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NARRATIVE REVIEW

Management of moderate to severe traumatic brain injury: an update for the intensivist

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Abstract

Traumatic brain injury (TBI) remains one of the most fatal and debilitating conditions in the world. Current clinical management in severe TBI patients is mainly concerned with reducing secondary insults and optimizing the balance between substrate delivery and consumption. Over the past decades, multimodality monitoring has become more widely available, and clinical management protocols have been published that recommend potential interventions to correct pathophysiological derangements. Even while evidence from randomized clinical trials is still lacking for many of the recommended interventions, these protocols and algorithms can be useful to define a clear standard of therapy where novel interventions can be added or be compared to. Over the past decade, more attention has been paid to holistic management, in which hemodynamic, respiratory, inflammatory or coagulation disturbances are detected and treated accordingly. Considerable variability with regards to the trajectories of recovery exists. Even while most of the recovery occurs in the first months after TBI, substantial changes may still occur in a later phase. Neuroprognostication is challenging in these patients, where a risk of self-fulfilling prophecies is a matter of concern. The present article provides a comprehensive and practical review of the current best practice in clinical management and long-term outcomes of moderate to severe TBI in adult patients admitted to the intensive care unit.

Keywords: Traumatic brain injury, Intracranial pressure, Cerebral perfusion pressure, Intensive care unit, Neuromonitoring, Pre-hospital management

Introduction

Traumatic brain injury (TBI) remains one of the most fatal and debilitating conditions in the world, affecting all ages, including children, the working-age population as well as the elderly. The actual incidence is difficult to determine but is estimated by the Global Burden of Disease study to be around 27 million cases per year, globally [1]. Most TBI cases occur in low- and middle-income countries, and huge disparity in outcomes continues to exist between and within these different settings. The quest for specific neuroprotective agents in TBI has been disappointing [2]. Consequently, the current clinical management approach in severe TBI patients is mainly focused on reducing secondary brain injury, a cascade of events caused by the physiologic responses following the initial injury, including edema and hematomas leading

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to elevations in intracranial pressure (ICP), mechanical distortion of surrounding brain tissue, or reduced energy substrate delivery, all of which potential causes of additional brain damage and worse clinical outcomes. Optimizing the balance between substrate delivery and consumption is the main therapeutic goal, a strategy which may be challenging as a continuous exercise, even in highly specialized centers, since optimal physiological targets may vary, not just between patients, but also within patients as the disease evolves over time. Over the past decades, multimodality monitoring has become more widely available, and clinical as well as research efforts are concentrated towards the development of management protocols based on individualized precision medicine, in the hope that this will improve the outcomes of individual patients. In the present review, the current state of the literature on severe adult TBI management is summarized, to provide a comprehensive and practical review of the current best practice in clinical management, and to identify areas where empirical evidence is lacking.

The first hours

Initial resuscitation targets

The early management of TBI is a continuum from the field to the trauma bay. Triage and transfer to specialized neuro-trauma-centers may be indicated depending on the local setting, but this is outside the scope of the present review. In the pre-hospital and early in-hospital phases, the main therapeutic goal is to avoid secondary brain insults (particularly brain hypoperfusion, hypoxia, and major bleeding) (Table 1).

Several studies reported worse neurological outcome in hypotensive TBI patients. The association of systolic hypotension (< 90 mmHg) and worse outcomes has been described earlier [3]. Across a wide pressure range (40–119 mmHg), a linear association between the lowest pre-hospital systolic blood pressure (SBP) and severity-adjusted probability of mortality exists [4]. Different guidelines differ in targets and thresholds, with recommendations to maintain mean arterial blood pressure (MAP) above 80 mmHg [5], or to keep the SBP above 100 mmHg for 50- to 69-year-old TBI patients and above 110 mmHg for younger (15–49 years) or older (> 70 years) patients [6, 7]. Whether the early blood pressure target should be individualized based on cerebrovascular autoregulation assessment, for instance by making use of transcranial Doppler (TCD) to optimize diastolic flow velocity (> 20 cm/s) and pulsatility index (< 1.4) [8], remains to be debated. Brain perfusion is also highly influenced by systemic partial pressure of carbon dioxide ($PaCO_2$). Hypo- as well as hypercapnia should be avoided. End-tidal CO_2 ($EtCO_2$) should always be monitored in intubated TBI patients [9], and ventilation adjusted to a target of 30–35 mmHg [7], which should later be adapted as soon as an arterial blood gas analysis is available.

Both the presence and duration of hypoxemic episodes (peripheral oxygen saturation (SpO_2) < 90%) are clearly associated with increased mortality and worse neurological outcome [4, 10]. Consequently, maintaining SpO_2 at minimum above this threshold is also an early resuscitation target.

Finally, it is imperative to stop bleeding from associated injuries, to maintain hemoglobin > 7 g/dL, and to treat coagulopathy, by rapidly reversing therapeutic anticoagulation, considering platelet supplementation in patients on anti-platelet agents, and supplementing platelets and clotting factors where needed [5]. Tranexamic acid has been reported to improve mortality and outcome in multiple trauma patients, and in a subgroup of moderate-to-severe TBI (see details below).

Table 1 Initial resuscitation targets

Parameter	Values/targets	Objectives
Blood pressure	MAP > 80 mmHg SBP > 100 or 110 mmHg	Preserving CBF
SpO_2	> 90%	Avoiding brain hypoxia
$EtCO_2$	30–35 mmHg	Preserving CBF
Hb	> 7 g/dl	Avoiding brain hypoxia
Anticoagulant	Reversal	Limiting blood loss and expansion of hemorrhagic contusions

Evidence for these target values is derived from associations between targets and outcome. Evidence for treatment according to these target values from randomized controlled trials, is currently lacking

SBP systolic blood pressure; *MAP* mean arterial blood pressure; *SpO_2* peripheral oxygen saturation; *$EtCO_2$* end tidal CO_2, *Hb* hemoglobin

Take-home message

The management of traumatic brain injury (TBI) has changed over the past decade, from a dogmatic approach where intracranial pressure control in isolation was confused with TBI management, to a multimodal approach, in which pathophysiological derangements are detected and treated accordingly.

In the intensive care unit

Secondary insults after trauma

Management of elevated intracranial pressure (including indications for monitoring)

ICP management is central to TBI care and ICP monitoring should be considered a default in severe TBI. ICP

monitoring may be by an external ventricular drain or intraparenchymal device. The former is inexpensive, readily available, and allows cerebrospinal fluid drainage. The latter is simple, of low-maintenance, and has a relatively low rate of complications, but is more expensive.

