventions fail, salvage measures such as secondary decompressive craniectomy, hypothermia or barbiturates can be tried, though their efficacy is unproven [30,31,32▪▪,33].

Neuroworsening should be immediately identified [30,31,32▪▪,33]. Manifestations may include decrease GCS, mydriasis, loss of pupillary reactivity, new focal deficit, seizures or changes in vital signs suggestive of craniocaudal herniation (Cushing triad) [30,31,32▪▪,33]. In such instances, intervention should occur without any delay, including acute hyperventilation (as brief as possible) and a bolus of osmotherapy, followed by CT to define the cause of the decline [30,31,32▪▪,33]. Is important to remember that patients with unilateral brain lesions (including patients with large subdural hemorrhage or very asymmetric hemorrhagic contusions) can develop major pressure gradients that may result in brain herniation without global ICP elevation [40]. Thus, ICP monitoring should not be considered a replacement, but rather a complement of serial physical examination and brain imaging. In Fig. 3, we delineate an algorithm of action based on an expert consensus [32▪▪].

There are no clear and validated guidelines regarding when to stop treatments for ICHt. However, we consider it prudent to begin to reduce it in a slow, progressive and stepwise manner, in the opposite direction of their initiation (i.e., starting from the most aggressive measure) to decrease the possibility of rebound effect [29–31,32▪▪,33,40].

We advocate starting therapy reduction only once clinical–neurological stability has been achieved for at least 48 h [29–31,32▪▪,33,40]. It is advisable to pursue an awakening test that allows full clinical evaluation. CT scan should ideally show open and uncompressed basal cisterns, absence of large mass lesions, no midline deviation and no signs of major cerebral edema [29–31,32▪▪,33,40].

HOW WE CAN AVOID THE BURDEN OF CEREBRAL HYPOXIA WITHOUT ADVANCED MONITORING?

Cerebral hypoxia is associated with poor short-term outcome in patients with severe TBI [68]. This association has been shown to be independent of ICP and cerebral prefusion pressure values [68]. In one study, the causes of cerebral hypoxia were ICHt (50%), arterial hypotension (25%), hypoxemia (8%), hypothermia (7%), hyperthermia (5%) and anemia (2%), while in 4% no cause could be identified [68]. In another study, a quarter of the episodes were secondary to hypocapnia [69].

Brain tissue oxygen pressure (PtO_2) can be monitored with an invasive catheter, though the

