Traumatic brain injury 1

Severe traumatic brain injury: targeted management in the intensive care unit

Nino Stocchetti, Marco Carbonara, Giuseppe Citerio, Ari Ercole, Markus B Skrifvars, Peter Smielewski, Tommaso Zoerle, David K Menon

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This is the first in a Series of four papers about traumatic brain injury

Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico, Department of Anaesthesia and Critical Care, Neuroscience Intensive Care Unit, Milan, Italy (Prof N Stocchetti MD, M Carbonara MD, T Zoerle MD); **University of Milan, Department of Pathophysiology and Transplants, Milan, Italy** (Prof N Stocchetti); **University of Milan–Bicocca, School of Medicine and Surgery, Milan, Italy** (G Citerio MD); **San Gerardo Hospital, Neurointensive Care, ASST, Monza, Italy** (G Citerio); **Addenbrooke's Hospital, Division of Anaesthesia, University of Cambridge, Cambridge, UK** (A Ercole MD, Prof D K Menon MD); **Monash University, Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Melbourne, VIC, Australia** (M B Skrifvars MD); **University of Helsinki and Helsinki University Hospital, Division of Intensive Care, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki, Finland** (M B Skrifvars); **and University of Cambridge Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neurosciences, Cambridge, UK** (P Smielewski PhD)

Correspondence to: Prof Nino Stocchetti, Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico, Department of Anaesthesia and Critical Care, Neuroscience Intensive Care Unit, Milan 20122, Italy
nino.stocchetti@policlinico.mi.it

Severe traumatic brain injury (TBI) is currently managed in the intensive care unit with a combined medical–surgical approach. Treatment aims to prevent additional brain damage and to optimise conditions for brain recovery. TBI is typically considered and treated as one pathological entity, although in fact it is a syndrome comprising a range of lesions that can require different therapies and physiological goals. Owing to advances in monitoring and imaging, there is now the potential to identify specific mechanisms of brain damage and to better target treatment to individuals or subsets of patients. Targeted treatment is especially relevant for elderly people—who now represent an increasing proportion of patients with TBI—as preinjury comorbidities and their therapies demand tailored management strategies. Progress in monitoring and in understanding pathophysiological mechanisms of TBI could change current management in the intensive care unit, enabling targeted interventions that could ultimately improve outcomes.

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.[1] About 10–15% of patients with TBI have serious injuries that require specialist care.[2] Patients with severe grades of TBI are commonly managed in the intensive care unit (ICU)[3] with a combined medical–surgical approach that has changed little over the past 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 interventions is weak or non-existent,[4] with few randomised controlled trials (RCTs) to guide treatment decisions. In view of 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.[5] Moreover, treatment targets incorporated into guidelines are usually derived from population studies and applied to all patients with TBI in the ICU. This approach reduces management variability but ignores differences in underlying pathological features. TBI is, in fact, a syndrome that includes a range of brain lesions with separate—sometimes diverging—pathophysiological pathways and therapeutic needs. As a result, undifferentiated interventions aimed at the overall population with TBI, rather than targeted to specific disease mechanisms and groups of patients, are likely to fail, as exemplified by repeated failures of clinical trials of neuroprotective agents.[6]

Furthermore, many patients with TBI who are now treated in the ICU differ greatly from those individuals from whom much of our accumulated clinical experience, research, and guidelines have been derived—ie, young (typically male) patients who sustained a TBI from high-velocity traffic injuries or assault. In high-income countries, TBI affects increasing proportions of people older than 65 years (who we arbitrarily indicate as elderly)—eg, in the USA, the rate of TBI-related hospital admissions for elderly people has risen by more than 50% from 2001 to 2010,[7] whereas this rate has remained stable or declined for individuals aged 15–44 years. This epidemiological change reflects increased life expectancy[8] coupled with risk factors typical of elderly people, such as age-related comorbidities and their pharmacological treatment. These older patients typically present after having sustained falls from a fairly low height, and the clinical course of these TBIs is complicated by multiple comorbidities and their treatment.

In this Review, we briefly describe the heterogeneity of pathological and pathophysiological features of TBI seen in the ICU, discuss how we might organise rational clinical care in view of the scarcity of conventional evidence from RCTs, and postulate how we could individualise care to aim for precision medicine approaches, considering pathophysiological diversity with use of advances in monitoring techniques. We focus on severe TBI in adults and, importantly, in addressing each of these issues, we examine how the rising age of patients with TBI in the ICU might require new evidence to strengthen clinical management.

Pathological and pathophysiological features

Primary and secondary injury

TBI is divided classically into two distinct phases: primary injury followed by delayed secondary injury. Primary injury arises from external physical forces applied to the head producing skull fractures, haematomas, and deformation and destruction of brain tissue, including contusions and axonal injury. Secondary injury develops over time with activation of multiple molecular and cellular pathways.[9,10] Axonal stretching

during injury can cause dysregulation of transmembrane ion fluxes and impaired axonal transport, and damaged axons could be vulnerable to secondary axotomy and demyelination. Changes in ionic permeability and release of excitatory neurotransmitters, particularly glutamate, propagate damage through energy failure and overload of free radicals. Altered cellular permeability also increases calcium influx, which causes mitochondrial dysfunction, triggering further energy defects and necrotic and apoptotic processes.[10]

These molecular and cellular changes might lead to development of cytotoxic or vasogenic brain oedema and disturbed autoregulation, whereby the volume of intracranial contents grows because of vascular dilation or water accumulation, or both.[11] Once this volume increase exceeds the compensatory capacities of the intracranial space, intracranial pressure (ICP) rises. Seizures early after trauma can exacerbate the imbalance between energy expenditure and supply.[12] Another electrical disturbance—spreading depolarisation—can occur in patients with TBI, and might be responsive to glutamate antagonists. Spreading depolarisation leads to anaerobic metabolism and energy substrate depletion, and it also seems to be associated with a worse outcome.[13]

Trauma affects the blood–brain barrier directly, with increased permeability favouring vasogenic oedema formation and activation of a proinflammatory state.[14] Inflammation, also promoted by resident microglia, could provide neuroprotection or aggravate secondary injury.[14] Patients with TBI often have extracranial injuries (eg, fractures and chest and abdominal trauma) and massive bleeding. These can cause hypoxia or arterial hypotension and trigger a systemic inflammatory response syndrome that can further aggravate the development of secondary injury.[15] This complex series of events starts minutes after trauma but lasts for weeks or even months, particularly for inflammation.[16]

Heterogeneity of TBI

TBI is typically classified according to clinical severity, with severe injury usually categorised on the basis of a total Glasgow Coma Scale (GCS) score of 8 or less.[17] TBI produces various lesions that range from mild injury to devastating damage. Expanding haematomas—extradural or subdural—might need emergency surgical removal in the first hours after injury; intraparenchymal contusions can increase over hours or days and need surgery as well. More subtle lesions such as traumatic axonal injury (the term commonly used, diffuse axonal injury, strictly only applies when involving three or more locations[18]) might not be evident from initial CT scans but, owing to neuronal network disruption, might have a serious effect on the quality of life of survivors, and can be seen on MRI.[19] These different lesion types typically arise in combination: for instance, cerebral contusions can develop underneath a subdural haematoma, and might also be associated with axonal injury. Figure 1 shows how the risk of high ICP, mortality, and disability can vary by lesion type.[20–23]

Several biomarkers of neuronal injury (eg, neuron-specific enolase, ubiquitin C-terminal hydrolase L1, spectrin breakdown products), axonal injury (eg, tau protein, neurofilaments), and glial injury (eg, glial fibrillary acidic protein, S100β) in serum and CSF are being investigated in patients with TBI.[24,25] These markers could—either individually or in combination—be used to characterise injury severity and type, and they might have prognostic importance.[24,25] Although preliminary evidence of cost-effectiveness is emerging for some biomarkers in mild TBI, their role in more severe injury remains uncertain. We need large-scale studies of the most promising biomarkers (or panels of biomarkers) to determine whether they can be used to refine initial characterisation of brain damage in critically ill patients with TBI.

Specific features of TBI in elderly people

TBI in older patients typically results from low-energy impacts such as ground-level falls,[26] with a higher

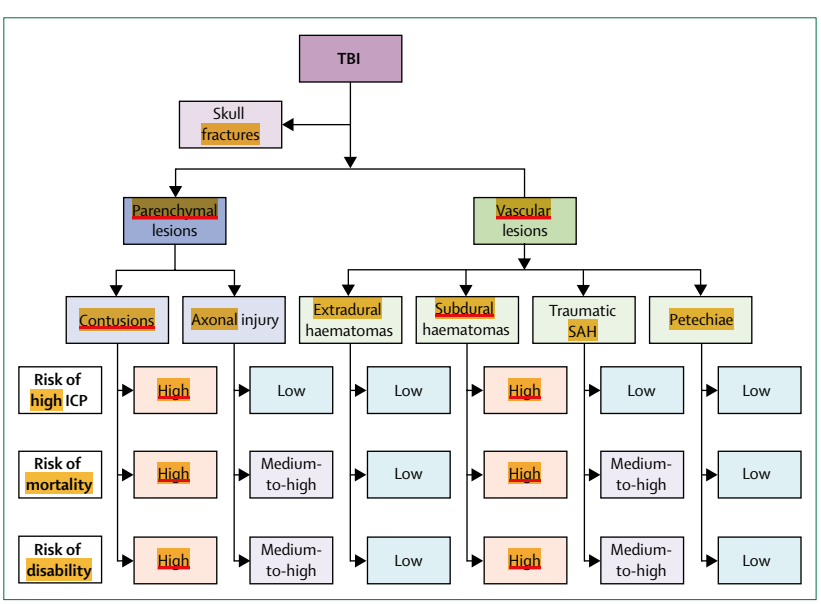

Figure 1: **Heterogeneity of traumatic brain injury**
Road accidents, intentional injuries, and falls can cause different types of head lesion; together with skull fractures, various parenchymal and vascular injuries often coexist. In this schematic diagram, lesions are presented separately for the purpose of classification, and estimates of risk of high ICP, mortality, and disability are shown. Some lesions, such as subdural haematomas, entail a substantial risk of elevated ICP, whereas others, such as axonal injury, are associated rarely with ICP disturbances[20] but might have a very severe effect on outcome. Axonal damage in multiple brain regions causes impairments in cognitive, motor, and sensory functions by disrupting neuronal connectivity. Pathological masses, such as contusions or intracranial haematomas, can vary in size and in their tendency to expand. When large pathological volumes accumulate, further compressing the brain, the probability of an unfavourable outcome, with high mortality and severe disability, is raised. Other vascular injuries, such as major vessel dissection or traumatic aneurysms, perhaps underdiagnosed with routine imaging, can be detected with appropriate investigations.[21] Mortality and disability are associated with several factors, such as age, comorbidities, and location and extent of the traumatic injury. Similarly, ICP rises might depend on multiple disturbances, such as hyponatraemia, and not just on the initial anatomical damage. Information on outcomes is from the IMPACT study.[22,23] ICP=intracranial pressure. SAH=subarachnoid haemorrhage. TBI=traumatic brain injury.

proportion of subdural haematomas and fewer contusions or epidural haematomas in this group than in younger patients.[27,28] Cerebral atrophy and increased CSF space could buffer new pathological intracranial masses, which could be linked to a lower incidence of raised ICP.[29,30] The GCS might underestimate the severity of brain injury in elderly patients,[31] making a case for higher score thresholds to trigger triage of older patients to specialist centres.[32] Furthermore, age-related comorbidities (eg, diabetes, chronic cardio-respiratory 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 treatments used for these chronic diseases (in particular, anticoagulant and antiplatelet drugs) might increase risk of haemorrhage or could worsen the evolution of intracerebral traumatic lesions (with the greatest risk from vitamin K antagonists).[33] Finally, the diminished brain reserve in these older patients[34] limits the potential for plasticity and neural repair and, hence, hampers the success of rehabilitation. The main differences between younger and older patients with TBI are summarised in the panel.[34–44]

Fundamentals of ICU monitoring and management

Patients with severe TBI are currently treated in the ICU with a specialised neurointensive approach combined with strategies used in general intensive care such as early enteral feeding, infection control and treatment, normalisation of respiratory exchanges with skilled nursing, physiotherapy, and artificial ventilation, and fluid optimisation for arterial pressure and splanchnic organ perfusion. This approach aims to prevent second insults and maintain cerebral homoeostasis. Some current strategies entail targeted approaches—eg, surgical haematoma 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 involves addressing both systemic threats (eg, hypoxia, hypercapnia, arterial hypotension, hyponatraemia, and pyrexia) and intracranial threats (eg, expanding haematomas or contusions and ICP rises). In this section, we focus on intracranial threats, which can be detected through clinical examination and ICP monitoring.