Indications for ICP monitoring and management are in evolution, with the concept of a fixed treatment threshold in question [11, 12]. In the latest edition of the Brain Trauma Foundation (BTF) Guidelines [6], "*Management of severe TBI patients using information from ICP monitoring is recommended to reduce in- hospital and 2-week post-injury mortality*" (Level IIB evidence). As for ICP thresholds, the same guidelines indicate 22 mmHg. Protocolized-care within- and between-specialties dealing with TBI care appears associated with improved outcome and efficiency. Across the world, considerable variability continues to exist in the use of ICP monitoring, even between centers from the same geographical region or income category [13]. Over the 146 intensive care units (ICUs) in 42 countries that participated in Synapse-ICU, 55% of TBI patients had an ICP monitor inserted. Six-month mortality was lower in patients who had ICP monitoring [441/1318 (34%)] than in those who were not monitored [517/1049 (49%); $p < 0.0001$], in particular in patients with at least one unreactive pupil [hazard ratio (HR) 0.35, 95% CI 0.26–0.47; $p < 0.0001$]. Patients with ICP monitoring were treated more aggressively, as evident from their higher Therapeutic Intensity Level (TIL) scores [9 (IQR 7–12)] compared to those who were not monitored (5 [3–8]; $p < 0.0001$). An increment of one point in TIL was associated with a reduction in mortality (HR 0.94, 95% CI 0.91–0.98; $p = 0.0011$).

Prompt detection and surgical evacuation of intracranial masses is crucial. Careful clinical observation and repeated brain computed tomography (CT) scans can be lifesaving. ICP management can be organized into tiers, as suggested by the recent Seattle Brain Injury Consensus Conference guidelines (SIBICC) [14, 15]. A modified version of the SIBICC algorithms is presented in Fig. 1. Tier 0 is the expected level of basic ICU care for all ICP monitored patients. When ICP remains elevated, Tier 1 treatments are suggested. Many cases are entirely manageable at Tier 1, and a general principle is to use "the lowest possible treatment tier". However, if ICP proves resistant to Tier 1, Tier 2 treatments are considered, including the assessment of pressure autoregulation and cerebral perfusion pressure (CPP) target-setting based on its status, as explained below. Tier 3 treatments have the highest risk of complications and include decompressive craniectomy, high-dose barbiturates, or mild hypothermia. These high-risk therapies should be reserved for the most severe situations, in patients where survival with an acceptable quality of life is still realistic.

When advancement above Tier 1 is required, ancillary monitoring such as brain tissue oxygen tension ($PbtO_2$) monitoring can be considered [15] and will be discussed below. Before advancing Tiers, the patient should be re-examined to assess the cause of the persistent ICP elevation, and to exclude obvious and easily remediable causes such as insufficient sedation or hypoventilation. In addition, a repeat CT scan of the brain to re-evaluate intracranial pathology should always be considered.

Remember that the pathophysiology of TBI includes much more than just intracranial overpressure. While avoiding ischemic or mechanical damage from elevated ICP is mandatory, lowering ICP does not treat the primary brain injury, nor other pathophysiological phenomena such as neuro-inflammation or excitotoxicity. Although still in development, adjusting treatment to fit the injury is the goal [11, 12]. The 22 mmHg ICP threshold may not be absolute and a recent CENTER-TBI study reported ICP levels of 18 ± 4 mm Hg to be associated with poorer outcome [16]. In addition, secondary brain damage resulting from intracranial hypertension is not merely a matter of crossing a certain threshold. Rather, observational studies suggest that the "dose of ICP", the combination of intensity and duration of episodes of intracranial hypertension, has an even better association with outcome [16, 17]. The availability of this parameter at the bedside could assist in clinical decision making before escalating therapy to a higher tier.

Cerebral perfusion pressure—hemodynamic management

CPP, calculated as the difference between median arterial pressure (MAP) and ICP, is a critical treatment target in the management of TBI. First, CPP is a key driver of oxygen [18] and substrate [19] delivery. As such, treatment of inappropriately low CPP values will avoid cerebral hypoperfusion. On the other hand, preventing excessive rises in CPP is important as well, as they could lead to increased perilesional edema. In TBI patients with intact cerebrovascular autoregulation, [20] increases and decreases in CPP can drive autoregulatory vasoconstriction and vasodilatation, respectively. Even while the resulting changes in cerebral blood volume are small, in a non-compliant intracranial cavity they can translate into significant changes in ICP. Attempts to establish a single universal CPP target, which avoids the harms of both a low and a high CPP, based on association with outcome in populations of patients, have led to conflicting recommendations. Previous guidelines [21] suggested a single CPP target of 70 mmHg, subsequently revised downwards to 60 mmHg due to the risk of cardiorespiratory complications. Current guidelines [6] recommend varying CPP targets between 60 and 70 mmHg, acknowledging that critical CPP thresholds vary with age and the

presence or absence of cerebrovascular autoregulation [22]. Individualized CPP targets based on neuromonitoring are often proposed as alternative, even while evidence from randomized controlled trials is lacking. Several physiological targets have been investigated, such as the $PbtO_2$, or the Pressure Reactivity Index (PRx). Target values for these metrics are based on historical associations between monitored values and outcome. The COGITATE trial [23] has explored safety and feasibility of a strategy to steer the CPP towards an optimal value (CPPopt) where cerebrovascular autoregulation is most active. In the intervention group of the trial, the CPP target was adapted every 4 h to a PRx-calculated CPPopt. COGITATE was not powered to demonstrate an outcome benefit for this strategy, but the COGITATE protocol can subsequently be studied in future interventional clinical trials.

Recent SIBICC [14, 15] guidelines have attempted to integrate multimodality monitoring (ICP, $PbtO_2$, and autoregulatory status) into decision support algorithms. The MAP challenge, a controlled trial of induced and reversible blood pressure augmentation followed by an evaluation of clinical and neuromonitoring parameters [14, 15, 24], is a pragmatic approach to integrate physiology in clinical practice. However, it should be emphasized not only that evidence for this approach is lacking, but also that this is a potentially risky intervention that should only be left to practitioners with experience in interpreting the results [24, 25].

Target CPP can be achieved by reducing ICP or by increasing MAP. In practice, ICP related interventions are most appropriate when ICP is elevated, and the interventions used in this context are discussed above. Augmentation of MAP can be achieved in many ways. Specific recommendations in the TBI population on the relative benefits and harms of fluid loading versus vasoactive drugs, and the choice of vasoactive drug used for this purpose, remain uncertain. The routine early administration of vasopressors to support CPP may mask under-resuscitation. Even while evaluating the volume status in critically ill patients is challenging, the volume status should be assessed before initiating vasopressors, and periodically thereafter. Using volume responsiveness of the MAP may result in fluid overload, which is undesirable since even a modestly elevated fluid balance is associated with worse outcome [26]. On the other hand, hypovolemia should be avoided as well. The choice of intravenous fluids is discussed below.

