Severe traumatic brain injury: targeted management in the Intensive Care Unit

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Abstract

Severe traumatic brain injury (TBI) is currently managed in the intensive care unit (ICU) by a combined medical-surgical approach. Treatment aims to prevent additional brain damage and to optimize conditions for brain recovery. TBI is considered and treated as a single pathological entity, though in fact it is a syndrome, comprising a range of lesions, which may demand different therapies and physiological goals. Thanks to advances in monitoring and imaging, there is now the potential to identify specific mechanisms of brain damage and to better target treatment to individual patients or subsets of patients. This is particularly relevant to elderly subjects, as TBI now affects an increasing proportion of aged patients. Pre-injury comorbidities and their therapies demand specific treatment, with strategies tailored to older cases. Advances in monitoring and in pathophysiological understanding may change the current ICU management with targeted interventions, ultimately improving outcome.
Introduction

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, with more than 13 million people estimated to live with disabilities related to TBI in Europe and the USA. Approximately 10–15% of patients with TBI have serious injuries that require specialist care. Severe grades of TBI are commonly managed in the intensive care unit (ICU) based on a combined medical-surgical approach, which has changed little over the last 20 years. A reassessment of this area of clinical practice is warranted on several grounds. First, recent expert reappraisals of such care have indicated that the evidence supporting most of our interventions is weak or non-existent, with few randomized controlled trials (RCTs) to guide treatment decisions. Given this dearth of evidence-based medicine to underpin clinical care, clinicians have had to rely on best practice statements from expert bodies, based on decades of accumulated and refined clinical experience. Moreover, treatment targets incorporated into guidelines are usually derived from population studies and applied to the entire ICU population of TBI patients. This approach reduces management variability, but ignores differences in the underlying pathology. TBI is in fact a syndrome that includes a range of brain lesions, with separate, sometimes diverging, pathophysiological paths and therapeutic needs. Consequently, undifferentiated interventions aimed at the overall population of TBI patients, rather than targeted to specific disease mechanisms and patient groups, are likely to fail, as exemplified by repeated failures of clinical trials of neuroprotective agents.

Furthermore, many patients with TBI now treated in the ICU are significantly different from those on which our accumulated clinical experience, research, and guidelines derives – young (typically male) patients who sustained a TBI from high-velocity traffic injuries or assault. In high-income countries (HICs), TBI affects increasing proportions of people older than 65 years (that we arbitrarily indicate as elderly): e.g., in the USA, the rate of TBI-related hospitalization for elderly people has increased by more than 50% from 2001 to 2010. This epidemiological change reflects increased life expectancy coupled with new risk factors typical of the elderly, such as anticoagulant medications. These older patients typically present after having sustained falls from a relatively low height, and have the clinical course of their TBI complicated by multiple comorbidities and their treatment.

This manuscript briefly reviews the heterogeneity of the pathology and pathophysiology of TBI seen in the ICU, explores how we might organize rational clinical care in view of the scarcity of conventional evidence.
from RCTs, and how we might individualize care to aim for precision medicine approaches, considering pathophysiological diversity with use of advances monitoring techniques. We focus on severe TBI in adults, and, critically, in addressing each of these issues, we examine how the rising age of TBI patients in the ICU might require new evidence to strengthen clinical management.

**Heterogeneity in pathology and pathophysiology**

*Primary and secondary injury*

TBI is classically divided into two distinct phases: a primary injury, followed by a delayed secondary injury. Primary injury arises from forces producing skull fractures, hematomas, and deformation and destruction of brain tissue, including contusions and diffuse axonal injury. Cell membranes are stretched, dysregulating trans-membrane ion fluxes, and impairing axonal transport. Secondary injury\(^9,10\) develops over time, with the activation of multiple molecular pathways, including excitotoxicity due to glutamate accumulation, activation of reactive oxygen species, ion channel and gap junction signaling, purinergic receptor signaling, intracellular calcium accumulation, and mitochondrial dysfunction. All these phenomena may damage the brain, from reversible disturbances up to necrosis or apoptosis. They may also be responsible for the development of cytotoxic or vasogenic brain edema and disturbed autoregulation, where the volume of intracranial contents increases because of vascular dilation and/or water accumulation\(^11\). Once this volume increase exceeds the compensatory capacities of the intracranial space, intracranial pressure (ICP) rises. Early seizures may exacerbate the imbalance between energy expenditure and supply\(^12\). Another electrical disturbance, spreading depolarization, has recently been attracting more attention. Spreading depolarization waves may occur in severe TBI patients and cause elevations in extracellular glutamate, increased anaerobic metabolism, and energy substrate depletion. They also seem associated with worse outcome\(^13\). Inflammation plays an important role, with the interplay of central nervous system resident or peripherally-derived inflammatory cells. Inflammation may provide neuroprotection or aggravate secondary injury\(^14\). Patients with TBI often suffer extra-cranial injuries (e.g. fractures, chest, and abdominal trauma) and massive bleeding. These may cause hypoxia or arterial hypotension and trigger a systemic inflammatory response syndrome that can further aggravate the development of secondary injury\(^15\).
Figure 1 summarizes the main pathophysiological changes following TBI and their dynamic progression over time.