Panel: Main differences between young adults and elderly people with traumatic brain injury

Preinjury factors

- Comorbidities are common in elderly people but rare in young adults with traumatic brain injury (TBI). Diabetes, chronic heart and renal failure, and chronic obstructive pulmonary disease might all increase the risk of systemic complications and second insults such as hypoxia and hypotension.
- Anticoagulant and antiplatelet drugs are used increasingly in the general population,[35] and particularly in elderly people; these drugs increase the risk of cerebral haemorrhagic lesions and might worsen the expansion of initial bleeding, even after modest TBIs.[36,37]
- Polypharmacy—including sedatives or hypnotics, antidepressants, benzodiazepines, and antihypertensive drugs—is common in elderly patients but not in young adults; these drugs might increase instability and predispose patients to a fall.[38]
- Elderly patients have less brain reserve than younger patients,[34] a vulnerability that amplifies the result of brain damage and hampers rehabilitation.
- Pre-existing neurodegenerative diseases that reduce cognitive reserve and impair motor function can increase the risk of TBI in affected elderly people.

Cause of injury

- Ground-level falls and low-energy impacts are typical of TBIs in the elderly population,[7,26,28,39] and these injuries are associated with impaired mobility and polypharmacy.[38]
- TBIs in young adults are often secondary to high-energy impacts from road traffic accidents or assaults.[7,39]

Type of lesion

- The proportion of subdural haematomas diagnosed in older patients is higher than in young adults; these haematomas are typically associated with lower severity and less underlying brain injury in older patients.
- The proportion of contusions, epidural haematomas, and axonal injury lesions diagnosed in young adults is higher than in elderly patients.[27,28]

Clinical course

- The initial Glasgow Coma Scale score might be inappropriately high and not reflect the severity of structural injury in elderly patients.[31]
- Older patients often have delays with CT imaging, are less likely to be transferred to specialist neurosurgical facilities, and are more usually cared for by junior medical staff.[44]
- Elderly patients have a lower incidence of raised intracranial pressure than do younger patients, which could be attributable to cerebral atrophy and an increased CSF space that buffers new pathological intracranial masses.[29,30]
- Post-traumatic seizures are more common in older patients than in young adults.[40]
- Compared with young adults, elderly people have poorer functional outcomes and higher mortality, more medical complications during their stay in the intensive care unit (requiring in-hospital procedures), and longer hospital stays and continued medical care.[27,41–43]

Neurological clinical examination

Clinical examination remains a fundamental monitoring procedure, even in patients who are comatose or sedated, to identify neurological deterioration and potential indications for surgical interventions. The basic examination relies on a GCS assessment coupled with investigation 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 can impede eye opening, so motor response remains the main assessable component of the GCS score. Neurological evaluation in patients who are deeply sedated can require a sedation hold (wake-up test), which might cause arterial hypertension and—in patients with reduced intracranial compliance—transient rises in ICP.[45] Whether these ICP spikes are detrimental for brain homoeostasis is uncertain.[46,47] Nevertheless, a wake-up test could help to identify important clinical changes—eg, signs of progressive brainstem impairment, rapid improvement after successful surgical removal of intracranial masses, or intoxication with alcohol or other substances. This test could affect a patient's management profoundly, with more aggressive intervention in patients who show deterioration or shorter intubation and ventilation times in those recovering favourably.

Assessments of pupillary diameter and reactivity are vital.[48] A dilated unreactive pupil usually discloses compression of the third cranial nerve due to midline shift and uncal herniation.[49] Pupillary reaction to light is assessed typically using a flashlight, although this method has poor inter-rater accuracy in clinical practice.[50] Automated pupillometry is a portable technique that measures pupil size and light reactivity automatically and with a high degree of precision.[51] This method might give more accurate measurements of reactivity, particularly when the pupil is small (eg, with opioid analgesia).[51]

Up to 40% of patients with TBI show substantial worsening during the first 48 h in the ICU.[52] Neurological worsening is currently defined as a decrease of 2 points on the GCS motor component, pupil asymmetry or loss of pupillary reactivity, or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.[18] Neurological worsening in TBI is associated significantly with high ICP and poor outcome.[53,54] This deterioration is typically due to a new or expanding intracranial lesion that might need surgical evacuation. Understanding of neurological worsening is becoming increasingly important because prompt access to early CT means that patients are usually scanned within minutes after the TBI, before lesions have had a chance to appear or evolve. Parenchymal lesions can expand over hours or days: in a series of 352 cases with contusions followed up with three CT scans, the volume of haemorrhage increased in 42% of patients.[55] A routine second CT scan is, therefore, recommended for all patients with TBI who are comatose, which might disclose surgical lesions in up to a third of cases.[56] Additionally, if any substantial clinical worsening occurs or ICP rises, a new CT scan must be done.[56]

ICP monitoring

ICP measurement is done through ventricular or intraparenchymal probes connected to a monitor.[11] This monitoring has been the cornerstone of TBI care since the 1980s. However, in a multicentre trial from South America (BEST:TRIP),[57] ICU management based on repeated clinical examination and CT scans was not inferior to management including continuous measurement of ICP. It would be entirely inappropriate to discard the role of ICP monitoring on the basis of the findings of this study,[58] but it does highlight the difficulties with postulating a direct link between monitoring and improvement of outcome, which can be too simplistic when considered in isolation.

In the 4th edition of the Brain Trauma Foundation guidelines, ICP monitoring is indicated in patients with severe TBI, because evidence suggests that ICP-guided treatment can reduce early mortality.[4] A variable proportion of patients with severe TBI develop raised ICP, generally depending on the definition. The historical and most widely accepted ICP threshold for therapy is 20 mm Hg, although the latest guidelines suggest 22 mm Hg.[4] This approach, which is based on population targets, provides little potential for optimising therapy according to the needs of individual patients. Indeed, available published work suggests that there could be subtle differences in critical ICP thresholds between young and old and male and female patients, even at an aggregated population level, with older patients (age ≥55 years) and females having lower ICP thresholds (18 mm Hg *vs* 22 mm Hg) for prediction of poor outcome.[59]

Protocols for ICP therapy vary in detail but generally include prevention of ICP rises using mechanical ventilation, sedation, and avoidance of pyrexia (figure 2), as well as active interventions.[11] For increases in ICP, first-tier strategies include oedema management with hyperosmotic infusions and drainage of CSF (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 can have harmful side-effects (figure 2).[60,61] ICP monitoring is fairly safe; complications such as haemorrhage and infection arise in 1–7% of cases,[62] driving a search for non-invasive alternatives. Several methods are under investigation for non-invasive ICP measurement but are not yet ready for clinical use.[11]

Maintenance of cerebral homoeostasis

Maintenance of cerebral homoeostasis and, in particular, optimisation of cerebral oxygen supply and demand are traditionally attempted using indirect variables such as cerebral perfusion pressure (CPP), which is the difference

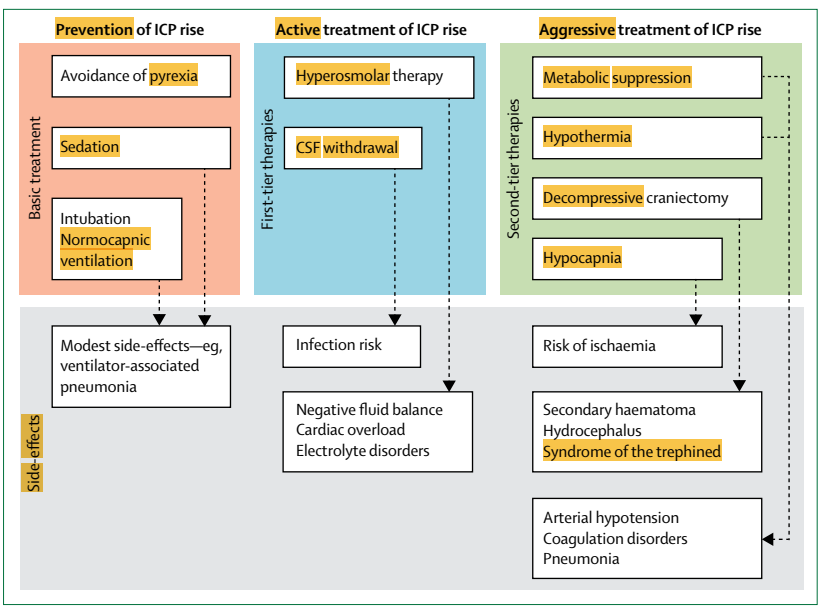

Figure 2: **Current prevention and treatment of intracranial hypertension after traumatic brain injury**
Surgical removal of intracranial masses is the most effective treatment for intracranial hypertension in the early phases after TBI. After surgery, strategies for ICP control are graded from prevention to progressively more intensive treatments. Prevention of high ICP is based on standard procedures in the intensive care unit, with fairly modest side-effects, such as ventilator-associated pneumonia for prolonged artificial ventilation. First-tier active interventions include CSF withdrawal (which requires a ventricular drain, with the risk of ventriculitis) and hyperosmolar drugs, such as mannitol or hypertonic saline (with the risks of cardiac overload during infusion and dehydration and hyperosmolar states due to induced diuresis).[11] Second-tier interventions include more aggressive treatments with associated risk of severe complications. Preventive measures are usually used for all patients with severe TBI, whereas active treatment is triggered by ICP rises. This approach is based mainly on clinical experience rather than on strong published evidence.[4] Because of side-effects, interventions effective at reducing ICP might not translate directly into improved outcomes.[60,61] ICP=intracranial pressure. TBI=traumatic brain injury.

between mean arterial blood pressure and ICP. Ideally, normal arterial pressure coupled with a physiological ICP value should be maintained. In cases of arterial hypotension, vasopressors and volume expansion are used to restore an adequate arterial pressure whereas ICP becomes a target when it exceeds a threshold. CPP of around 60 mm Hg is generally targeted, although the latest guidelines suggest some discrimination between individuals with and without preserved autoregulation.[4] However, as with ICP, these guidelines do not account for differences in CPP thresholds between groups of patients.[59]

Modulatory effects of age

A clear association has been noted between older age and worse outcome,[42,43] which could be accounted for, at least in part, by the effects of age-related comorbidities,[63] use of pharmacotherapies to treat comorbidities (particularly antithrombotic drugs),[37] and reduced brain reserve in elderly patients.[34] Treatment and monitoring of comorbidities might, therefore, be as important as management of TBI in determining outcome.[63] Treatment of drug-induced coagulopathy with reversal of anticoagulant or antiplatelet therapy is essential if an intracranial haemorrhage is present.[64,65] Post-traumatic seizures are common in older patients with TBI;[40] however, the optimum therapy and length of seizure prophylaxis in this population is still not clear.

An unfavourable outcome in older patients could be, at least in part, a self-fulfilling prophecy. Data gathered for 4387 patients with TBI in the UK indicate suboptimum care for older patients, including delayed CT scans, assessment more commonly by junior medical staff, and a reduced likelihood of being transferred to neurotrauma centres (panel).[44] However, when older patients are treated aggressively and promptly after admission to the ICU, favourable outcomes are seen in 39% of patients aged 60–69 years,[27] suggesting that this nihilistic attitude is not justified.

The lower ICP threshold associated with poor outcome in older patients compared with younger people (18 mm Hg *vs* 22 mm Hg)[59] might reflect the greater vulnerability of the aged brain, or a given rise in ICP might denote a worse brain injury in older patients, since age-related atrophy and increased CSF space allows lesion expansion and brain oedema before ICP rises. Notwithstanding the cause, these data provide the rationale for investigating whether a reduced threshold for ICP control might be beneficial in older patients. However, because increased ICP is less frequent in elderly populations, and tissue penetration by intracranial probes is riskier in patients who have received anticoagulant and antiplatelet drugs, there is a case for revised (reduced) indications for ICP monitoring in these patients.

Elderly patients might also have compromised autoregulation because of arterial hypertension, with the autoregulatory curve shifted towards higher arterial pressure. Indeed, available data suggest that CPP thresholds for survival are higher in patients older than 55 years than in younger patients,[59] and a higher CPP might be desirable, particularly in patients with a history of arterial hypertension.[4,59]

It is worth noting that the current conceptual basis of ICU management of TBI is based on a body of experience accumulated over the past four decades, which derives overwhelmingly 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 see with different injury mechanisms (panel), and there is a pressing need to develop optimum management strategies targeted to these patients.