There is equally limited evidence to support the choice of a particular vasoactive drug in this situation, but norepinephrine appears to be the most used in practice, compared to other inotropes [27]. While cardiac output may be independently associated with cerebral perfusion, [28] it is rarely monitored, and MAP remains the most common target for circulatory management in TBI. Several vasopressors have been used for CPP augmentation (norepinephrine, phenylephrine, dopamine, and vasopressin) [29], but evidence to support a choice of any individual agent is lacking [30]. Dopamine produces less predictable CPP augmentation than norepinephrine [31]. Vasopressin and analogues (such as terlipressin) should be used with caution because of risk of hyponatremia (and subsequent cerebral oedema), and excessive vasoconstriction. Given the importance of maintaining CPP, inodilatators such as phosphodiesterase inhibitors are probably best avoided unless specific indications, and always combined with vasopressors. Escalations of

(See figure on next page.)

Fig. 1 An algorithm for treating intracranial pressure (ICP) (modified from The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC)). In patients with ICP monitoring (with/without additional brain oxygen monitoring) the four represent the starting points for deciding a treatment strategy. Tier 0, i.e. basic strategies (not included in the flowchart), apply to TBI patients who are admitted to an intensive care unit (ICU) for whom the decision to monitor ICP has been made. The goal of tier-zero is to establish a stable, neuroprotective physiologic baseline regardless of eventual ICP readings. Tier-zero sedatives and analgesics target comfort and ventilator tolerance, temperature management targets the avoidance of fever and CPP > 60 mm Hg. Lower tier treatments are viewed as having a more favorable side effect profile than higher tiers and generally should be employed first. Treatments in any given tier are considered equivalent, with the selection of one treatment over another based on individual patient characteristics and physician discretion and multiple items from a single tier can be trialed individually or in combination with the goal of a rapid response. The provider should consider moving to more aggressive interventions in a higher tier quickly if the patient is not responding. Panel **A** Patients with ICP below the threshold usually do not need treatment except for conditions in which a high intracranial pressure–time burden is present because this condition is associated with worse outcomes. Refer to [1] for details. Therefore, in this setting, treatment could be considered also below the classical threshold of 22 mmHg. Panel **B** Consensus-based algorithm for the management of severe traumatic brain injury with brain hypoxia and normal intracranial pressure. Panel **C** Consensus-based algorithm for the management of severe traumatic brain injury with intracranial hypertension and brain hypoxia. Panel **D** Consensus-based algorithm for the management of severe traumatic brain injury with intracranial hypertension and normal brain oxygenation. Inter-tier recommendations encourage patient reassessment for remediable causes of treatment resistance. Stepping to a higher tier is a potential indicator of increased disease severity. As higher tiers represent interventions with increased associated risks, we recommend reassessing the patient's basic intra-and extra-cranial physiologic status and reconsidering the surgical status of intracranial mass lesions not previously considered operative

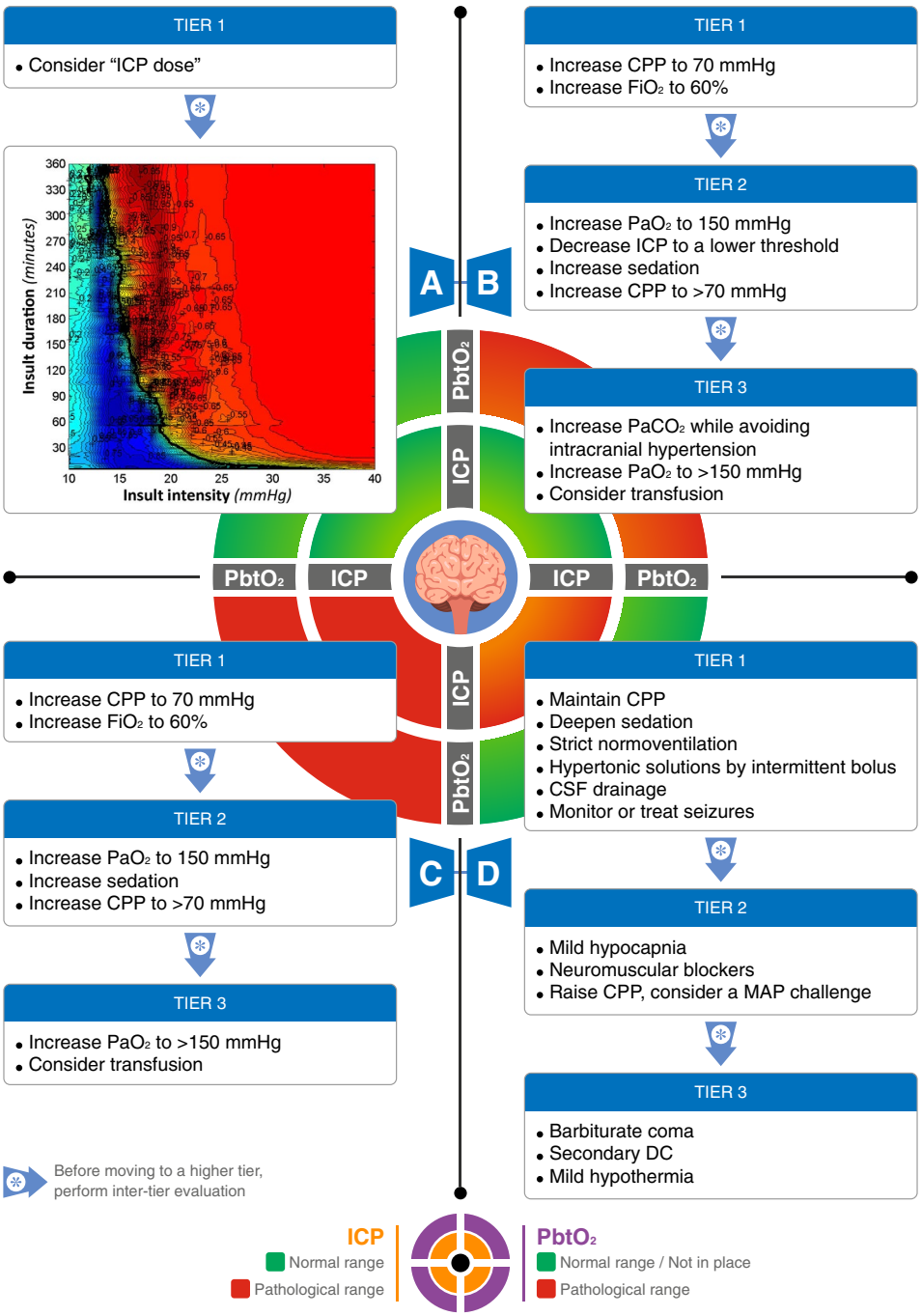

Fig. 1 (See legend on previous page.)

the need for vasopressors may occur and should prompt a thorough hemodynamic evaluation (including echocardiography or invasive monitoring) and a suspicion of associated sepsis or pituitary-adrenal insufficiency. For the latter, the cortisol/C-reactive protein ratio may be a useful index [32].