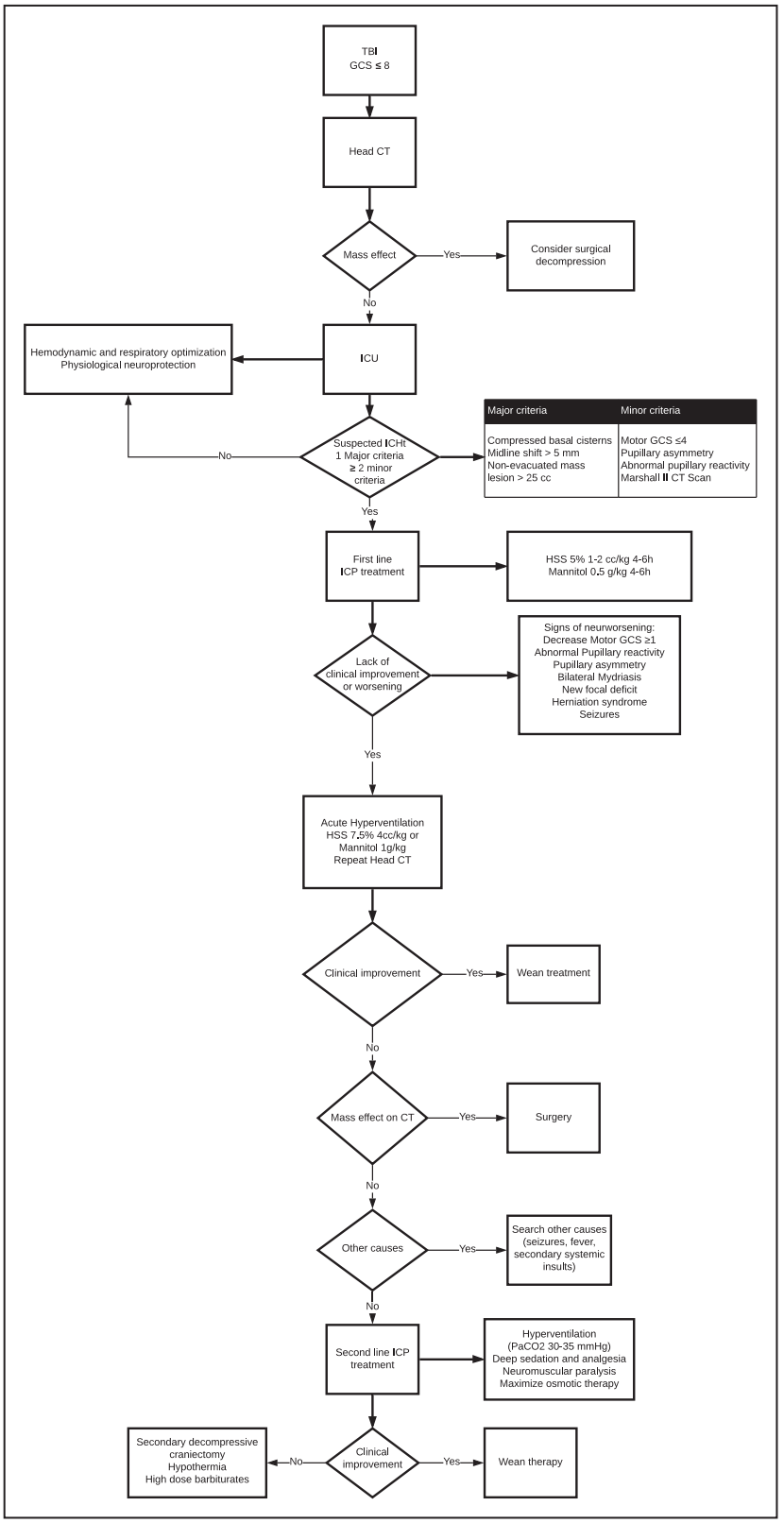


FIGURE 3. Algorithm for intracranial hypertension management without intracranial pressure monitoring.