Targeted ICU management based on physiological monitoring

Clinical pathophysiology of TBI is dependent on the patient, the treatment given, and the type of injury and, therefore, is highly heterogeneous. A one-size-fits-all management strategy is unlikely to be optimum. More precise understanding of intracranial disturbances might indicate specific targets and, hopefully, targeted therapies. A panoply of monitoring techniques (table 1) and imaging modalities (table 2) can be used to obtain this information, including measurement of brain tissue partial tension

	Variable monitored	Variable derived	Focal or global measure	Time resolution	Risk of brain damage	Running costs (€)*	Other limitations
Intracranial pressure monitoring with intraparenchymal monitor or ventricular catheter	Intracranial pressure	Intracranial volumes, cerebral perfusion pressure, pressure-reactivity index, intracranial compliance	Global	Continuous	Yes	<50	None
Brain tissue oxygen measurement with parenchymal probe	Brain tissue partial tension of oxygen	Oxygen diffusion and balance between oxygen supply and demand	Focal	Continuous	Yes	50–500	None
Cerebral microdialysis	Brain metabolites and biomarkers	Aerobic or anaerobic metabolism, brain injury severity and inflammation	Focal	Intermittent	Yes	>500	None
Temperature monitoring via intraparenchymal probe	Brain temperature	Gradient between core and brain temperature	Focal	Continuous	Yes	50–500	None
Intraparenchymal thermal diffusion flowmetry	Cerebral blood flow	Hypoperfusion or hyperperfusion	Focal	Continuous	Yes	>500	Non-standard technique
Electrocorticography	Cortical and depth electrical activity	Seizure activity, spreading depolarisation	Focal	Continuous	Yes	>500	Requires specific surgical placement
Jugular bulb oximetry	Oxygen saturation of venous jugular haemoglobin	Cerebral arterojugular difference in oxygen content	Global	Intermittent (continuous with fibreoptic catheters)	No	<50 (50–500 for fibreoptic catheters)	None
EEG	Cortical electrical activity	Seizure activity, abnormal patterns	Global	Continuous	No	<50	Training needed
Transcranial doppler	Cerebral blood velocity	Critical closing pressure, cerebral arterial impedance	Global	Intermittent	No	<50	Operator-dependent
Optic-nerve sheath ultrasonography	Optic nerve-sheath diameter	Intracranial pressure	Global	Intermittent	No	<50	Operator-dependent
Near-infrared spectroscopy	Cerebrovascular oxygen saturation and relative blood volume	Cerebral blood flow, cerebral autoregulation	Focal	Continuous	No	50–500	Extracerebral contamination of signal

The most commonly used bedside technologies are listed.[66] *Based on information provided by device vendors in most European countries; monitors, personnel, and maintenance are not considered.

Table 1: **Current bedside neuromonitoring modalities for traumatic brain injury**

of oxygen ($PbtO_2$), microdialysis, and autoregulation assessment.[66] In isolation, these techniques generally provide indirect measures of TBI pathological processes. For example, raised ICP is not a diagnosis by itself: it results from many (usually coexisting) mechanisms, including oedema (either cytotoxic or vasogenic), increased cerebral blood volume (which itself might result from many disparate mechanisms, including excessive metabolic demand, hypercapnia, or disordered autoregulation), or impaired CSF reabsorption. Methods to better characterise pathophysiological derangements have been available in the past two decades; however, they have been used rarely, even in the most specialised neurological ICUs. Findings of a survey of 31 specialised ICUs in the UK showed that ICP monitoring was used frequently in all but one institution, $PbtO_2$ measurement in eight (26%), and microdialysis in only four (13%) centres.[67]

Measurement of $PbtO_2$

ICP and CPP provide information on the driving pressure for blood flow through the cerebral circulation. However, downstream metabolic events can also be monitored using several probes, typically through a common insertion device. One such example is measurement of $PbtO_2$,[68–70] which provides a continuous (albeit localised) 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. It is affected further by the ability of oxygen to diffuse.[71,72] For example, in pericontusional tissue, diffusion of oxygen might be affected not only by tissue and endothelial oedema but also by microvascular collapse, which increases the mean intercapillary distance for diffusion, reducing average oxygen tension.[72]

Determining appropriate target values for $PbtO_2$ is clearly methodologically difficult: oxygen tensions of around 23 mm Hg are recorded during or after functional neurosurgery.[73] Values between 15 mm Hg and 20 mm Hg are typically regarded as thresholds for inadequate oxygen supply[74–76] and are associated with worse outcome after TBI.[72] Therapeutic approaches have been described that aim to return $PbtO_2$ to normal levels by increasing either arterial pressure or arterial oxygen tension, or both.[77,78] Those strategies seem to be associated with better outcomes than strategies focused only on ICP and CPP. However, without large controlled trials, evidence is inconclusive.[79]

Microdialysis

Measurement of glucose, lactate, and pyruvate in the extracellular space of the brain using cerebral microdialysis provides information on energy metabolism. A high lactate:pyruvate ratio after TBI is a marker of anaerobic glucose utilisation, resulting from low $PbtO_2$ due to ischaemia or diffusion hypoxia or, under normoxic conditions, mitochondrial dysfunction.[80–82] A high

	Variable monitored	Information derived	Spatial resolution	Radiation absorption	Acquisition time (min)	Other limitations
CT	Structural integrity	Space-occupying lesions, CSF space modifications, skull fractures, brain swelling	Medium	Low	<5	Limited resolution for posterior fossa pathology
CT angiography	Cerebral vessel patency and integrity	Thrombosis and dissection in main intracranial vessels	Medium	Medium	<5	Contrast medium injection needed
Perfusion CT	Cerebral perfusion	Hypoperfusion or hyperperfusion	Low	High	<5	Contrast medium injection needed
MRI	Structural, functional, and biochemical integrity, cerebral vessel patency	Space-occupying lesions, CSF space modifications, brain swelling, thrombosis and dissection in main intracranial vessels, hypoperfusion or hyperperfusion, traumatic axonal injury, functional and chemical information	High	None	>20	Magnetic field environment might be contraindicated in some patients,* high cost

*MRI use is not possible in patients who have indwelling probes containing ferromagnetic material or in patients who are dependent on ventilators, infusion pumps, or monitors used in the intensive care unit for which magnetic resonance safety is unknown. Some magnetic resonance studies can be prolonged and might be contraindicated in unstable patients.

Table 2: **Current imaging modalities for traumatic brain injury**

lactate:pyruvate ratio indicates an energy metabolism crisis and is an independent predictor of mortality.[83] Improvement in the lactate:pyruvate ratio might indicate a beneficial effect of treatment. The effects of various interventions—eg, hyperoxia and hypertonic lactate—on brain energy metabolism have been investigated. Normobaric hyperoxia, which is usually induced by increasing the fraction of inspired oxygen, can typically raise a low $PbtO_2$, but inconsistent benefits on microdialysis variables have been reported.[84,85] However, findings of imaging studies suggest improvements in the cerebral metabolic rate of oxygen[86] and reversal of pericontusional cytotoxic oedema with this intervention.[87] Attempts to improve brain glucose metabolism with hypertonic lactate infusions show a clear cerebral glucose-sparing effect, but mainly in patients with a pathological lactate:pyruvate ratio.[88] These preliminary clinical trial results need to be confirmed with larger numbers of participants, but early findings indicate the possibility for targeted interventions.

Autoregulation assessment

Methods for online real-time assessment of cerebrovascular autoregulation, a physiological mechanism that serves to maintain adequate cerebral perfusion in the presence of blood pressure changes, have been studied.[66] Under typical conditions, with normal autoregulation, the diameter of cerebral vessels changes to adjust for alterations in arterial pressure (eg, vasoconstriction in response to arterial hypertension) and these changes can affect ICP. In the case of vasoconstriction, ICP should remain unaffected or it could decrease. ICP measurements can, therefore, be used to assess how brain vessels react to variations in arterial pressure. In pathological conditions such as severe TBI, autoregulation can be altered or totally lost. Probably the best known measurement is the pressure-reactivity index (PRx)—ie, the correlation coefficient between ICP and arterial pressure readings using a moving data window, which is usually a negative number.[89–91] The PRx typically shows a U-shaped relation when plotted against spontaneous changes in CPP over time, with the lowest PRx noted in the optimum autoregulatory range. The CPP for which the PRx is a minimum is, therefore, deemed to represent a state of optimum autoregulation, and CPP-based management that targets this level has been associated with better outcomes.[92,93]

An autoregulation-guided approach to individualise CPP might be helpful in preventing cerebral hypoperfusion while avoiding the risks of excessive cerebral blood flow. An approach based on optimisation of autoregulation is physiologically attractive and has the potential to reconcile perfusion-supporting and oedema-minimising treatments. However, autoregulation can be impaired in a region-specific way that might not be captured by the PRx, which is a global average. Alternative measures based on assessment of blood flow or brain tissue oxygen reactivity have the opposite limitation of restricted global spatial coverage. Prospective evidence from clinical studies is urgently needed before definitive guidelines can be drawn up.

Multimodal monitoring for individualised management

Simultaneous use of several monitoring modalities could provide a means of targeting patient-specific ICP thresholds.[66] Concordant changes identified from different measures provide cross-validation of the physiological state of the injured brain. For example, a critical $PbtO_2$ reduction could be used to individualise thresholds for more aggressive methods for correcting low CPP due to high ICP. Conversely, discordant findings, although potentially posing a clinical dilemma in terms of treatment compromise, might sometimes offer clues to the presence of pathophysiological heterogeneity and stimulate the

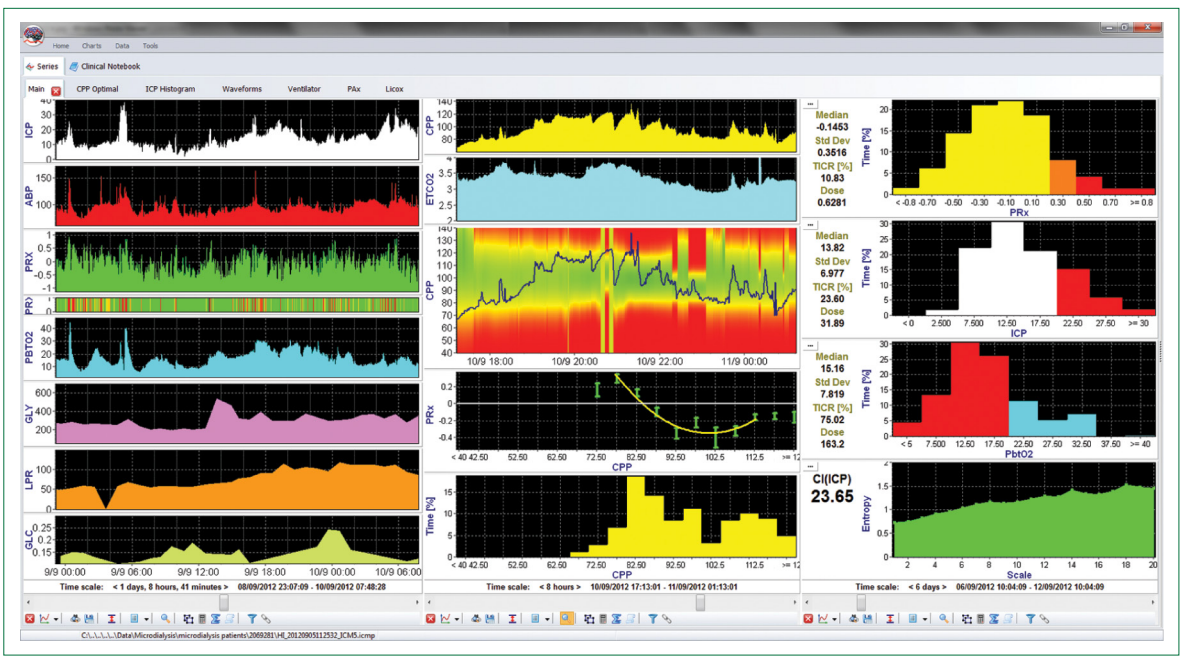

Figure 3: **Screenshot showing computerised multimodal monitoring for traumatic brain injury**
Advanced invasive monitoring for patients with traumatic brain injury (TBI) can simultaneously provide time trends for mean intracranial pressure (ICP), arterial blood pressure (ABP) readings, the pressure-reactivity index (PRx), a derived autoregulation index (presented both as a time trend and as a colour-coded warning bar), measures of brain tissue partial tension of oxygen ($PbtO_2$), and three microdialysis variables (glycerol [GLY], lactate:pyruvate ratio [LPR], and glucose [GLC]), all shown in the first column. It is helpful to integrate the signals into one bedside screen with trend charts showing current and historical values to allow early detection and accurate assessment of newly developing second insults. Other crucial information can be obtained from the neuromonitoring signals and presented on the same screen (second column) to further facilitate decision making. This includes information about the current (and historical) state of cerebral autoregulation and the related cerebral perfusion pressure (CPP) safe zone recommendation. These are depicted in the second column as CPP; end tidal CO_2 (an estimate of partial pressure of CO_2 in the blood [$ETCO_2$]); two optimum CPP representations (the estimated CPP range corresponding to intact autoregulation [in green] and an error bar chart summarising the PRx /CPP relation [the optimum CPP value is at the vertex of the fitted curve]); and the time percentage of a given CPP value (represented by the histogram at the bottom of the second column). Total (or recent) doses of intracranial hypertension or brain hypoxia (as indicated by PRx, ICP, and $PbtO_2$, with insult regions highlighted in red), and the state of homoeostatic decomplexification (as indicated by the ICP complexity chart [CI(ICP)], a multiscale entropy representation) are shown in the third column.

search for less well recognised routes to energy failure, such as diffusion hypoxia,[71,72] mitochondrial dysfunction,[94] and low cerebral glucose levels[83,95] as downstream markers of compromised cerebral perfusion.