Hopefully, future trials will be able to provide evidence that current expert-opinion based CPP policies have impact on clinical outcomes. It remains striking that even fundamental aspects of CPP management, such as the level at which MAP is referenced (mid-axillary line versus external auditory meatus), remain inconsistently applied, both in reported studies and in clinical practice [33]. It should be clear that for appropriate CPP calculation, both MAP and ICP should be calibrated at the level of the foramen of Monro, corresponding to the external meatus acusticus.

Table 2 Proposed target values for some neuromonitoring modalities

	Normal	Desirable	Critical
ICP	~10 mmHg	< 18–22 mmHg	> 25 mmHg
CPP	50–60 mmHg	60- (80) mmHg	< 50 mmHg
$PbtO_2$	~30 mmHg	20–25 mmHg	< 15 mmHg
Lactate/Pyruvate Ratio	< 25	< 25	> 40
Brain Glucose	> 1 mmol/l	> 0.8 mmol/l	< 0.5 mmol/l
Brain temperature	~36.5 °C	36.5–37 °C	> 37.5 °C

Evidence for these target values is derived from associations between targets and outcome. Evidence from randomized controlled trials that treating TBI patients according to these target values impacts their outcomes is currently lacking

ICP intracranial pressure; *CPP* cerebral perfusion pressure; *$PbtO_2$* brain tissue oxygen

Multimodality monitoring targets and management

Additional physiological information can be obtained from different monitors to support clinical decision-making in TBI patients. In some cases, ICP and CPP targets can be beneficially adjusted and followed based on multimodality monitoring. Huge variability in the application of multimodality monitoring exists [27], which can be related to the current lack of scientific evidence from clinical trials on which processes to monitor, and whether monitoring these processes is cost-effective or impacts outcome [34]. As such, universal recommendations on the indications for ancillary monitoring cannot be made, but, if applied, multimodality monitoring should be focused on determining the pathology underlying the ICP elevation (e.g., ischemia, hyperemia, edema, cerebrospinal fluid dynamics disruption) as well as determining the toxicity of the ICP elevation (e.g., hypoperfusion, herniation). Nevertheless, apart from the potential benefit for clinical management, neuromonitoring can have an additional important role in the quest for appropriate neuroprotective treatments, the identification of subgroups of patients that could most benefit from certain therapies, or to gain insight in the still incompletely understood underlying pathophysiological processes following severe TBI. Table 2 summarizes currently advised target values for some neuromonitoring modalities.

Brain tissue oxygen tension monitoring

Non-invasive tools to measure brain oxygen are currently not recommended in TBI. Invasive $PbtO_2$-monitoring is gaining favor as a second monitoring parameter in TBI, added to ICP monitoring [35, 36]. Brain oxygenation depends on a complex interplay of oxygen delivery, diffusion, consumption, and metabolism. $PbtO_2$-values below 20 mmHg are associated with worse outcome [36]. Multiple interventions can be used individually or in combination to manage brain hypoxia. The BOOST-II [37] trial has demonstrated feasibility of a combined ICP-$PbtO_2$ protocol. Based on the ICP and $PbtO_2$ values of the patient, four situations are defined, where both, none, or only one parameter are/is out of range; and this framework has been incorporated in the SIBICC guidelines as well [15] (Fig. 1).

There are currently three randomized controlled trials investigating the treatment of low $PbtO_2$ values in TBI as follows: the subsequent BOOST-III trial (NCT03754114) [38], the Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment Trial (BONANZA) (ACTRN12619001328167p) [39] and the French OXY-TC trial [40] (NCT02754063).

Cerebral microdialysis

Cerebral microdialysis allows measurement of small molecular weight substances (glucose, lactate, pyruvate, glycerol, glutamate) in brain tissue to identify neuroglycopenia, energy metabolic crisis, cerebral ischemia, or excitotoxicity and, which are independent predictors for mortality and sometimes precede intracranial hypertension [41]. Recommendations to implement microdialysis in clinical practice were summarized in a 2014 expert consensus statement [42]. However, use is still limited to academic centers, mostly to gain pathophysiological insights, rather than as a clinical tool. In this perspective, it is worth mentioning that cerebral microdialysis can also be used to measure neuronal/axonal proteins (i.e., neurofilament light (NFL) and tau) and proteins of glial activation or blood brain barrier dysfunction (i.e., glial fibrillary acidic protein (GFAP)), with potentially

important implications in getting insights on injury evolution [43].

Pupillometry

The serial evaluation of pupillary size and reactivity is a fundamental component of the neurological assessment of TBI patients. Currently, assessment is mostly performed by nurses or physicians using manual flash penlights, which is non-quantitative, and inter-operator dependent [44].

Using an infrared light-emitting diode and a digital camera, automated pupillometry can provide quantitative and objective information on pupillary asymmetry, size, constriction variation, latency, constriction, and dilation velocity [45].

Automated pupillometry may have several applications in TBI patients. First, by reducing errors in the evaluation of pupillary function [46, 47], a more precise and early detection of neuroworsening and neurological complications is possible. Second, a relationship between the Neuroptics® NPi-200 Neurological Pupil Index (NPi) and ICP has been demonstrated, with values < 3 being indicative of increased ICP > 20 mmHg [48]. Finally, an ongoing multicenter study will assess whether pupillometry could be used for neuroprognostication in TBI patients [49], like its use in cardiac arrest patients [50].

Brain ultrasonography

In TBI, transcranial color-coded duplex ultrasonography (TCCD) may be a helpful bedside tool to detect intracranial hemorrhage, midline shift, hydrocephalus, and cerebrovascular alterations [51].

Intracranial hypertension can be estimated non-invasively through ultrasound, although these methods are not accurate enough to substitute invasive monitoring. An optic nerve sheath diameter (ONSD) above 6 mm (measured 3 mm behind the retina using a high frequency probe of at least 7.5 MHz), is indicative of increased ICP [52]. Waveform analysis of the middle cerebral artery (MCA) diastolic flow velocity, and an increased Pulsatility index (PI, defined as: systolic flow velocity (FV) – diastolic FV/mean FV), can also raise suspicion of increased ICP [51, 53]. These tools could be useful when invasive methods are not available (i.e., low-in-come countries) or contraindicated (i.e., severe coagulopathy), or in borderline situations to discriminate patients at risk of developing intracranial hypertension.

Electro-encephalography (EEG)

Convulsive and non-convulsive seizures occur frequently after TBI [54], often remain undetected, and are a treatable cause of neurological deterioration. For this reason, it can be useful to use continuous or intermittent EEG monitoring, which is also recommended as inter-tier evaluation in the SIBICC guidelines [14, 15]. In addition, invasive electrophysiological monitoring can identify cortical spreading depolarizations, which occur in up to 50% of TBI patients and are associated with poor outcome [55].