**Heterogeneity of TBI**

TBI is often classified according to clinical severity, with severe TBI usually categorized on the basis of a total Glasgow Coma Scale (GCS) score of 8 or less. TBI produces a spectrum of lesions that range from mild injury to devastating damage. Expanding hematomas, extradural or subdural, may require emergency surgical removal in the first hours after injury; intraparenchymal contusions may increase over hours or days and require surgery as well. More subtle lesions such as traumatic axonal injury (TAI; the term commonly used for diffuse axonal injury [DAI] only strictly applies when involving three or more locations) may not be evident from initial computed tomography (CT) scans but, due to the neuronal network disruption, it may have a heavy effect on the quality of life of survivors, and is disclosed by magnetic resonance imaging (MRI). These different lesion types often occur in combination: for instance, cerebral contusions may develop underneath a subdural hematoma, and may also be associated with axonal injury. Figure 2 shows how the outcome, and the risk of high ICP, can vary by lesion type.

A number of serum and CSF biomarkers of neuronal (neuron-specific enolase; ubiquitin C-terminal hydrolase L1; spectrin breakdown products), axonal (τ protein; neurofilaments) and glial (glial fibrillary acidic protein; S100β) injury are currently being investigated in TBI patients and could, either individually or in concert, be used to characterize injury severity and type and may have prognostic significance. While preliminary evidence of cost effectiveness is emerging for some biomarkers in mild TBI, their role in more severe TBI remains uncertain. We need large-scale studies of the most promising biomarkers (or panels of biomarkers) to demonstrate that they can be used to refine initial characterization of brain damage in critically ill patients with TBI.

**Specific features of TBI in the elderly**

TBI in older patients often results from low-energy impacts such as ground level falls, with a higher proportion of subdural hematomas and less contusions or epidural hematomas. Cerebral atrophy and increased CSF space may buffer new pathological intracranial masses, with a lower incidence of raised
ICP\textsuperscript{28,30}, and the GCS may underestimate the severity of brain injury\textsuperscript{31}, making a case for higher GCS thresholds to trigger the triage of older patients to specialist centers\textsuperscript{32}. Further, age-related co-morbidities (e.g. diabetes, chronic cardiorespiratory disease, and renal dysfunction) reduce physiological reserve and increase the incidence and severity of brain damage due to second insults, such as hypoxia and hypotension. Many of the therapies used for these chronic diseases (in particular, anticoagulants and antiplatelet agents) may predispose to an increased incidence of hemorrhage or may worsen the evolution of intra-cerebral traumatic lesions (with the greatest risk from vitamin K antagonists)\textsuperscript{33}. Finally, the diminished brain reserve in these patients\textsuperscript{34} limits the potential for plasticity and neural repair, and hence hampers the success of rehabilitation. The main differences between young and older TBI patients are listed in Panel 1.

**Fundamentals of ICU monitoring and management**

Patients with severe TBI are currently treated in the ICU combining strategies used in general intensive care (such as early enteral feeding; infection control and treatment; normalization of respiratory exchanges, with skilled nursing, physiotherapy, and artificial ventilation; fluid optimization for arterial pressure and splanchnic organ perfusion, etc.) and a specialized neuro-intensive approach. This aims at prevention of second insults and maintenance of cerebral homeostasis. Some current strategies involve targeted approaches, such as surgical hematoma removal, whereas many medical therapies (for instance treatments for controlling high ICP) are prescribed for all cases.