However, current multimodal monitoring generates vast amounts of data, which might need to be summarised for clinicians to extract information that can be used to guide patients' care (figure 3). Advances in monitoring will probably also depend on advances in neuroinformatics and data analysis.[96] Computer visualisation techniques offer a promising way to reduce complex datasets to a form that can be interpreted by clinicians and have been applied in various areas, including investigation of the cumulative burden of intracranial hypertension[97] and assessment of autoregulation.[98] Such complex multidimensional problems are not new outside medicine, and other so-called big data techniques will very likely find increasing application in the intensive care of patients with TBI.[99]

Physiological monitoring in elderly people

Use of advanced multimodal monitoring to guide management in older patients is conceptually appealing, but experience in this area is scarce. This lack of experience is in part accounted for by the increased risks of invasive intracranial monitoring in older patients, who frequently present on anticoagulant and antiplatelet drugs (panel), and in part by the expectation of poor outcome that has made aggressive monitoring and therapy less frequent in this age group. Changing attitudes might provide more data to guide individualisation of treatment for older patients in the future, and development of less invasive monitoring methods would be particularly beneficial in this group.

Targeted ICU management with aggressive therapies

No treatments in the ICU are risk free, and the more aggressive interventions for restoring cerebral homoeostasis have substantial potential to cause harm (figure 2). Multimodal monitoring can show that aggressive interventions are justified by proving that cerebrovascular physiology is seriously compromised (eg, ICP and CPP outside the thresholds, $PbtO_2$ reductions, or elevations in lactate and lactate:pyruvate ratio), and not amenable to therapy with less risky interventions. Once a therapeutic

target has been identified, careful measurement of physiological variables can minimise harm for some interventions.

Augmentation of CPP

Pharmacological augmentation of CPP might improve cerebral oxygenation but at the expense of serious cardiopulmonary complications.[100] Advanced cardiovascular monitoring—including intravascular volume assessment, echocardiography, or cardiac output—beyond standard pulse oximetry and invasive arterial pressure monitoring might be necessary.[66]

Hypocapnia

A brief period of hypocapnia could be justifiable in the face of an episode of dangerously high ICP but it might cause ischaemia through vasoconstriction,[101] particularly in the early phases after injury. For this reason, measurement of cerebral oxygenation—most commonly by $PbtO_2$ monitoring—is recommended when hypocapnia is used, to minimise the ischaemic risk.[66]

Metabolic suppression

Barbiturates for metabolic suppression are effective in reducing ICP but carry substantial risks of cardiovascular instability and other end-organ dysfunction or metabolic disturbances.[102] Advanced cardiovascular monitoring and support—including fluid titration, inotropes, and use of 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 moderate hypothermia (32–35°C) was used as an early ICP intervention, the treated group had a worse outcome than did controls.[61] Despite the results of this trial, hypothermia continues to be used in some centres but typically with higher ICP thresholds (25–30 mm Hg),[104] denoting an implicit acceptance that the risks of hypothermia demand more deranged physiology before the risk:benefit ratio becomes favourable.

Decompressive craniectomy

Decompressive craniectomy is effective at reducing ICP, but results of RCTs have shown differences in outcome depending on the target group. In the DECRA trial,[60] decompressive craniectomy did not improve outcome when used for modest ICP increases. However, the balance of risk and benefit changes in circumstances for which aggressive therapies are justified by the presence of refractory severe intracranial hypertension. For example, in the RESCUE-ICP study,[105] decompressive craniectomy targeted to patients with refractory severe ICP was shown to reduce mortality and shift 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 emphasise the importance of following a graded sequence for aggressive interventions, beginning with those with least potential for harm before escalating to higher—and potentially more harmful—therapeutic intensity (figure 2). Furthermore, the evidence highlights the need to select interventions on the basis of 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 older patients with impaired physiological reserve (panel). The high incidence of cardiorespiratory comorbidities in such individuals might further reduce the ability of patients to tolerate some of the aggressive interventions (eg, augmentation of CPP, barbiturates, and hypothermia) used in the critical care of TBI. Therefore, careful monitoring of systemic physiology is mandatory, and caution is needed with haemodynamic augmentation and second-tier therapies for high ICP in these patients.

In two major RCTs on decompressive craniectomy for TBI,[60,105] patients older than 65 years were excluded, probably reflecting the scepticism of the neurotrauma community about use of aggressive therapies in older people. In another study, decompressive craniectomy was used to treat unilateral or bilateral brain swelling in 44 patients with TBI older than 66 years;[106] however, mortality was 77% and overall unfavourable outcomes were recorded in 82%, leading to this approach being abandoned in clinical practice for elderly patients who present with a GCS of 8 or less.

Emerging opportunities in the 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 used widely in clinical practice. However, emerging advances could deliver additional refinement, or even paradigm changes, in how we treat these patients, with respect to better characterisation of TBI, identification of novel therapeutic targets, and generation of evidence to support changes in management. Pharmacological trials of erythropoietin[107,108] and progesterone[109,110] for TBI failed to show improvement in neurological outcome despite experimental evidence of multiple neuroprotective mechanisms, thus underlining the importance of targeting treatments to selected groups of patients. Enrolment criteria in these trials were based on severity of TBI, and the benefits of compounds acting on specific pathways might not have been demonstrable in a heterogeneous population of patients with TBI.

Future trials should aim to select patients on the basis of specific mechanisms of brain damage in individual patients to maximise potential for improved outcomes.

The growing use of MRI in TBI promises to provide better definitions of injury location, type, and severity;[111] moreover, accumulating data linking genetic variability to outcome[112] suggest that we might be able to identify patients in whom specific therapies could be effective. For instance, once the pathological role of spreading depression is clarified better and patient groups who are likely to be affected have been identified, specific interventions—eg, nimodipine or ketamine—could be envisaged to correct spreading depression.[113] Promising therapeutic targets are emerging from more rigorous preclinical evaluation of new interventions for TBI, such as those delivered by Operation Brain Trauma Therapy, a multicentre multiplatform collaboration for experimental evaluation of therapies.[114] Other basic biology research that might advance clinical interventions for mitigation of secondary injury includes identification of the sulfonylurea receptor (SUR1), which is implicated in oedema formation and contusion expansion,[115] preclinical assessment of novel brain fuels that bypass impaired energy metabolism,[116] and more precise targeting of the inflammatory response,[117] which is emerging as a key player in TBI pathophysiology.

Conclusions and future directions

Advances in monitoring provide a paradigm that could enable us to move treatment of TBI in the ICU from a standard one-size-fits-all approach to more individualised treatment. Better identification of disease mechanisms as potential targets for intervention seems a reasonable aspiration. Improved characterisation of mechanisms might also offer new goals for neuroprotective drug development. However, translational failure of a few biologically and experimentally well founded interventions[118] suggests that uncharacterised patient factors are still a major stumbling block in terms of tailoring aggressive treatments to maximise benefit and minimise harm at an individual level. Despite the wealth of data, stratification of patients into subgroups with more homogeneous pathophysiology, disease course, and expected outcome is still at an early stage.

Integration of newer monitoring modalities could provide further individualisation of therapy, but these approaches rely on data that do not come from RCTs based on targeted approaches. Indeed, the results and subsequent discussion of the BEST:TRIP trial of ICP monitoring[57,58] highlight the difficulties with using classic RCTs to evaluate monitoring devices and treatment thresholds, and we might need to rely on other means of evidence generation—eg, comparative effectiveness research—to provide strong frameworks for use of newer monitoring devices in TBI. Such approaches will need large, well characterised populations of patients with rigorous outcome assessment. International initiatives—eg, the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) and other partner studies in the International Traumatic Brain Injury Research initiative (InTBIR)—could generate the large samples needed to address this aim and provide the context 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 high-income countries calls for varying preventive approaches, such as measures aimed at frailty and falls,[119] and suggests the need for changes in ICU management approaches. Less-invasive monitoring methods, for instance, might improve care and reduce side-effects during the acute phase. Techniques for quick and efficient restoration of coagulation could limit brain injury progression in patients on anticoagulant and antiplatelet drugs, 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—eg, decompressive craniectomy and neuroprotective drugs[52,60,105,108,120]—leading to the paradox that a population segment at increased risk of TBI has not been exposed to possible therapeutic interventions. In view of the logistic complexities of undertaking RCTs in TBI generally, and specifically in older patients, comparative effectiveness research approaches might also facilitate assessment of interventions in older patients, with differences in management of these individuals in various centres providing an appropriate context to undertake such studies.

The changes described here hold promise for reshaping current management in the ICU and potentially improving outcome. However, showing that this promise can be fulfilled requires rigorous research evaluation and proof of cost-effectiveness.

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 2010, and March 6, 2017, with the terms "head injury", "traumatic brain injury", "intensive care", "epidemiology", "intracranial pressure", and "head injury OR traumatic brain injury AND elderly". Only papers published in English were included, and except for a review on neuroprotection based on experimental data, animal studies were excluded. Additional papers or websites were identified by searching the authors' personal files.

For more on **CENTER-TBI** see https://www.center-tbi.eu

For more on **InTBIR** see https://intbir.nih.gov

For more on **Operation Brain Trauma Therapy** see http://www.safar.pitt.edu/obtt

Contributors

NS designed the review structure and did 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 current ICU treatment. AE, PS, and DKM focused on targeting

mechanisms and multimodal monitoring. TZ and MC collected and discussed evidence concerning the ageing population. DKM extensively edited the paper. All authors reviewed and commented on several preliminary drafts and approved the final version of the review.

Declaration of interests

MBS reports speakers' fees from COVIDIEN, Astellas Pharma, Axis Shield, and Orion and a grant from GE Healthcare, outside the submitted work. PS receives part of the licensing fees for multimodal brain monitoring software ICM+, licensed by Cambridge Enterprise Ltd, University of Cambridge, UK. DKM reports personal fees for consultancy work or as a member of data monitoring committees for Solvay, GlaxoSmithKline, Brainscope, Ornim Medical, Shire Medical, and Neurovive, and honorarium for a lecture at the London Hospital, UK, reimbursed to organisers by GlaxoSmithKline. NS, MC, GC, AE, and TZ declare no competing interests.

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Traumatic brain injury 2

Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management

Marc Maegele, Herbert Schöchl, Tomas Menovsky, Hugues Maréchal, Niklas Marklund, Andras Buki, Simon Stanworth

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Department for Trauma and Orthopaedic Surgery, Cologne–Merheim Medical Center, University Witten/Herdecke, Cologne, Germany (Prof M Maegele MD); **Institute for Research in Operative Medicine, University Witten/Herdecke, Cologne, Germany** (Prof M Maegele); **Department for Anaesthesiology and Intensive Care Medicine, AUVA Trauma Academic Teaching Hospital, Paracelsus Medical University Salzburg, Salzburg, Austria** (H Schöchl MD); **Department for Neurosurgery, Antwerp University Hospital, University of Antwerp, Edegem, Belgium** (Prof T Menovsky MD); **Department of Anaesthesiology and Intensive Care Medicine, CRH La Citadelle, Liège, Belgium** (H Maréchal MD); **Department of Clinical Sciences, Division of Neurosurgery, University Hospital of Southern Sweden, Lund University, Lund, Sweden** (Prof N Marklund MD); **Department of Neurosurgery, The MTA-PTE Clinical Neuroscience MR Research Group, Janos Szentagothai Research Center, Hungarian Brain Research Program, University of Pécs, Pécs, Hungary** (Prof A Buki MD); **and NHS Blood and Transplant/Oxford University Hospitals NHS Foundation Trust, University of Oxford, John Radcliffe Hospital, Oxford, UK** (S Stanworth MD)

Correspondence to:
Prof Marc Maegele, Department of Trauma and Orthopaedic Surgery, Cologne–Merheim Medical Center, University Witten/Herdecke, Cologne D-51109, Germany
marc.maegele@t-online.de

Normal haemostasis depends on an intricate balance between mechanisms of bleeding and mechanisms of thrombosis, and this balance can be altered after traumatic brain injury (TBI). Impaired haemostasis could exacerbate the primary insult with risk of initiation or aggravation of bleeding; anticoagulant use at the time of injury can also contribute to bleeding risk after TBI. Many patients with TBI have abnormalities on conventional coagulation tests at admission to the emergency department, and the presence of coagulopathy is associated with increased morbidity and mortality. Further blood testing often reveals a range of changes affecting platelet numbers and function, procoagulant or anticoagulant factors, fibrinolysis, and interactions between the coagulation system and the vascular endothelium, brain tissue, inflammatory mechanisms, and blood flow dynamics. However, the degree to which these coagulation abnormalities affect TBI outcomes and whether they are modifiable risk factors are not known. Although the main challenge for management is to address the risk of hypocoagulopathy with prolonged bleeding and progression of haemorrhagic lesions, the risk of hypercoagulopathy with an increased prothrombotic tendency also warrants consideration.