Extracranial complications

Respiratory management

The setting of mechanical ventilation in TBI is important [6] and may contribute to secondary brain injury, due to the tight interactions between cerebral and respiratory dynamics, affecting CPP, venous return, vasomotor tonus, and oxygen delivery. Pulmonary complications such as ventilator-associated pneumonia (VAP) are relatively common in TBI patients, complicating up to 30% of cases [56]. Lung protective strategies (LPS), especially low tidal volume and plateau pressures, might be beneficial [57] in this population (Table 3), even while they carry the risk of increasing $PaCO_2$ and ICP. The use of positive end expiratory pressure (PEEP) may improve oxygenation, alveolar recruitment, and ventilation–perfusion mismatch, and can be safely applied in TBI patients provided hemodynamic stability is maintained and alveolar hyperdistention avoided. The roles of recruitment maneuvers, prone positioning, and other rescue therapies are less well established as they can have detrimental effects on ICP and CPP (Table 3). These more aggressive strategies should be considered on a case-by-case basis, evaluating risks and benefits after multidisciplinary assessment. In selected cases, extracorporeal systems (carbon dioxide removal or extracorporeal membrane oxygenation) have been used [58], albeit with minimum or no systemic anticoagulation because of the risk of intracranial bleeding.

The central goal of mechanical ventilation in TBI is the avoidance of both hypoxia and hyperoxia. Current guidelines recommend that the optimal target range of PaO_2 in patients with TBI is 80–120 mmHg. Similarly, hypercapnia should be avoided (optimal target in absence of ICP elevation is 35–45 mmHg). However, mild-short term hypocapnia and has been suggested as part of the management of refractory intracranial hypertension, [6] and centers who use this strategy in combination with ICP monitoring report similar outcomes than those who do not [59] In summary, when defining mechanical ventilation setting and targets in TBI, a balance needs to be found between brain and lung protection. $PbtO_2$-monitoring may help the intensivists to target specific values of $PaCO_2$ and PaO_2.

Fluid and transfusion management

The standard fluid management in patients with TBI is aimed at maintaining a normal hemodynamic status,

Table 3 Respiratory management: an overview

Parameter	Key messages	Clinical recommendation
PaO_2	Hypoxia is a well-known cause of secondary brain damage Hyperoxia seems to worsen outcome by increasing cerebral inflammation and reactive oxygen species	Target PaO_2 = 80–120 mmHg
$PaCO_2$	Hypercapnia may cause cerebral vasodilation and increased ICP Hypocapnia may reduce ICP but can cause cerebral vasoconstriction and ischemia	Target $PaCO_2$ = 35–45 mmHg In case of intracranial hypertension: $PaCO_2$ = 35–38 mmHg as Tier 1 $PaCO_2$ = 32–35 mmHg as Tier 2, preferably with additional $PbtO_2$-monitoring $PaCO_2$ = 30–32 mmHg (briefly) as rescue for refractory intracranial hypertension (not routinely recommended)
TV/Pplat	High TV and Pplat increase the risk of ventilator-induced lung injury in brain injured patients Low TV may cause hypercapnia and increased ICP	TV = 6–8 mL/kg PBW, driving pressure < 15 cmH_20, Pplat 18–25 cmH_20
PEEP	PEEP can improve oxygenation and prevent atelectasis PEEP can lead to increased intrathoracic pressure, reduced jugular venous outflow, and hemodynamic instability Alveolar hyperdistention caused by excessive levels of PEEP can increase $PaCO_2$ values	PEEP should be set according to the principles applied in the general ICU population, considering systemic oxygenation, respiratory mechanics (compliance), and hemodynamic status
Recruitment manoevers	RM may improve oxygenation RM can cause hemodynamic instability and reduction of CPP RM can increase intrathoracic pressure and reduce jugular venous outflow	RM only as rescue therapy (hypoxemia responsive to PEEP, and considering/preventing the risk of hemodynamic instability)
Prone positioning	May improve oxygenation and improve outcomes in hypoxemic respiratory failure May improve cerebral oxygenation Risk of hemodynamic instability Risk of ICP catheter dislocation	May be taken in consideration as rescue therapy, considering risks and benefits to improve systemic and cerebral oxygenation
iNO	May improve systemic and cerebral oxygenation No definite evidence regarding outcome benefit	Should be considered in case of refractory hypoxemia with pulmonary hypertension
$ECCO_2R$	Can allow protective ventilation with $PaCO_2$ control Quick reduction of $PaCO_2$ could lead to cerebral vasoconstriction	Can be considered in TBI without active intracranial bleeding None or reduced dose of heparin for cannulation should be applied
ECMO	Can improve oxygenation and control $PaCO_2$, but often requires systemic anticoagulation and thus increases the risk of bleeding Quick changes in $PaCO_2$ and PaO_2 can lead to cerebral vasoconstriction, loss of autoregulation and intracerebral complications	Can be considered in TBI without active intracranial bleeding None or reduced dose of heparin for cannulation should be applied

PaO_2 arterial oxygen tension; *$PaCO_2$* arterial carbon dioxide tension; *TV* tidal volume; *Pplat* plateau pressure; *ICP* intracranial pressure; *PBW* predicted body weight; *PEEP* positive end-expiratory pressure; *RM* recruitment manoevers; *CPP* cerebral perfusion pressure; *iNO* inhaled nitric oxide; *$ECCO_2R$* extracorporeal carbon dioxide removal; *ECMO* extracorporeal membrane oxygenation

guided by invasive and non-invasive monitoring, including arterial blood pressure, fluid balance and urinary output [60], and even oxygen venous saturation, blood lactate and cardiac output or other hemodynamic monitoring if necessary. Crystalloids are the preferred maintenance and resuscitation fluids, while hypotonic fluids and albumin are not recommended [60]. Hypertonic saline solutions as maintenance or resuscitation fluids confer no benefit over saline or balanced solutions [61]. Concerning the management of intracranial hypertension, the choice of the "optimal" hypertonic fluid between mannitol and hypertonic saline remains uncertain; both agents showing comparable efficacy in reducing ICP in most studies [62]. To help address this uncertainty, a multicenter comparative study is ongoing (ISRCTN16075091) [63].

Red blood cell transfusions (RBCT) are generally safe, but have a small risk of immune, hemolytic, or infectious complications. The hemoglobin (Hb) threshold to administer RBCT in patients with TBI remains controversial [64], while randomized trials have conflicting results. In the EPO Severe TBI trial (n = 200), targeting Hb concentrations > 10 g/dL did not improve 6-month neurological outcome when compared to a restrictive strategy initiating RBCT for Hb > 7 g/dL [65]. However, in this study, Hb values of the "restrictive" control group were in the 8–9 g/dL range, thereby questioning how these findings should be interpreted and translated to clinical practice.

In contrast, in a smaller feasibility study ($n=44$), outcome (hospital mortality and 6-month neurological status) was better in the liberal (RBCT if Hb < 9 g/dL) than the restrictive (RBCT if Hb < 7 g/dL) group [66]. This controversy is reflected by variable ICU practices for RBCT [64]. While awaiting larger randomized trials, RBCT decision in severe TBI patients, may be best based on individual systemic and cerebral physiological triggers, targeted to multimodal monitoring [14, 15].