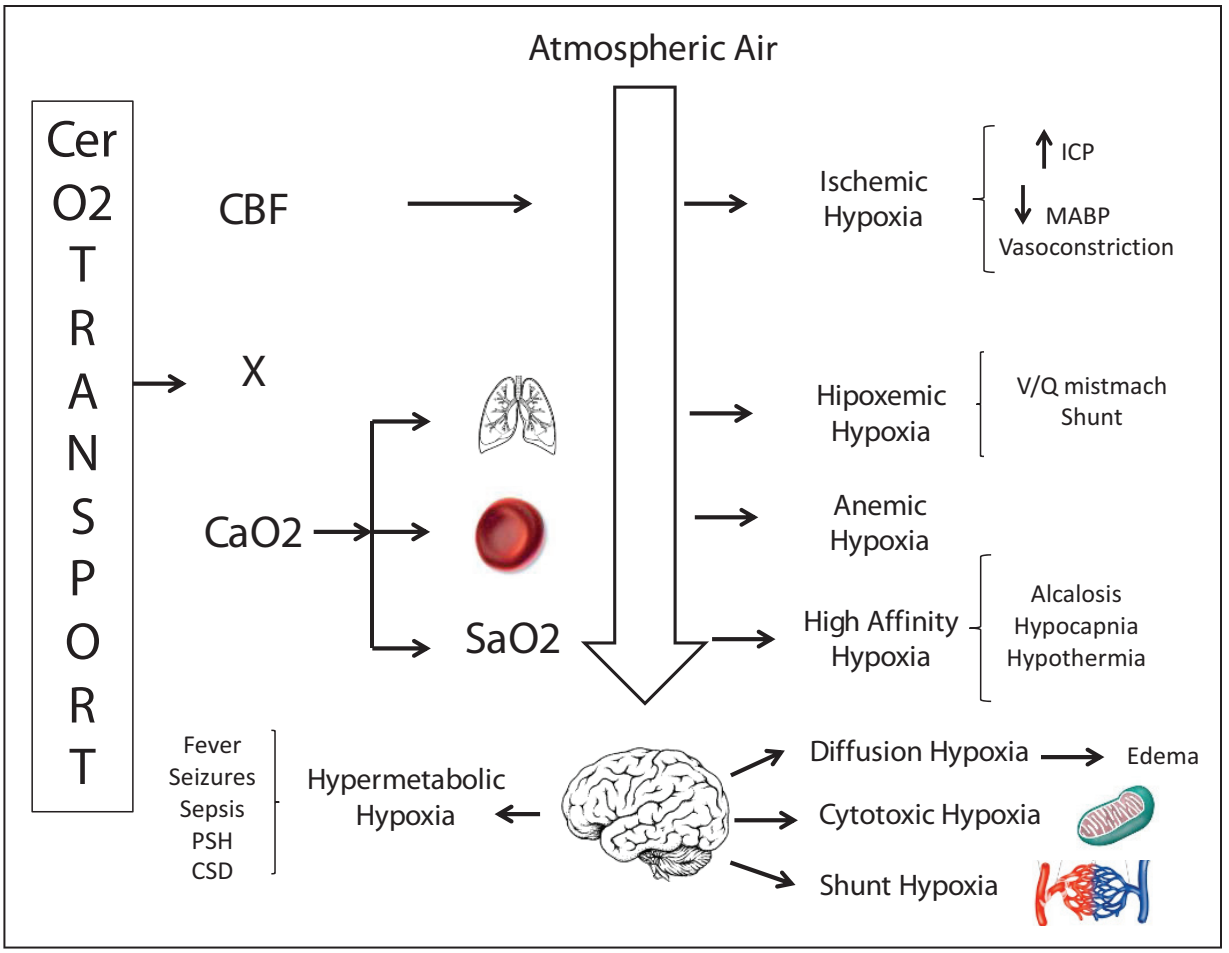


FIGURE 4. Oxygen route. Pathophysiology of brain hypoxia: causes and types. CaO_2, oxygen arterial content; CBF, cerebral blood flow; $CerO_2$, cerebral oxygen transport; CSD, cortical spreading depolarizations; ICP, intracranial pressure; MABP, mean arterial blood pressure; PSH, paroxysmal sympathetic hyperactivity; SaO_2, arterial oxygen saturation; V/Q, ventilation/perfusion.

measurement only applies to the tissue immediately surrounding the monitor (i.e., it is a local measurement of oxygenation that does not necessarily represent the degree of oxygenation in the rest of the brain). A survey conducted in trauma centers of Canada, United States and Europe reported a monitoring utilization rate of PtO_2 of 19% [70]. Yet, in another study the use of brain oxygen monitoring techniques (PtO_2, oxygen saturation in the jugular vein or near infrared spectroscopy) was much lower [71]. There are no data from LMICs; however, it is fair to assume that the use of these oxygen monitoring modalities is extremely infrequent in centers with less resources.

Most episodes of hypoxia are due to common clinical situations that can be potentially prevented. To avoid brain hypoxia episodes, we recommend following the physiology of oxygen route (Fig. 4). Clinical targets should be achieved as delineated in Fig. 5 [40].

RECOMMENDATIONS FROM LOW-INCOME AND MIDDLE-INCOME COUNTRIES

A recent review summarizes the evidence for severe TBI management in LMICs [72▪▪]. CREVICE protocol, based on an expert consensus approach, includes three levels of interventions and recommendations for monitoring, general measures, goals for cerebral perfusion and oxygenation treatment and for escalation or tapering therapies [32▪▪]. Meanwhile, 'BOOTStraP' reported protocols in different scenarios (from high to lower resources) [73▪▪]. 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 [48▪▪]. The document provides updated recommendations on general clinical ICU measures [48▪▪]. An example of the algorithm for severe TBI management in LMICs is presented in Fig. 6.