Introduction

Traumatic brain injury (TBI) remains one of the leading causes of trauma deaths and will surpass many other disorders as a major cause of death and disability by the year 2020.[1,2] However, improvements are needed in our understanding of the nature and optimal management approaches to TBI. Coagulopathy is a common finding in patients with TBI that affects its clinical course, with nearly two-thirds of patients with severe TBI having abnormalities on conventional coagulation tests on admission to the emergency department.[3,4] Coagulopathy can refer to both hypocoagulopathy associated with prolonged bleeding and haemorrhagic progression[5] and hypercoagulopathy with an increased prothrombotic tendency,[6,7] both of which can occur—often simultaneously—after TBI. Here, we focus mainly on hypocoagulable states (referred to as coagulopathy) and increased risk of bleeding, although it should be noted that the contribution of prothrombotic states and the interactions between the two states are also relevant to the causes of increased bleeding risk.

The coexistence of TBI and coagulopathy of varying degrees has repeatedly been linked to detrimental outcomes with reported mortality rates of between 17% and 86%, reflecting the heterogeneity of TBI (table 1).[4,8–26] Historically, TBI predominantly affected young people. Now, the median age of people with TBI is increasing worldwide, and approximately half, or even more, of patients affected are over 50 years old at the time of injury.[27] In these older age groups, comorbidities and increased preinjury use of pharmacotherapies such as platelet inhibitors and oral anticoagulants, which are linked to an increased risk of bleeding, are common. Moreover, falls are a common cause of TBI in the elderly, leading to a higher number of contusional injuries, which are prone to haemorrhagic progression.[27,28]

Regardless of the patient age, the force of impact at the time of TBI can cause shearing of large and small vessels and can result in extradural, subdural, subarachnoid, or intracerebral haemorrhages, or a combination of haemorrhagic types, which can require surgical treatment. More subtle disruption of cerebral blood vessels, mainly in the microvasculature, or a blood–brain barrier (BBB) breakdown, is also common and results in the evolution or progression of haemorrhagic lesions, often on a background of contusions.[29] TBI-associated factors might then alter the intricate balance between bleeding and thrombosis formation in the later sequelae leading to impaired haemostasis with exacerbation of the initial injury.[5] Numerous mechanisms that are potentially linked to haemostatic disturbances after TBI have been studied[5]—including disorders of platelet number and function, changes in endogeneous procoagulant and anticoagulant factors, endothelial cell activation, hypoperfusion, and inflammation—but the effects of these mechanistic changes on survival and functional outcomes and whether they might be targeted to improve outcomes remain to be elucidated.

Management approaches need to focus primarily on hypocoagulopathy with prolonged bleeding, including haemorrhagic progression,[5] but this needs to be balanced against the risk of hypercoagulable states with an increased prothrombotic tendency.[6,7] Coagulopathy is a common occurrence after severe systemic trauma in the absence of TBI,[30] and management approaches in these patients include damage-control surgery[31] and

	Number of patients	Definition of TBI	Definition of coagulopathy	Prevalence of coagulopathy in patients with TBI	Mortality in patients with coagulopathy after TBI	Odds ratio for mortality [unfavourable outcome] in patients with coagulopathy after TBI (95% CI)
Harhangi et al (2008)[4]*	5357	Heterogeneous	Heterogeneous	32·7% (10·0–97·5)	51% (25–93)	9·0 (7·3–11·6) [36·3 (18·7–70·5)]
Epstein et al (2014)[8]†	7037	Heterogeneous	Heterogeneous	35·2% (7–86·1)	17–86%	Between 3·0 (2·3–3·8) and 9·6 (4·1–25·0)
Zehtabchi et al (2008)[9]	224	AIS_{head} >2 or any intracranial haematoma on CT	aPTT >34 s or INR >1·3	17% (8–30)	..	..
Talving et al (2009)[10]	387	AIS_{head} ≥3 and extracranial AIS <3	aPTT >36 s or INR >1·1 or <100 × 10^9 platelets per L	34%	34·7%	9·6 (4·1–25·0)
Lustenberger et al (2010)[11]	278	AIS_{head} ≥3 and extracranial AIS <3	aPTT >36 s or INR >1·4 or <100 × 10^9 platelets per L	45·7%	40·9%	5·0 (1·5–17·0) [12·0 (4·0–29·4)]
Lustenberger et al (2010)[12]	132	AIS_{head} ≥3 and extracranial AIS <3	aPTT >36 s or INR >1·2 or <100 × 10^9 platelets per L	36·4%	32·5%	3·8 (1·1–13·5)
Wafaisade et al (2010)[13]	3114	AIS_{head} ≥3 and extracranial AIS <3	PT_R <70% or <100 × 10^9 platelets per L	22·7%	50·4%	3·0 (2·3–3·9)
Chhabra et al (2010)[14]	100	GCS <13	Fibrinogen <2·0 g/L	7%	..	..
Greuters et al (2011)[15]	107	Brain tissue injury on CT and extracranial AIS <3	aPTT >40 s or INR >1·2 or <120 × 10^9 platelets per L	24% (54%‡)	41%	3·8 (1·1–13·5)
Shehata et al (2011)[16]	101	Isolated TBI on admission CT	PT >13 s or INR ≥1·2 or D-dimer-positive or <100 × 10^9 platelets per L	63%	36%	..
Schöchl et al (2011)[17]	88	AIS_{head} ≥3 and extracranial AIS <3	aPTT >35 s or PT_R <70% or fibrinogen <1·5 g/L or <100 × 10^9 platelets per L	15·8%	50%	9·1 (2·2–37·3)‖
Franschman et al (2012)[18]	226	Isolated TBI on CT and extracranial AIS <3	aPTT >40 s or PT >1·2 s or <120 × 10^9 platelets per L	25% (44%‡)	33%	9·7 (3·1–30·8)
Genet et al (2013)[19]	23	AIS_{head} ≥3 and extracranial AIS <3	aPTT >35 s or INR >1·2	13%	22%	..
Alexiou et al (2013)[20]	149	Isolated TBI on CT with exclusion of multisystem trauma	aPTT >40 s or INR >1·2 or <120 × 10^9 platelets per L	14·8% (22·8%‡)	..	..
Joseph et al (2014)[21]	591	AIS_{head} ≥3 and extracranial AIS <3	aPTT ≥35 s or INR ≥1·5 or ≤100 × 10^9 platelets per L	13·3%	23%	2·6 (1·1–4·8) [4·0 (1·7–10·0)]
Epstein et al (2014)[22]	1718	AIS_{head} ≥3 and extracranial AIS <3	INR ≥1·3	7·7%	45·1%	..
De Oliveira Manoel et al (2015)[23]	48	AIS_{head} ≥3 and extracranial AIS <3	aPTT ≥60 s or INR ≥1·5 or <100 × 10^9 platelets per L§	12·5%	66%	11·5 (3·9–34·2)
Dekker et al (2016)[24]	52	AIS_{head} ≥3	aPTT >40 s or INR >1·2 or <120 × 10^9 platelets per L	42%	45·5%	..

Studies reporting the prevalence of coagulopathy in patients with clinical moderate-to-severe and/or CT-confirmed TBI, including mortality rates (and unfavourable outcome if available) for TBI in the presence of coagulopathy. ..=Data not available. TBI=traumatic brain injury. AIS=Abbreviated Injury Scale. GCS=Glasgow Coma Scale. aPTT=activated partial thromboplastin time. INR=international normalised ratio. PT=prothrombin time. PT_R=prothrombin ratio. *Meta-analysis (1966–2007); n=34 studies included. †Meta-analysis (1990–2013); n=22 studies included. ‡After 24 h. §Additional coagulation tests: fibrinogen ≤1·0 g/L, any clotting factor <0·5 (<50% activity), and abnormal viscoelastic test results. ||Based on viscoelastic test results.

Table 1: **Studies of the prevalence of coagulopathy after traumatic brain injury**

haemostatic resuscitation[32] with timely and balanced use of blood-component and fluid therapies.[33] However, it is unclear whether the same principles of haemostatic resuscitation developed for the systemic trauma population might also apply to patients with TBI. This might reflect not only the nature of bleeding after TBI, which could be small in volume although presenting at a critical site, but also the belief that haemostatic disorders can be an almost inevitable occurrence after TBI.[34] Nevertheless, haemostatic resuscitation might have particular relevance in TBI as the progression of haemorrhagic lesions in the intracranial compartment can be life-threatening.[5]

In this Series paper, we explore current understanding of the clinical course and underlying mechanisms of coagulopathy in TBI. We aim to highlight novel perspectives and approaches to diagnosis beyond conventional methods. Furthermore, management strategies are reviewed, including the traditional use of blood products and more novel approaches, as well as thrombosis prophylaxis in view of the susceptibility to prothrombotic states alongside coagulopathy in these patients. Improved understanding of mechanisms and novel diagnostic strategies might facilitate targeted approaches to treatment of individual patients or groups of patients with TBI. Finally, we also emphasise opportunities for the future research agenda.

Epidemiology and definitions

The published findings on the reported prevalence of coagulopathy associated with TBI inevitably depend on the techniques and definitions used to document coagulopathy and TBI. Most commonly, coagulopathy is defined by abnormalities on conventional coagulation assays (CCAs), typically the prothrombin time (PT), which is sometimes reported as a ratio (PT_R). Although this assay is often considered interchangeably with the international

	Odds ratio (95% CI)	Study
Age ≥75 years	1·02 (1·01–1·03), 2·30 (1·79–2·96)*	Epstein et al (2014),[22] Wafaisade et al (2010)[13]
Intravenous fluids before hospital admission ≥2 L	2·15 (1·63–2·84)	Wafaisade et al (2010)[13]
Intravenous fluids before hospital admission ≥3 L	3·48 (2·13–5·68)	Wafaisade et al (2010)[13]
GCS ≤8 at scene of injury (before intubation)	2·27 (1·34–3·84), 1·71 (1·38–2·12)*	Talving et al (2009),[10] Wafaisade et al (2010)[13]
Injury Severity Score ≥16	4·06 (2·13–8·25)	Talving et al (2009)[10]
AIS_{head} =5	2·25 (1·63–3·10), 3·15 (1·47–6·76)*	Wafaisade et al (2010),[13] Lustenberger et al (2010)[12]
Subarachnoid haemorrhage on CT	1·99 (1·22–3·25)	Talving et al (2009)[10]
Brain oedema on CT	3·23 (1·66–6·41)	Talving et al (2009)[10]
Midline shift on brain CT	2·43 (1·09–5·53)	Talving et al (2009)[10]
Abnormal pupils	8·33 (4·50–15·89)	Epstein et al (2014)[22]
Systolic blood pressure ≤90 mm Hg	11·41 (2·55–83·9), 2·34 (1·64–3·34)*	Talving et al (2009),[10] Wafaisade et al (2010)[13]
Haemoglobin <12·4 mg/dL	9·2 (1·34–63·85)	Alexiou et al (2013)[20]
Serum glucose >151 mg/dL	29·5 (4·97–175·31)	Alexiou et al (2013)[20]
Arterial base deficit >6 mmol/L†	2·34 (1·02–5·35)	Lustenberger et al (2010)[12]
SI ≥1	1·68 (1·01–2·79)	Epstein et al (2014)[22]
Presence of at least two factors, of age >50 years, SI ≥1, or abnormal pupils	97·54 (96·6–98·2)	Epstein et al (2014)[22]

GCS=Glasgow Coma Scale. AIS=Abbreviated Injury Scale. SI=shock index (heart rate/systolic blood pressure). *Odds ratios correspond to each of the two references in the study column. †Arterial base deficit is indicative of hypoperfusion.

Table 2: **Predisposing risk factors associated with coagulopathy in isolated blunt traumatic brain injury**

normalised ratio (INR), strictly the INR is an assay that is optimised for monitoring anticoagulation therapy.

The prevalence of coagulopathy in TBI at admission to hospital ranges from 7%[14] to 63%,[16] reflecting the wide variation in definitions of TBI and coagulopathy (table 1). Coagulopathy occurs in more than 60% of patients with severe TBI,[3,4] but is uncommon in mild head injury (<1%).[35] Although the prevalence of coagulopathy in isolated TBI (ie, in the absence of additional traumatic injuries) is not higher when compared with systemic injuries of similar severity, the coincidence of both TBI and systemic injury could substantially increase the magnitude of coagulopathy beyond that seen in the isolated condition.[19,23,36–38] The incidence of coagulopathy after TBI also increases with injury severity[12,13,20] and is seen more frequently after penetrating injuries than after blunt trauma.[10,12] Predisposing risk factors that have been identified for the development of coagulopathy after isolated blunt TBI are summarised in table 2.