Renal complications

Acute kidney injury (AKI) occurs early after TBI, and affects around 10% of patients, with a 20% incidence of severe AKI, often requiring renal replacement therapy [67, 68]. AKI is an independent determinant of mortality and poor long-term neurological outcome [67], while severe AKI is associated with the need for tracheostomy and prolonged hospital length of stay [68]. Together with pre-existing risk factors (such as chronic renal disease and diabetes), potentially modifiable determinants of AKI are the use of mannitol [69], and the presence of hyperchloremia [70]. Whether therapeutic strategies aiming at preventing AKI in TBI patients can also improve long-term outcomes remains to be further elucidated.

At the other side of the renal function spectrum, augmented renal clearance is notably prevalent in neurocritical care and trauma patients, and should warrant particular attention to dosage of hydrophilic drugs, in particular antibiotics [71].

Nutrition and glucose control

While pre-clinical neurophysiological data are encouraging, there is no hard evidence for nutritional interventions improving outcome in TBI [72]. As such, nutritional management should prioritize the prevention of nutrition-induced harm [73]. Initiation of enteral nutrition (EN) within 48 h might reduce infectious morbidity, but not mortality, as compared to late initiation of EN and to early parenteral nutrition (PN) [74, 75]. The limited amounts of EN provided due to delayed gastric emptying -occurring particularly during therapeutic hypothermia- should raise no concern. They may be adaptive to critical illness and the reduced metabolic rate with hypothermia [73, 76].

Modest micronutrient-doses provided by standard EN-preparations might not compensate early losses or premorbid deficiencies [77]. Particularly in comatose patients, clinical hallmarks of micronutrient deficiency will be easily overlooked [78]. Strategies of early generous micronutrient administration versus targeted corrections have not been investigated after TBI [78].

Guidance on glucose control has fluctuated over the past decades. A subgroup analysis of the Leuven landmark randomised controlled trial (RCT) reported that tight glucose control (TGC) improved short and long-term outcome in 63 patients with isolated TBI [79]. In a meta-analysis of 7 RCTs ($N=1013$) TGC beneficially impacted the occurrence of new infections, ICU length of stay and long-term neurological outcome, despite hypoglycemia occurring more often [80]. These trials, however, were mostly conducted before 2011, providing early generous EN and/or PN. In contrast, a sub-study analysis of 391 patients with TBI in the NICE-SUGAR study comparing intensive (glucose < 6 mmol/L or 106 mg/dl) versus conventional (glucose < 10 mmol/L or 180 mg/dl) glucose control found no difference in outcomes but a higher incidence of hypoglycemia in the intensive control group [81]. A meta-analysis of 10 RCTs ($N=1066$) confirmed this higher risk of severe hypoglycemia associated with intensive control, while at the same time TGC reduced the risk of poor neurological outcome, but not mortality [82]. Based on these studies, a universal glucose target is difficult to establish and TGC should probably only be performed in centers capable of performing intensive control while avoiding hypoglycemia. Else, a glucose goal that avoids hypoglycemia while targeting levels < 10 mmol/L (180 mg/dl) should be acceptable.

Early mobilization and rehabilitation

In non-brain injured critically ill patients, early mobilization in the ICU is feasible, safe, and leads to better functional and neurocognitive outcomes [83]. Early ICU mobilization in TBI patients, and severely brain-injured patients in general, remains poorly investigated. Currently, evidence from randomized controlled trials for early head-up mobilization is lacking [84], although observational data suggest a potential benefit [85], and one small prospective trial has demonstrated the feasibility [86].

Huge differences in rehabilitation referrals after severe TBI continue to exist across and within different health care systems [87], making conclusions about optimal trajectories and indications for early rehabilitation referral difficult. According to a Cochrane analysis in 2015, a limited benefit of starting rehabilitation early after TBI is suggested, while more intense programs might be associated with earlier functional gains [88].

Coagulopathy

Trauma-induced coagulopathy (TIC) is a complex multifactorial failure of hemostasis that occurs in 25% of severely injured patients and is associated with higher morbidity and a fourfold increase in mortality [89]. TIC occurs immediately after trauma and is characterized by hypofibrinogenemia, hyperfibrinolysis, systemic anticoagulation, endothelial dysfunction, and platelet

consumption and dysfunction [90]. Initial management should focus primarily at stopping eventual bleeding, in most cases from extracranial sources, and addressing the lethal triad of coagulopathy, acidosis, and hypothermia. Tranexamic acid should be administered in all bleeding multiple trauma patients, as early as possible, and within the first 3 h. In isolated TBI, the CRASH3 trial showed a reduction in TBI-related death when tranexamic acid (TXA) was administered in the subgroup of patients with mild-to-moderate TBI (Glasgow Coma Score (GCS) 9–15) within the first 3 h [91], but not in severe TBI. Moreover, a systematic review of 9 RCTs (including CRASH3) in 14,747 isolated TBI patients [92] did not find such mortality benefit of TXA (even while there was a reduction in hematoma expansion), and no increased risk of adverse events. As such, TXA is not indicated in severe isolated TBI, but can be considered in mild-to-moderate TBI, when administered within the first 3 h [93].

Early and targeted hemostatic resuscitation can be accomplished with timely and balanced use of blood components and resuscitation fluids, damage control surgery, hemostasis monitoring with viscoelastic assays, and early hemodynamic monitoring to maintain a neutral fluid balance [94]. Obviously, this is even more relevant in TBI as the progression of hemorrhagic lesions in the intracranial compartment can become life-threatening [95]. Treatment strategies for coagulopathy in TBI patients are the same as for extracranial injuries, although some experts advocate a higher platelet count (>100 G/L) [90]. Early empirical and ratio-driven blood transfusion (1:1:1) is also crucial in TBI. A recent RCT showed a decrease in mortality in TBI patients (especially those having extracranial injuries) receiving early plasma in the pre-hospital setting [96].

TBI is an independent risk factor of venous thromboembolic events (VTE). Hypercoagulability is driven by excessive thrombin generation and inflammation [89]. In the early phase, before low-molecular weight heparin (LMWH) can be started, intermittent pneumatic compression should be used for VTE prophylaxis. After 24–72 h, once hemostasis is achieved, LMWH can probably be safely initiated with no increased risk of hemorrhage provided that repeated neuroimaging shows no evidence of hematoma progression, although significant variability in the timing of LMWH initiation exists, ranging from 1 to 7 days [97].