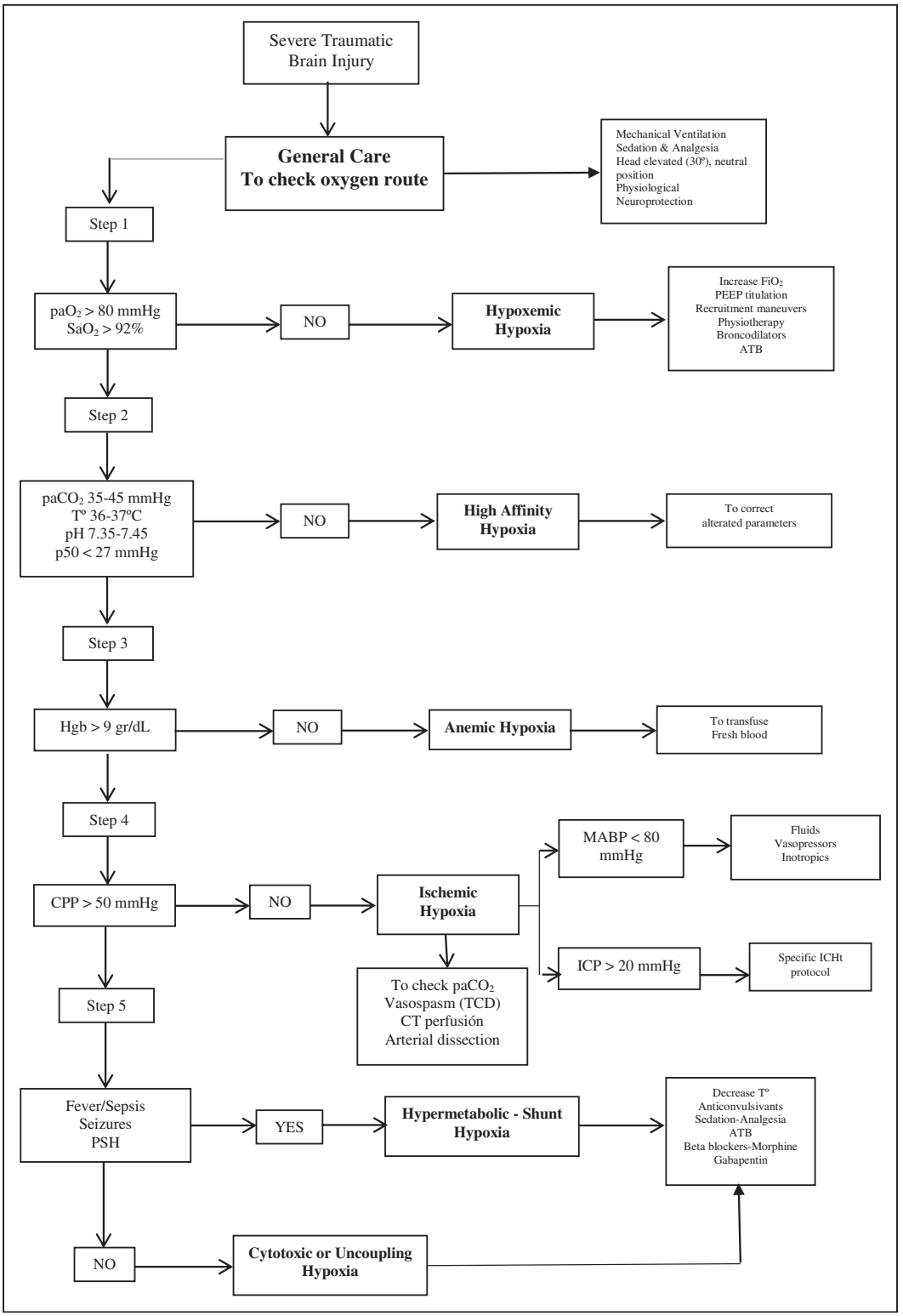


FIGURE 5. Clinical pathway to avoid brain hypoxia when monitoring is not available. ATB, antibiotics; CPP, cerebral prefusion pressure; FiO_2, oxygen inspirated fraction; Hgb, hemoglobin; ICHt, intracranial hypertension; ICP, intracranial pressure; MABP, mean arterial blood pressure; $paCO_2$, arterial carbon dioxide pressure; PaO_2, arterial oxygen pressure; PEEP, positive end expiratory pressure; PSH, paroxysmal sympathetic hyperactivity; SaO_2, arterial oxygen saturation; T°, central temperature; TCD, transcranial Doppler.