Coagulopathy and clinical course of TBI

Clinical presentation and haemorrhagic progression

The number of patients with TBI and coagulopathy doubles within 24 h of injury.[15] Coagulopathy in TBI has been strongly associated with progressive haemorrhagic injury (PHI)[38] and intracranial haemorrhage (ICH),[39] with approximately half of all patients with TBI and coagulopathy subsequently displaying haemorrhagic progression of initial brain contusions and ongoing ICH within 48 h.[40–43] The interval to onset of coagulopathy is inversely related to injury severity, and alterations in the coagulation system can persist at least until the third day after injury[11] or even longer.[44] Haemorrhagic progression of brain contusions can involve not only the expansion of existing contusions but also the delayed appearance of non-contiguous haemorrhagic lesions.[45] Elderly patients with coagulopathy and intraparenchymal contusions on admission are more likely to have PHI than younger patients.[46] Coagulopathy at presentation is a powerful predictor of outcome and overall prognosis in TBI,[4,8,13,15] resulting in a nine-times higher risk of mortality and a 30-times higher risk of unfavourable outcome than in patients with TBI without coagulopathy.[4,10] The association between coagulopathy and ICH,[38,39] in particular, has a detrimental effect on TBI outcome since ICH is one of the greatest causes of mortality associated with TBI.[47]

Effects of preinjury pharmacotherapies

The demographic change towards TBI in older age is accompanied by an increased incidence of comorbidities in patients with TBI,[27,48] and modern treatment of chronic cerebrovascular and coronary artery disease means that these patients are often taking anticoagulant or antiplatelet drugs, both of which have been explored as causes of increased bleeding and worse outcome after TBI.[27,49–53] According to a meta-analysis,[49] patients taking warfarin at the time of TBI have double the risk of poor outcome than patients not taking warfarin, but a similar analysis of antiplatelet therapy did not show a clear increase in risk.[50] Although retrospective evidence echoes this observation,[52] other studies[51,54,55] have suggested that preinjury use of antiplatelet therapy could result in a two-times higher occurrence of traumatic ICH even after mild TBI than in patients not taking antiplatelet therapy, particularly in the elderly population. Preinjury clopidogrel or warfarin intake are independent predictors of immediate traumatic

ICH, disease progression, and worse outcomes.[56–58] So far, we do not know the risks to patients with TBI of taking the newer target-specific direct oral anticoagulants (DOACs).[59] Although the risk of spontaneous non-traumatic ICH is lower with these treatments, their effect on incidental TBI is poorly quantified. The results from a retrospective study[60] provided the first evidence for reduced mortality and fewer operative interventions in patients with blunt traumatic ICH associated with preinjury intake of DOACs versus warfarin. Other commonly prescribed drugs, such as selective serotonin reuptake inhibitors, might also have effects on haemostasis,[61] but their effect on TBI course and outcome remains poorly investigated.

Potential mechanisms of coagulopathy after TBI

The clinical course of coagulopathy and increased bleeding after TBI has often been considered to reflect rapid progression from a hypercoagulable to a hypocoagulable state—ie, coagulopathy develops as procoagulant tissue factor (TF) is released from the damaged brain and coagulation factors are then consecutively consumed, leading to ICH expansion. However, this is likely to be an oversimplification of a much more complex series of events occurring either simultaneously or sequentially after TBI and involving both coagulopathy and prothrombotic states (figure 1). The proposed pathophysiological mechanisms that trigger haemostatic disorders after trauma with or without brain involvement include platelet dysfunction, endogenous anticoagulation, endothelial activation, fibrinogen modifications, inflammation, and hyperfibrinolysis,[5,25,34,37,38,45,62–70] which can elicit increased and potentially dangerous bleeding. Evidence for these mechanisms is based mainly on correlative data, and causation has generally not been established.[5,25,34,37,68,69] Uncertainties about mechanisms of coagulopathy in isolated TBI also contribute to inconsistencies in epidemiological data (table 1).[38] Better characterisation of these mechanisms and pathways can inform the development of novel diagnostic strategies and might enable identification of potential therapeutic targets for coagulopathy. Here, we summarise the principal pathomechanisms that form our current understanding of the events that drive haemostatic disorders in the context of TBI.

Direct effects of injury

Microvascular failure, BBB disruption, and haemorrhagic progression

Coagulopathy itself does not result in haemorrhage within the brain in the absence of vascular or microvascular injury or failure including BBB breakdown. In a typical contusion, stress and rupture of microvessels result in an immediate haemorrhagic contusion. In the penumbra and other surrounding regions, where the effect of injury is lower, mechanosensitive molecular processes can be activated, mostly in microvessels, thereby triggering cascades that could later result in the delayed structural failure of microvessels, better termed haemorrhagic progressive contusions.[45,71,72] These processes might also occur in other areas of the brain that are not primarily injured and where haemorrhagic contusions are not initially apparent but are visible on repeated CT scans.[45] Numerous signalling pathways involving integrins, ion channels, and transcription factors contribute to the high mechanosensitivity of vascular smooth muscle and endothelial cells in blood vessels in the brain.[71] Transcriptional events usually require hours to display their effects and this could be a rational molecular explanation for the interval between the initial injury and the occurrence of delayed haemorrhage.

Platelet–endothelial interactions and platelet dysfunction

Damage to the microvasculature and BBB disruption further trigger interactions between platelets and the pertubated endothelium or the exposed subendothelial matrix, leading to platelet adhesion—either directly or via platelet ligands such as von Willebrand factor (vWF; a component of the vessel wall)—platelet activation, and formation of a platelet plug at the injury site, which together comprise primary haemostasis.[73,74] Low platelet counts and platelet dysfunction appear to be major contributors to coagulopathy, and these conditions increase risk of bleeding complications after TBI.[62,65,75–78] For example, counts of fewer than 175×10^9 platelets per L have been shown to increase the risk of ICH progression and counts of fewer than 100×10^9 platelets per L are associated with a nine-times increased risk of death compared with patients with higher platelet counts.[21,76] Low platelet counts and spontaneous platelet aggregation have been seen in the absence of bleeding, even days after the initial injury, and might be explained by platelet hyperactivity in TBI.[66] Reports of a profound reduction in pericontusional blood flow after experimental intravascular microthrombosis in mice with TBI could support this assumption.[79,80] Brain-derived platelet-activating factor (PAF) contributes to hypoxia-induced BBB breakdown, which could promote the release of additional PAF and other brain-derived procoagulative molecules such as TF.[81] The precise role of principal platelet ligands such as vWF, which facilitate platelet capture at injury sites in the downstream microvasculature, remains unknown.[73,74] Platelet hyperactivity, with subsequent platelet consumption, might also result in secondary platelet depletion and, at later stages, to platelet exhaustion with increased risk for bleeding.[65]

Clinically significant platelet dysfunction has also been detected with normal platelet counts.[62,75] Platelet dysfunction is indicated by a reduced ability of the agonists adenosine diphosphate (ADP) or arachidonic acid (AA) to activate platelets owing to inhibition of the ADP and AA receptors.[65,77] This receptor inhibition has been characterised as a common feature of haemostatic failure in isolated TBI and occurs in the absence of

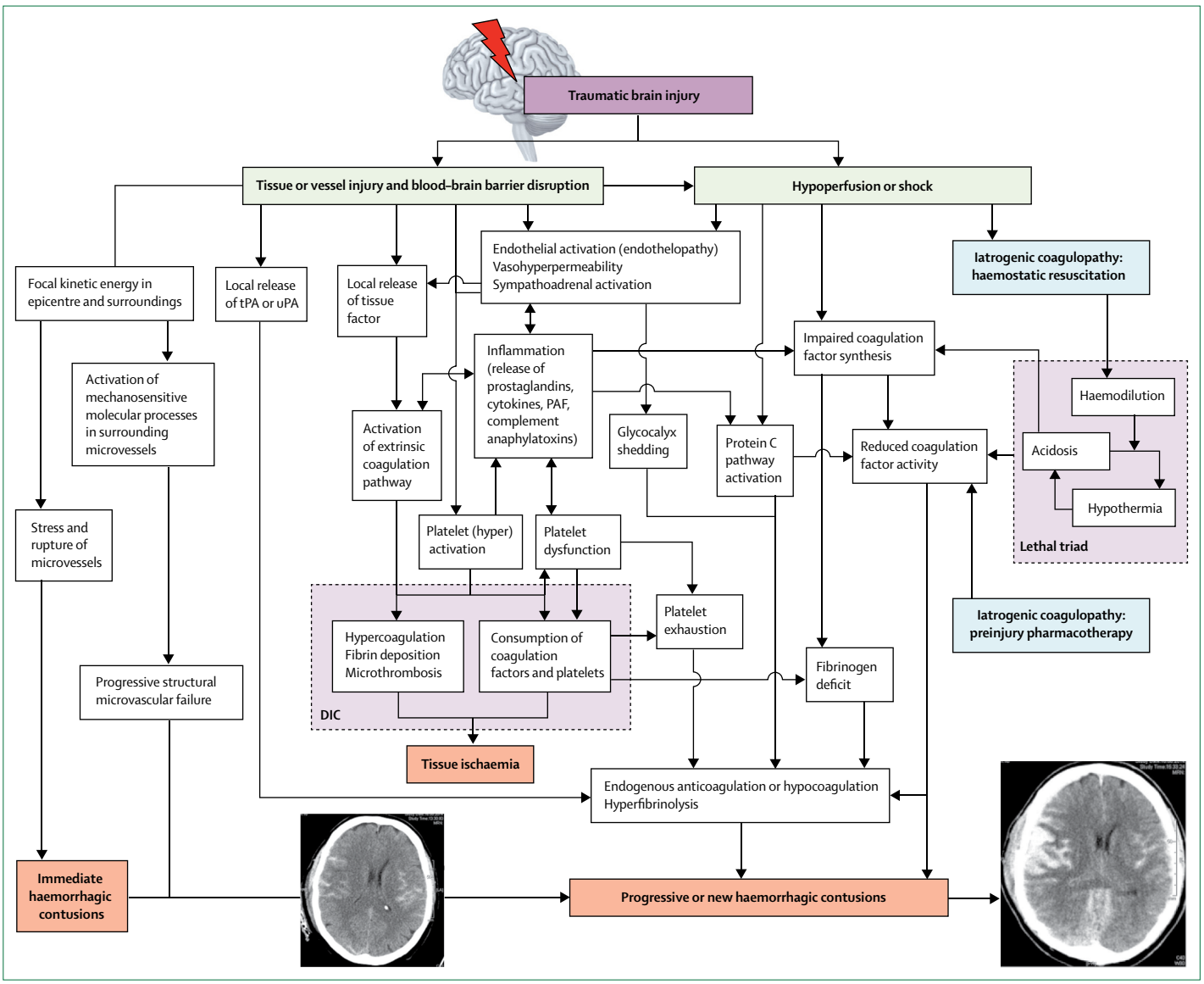


Figure 1: **Current understanding of the mechanisms underlying coagulopathy and haemorrhagic contusions after traumatic brain injury**
Apart from the mechanical force of the impact on the brain, tissue and vessel injuries including blood–brain barrier disruption trigger multiple, highly complex, interactive pathways that can result in haemostatic failure and haemorrhagic progression. Hypoperfusion and shock aggravate coagulopathy and progressive haemorrhagic contusions via endotheliopathy and activation of the protein C pathway, thereby promoting endogenous anticoagulation and hyperfibrinolysis. Loss, consumption, dilution, and dysfunction of coagulation factors and platelets further aggravate the bleeding. Iatrogenic liberal volume resuscitation might trigger the so-called lethal triad consisting of coagulopathy, hypothermia, and acidosis. Understanding of mechanisms is based on multiple sources.[5,25,34,37,38,45,62–70] DIC=disseminated intravascular coagulation. PAF=platelet-activating factor. tPA=tissue-type plasminogen activator. uPA=urokinase-type plasminogen activator.

shock, hypoperfusion, or multisystem trauma.[65] This finding indicates that TBI by itself might be sufficient to induce profound platelet dysfunction by a mechanism distinct from that leading to platelet dysfunction observed in multisystem trauma and shock. Brain tissue and vessel damage also activate inflammation pathways via perturbed endothelium, and platelet dysfunction is thought to aggravate coagulopathy by contributing to interactions between the coagulation and inflammation pathways via the complement system, with activation of one system amplifying activation of the other.[70,82–84]