Inflammation

Coagulation and inflammation are interrelated processes. Brain secondary insults can be triggered by the inflammatory response to TBI. Figure 2 explains the acute damage-related inflammatory molecular cascade that leads to brain injuries worsening and extracranial complications [98]. In addition, a complex poly-antigenic response has been described in both the acute and chronic phases persisting years after injury; and acute elevation of anti-myelin associated glycopeptide (MAG) IgM autoantibodies is associated with worse outcomes [99]. The persistence of MAG IgM is associated with chronic neurofilament light level, a marker of axonal injury which has been associated with white matter neurodegeneration [43].

While this response is still incompletely understood, the quest for specific treatment addressing the inflammatory cascade has been unsuccessful to date [2], and research is still ongoing.

Fever is prevalent in TBI patients, occurring in up to 79% of patients [100], and can be a sign of infectious complications, or central disturbed thermoregulation. Infection management is beyond the scope of this review, but is obviously crucial. Targeted temperature management outside ICP control, aimed at avoiding fever or maintaining strict normothermia, may be neuroprotective, but evidence from interventional trials is currently lacking to demonstrate the impact of such approach on patient outcomes [101]. $PbtO_2$ values appear to be unaffected during episodes of fever unless hypotension is present [100].

Long-term outcome

Neuroprognostication

The ancient Hippocratic aphorism *"No head injury is too severe to despair of, nor too trivial to ignore"* still holds to this day. Unfortunately, preventable deaths in patients with head injury who "talk and die" still present, while at the other severe end of the TBI spectrum (GCS 3–5), some patients ultimately recover. Caution is advised against too early withdrawal of care. Eighty-six percent of TBI patients who die in the ICU do so following withdrawal of life-sustaining measures [102]. Withdrawal occurred within 72 h of injury in around half of the patients. This is of concern given the risk of self-fulfilling prophecies, the withdrawal of life-sustaining measures as a result of a predicted or estimated poor outcome [103], in a reality of imperfect prognostic models.

Advances in pathophysiological insight may improve prognostic modelling, while the increasing availability of big data and computational science pave the way towards more accurate prognostic estimates than can be obtained from clinical experience of physicians. Such estimates can be used to provide patients and relatives objective information on the expected outcome, to stratify patients for clinical trials, to support medical decision making and to benchmark quality of care. For predicting outcome with baseline characteristics, the IMPACT and CRASH prognostic models are robust and have been

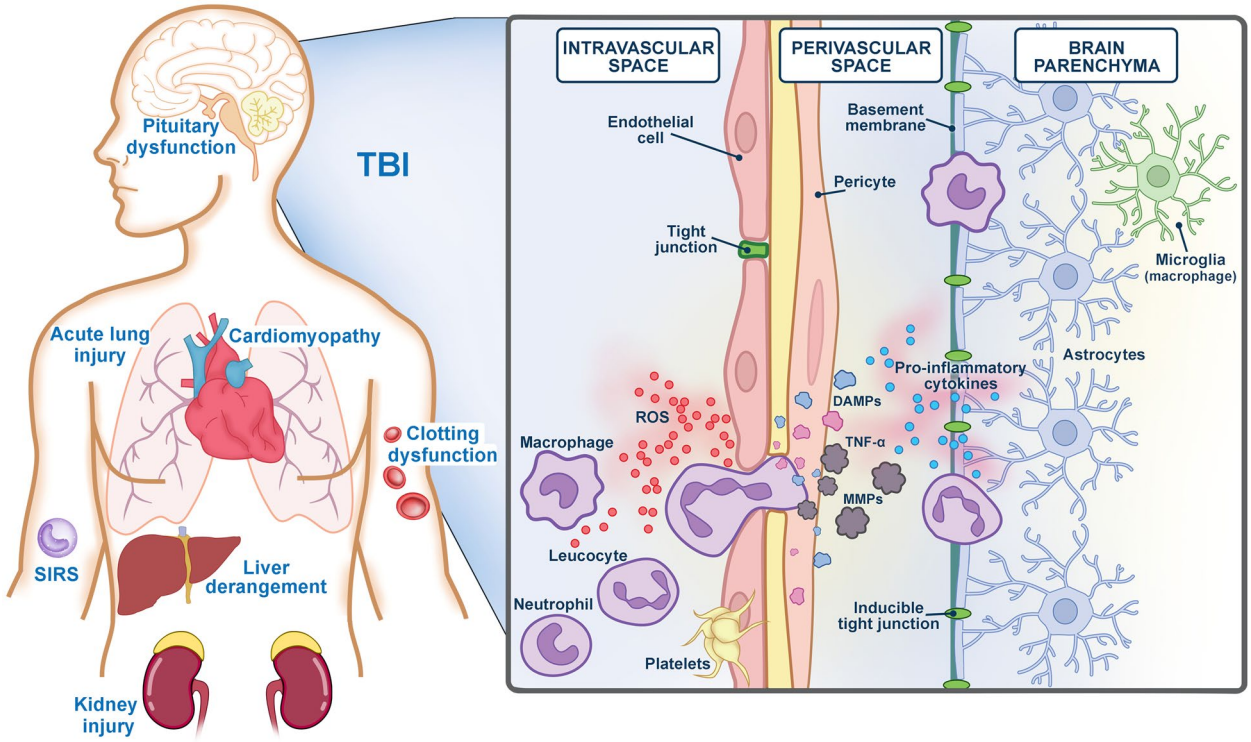

Fig. 2 Acute inflammatory response after TBI. The local inflammatory process starts with the activation of the immunological pro-inflammatory and coagulative cascades into the intravascular space. This triggers the activation of a cascade of events leading to blood–brain barrier disruption and infiltration of peripheral macrophages and neutrophils into the brain parenchyma with activation of microglia and recall of other peripheral immune cells into the cerebral microcirculation. The local inflammatory activation leads to peripheral organ dysfunction by crossing the damaged blood–brain barrier and passing into the systemic circulation. *ROS* Reactive oxygen species; *TNF-α* tumor necrosis factor alpha; *MMPs* matrix metalloproteinases; *DAMPs* danger-associated molecular patterns, *SIRS* systemic inflammatory response syndrome

extensively validated externally [104]. They, however, only explain 35% of variance in outcome [105]. Work is currently ongoing to update the models to current practice and to explore the added value of other predictors such as blood-based biomarkers, in-depth information from CT and magnetic resonance imaging (MRI) scans, and advanced EEG techniques. For example, the presence of deeper lesions on MRI, at the level of bilateral thalamus or brainstem, increases the risk of poor neurological outcome [106, 107]. The precise location of lesions is likely to be important; with those in the dorsal brainstem seeming to be more predictive than brainstem lesions elsewhere [108]. Diffusion MRI, a technique able to detect occult structural damage in grey and white matter not visible on conventional sequences, holds promise for predicting emergence from coma in patients with very severe TBI [109]. Advanced EEG with machine-learning techniques has been able to identify brain activation and responsiveness of comatose patients, which may potentially guide rehabilitative interventions [110]. Blood biomarkers, including neurofilament light (NFL, associated with axonal injury) and glial fibrillary acid protein (GFAP), secreted from astrocytes and microglia after injury are associated with the burden of injury defined on CT [111]. The peak of NFL (~ 10 days to 6 weeks after injury) is associated with the extent of white matter neurodegeneration and functional outcome at 1 year in patients with moderate-to-severe TBI. [43]

Over the past decades, the proportion of elderly TBI patients has increased [112]. Independent from age, frailty is associated with an increased risk of unfavorable outcome, and the recently developed CENTER-TBI frailty index [113] could be helpful in stratifying elderly patients.