**Prevention of second insults**

Prevention of second insults deals both with systemic (as hypoxia, hypercapnia, arterial hypotension, hyponatremia, pyrexia, etc.) and intracranial threats (such as expanding hematomas or contusions, ICP rises, etc.). Here, we focus on detection of intracranial threats through clinical examination and ICP monitoring.

**Neurological clinical examination**: Clinical examination remains a fundamental monitoring tool, even in the comatose or sedated patient to identify neurological deterioration and potential indications for surgical interventions. The basic examination relies on a GCS evaluation coupled with assessment of pupil diameter and reactivity to light. There are some obstacles to a complete GCS assessment: tracheal intubation precludes
a verbal response and facial injuries may impede eye opening, so motor response remains the main
assessable component of the GCS score. Neurological evaluation in deeply sedated patients may require a
sedation hold (wake-up test), which may cause arterial hypertension and, in patients with reduced
intracranial compliance, transient ICP rises. It is currently debated whether these ICP spikes are detrimental
for brain homeostasis or not.

On the other hand, a wake-up test may identify important clinical changes, in cases showing signs of
progressive brain stem impairment or in those with rapid improvement, as after successful surgical removal
of intracranial masses and patients with alcohol or other intoxications. This may profoundly influence their
management, with more aggressive intervention in case of deterioration or shorter intubation and ventilation
times in cases evolving favorably.

Pupillary diameter and reactivity are vital. A dilated, unreactive pupil usually discloses compression of the
third cranial nerve due to midline shift and uncal herniation. Pupillary reaction to light is commonly
assessed using a flashlight which, however, has poor inter-rater accuracy in clinical practice. Automated
pupillometry is a portable technique that measures pupil size and light reactivity automatically, and with a
high degree of precision. It may give more accurate measurements of reactivity, especially when the pupil
is small, as with opioid analgesia.

Up to 40% of patients experience significant worsening during the first 48 hours in the ICU. Neurological
worsening is currently defined as 1) a decrease of 2 points of the GCS motor component, or 2) loss of
pupillary reactivity or asymmetry, or 3) deterioration in neurological or CT status sufficient to warrant
immediate medical or surgical intervention. Neuroworsening in TBI is significantly associated with high
ICP and poor outcome. This is often due to a new or expanding intracranial lesion that may require
surgical evacuation. This progression is becoming increasingly important because prompt access to early CT
means that patients are often scanned within minutes after the TBI, before lesions had a chance to appear or
evolve. Parenchymal lesions may evolve in hours to days: in a series of 352 cases with contusions followed
up with three CT scans, the volume of hemorrhage increased in 42% of patients. A routine second CT scan
is therefore recommended for all comatose TBI patients, where it may disclose surgical lesions in up to one
third of cases. Additionally, if there is any substantial clinical worsening and/or ICP elevation, a new CT
scan must be performed.
ICP monitoring: ICP measurement is performed through ventricular or intraparenchymal probes connected to monitor\(^\text{11}\). This monitoring has been the cornerstone of TBI care since the 1980s, although it has been questioned recently in a multicenter trial (BEST:TRIP) in South America, where ICU management based on repeated clinical examination and CT scans was not inferior to management including continuous measurement of ICP\(^\text{57}\). It would be entirely inappropriate to discard the role of ICP monitoring based on this study\(^\text{58}\), but it does illustrate the fact that postulating a direct link from monitoring to improving outcome is too simplistic when considered in isolation.

In the latest edition of the Brain Trauma Foundation (BTF) guidelines, ICP monitoring is indicated in patients with severe TBI, because evidence suggests that ICP-guided treatment may reduce early mortality\(^\text{4}\). A variable proportion of severe TBI patients develops raised ICP, often depending on the definition. The historical and most widely accepted ICP threshold for therapy is 20 mmHg, though recent guidelines suggest 22 mmHg\(^\text{4}\). This approach, which is based on population targets, provides little potential for optimizing therapy based on the needs of individual patients. Indeed, the available literature suggests that there may be subtle differences in critical ICP thresholds between young and old patients and males and females, even at an aggregated population level, with older patients (≥55 years of age) and females having lower ICP thresholds (18 vs. 22 mmHg) for prediction of poor outcome\(^\text{59}\).