TF activation

Brain TF is normally isolated by the BBB and thereby not exposed to coagulation factors and largely unsaturated by factor VIIa.[85] If exposed to blood and platelets as a result of direct vessel injury or defragmentation from microvascular failure, TF might be released and bind extensively to factor VIIa. This binding then triggers the extrinsic coagulation pathway, which results in thrombin generation during the initiation phase of clotting and subsequent platelet dysfunction and exhaustion[65,86] as well as disseminated intravascular coagulation. Disseminated

intravascular coagulation could occur within 6 h after TBI and is characterised by systemic activation of the clotting cascade, resulting in fibrin deposition and intravascular microthrombosis, and potentially post-traumatic cerebral infarction,[6,7,87] as well as increased consumption of coagulation factors and platelets,[5,19,88] leading to further platelet exhaustion.[5,19,88]

Small amounts of biologically active TF are also present in circulating blood as blood-borne soluble TF and together with traumatically activated and released TF can be integrated into the surface of activated platelets as well as platelet-derived and endothelial-derived microparticles, which might augment the ongoing initial amplification of coagulation.[89–91] Microparticles have been characterised as small 0·1–1 mm phospholipid vesicles released from membranes of various cell types following cell death or stimulation via damage and stress; after TBI, the pattern of circulating microparticles is altered as both platelet-derived and endothelial-derived microparticles are generated in the injured brain.[92] Platelet-derived microparticles are also enriched in phosphatidylserine, which facilitates the binding of coagulation factors to membranes enabling the formation of procoagulant complexes.[93] As multiple clots form, the systemic consumption of clotting factors and platelets results in a decline in fibrinogen concentration and platelet counts early after TBI, which might lead to increased bleeding.[40,41]

Endogenous plasminogen activator release

Although overactivation of clotting via TF has been suggested to drive hyperfibrinolysis after TBI,[40,41] alternative mechanisms have been proposed, such as local release of endogeneous tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) from contusional brain tissue[94] or depletion of alpha-2-plasmin inhibitor with an increase in plasmin.[5] Plasmin is the main effector of fibrinolysis, the cleavage product of circulating plasminogen. Both tPA and uPA concentrations have been reported to be transiently increased in experimentally lesioned mouse brains but with different temporal profiles.[94] More recently, the role of fibrinolytic shutdown has been suggested as another mechanism that makes patients with TBI potentially prone to a hypercoagulable state.[95]

Effects of hypoperfusion and shock

Endotheliopathy, inflammation, and glycocalyx shedding

Endothelial activation and inflammation are triggered not only by brain tissue and vessel damage, but also by hypoperfusion and shock.[67,96–99] Additionally, endotheliopathy is associated with a strong sympathetic nervous system response with profuse secretion of catecholamines resulting in a hyperadrenergic state that is linked to immunomodulation both locally and systemically.[67,97,98] Biomarker profiles in patients with TBI with poor outcomes have indicated haemostatic failure, endothelial damage including damage to the inner endothelial layer (glycocalyx), vascular activation, inflammation, and hyperfibrinolysis with catecholamine concentrations correlating with endotheliopathy and markers of coagulopathy within the first 24 h after TBI.[97] Degradation of the endothelial glycocalyx has been shown to induce autoheparinisation, thereby contributing to endogenous anticoagulation and bleeding.[99]

Protein C pathway activation

Combined TBI and shock might also result in an immediate activation of coagulation pathways with subsequent protein C pathway activation promoting inhibition of coagulation factors Va and VIIIa,[5] hyperfibrinolysis,[5] and inflammation.[5,96] TBI-related coagulopathy is more profound in patients with acidosis and high lactate concentrations, and hypoperfusion has been associated with an increased risk of hyperfibrinolysis via activation of the protein C pathway.[24] Conversely, in the later sequalae, the post-traumatic inflammatory response might result in chronic protein C depletion, which can result in enhanced susceptibility to infection and thromboembolism.[5]

Iatrogenic coagulopathy

Uncritical haemostatic resucitation with liberal use of intravenous fluids promotes iatrogenic coagulopathy via haemodilution and increases mortality risk owing to the so-called lethal triad, which consists of coagulopathy, hypothermia, and acidosis.[100] Hypothermia primarily inhibits the initiation of thrombin generation and fibrinogen synthesis,[101] whereas acidosis disrupts the interplay of coagulation factors with the negatively charged phospholipids on the surface of activated platelets.[102] Additionally, patients with TBI with preinjury intake of pharmacological anticoagulants might have coagulopathy because of a reduction or block in activity of coagulation factors (direct factor Xa or thrombin inhibitors) or platelets (antiplatelet agents), or inhibition of their synthesis (vitamin K antagonists [VKAs]).

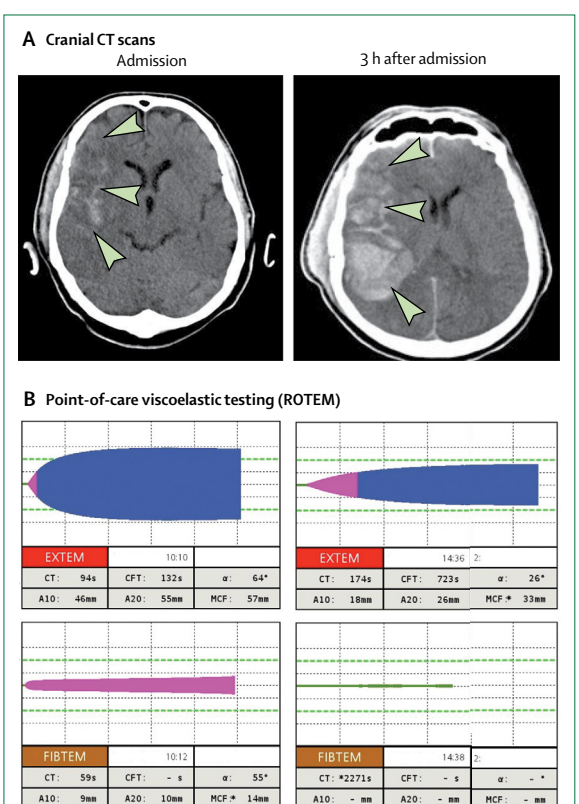
Novel diagnostic approaches to coagulopathy

CCAs are still the most commonly used assessment of coagulation, and detection of coagulation abnormalities can facilitate prediction of outcome after TBI.[21] However, they provide no information on some of the underlying mechanisms associated with haemostatic failure after TBI, such as platelet dysfunction, and might not enable accurate diagnosis of fibrinogen deficiency. Furthermore, CCAs monitor the initiation of blood coagulation, and characterise only the first 4% of thrombin generation in secondary haemostasis.[103] PT, activated partial thromboplastin time (aPTT), and the INR can be used to measure derangements in individual pathways but not to assess complex interactions between multiple pathways, and have not been validated for patients who are critically ill.[104] Standard coagulation screens might appear normal even when the overall state of blood haemostasis is

abnormal.[105] According to a meta-analysis,[38] coagulation tests, in particular aPTT and PT, are inconsistent in detecting haemostatic alterations during blood monitoring. Low initial haemoglobin concentrations should be considered as an indicator for severe bleeding and coagulopathy, and repeated measurements are recommended since an initial value in the reference ranges might mask signs of bleeding.[33]

By contrast, global haemostatic assays, such as viscoelastic (ROTEM and TEG) and thrombin generation tests, which can be done in whole blood, are often considered to provide a better assessment, and include information about the overall haemostatic potential, clot formation kinetics, and clot stability during dynamic clot formation (figure 2).[17,106–110] There is an increasing clinical interest in the use of these tests to monitor and guide blood-product replacement during the acute resuscitation of injured patients.[111,112] Global haemostatic assays have been reported to be better for predicting prognosis and outcome in patients with severe TBI[17,113] and to provide results in more rapid turnaround times compared with CCAs,[105,114,115] which could lead to more timely correction of haemostatic defects. Fibrinogen is increasingly recognised as important in trauma-related bleeding and is not only the precursor of fibrin, but also an important mediator of platelet aggregation.[116] Fibrinogen levels of less than 2·0 g/L have been reported as a risk factor for the development of PHI,[40] and functional deficits in fibrin polymerisation can be more rapidly assessed with global assays than with CCAs (figure 2).[115] Signs of clot lysis on global assays and systemic presence of fibrinolytic fragments on CCAs have been associated with PHI,[39–41] outcome (as measured with the Rankin scale for disability and level of functional independence),[42,117] and the need for neurosurgical procedures.[43] Additionally, patients with abnormal clot formation dynamics on global assays had approximately five times the odds of dying from ICH progression than those with normal clot dynamics.[43]

Point-of-care platelet function tests, such as the Platelet Function Analyzer (PFA-100), Multiplate, and platelet mapping, could have a role in detecting platelet dysfunction or therapeutic platelet inhibition.[53,65,77] Platelet ADP inhibition distinguished survivors from non-survivors and both ADP and AA receptor inhibition have been strongly correlated with TBI severity.[77] Furthermore, significant derangements in CCAs were not found for 70 patients with isolated moderate-to-severe TBI but significant injury severity-dependent platelet dysfunction was indicated by



Haemoglobin	12·6 g/dL↓	6·6 g/dL↓
Platelets	174×10⁹/L	55×10⁹/L↓
pH	7·33↓	7·22↓
BE	−2·7 mmol/L	−8·7 mmol/L↓
Lactate	0·99 mmol/L	6·99 mmol/L↑
PTr	60%↓	15%↓
PT	16·3 s↑	45·3 s↑
aPTT	40 s↑	161 s↑
Fibrinogen	135 mg/dL↓	81 mg/dL↓

Figure 2: **Clinical assessment of progression of haemorrhagic injury and coagulopathy after traumatic brain injury**
A 45-year-old male patient with severe traumatic brain injury had cranial CT scans and coagulopathy assessments with viscoelastic assays and conventional coagulation assays at emergency department admission and 3 h after admission. (A) Clinical CT scans show deteriorating intracranial haemorrhage. (B) Clinical viscoelastic assessments using ROTEM were based on the EXTEM and FIBTEM subtests: the EXTEM test is used as a screening test for the (extrinsic) haemostasis system and the FIBTEM test is an assay for the fibrin part of the clot. Assay results are assessed along the time axis from left to right. The patient viscoelastic findings at admission indicate early signs of coagulopathy, with abnormal clot formation reflected in prolonged EXTEM clotting times (CT, 94 s) and a reduced FIBTEM clot amplitude after 10 min (A10, 9 mm), indicative of reduced clot stability due to fibrinogen deficiency. At 3 h after admission, findings indicate delayed and insufficient clotting, reflected in prolonged EXTEM CT (174 s) and absent FIBTEM A10, suggesting the development of complicating hypotensive (multifactorial) coagulopathy associated with the deteriorating haemorrhage. The flat line in the FIBTEM channel reflects complete absence of fibrin polymerisation. Abnormal clot formation can also be indicated by a prolonged CFT, a reduced angle reflecting the speed of clot formation (α), or a reduced MCF, which reflects overall clot stability and sustainability (for more on assessment parameters for viscoelastic tests, see appendix). (C) The results from standard laboratory assays and CCAs at 3 h confirm severe shock with coagulation failure along with hypofibrinogenaemia and thrombocytopenia (arrows indicate abnormal findings). The more rapid availability of viscoelastic test results compared with CCA and standard laboratory test results enabled timely, targeted treatment of bleeding in this patient. BE=base excess. PTr=prothrombin ratio. PT=prothrombin time. aPTT=activated partial thromboplastin time. CFT=clot formation time. MCF=maximum clot firmness. CCAs=conventional coagulation assays.

See Online for appendix

platelet ADP and AA receptor inhibition in the early phase after injury.[65] One particular role for platelet reactivity tests might be in detecting and monitoring the effects of antiplatelet agents, which vary greatly between individuals.[118,119] However, platelet function assays are not readily available outside the research setting, quality-control protocols are poorly established, and these tests are less reliable in the presence of low platelet counts. There is little experience with monitoring the activity of DOACs,[120] and the use of the above testing approaches for patients with acute injuries remains a work in progress.[121]

Treatment of coagulopathy after TBI

The early correction of coagulopathy in TBI has been independently associated with survival[122] and monitoring, and measures to support coagulation should be initiated immediately on hospital or emergency department admission.[33] The most common options for the treatment of TBI-associated coagulopathy are blood components, including plasma and platelet concentrates, although there is increasing interest in the role of purified or recombinant factors (eg, coagulation factor concentrates) and haemostatic drugs such as tranexamic acid (TXA) and desmopressin. In the absence of specific guidelines, TBI treatment strategies for coagulopathy follow those for systemic trauma except for targeting a higher mean arterial pressure of 80 mm Hg or greater[33] because of the susceptibility of the injured brain to even small reductions in perfusion pressure[12,24,37,123,124] and the proposed need to maintain higher platelet counts (>100×10^9 platelets per L).[33] Treatment protocols and algorithms including massive transfusion and major haemorrhage protocols for the management of bleeding in patients with systemic trauma have been introduced[33,125,126] and their adherence was linked to improved delivery of blood-component therapies and outcomes.[127] Standardised approaches are generally based on the administration of packed red-blood-cell (pRBC) concentrates, fresh frozen plasma (FFP), and platelet concentrates in a 1:1:1 ratio. However, best-practice use of blood products continues to evolve and should be guided by goal-directed strategies using CCAs or viscoelastic assays rather than by empirical administration.[33] Below, standardised and more novel approaches to the treatment of coagulopathy, including haemostatic agents and viscoelastic-based treatment algorithms in the context of TBI, are discussed. Since many patients with TBI have coagulopathy and ICH associated with preinjury pharmacotherapies—particularly anticoagulant or anti-platelet drugs—strategies for the reversal of anti-thrombotics are also discussed.