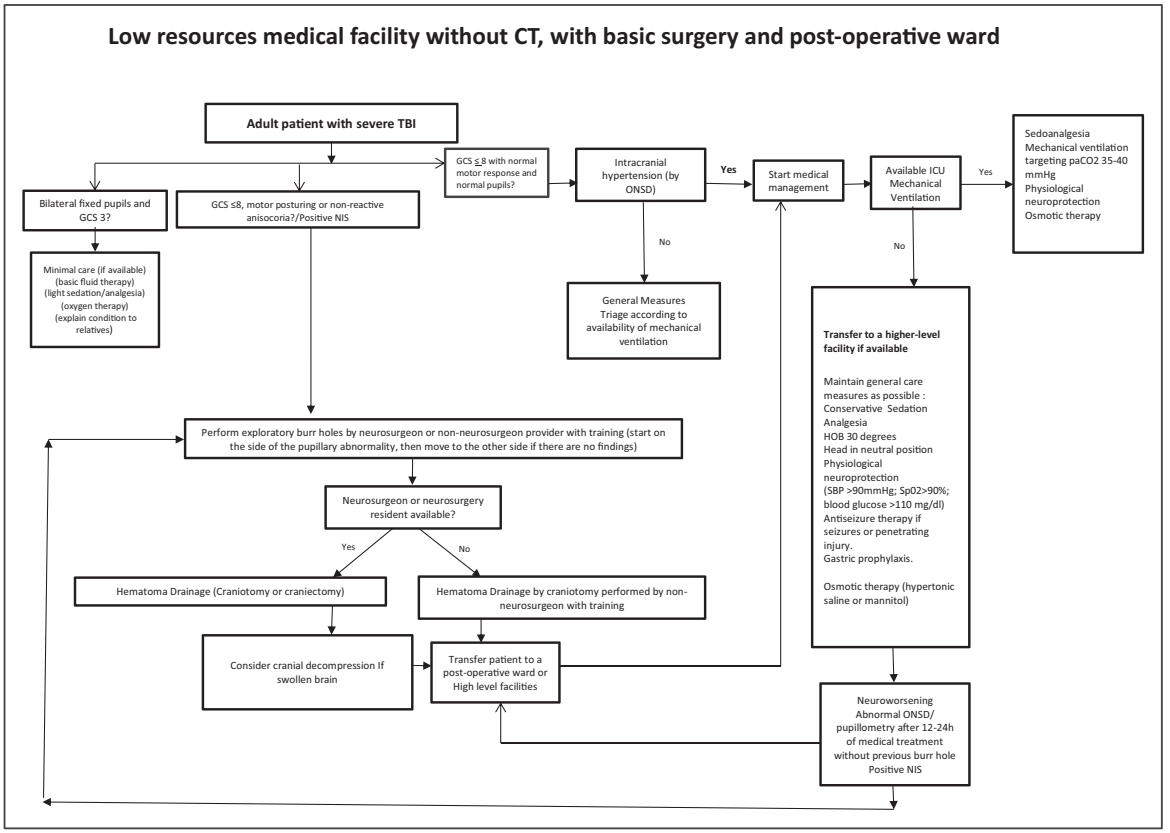


FIGURE 6. Pathway for severe traumatic brain injury management in low-income and middle-income countries without computed tomography scan, basic surgery and postoperative ward. GCS, Glasgow Coma Scale; HOB, head of bed elevation; NIS, near infrared scanner; ONSD, optic nerve sheath diameter; $paCO_2$, arterial carbon dioxide pressure; SaO_2, arterial oxygen saturation; TBI, traumatic brain injury; TCD, transcranial Doppler. *The available evidence places the cohort point in monitoring of the optic nerve sheath diameter with the highest correlation and predictive power to determine the presence of intracranial hypertension (intracranial pressure >20 mmHg) between 4.5 and 6.4 mm, while the correlation with the transcranial Doppler through the analysis of the pulsatility index more than 1.25 is not as consistent, lacks sufficient sensitivity and specificity and was not validated on a large scale [74,75].

CONCLUSION

TBI is a major global public health problem that disproportionally affects poorer countries with more limited healthcare resources. Treatment strategies recommended in current professional guidelines may not be applicable in LMICs and local adjustments are necessary. Emerging simple and portable technology may help bridge some of these gaps by facilitating the selection of patients who may benefit from early decompressive surgery and guiding triage decisions. Yet, the most impactful interventions to improve the outcomes of patients with TBI in LMICs would be the development of regional systems of care adapted to the local availability of resources and the focused analysis of the most pressing current deficiencies in each region to identify feasible solutions.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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- ■■ of outstanding interest

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