Protocols for ICP therapy vary in detail but generally include the prevention of ICP rises, with mechanical ventilation, sedation, and avoidance of pyrexia, as well as active interventions\(^\text{11}\). For ICP elevations, first-tier strategies include edema management with hyperosmotic infusions and CSF drainage (when a ventricular drain is available). More aggressive therapies are required for refractory ICP, including hypothermia, metabolic suppression with deep sedation, decompressive craniectomy, and hypocapnia, but these have more harmful side effects, as illustrated in Figure 3 (and discussed below). ICP monitoring is relatively safe; complications (hemorrhage and infection) arise in 1-7% of cases\(^\text{62}\), driving a search for non-invasive alternatives. Several methods are under investigation for non-invasive ICP measurement, but are not ready for clinical use yet\(^\text{11}\).

*Maintenance of cerebral homeostasis*
Maintenance of cerebral homeostasis and, in particular, optimization of cerebral oxygen supply and demand, is traditionally attempted using indirect parameters such as cerebral perfusion pressure (CPP), the difference between mean arterial blood pressure (ABP) and ICP. Ideally a normal arterial pressure, coupled with a physiological ICP value, should be maintained. In case of arterial hypotension, vasopressors and volume expansion are used to restore an adequate arterial pressure, while ICP becomes a target when it exceeds a threshold (see above). CPP around 60 mmHg is generally targeted, though the latest guidelines suggest some discrimination between individuals with and without preserved autoregulation, but, as for ICP, do not account for differences in CPP thresholds between patient groups.

**Modulatory influences of age**

There is a clear association between older age and worse outcome, which might be explained, at least in part, by the effects of age-related co-morbidities, use of pharmacotherapies to treat comorbidities (especially antithrombotic drugs), and reduced brain reserve in elderly patients. Care of comorbidities may therefore be as important as management of TBI in determining outcome. Treatment of drug-induced coagulopathy in particular is essential with reversal of anticoagulant and antiplatelet therapy if there is significant hemorrhage. Post-traumatic seizures are common in older TBI patients; however, the optimal therapy and length of seizure prophylaxis in this population is still not clear.

Unfavorable outcome in older patients could be, at least in part, a self-fulfilling prophecy. Data collected on 4387 TBI patients in the UK indicates suboptimal care for older patients (including delayed CT scans), assessment by more junior medical staff, and a reduced likelihood of being transferred to neurotrauma centers. However, when older patients are treated aggressively and promptly following ICU admission, favorable outcomes are seen in 39% of patients between the ages of 60 and 69 years, suggesting that this nihilistic attitude is not justified.

The lower ICP thresholds associated with poor outcome in older patients might reflect the greater vulnerability of the aged brain, or a given ICP elevation may denote a worse brain injury in older patients, since age related atrophy allows space lesion expansion and brain edema before ICP rises. Notwithstanding the cause, these data make a case for exploring whether a reduced threshold for ICP control might be beneficial in the older patient. However, since elevated ICP is less frequent in the elderly and tissue...
penetration by intracranial probes is riskier in patients with anticoagulant and antiplatelet therapy, there is a case for revised (reduced) indications for ICP monitoring in these patients. Elderly patients may also have compromised autoregulation because of arterial hypertension, with the autoregulatory curve shifted toward higher arterial pressures. Indeed, the available data suggest that CPP thresholds for survival are higher in patients over the age of 55 years (75 vs 70 mmHg), suggesting that a higher CPP may be desirable, particularly in patients with a history of arterial hypertension.

It is worth noting that the current conceptual basis of ICU management of TBI is based on a body of experience accumulated over the last four decades, which overwhelmingly derives from younger patients, with high velocity injuries. It would be wrong, or at least unsafe, to assume that this experience can be directly applied to the older patients we now see with different injury mechanisms, and there is a pressing need to develop optimum management strategies targeted to these patients.