In the ICU setting with a rich data environment, prognostic modelling can be taken a step further to predict derangements of physiological functioning, such as increased ICP, before such derangements are clinically evident [114, 115]. Therapeutic interventions can then be initiated before critical thresholds are reached. We suggest that future research should focus on dynamic prediction modelling, incorporating new information as it becomes available over time. For high dimensional

datasets, advanced computational approaches in the field of machine learning offer opportunities.

TBI: a chronic condition?

Most of the recovery after TBI takes place in the first months, up to the first 2 years. However, substantial change can occur even as late as two decades after injury [116]. Considerable variability with regard to the trajectories of recovery exists, [117] where patients may show both improvement and deterioration in the months and years following injury [116, 118]. As mentioned above, caution is needed when predicted probabilities from prognostic tools are translated into management decisions for individual patients, even in apparently devastating injuries [119].

Although outcome is strongly dependent on the initial severity of TBI, recent literature demonstrates that even patients with mild injuries may suffer from significant long-term consequences. Incomplete recovery is often defined as a Glasgow Outcome Score-Extended (GOSE) rating of less than 8, because this means that the individual has not returned fully to normal life. At 6 months post-injury, a GOSE less than 8 has been found in more than 60% of patients presenting with a mild TBI (GCS 13–15) who met criteria for a CT scan [120]. Even in patients managed as an outpatient in the emergency department, approximately every third person has a GOSE of less than 8, at 6 months [121]. Since most TBI presents as mild, these findings point to a substantial socioeconomic burden, which is often insufficiently addressed by existing health care services. Moreover, predictive models for functional outcome and persistence of post concussive symptoms for mild TBI are particularly imprecise and need further refinement of relevant endpoints and predictors [122].

Long-term consequences after TBI also include a higher risk for developing neurological diseases including epilepsy and stroke [123]. Furthermore, TBI has been linked to cognitive deficits, often affecting executive function, working memory, leading to chronic degenerative processes. Dementia is not uncommon, [124–126] even in patients with apparently mild TBI, especially those patients with repeated concussions [125]. This is supported by long-term neuropathological studies and argues for recognizing TBI as chronic disease with lifelong consequences in survivors [126].

Neurorepair: experimental therapies

Experimental efforts to promote repair in TBI have been directed towards reawakening mechanisms of neural development, to reprogram the local microenvironment from a detrimental function to a beneficial role by cell-based or gene therapy, or to promote adaptive plasticity [127]. Among cell-based therapies, mesenchymal stromal cells (MSC) are most promising. Preclinical studies have demonstrated favorable effects of MSC on favorable outcomes [128]. Clinical studies are at their infancy. Results from a first randomized phase 2 trial, testing intracerebral implantation of allogeneic modified MSC in TBI patients with chronic motor deficits, has demonstrated preliminary efficacy on motor dysfunction [129]. MSC are immune-privileged. As such, it can be envisaged that MSC from donors, can be stored as an "off the shelf" cell medicinal product, and made available to TBI patients with no delay in therapy.

The development of acellular scaffolds which are compositionally like brain extracellular matrix (ECM) is also gaining attention [130]. Chondroitin sulfate glycosaminoglycans (CS) are major constituents of the ECM and key regulators of growth factor signaling and neural stem cell homeostasis in the brain. Recent studies show that engineered CS (eCS) matrices can potentiate brain repair after TBI. Furthermore, neurotrophic factor – laden eCS matrix implants promote angiogenesis, support synaptic stability, and foster cognitive recovery, and could represent a rational approach to promote repair in TBI.

Self-repair processes occur after TBI, are stimulated by endogenous growth-related factors, and may last for weeks. However, those are usually insufficient to contrast injury progression in TBI [131]. Accordingly, providing the tissue with a milieu able to restore, replace, or regenerate injured brain and immune cells has become an important therapeutic target.

Conclusion

TBI management has changed over the past decade, from a dogmatic approach where ICP control in isolation was confused with TBI management, to a more multimodal approach, in which pathophysiological derangements are detected and treated accordingly (Table 4). Further research into these pathophysiological mechanisms is still needed, quantifying temporal relations and dependencies. Also, addressing the systemic complications of TBI, such as hypercoagulation or malnutrition, is now part of standard management protocols. Unfortunately,

Table 4 Management of severe TBI: conceptual highlights

Initial management	
Initial pre-and in-hospital resuscitation	Avoid and treat hypotension, hypoxia, anemia
Secondary injury management	
Management of elevated ICP	ICP monitoring allows to titrate therapy to severity of intracranial hypertension in severe TBI patients SIBICC algorithms provide a conceptual framework for a tiered approach Treating TBI involves more than just treating elevated ICP
Management of CPP	Optimizing brain perfusion can be challenging, and ancillary monitoring of brain tissue oxygen or cerebrovascular autoregulation may be helpful
Multimodality monitoring	Should be applied to answer a specific pathophysiological question
Extracranial complications	
Respiratory management	Lung protective ventilation is the preferred strategy Avoid hypoxia, hyperoxia, hypocapnia, hypercapnia
Fluid management	Assessment of volume status like general critically ill patients Choice of optimal hypertonic solution still uncertain
Transfusion	Variation in transfusion triggers reflects lack of evidence
Acute kidney injury	Occurs in 10% of TBI patients and is associated with poor long-term outcomes
Nutrition management	Nutrition management should prioritize the prevention of nutrition induced harm: avoid hyperglycemia, administer micronutrients early on, and delayed enteral nutrition should raise no concern
Mobilization and rehabilitation	Early mobilization is feasible, but benefit is unknown Early rehabilitation referrals might be associated with earlier functional gain
Coagulation management	TXA should be administered in all bleeding multiple trauma patients < 3 h. TXA may be considered in isolated mild-to-moderate but not severe TBI Significant variability in the timing of LMWH initiation exists. Before LMWH can be started, intermittent pneumatic compression should be applied

ICP intracranial pressure, *TBI* traumatic brain injury, *SIBICC* Seattle International Severe Traumatic Brain Injury Consensus Conference. *CPP* cerebral perfusion pressure, *TXA* tranexamic acid, *LMWH* low molecular weight heparin

evidence from randomized clinical trials is still lacking for many of the recommended interventions. However, the SIBICC guidelines now provide a clear standard of therapy where novel interventions can be added or be compared to.

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Declarations

Conflict of interest
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