**Targeted ICU management: the role of physiological monitoring**

Clinical TBI pathophysiology is host-, treatment- and injury-dependent and therefore highly heterogeneous. A “one size fits all” management strategy is unlikely to be optimal. More precise understanding of intracranial disturbances might indicate specific targets and, hopefully, targeted therapies. A panoply of monitoring techniques and imaging modalities have been employed to achieve this information, including measurement of brain tissue partial tension of oxygen (PbtO$_2$), microdialysis, and autoregulation assessment (Table 1). In isolation, these techniques are at best indirect surrogates for a complex condition in our most complex organ. For example, raised ICP is not a diagnosis by itself. It results from many (often coexisting) mechanisms, including edema (either cytotoxic or vasogenic), increased cerebral blood volume (which itself may result from many disparate mechanisms including excessive metabolic demand, hypercapnia, or disordered autoregulation, to name but a few), or impaired CSF reabsorption. Tools for better characterization of pathophysiological derangements have been available in the last two decades; however, they have been rarely used even in the most specialized neuro ICU. A recent survey of monitoring modalities in 31 UK specialized ICUs found that ICP was commonly used in all but one institution, PbtO$_2$ in 26% and microdialysis only in 13%.
Brain tissue partial tension of oxygen measurement

ICP and CPP provide information on the driving pressure for blood flow through the cerebral circulation. However, downstream metabolic event can also be monitored using several probes, often through a common insertion device. One such example is the measurement of PbtO$_2$ based on seminal studies of pioneer European groups$^{68-70}$. This provides a continuous (albeit localized) spatial average of extracellular oxygen tension as an indicator of the adequacy of oxygen delivery. PbtO$_2$ depends on the balance between oxygen delivery and consumption, and the cerebral metabolic rate of oxygen (CMRO$_2$). It is further influenced by the oxygen’s ability to diffuse$^{71,72}$. For example, in pericontusional tissue this may be influenced not only by tissue and endothelial edema, but also by microvascular collapse which increases the mean inter-capillary distance for diffusion, reducing average oxygen tension$^{72}$.

Determining appropriate target values for PbtO$_2$ is clearly methodologically difficult: oxygen tensions around 23 mmHg are recorded during/after functional neurosurgery$^{73}$. Values between 15 and 20 mmHg are typically regarded as thresholds for inadequate oxygen supply$^{74-76}$ and are associated with worse outcome after TBI$^{72}$. Therapeutic approaches aimed at normalization of PbtO$_2$, either by increasing arterial pressure and/or arterial oxygen tension, have been published$^{77,78}$. Those strategies seem to obtain better outcomes than strategies only focused on ICP and CPP. However, in absence of large, controlled trials, evidence at the moment is inconclusive$^{79}$.

Microdialysis

Measurement of glucose, lactate and pyruvate in the brain extracellular space using cerebral microdialysis provides information on energy metabolism. A high lactate/pyruvate ratio (LPR) after TBI is a marker of anaerobic glucose utilization, resulting from low PbtO$_2$ due to ischemia or diffusion hypoxia or, under normoxic conditions as a consequence of mitochondrial dysfunction$^{80,82}$. A high LPR indicates an energy metabolism crisis and is an independent predictor of mortality$^{83}$. Improvement of the LPR may indicate a beneficial effect of treatment. Various interventions, like hyperoxia and hypertonic lactate, have been tested on the brain energy metabolism. Normobaric hyperoxia, usually induced by increasing the fraction of inspired oxygen (FiO$_2$), can normally raise a low PbtO$_2$, but shows variable benefit on microdialysis
parameters in different studies\cite{84,85}, though imaging studies suggest improvements in CMRO$_2$\cite{86} and reversal of pericontusional cytotoxic edema\cite{87}. Attempts to improve brain glucose metabolism by hypertonic lactate infusions show a clear cerebral glucose-sparing effect, but mainly in patients with a pathological LPR\cite{88}. These preliminary clinical trials require larger numbers for confirmation, but indicate the possibility of targeted interventions.

**Autoregulation assessment**

One area that has received attention is on-line real-time assessment of cerebrovascular autoregulation, a physiological mechanism that serves to maintain adequate cerebral perfusion in the presence of blood pressure changes\cite{66}. Under normal conditions, with a normal autoregulation, the diameter of cerebral vessels changes to adjust for arterial pressure alterations (vasoconstriction in response to arterial hypertension, for instance), and these changes may impact ICP. In case of vasoconstriction ICP should remain unaffected or it may decrease. ICP may be therefore used for assessing how the brain vessels react to arterial pressure variation. In pathological conditions, as severe TBI, autoregulation can be altered or totally lost. Probably the measurement best known is the pressure-reactivity index (PRx): the correlation coefficient between samples of ICP and arterial pressure using a moving data window, which is normally a negative number\cite{89,90}. Furthermore, PRx often shows a U-shaped relationship when plotted against spontaneous changes in CPP over time, with the lowest PRx observed in the optimal autoregulatory range. The CPP for which PRx is a minimum is therefore felt to represent a state of optimal autoregulation, and management close to this has been associated with better outcomes\cite{92,93}. An autoregulation-guided approach to individualize CPP may be helpful in preventing cerebral hypoperfusion while at the same time avoiding the risks of excessive CBF. An approach based on optimization of autoregulation is physiologically attractive and has the potential to reconcile perfusion-supporting and edema-minimizing treatments. However, autoregulation may be impaired in a region-specific way which may not be captured by PRx, which is a global average. Alternative measures based on assessment of blood flow or brain tissue oxygen reactivity suffer the opposite limitation of limited global spatial coverage. Prospective evidence from clinical studies is urgently required before definitive guidelines can be drawn up.
Multimodal monitoring for tailoring therapies

There is consensus\textsuperscript{66} that simultaneous use of several monitoring modalities may provide a means of targeting patient specific ICP thresholds. Concordant changes documented by different sources provide cross-validation of physiology in the injured brain. For example, a critical PbtO$_2$ reduction may be used to individualize thresholds for more aggressive methods for correcting low CPP due to high ICP. Conversely, discordant findings, while potentially posing a clinical dilemma in terms of treatment compromise, may sometimes offer clues to the presence of pathophysiological heterogeneity and stimulate the search for less well-recognized routes to energy failure, such as diffusion hypoxia\textsuperscript{71,72}, mitochondrial dysfunction\textsuperscript{94}, and low cerebral glucose levels\textsuperscript{83,95} as downstream markers of compromised cerebral perfusion.\textsuperscript{71}

However, current multimodality neuromonitoring generates vast amounts of data which may need to be summarized for clinicians to extract information that can be used to guide patient care (Figure 4). Advances in monitoring will probably also require advances in neuroinformatics and data analysis\textsuperscript{96}. Computer visualization techniques offer one promising way to reduce complex datasets to a form that can be interpreted by a human, and have been applied in various areas including assessment of the cumulative burden of intracranial hypertension\textsuperscript{97} and autoregulation assessment\textsuperscript{98}. Such complex multidimensional problems are not new outside medicine, and other techniques from the field of ‘big data’ will very likely find increasing application in the intensive care of TBI patients\textsuperscript{99}.

Physiological monitoring in the elderly

The use of advanced multimodality monitoring to guide therapy in older patients is conceptually appealing, but experience in this area is limited. This lack of experience is in part explained by increased risks of invasive intracranial monitoring in older patients who commonly present on anticoagulants and anti-platelet therapies, and in part by the expectation of poor outcome that has made aggressive monitoring and therapy less frequent in this age group. Changing attitudes may provide more data to guide therapy individualization for older patients in the future, and development of less invasive monitoring tools would be particularly beneficial in this group.

Targeted ICU management with aggressive therapies
None of our therapies in the ICU are risk free, and the more aggressive interventions for restoring cerebral homeostasis have substantial potential to cause harm. Multimodal monitoring can demonstrate that aggressive interventions are justified, by proving that cerebrovascular physiology (ICP and CPP outside thresholds, and/or PbtO$_2$ reductions and elevations in lactate and lactate/pyruvate ratio) is seriously compromised, and not amenable to therapy with less risky interventions. Once a therapeutic target has been identified, for some interventions, careful measurement of physiological variables may minimize harm.

**CPP augmentation**

Pharmacological augmentation of CPP may improve cerebral oxygenation but at the expense of serious cardiopulmonary complications$^{100}$. Advanced cardiovascular monitoring, including intravascular volume assessment, echocardiography, cardiac output etc. beyond standard pulse oximetry and invasive arterial pressure monitoring, may be necessary$^{66}$.

**Hypocapnia**

Brief period of hypocapnia may be justifiable in the face of an episode of menacingly high ICP but it may cause dangerous ischemia through vasoconstriction$^{101}$, especially in the early phases after injury. For this reason, measurement of cerebral oxygenation, most commonly using PbtO$_2$ monitoring, is recommended when hypocapnia is used, to minimize the ischemic risk$^{66}$.

**Metabolic suppression**

Barbiturates for metabolic suppression are effective in reducing ICP but carry significant risks of cardiovascular instability and other end-organ dysfunction or metabolic disturbances$^{102}$. Advanced cardiovascular monitoring and support (including fluid titration, inotropes, and vasopressors) is advisable to avoid arterial hypotension.

**Hypothermia**

Hypothermia, a treatment with strong neuroprotective action in animal models$^{103}$, failed to show outcome benefit in clinical trials$^{61}$. When, recently, moderate hypothermia (32 to 35°C) was used as early ICP intervention, the treated group had a worse outcome than controls$^{61}$. Despite the results of this trial, hypothermia continues to be used in some centers, but often with higher ICP thresholds (25-30 mmHg)$^{104}$, denoting an implicit acceptance that the risks of hypothermia demand more deranged physiology before the risk-benefit ratio becomes favorable.
Decompressive craniectomy

Decompressive craniectomy (DC) is effective in reducing ICP, but results of RCTs have shown differences in outcome depending on the target group. The DECRA trial showed that it did not improve outcome when used for modest ICP increases\(^{60}\). However, the balance of risk and benefit changes in circumstances where aggressive therapies are justified by the presence of refractory severe intracranial hypertension. For example, the RESCUE-ICP\(^{105}\) study showed that DC targeted to patients with refractory severe ICP reduced mortality, and shifted neurological outcomes so that more patients could at least function independently at home, although these gains were achieved at the expense of increases in survival with severe disability. These findings emphasize the importance of following a graded sequence for these aggressive interventions, beginning with those with least potential for harm before escalating to higher - and potentially more harmful - therapeutic intensity (see Figure 2). Furthermore, the evidence highlights the need to select interventions based on the clinical picture in individual patients, and the circumstances at the time of intervention. Further research into the contribution of the physiological monitoring methods might enable more refined stratification of patients for these more aggressive therapies.

Aggressive therapies in elderly patients

Aggressive therapies are linked to severe side-effects, and might not be tolerated by frail old patients with impaired physiological reserve. The high incidence of cardiorespiratory comorbidities in such individuals might further reduce the ability of patients to tolerate some of the aggressive interventions (such as CPP augmentation, barbiturates, and hypothermia) used in the critical care of TBI. Therefore, careful monitoring of systemic physiology is mandatory, and caution is needed with hemodynamic augmentation and second stage therapies for high ICP in these patients. The two major RCTs\(^{60,105}\) on DC for TBI excluded patients older than 65 years, probably reflecting the skepticism of the neurotrauma community against extreme therapies in the elderly. Another study, where DC was used for the treatment of unilateral or bilateral brain swelling in 44 TBI patients over the age of 66 years, resulted in 77% mortality and 82% overall unfavorable outcomes, leading to this approach being abandoned in clinical practice for elderly patients who present with a GCS \(< 8\)^\(^{106}\).
Emerging opportunities in management of severe TBI

The focus of this review has been on how we might improve clinical management of TBI using techniques that are already available, even if not widely used in clinical practice. However, emerging advances could deliver additional refinement, or even paradigm changes, in how we treat these patients, with regard to better characterization, identification of novel therapeutic targets, and the generation of evidence to support changes in management. The failure of four recent pharmacological trials, two on erythropoietin\textsuperscript{107,108} and two on progesterone\textsuperscript{109,110}, to improve neurological outcome despite experimental evidence of multiple neuroprotective mechanisms underlines the importance of targeting treatments to selected patient groups. Enrolment criteria in these trials were based on TBI severity, and the benefits of compounds acting on specific pathways may not have been demonstrable in a heterogeneous population of TBI patients. Future trials should aim to select patients on the basis of specific mechanisms of brain damage in individual patients to maximize potential for improved outcomes.

The growing use of magnetic resonance imaging in TBI promises to provide better definitions of injury location, type and severity\textsuperscript{111}, and accumulating data linking genetic variability to outcome\textsuperscript{112} suggests that it may prove possible identify patients in whom specific therapies could be effective. For instance, once the pathological role of spreading depression is clarified better, specific interventions -such as nimodipine or ketamine - could be envisaged to correct it\textsuperscript{113}. Promising new therapeutic targets are emerging from more rigorous preclinical evaluation of new interventions in TBI, such as those delivered by Operation Brain Trauma Therapy, a multicenter, multiplatform collaboration for experimental evaluation of new therapies\textsuperscript{114}.

Other basic biology that may rapidly translate to clinical intervention includes the sulphonylurea receptor (SUR1) which is implicated in edema formation and contusion expansion\textsuperscript{115}, novel brain fuels that bypass identified blocks in energy generation\textsuperscript{116}, more precise action on the host immune response\textsuperscript{117} (which is emerging as a key player in pathophysiology), and characterizing the acute pathophysiological role of neurodegenerative processes such as amyloid, which are now clinically detectable hours to days following TBI\textsuperscript{118}.

Conclusions
Advances in monitoring provide a paradigm that could enable the ICU care of TBI to move from a standard “one size fits all” approach to more individualized treatment. Better identification of mechanisms as potential targets for intervention seems a reasonable aspiration. Improved characterization of disease mechanisms might also offer new goals for neuroprotective drug development. But the translational failure of a few biologically and experimentally well-founded interventions suggests that uncharacterized patient factors are still a major stumbling block in terms of tailoring aggressive treatments to maximize benefit and minimize harm at an individual level. Despite the wealth of data, the stratification of patients into subgroups with more homogeneous pathophysiology, disease course and expected outcome is still at an early stage. The integration of newer monitoring modalities can provide more individualization of therapy, but these approaches are based on data that do not come from directly targeted RCTs. Indeed, the results and subsequent discussion of the BEST-TRIP trial highlight the difficulties with using classical RCTs to evaluate monitoring devices and treatment thresholds, and we may need to rely on other means of evidence generation, such as comparative effectiveness research (CER), to provide strong frameworks for use of these devices. Such approaches will require large, well characterized populations of patients, with rigorous outcome assessment. International initiatives such as the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI, https://www.center-tbi.eu) and other partner studies in the International Traumatic Brain Injury Research initiative (InTBIR, https://intbir.nih.gov/) could provide the large samples needed to address this aim, and provide the substrate for developing and testing precision-medicine approaches in severe TBI.

The epidemiological shift towards a larger proportion of physiologically fragile elderly patients with TBI in HICs calls for varying preventive approaches, such as measures aimed at frailty and falls, and suggests the need for changes in ICU management approaches. Less invasive monitoring tools, for instance, may improve care and reduce side effects during the acute phase. Methods for quick and efficient restoration of coagulation may limit brain injury progression in patients on anticoagulant and antiplatelet agents, thus improving outcomes. Provision of care based on measured, rather than assumed, outcome could avoid self-fulfilling prophecies of inevitable poor outcome for older patients. Age older than 65 years has often been an exclusion criterion in clinical trials of interventions for TBI, such as DC and of neuroprotective drugs, leading to the paradox that a population segment at increased risk of TBI has not been
exposed to possible therapeutical interventions. Given the logistic complexities of conducting RCTs in TBI
generally and specifically in the older patient population, CER approaches might also facilitate assessment of
interventions in older patients, with differences in management of these patients in different centers
providing an appropriate context to undertake such studies.
The changes described here hold the promise of reshaping current ICU management, and potentially
improving outcome. However, demonstration that this promise can be fulfilled requires rigorous research
evaluation and proof of cost-effectiveness.
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Authors’ contributions

NS designed the review structure and made a preliminary bibliographic search. All authors discussed the general outline of the review and agreed on a writing plan. NS, MC and TZ coordinated the writing and the literature search, assembled a preliminary draft and incorporated further contributions from each author into subsequent versions. GC and MBS reviewed the current ICU treatment; AE, PS and DM focused on targeting mechanisms and multimodal monitoring; TZ and MC collected and discussed the evidence concerning the aging population. DM extensively edited the paper. All authors reviewed and commented several preliminary drafts and approved the final version of the manuscript.

Search strategy and selection criteria

We identified references for this review by searching PubMed for articles published between Jan 1, 2010, and March 6, 2016. The search terms used were “head injury”, “traumatic brain injury”, “intensive care”, “epidemiology”, “intracranial pressure”, “head injury or traumatic brain injury and elderly”. Animal studies and papers not in English were excluded. A review on neuroprotection based on experimental data was also used. Additional papers or web-sites were identified by searching the authors’ personal files.

Declaration of conflict of interest

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