Red-blood-cell transfusions

Red blood cells, which are the most commonly transfused blood component, have an important role in haemostasis to rapidly increase haemoglobin concentrations, but there is no consensus on haemoglobin targets or transfusion strategies (eg, restrictive *vs* liberal) in patients with TBI who are critically ill.[128–130] Few clinical studies on the optimal transfusion strategy have been done and those that exist are likely to be biased by substantial confounders.[130] Increasing the haematocrit to more than 28% during initial surgery after severe TBI was not associated with improved or worse outcomes, calling into question the need for aggressive transfusion in these patients.[131] In a randomised trial, neither the administration of erythropoietin nor maintaining haemoglobin concentrations above 10 g/dL resulted in an improved neurological outcome at 6 months in patients with TBI; however, the transfusion threshold of 10 g/dL versus 7 g/dL was associated with a higher incidence of adverse events including PHI.[132,133] Furthermore, a mean 7-day haemoglobin concentration of less than 9 g/dL has been associated with increased hospital mortality in patients with severe TBI.[134] The pathophysiology of such complications is complex and even when red-blood-cell transfusion produces an improvement in cerebral oxygenation, this finding has not always been associated with changes in brain metabolism.[135,136]

Red-blood-cell transfusions have been associated with poor long-term functional outcomes in patients with TBI with moderate anaemia, and remain controversial.[137,138] A restrictive red-blood-cell transfusion strategy should be implemented unless poor tolerance to anaemia is present.[130,139] A systematic review[140] on red-blood-cell transfusion in patients with TBI underpinned the heterogeneity of the literature and the overall shortage of clinical evidence guiding transfusion strategies in TBI.[140] Clinicians must assess patients and initiate transfusion on the basis of the clinical setting and patient haemodynamic state rather than using a specific threshold.[141] If indicated, patients should receive red-blood-cell transfusion units selected at any timepoint within their licensed dating period rather than restricting transfusion to only fresh units with storage age less than 10 days.[139] In the modern era of transfusion, including the use of balanced transfusion protocols, the age of stored blood might not affect outcomes as shown historically,[136] and the safety of transfusion products is not likely to be affected before 21 days of storage.[141]

FFP transfusions

In the general (non-TBI) trauma literature, there has been much interest in the early empirical use of plasma, but whether these strategies should be applied to the TBI population remains unclear.[142–145] The empirical infusion of FFP concentrates in patients with severe TBI[143] or the use of FFP in patients with TBI and moderate coagulopathy either alone or combined with pRBCs has been associated with adverse effects or poorer functional outcomes.[138] Evidence from two retrospective studies suggests a survival benefit with early plasma administration in patients with multifocal ICH[142] or with ratio-based blood-product transfusion in patients with

TBI as the only major injury.[144] In the context of a plasma-based coagulation resuscitation strategy in patients with TBI without preinjury anticoagulation, plasma could be administered to maintain PT and aPTT at less than 1·5 times the normal control level and should be avoided in patients without substantial bleeding.[33]

Platelet-concentrate transfusions

The role of platelet-concentrate transfusions is a controversial topic. The effect of blood-component ratios was retrospectively assessed in over 200 patients with TBI with massive transfusion and a high platelet ratio was associated with improved survival.[145] In less serious circumstances, in patients with TBI with moderate thrombocytopenia, platelet-concentrate transfusion did not result in improved outcomes[138] and was inferior to standard care for patients taking antiplatelet therapy before ICH.[146] Platelet-concentrate transfusions in patients with mild TBI, ICH, and preinjury intake of antiplatelet therapy was not associated with improved short-term outcomes and could have exposed these patients to unnecessary risks of transfusion, which include allergic reactions (anaphylaxis), fluid overload, lung injury, and infection.[147] Five retrospective registry studies provide inadequate evidence to support the routine use of platelet-concentrate transfusions in patients with traumatic ICH and preinjury antiplatelet use.[56] Prospective evidence might suggest that platelet-concentrate transfusion in TBI is more likely to improve aspirin-induced, but not trauma-induced, platelet dysfunction.[78] Although platelet-concentrate transfusion in patients with TBI with preinjury intake of antiplatelet therapy is often considered, the current data on its effects on platelet function are still conflicting and inconclusive.[148–150]

Coagulation factor concentrates

Prothrombin complex concentrate

Prothrombin complex concentrate (PCC) is an inactivated concentrate of factors II, IX, and X, with variable amounts of factor VII. At present, PCC cannot be recommended for first-line therapy in patients with traumatic haemorrhage including TBI except for refractory bleeding.[151] However, for the emergency reversal of VKA anticoagulant therapy (eg, warfarin), its early use is effective and it is recommended as a primary treatment in patients with life-threatening bleeding and increased INR.[33,152–154] Use of PCC in different clinical situations has been associated with a very low prevalence of thrombotic complications (0·9%); however, risk of thrombosis and disseminated intravascular coagulation might increase with repeated dosing.[154] A moderate PCC dose of 35 IU/kg compared with a lower dose of 25 IU/kg was associated with a higher percentage of INR reversal and more rapid INR normalisation in patients with TBI taking VKAs.[155] If both three-factor and four-factor PCC are available for the acute management of life-threatening bleeding and to improve thrombin generation, four-factor PCC is preferred,[156] but when this product is not available it is advisable to use a three-factor product together with a small amount of FFP (as it is a source of factor VII).[157] In the context of TBI, the administration of PCC in patients both with and without preinjury VKA intake was superior to recombinant factor VIIa in reducing the need for allogeneic blood transfusions and costs,[158] and when PCC was used as an adjunct to FFP the time to surgical intervention (ie, craniotomy) was reduced with faster correction of INR.[159] Whether PCC can be effective as an adjunct in patients who require a massive blood transfusion is not known.[160]

Fibrinogen (factor I)

Fibrinogen, known as coagulation factor I, is the substrate for clot formation. Fibrinogen concentrations decline initially after TBI because of increased early coagulation factor consumption and recover beyond normal amounts 2–3 days later.[87] Reduced fibrinogen concentrations in the acute phase have been associated with mortality in patients with traumatic haemorrhage without TBI,[161] and concentrations should be kept within 1·5–2 g/L either through administration of fibrinogen concentrates or cryoprecipitate.[33] Increased plasma concentrations of fibrinogen, which can occur during later stages of TBI, can cause inflammation with increased cerebrovascular permeability in the injury penumbra;[162] supplementation to above normal concentrations should be avoided since it might impair the healing process.

Recombinant factor VIIa

One study[163] has shown less haematoma progression in patients with TBI who were treated with recombinant factor VIIa compared with placebo, but the clinical relevance of this finding is unclear, since the effect size and patient numbers were small and the treatment was associated with a higher incidence of thrombosis.[163] Two other small studies[164,165] showed correction of coagulopathy with recombinant factor VIIa in patients with severe TBI requiring emergency craniotomy, which allowed shorter transit times to surgical intervention. However, a systematic review published in 2010[166] included only two trials of recombinant factor VIIa and did not provide reliable evidence to support its use in reducing mortality or disability in patients with TBI. In a small prospective study[167] involving 87 patients with isolated TBI and coagulopathy on hospital admission, single low dose recombinant factor VIIa (20 mg/kg intravenously) and blood products were effective for correcting coagulopathy and preventing the occurrence of PHI without an increase in thromboembolic events. In patients with preinjury VKA intake, the use of recombinant factor VIIa has been associated with a decreased time to normal INR but no difference in mortality.[168] At present, data are inconclusive and general recommendations about management with recombinant factor VIIa cannot be made. The off-label use of

recombinant factor VIIa might be considered if major bleeding and coagulopathy persist despite best-practice use of conventional haemostatic measures and all other attempts to control bleeding.[33]

Factor XIII

Coagulation factor XIII has an important role in maintaining clot stability. After activation of factor XIII via thrombin in the presence of calcium, factor XIII crosslinks fibrin monomers into stable polymers to form a stable clot.[169] Factor XIII deficiency by coagulation factor dilution or consumption has been associated with clinically relevant coagulopathy including bleeding after neurosurgical procedures.[170,171] In-vitro studies have documented the postive effect of factor XIII supplementation on viscoelastic clot dynamics, firmness, and stability,[172] and a potentially inhibitory effect on tPA-evoked hyperfibrinolysis;[173] however, whether these findings could be translated into clinical benefits or treatment options for patients with TBI remains speculative.[174]

Haemostatic agents

TXA

A subanalysis of data from the CRASH-2 trial on intracranial bleeding in TBI suggested that the lysine analogue TXA could be associated with a reduction in haemorrhage growth, fewer focal ischaemic lesions, and fewer deaths compared with placebo.[175] The overall benefit from TXA in the CRASH-2 trial was limited to patients who were treated within 3 h of injury and treatment resulted in more deaths due to bleeding when administered after 3 h.[176] In mice with experimental TBI, TXA has been shown to block tPA-mediated fibrinolysis and ICH in the acute phase, but it potentiated the effect of uPA, thereby promoting ICH, beyond the 3-h window;[94,177] this selective increase in uPA-mediated plasminogen activation at later stages might explain the different responses to TXA over time.[178] Whether this finding also applies to TBI is unclear. The ongoing CRASH-3 study could provide further guidance.[179] Pooled data from two randomised trials[180] on the use of TXA in patients with TBI showed a significant reduction in ICH progression but no improvement in clinical outcomes with early administration of TXA.[180] However, a small randomised trial reported no reduction in PHI with TXA in patients with severe TBI.[181]

A clinical concern with the use of TXA is the potential risk of thromboembolic events, which has not been studied in the context of TBI. The CRASH-2 trial showed no increase in thrombotic events with TXA in the trauma setting; indeed, there was a reduction in myocardial infarction.[176] A trial of TXA in patients undergoing coronary artery surgery[182] showed no higher risk of thrombotic complications within 30 days of surgery but a higher risk of postoperative seizures in treated patients compared with those given placebo.[182] However, trials of TXA in a surgical setting have not adequately studied its effects on the risk of post-operative venous thromboembolism (VTE) and potential reduction in arterial thromboembolism, and this needs further research.[183]

Desmopressin

Use of desmopressin has been investigated in a small number of patients with acute ICH and has resulted in improved platelet function test results,[184] but further studies are needed to identify its role in TBI, particularly in the context of antiplatelet therapy. To date, the use of desmopressin is not suggested routinely in bleeding trauma patients including those with TBI owing to the risk of aggravating cerebral oedema and intracranial hypertension.[33]

Additional strategies for the reversal of antithrombotics

In addition to the strategies discussed above, current guidelines[33,154] suggest the use of several other options to correct coagulopathy in TBI specifically related to the reversal of antithrombotics. In general, all antithrombotic agents should be discontinued when ICH is present or suspected.[154] Vitamin K is recommended to ensure durable INR reversal after VKA-associated ICH in patients with an INR of 1·4 or greater. Vitamin K should be given as soon as possible or concomitantly with other reversal agents. Three-factor and four-factor PCC is preferred to FFP, but FFP can be considered if PCC is not available or contraindicated. The management of patients with TBI on preinjury DOACs is challenging because until recently there were no options for rapid reversal in the event of bleeding. The emergence of a range of reversal agents is likely to improve the safety profile of DOACs,[185] and in 2015, evidence was published for the safety and efficacy of the monoclonal antibody fragment idarucizumab, the first specific agent for the acute reversal of the direct factor IIa (thrombin) inhibitor (DTI) dabigatran.[186] Factor Xa inhibitor antidotes such as andexanet alfa and ciraparantag are in phase II and phase III trials and might be approved in the near future.[187] Protamine sulfate is indicated for the reversal of unfractionated and low-molecular-weight heparin (LMWH). Urgent reversal is recommended if ICH develops during full-dose heparin infusion, whereas routine reversal of prophylactic subcutaneous heparin is not recommended unless the aPTT is substantially prolonged.[154] Similarly, LMWH reversal with protamine sulfate in patients with ICH is recommended for therapeutic doses of LMWH but not for prophylactic dosing.[154] Obtaining information on the time and amount of the last ingested doses, renal and liver function, and possible interactions between medications assists in estimating the degree of anticoagulation exposure. Table 3 summarises current recommendations on reversal agents to restore coagulation function in patients with TBI and ICH associated with antithrombotic medication.[154]

Viscoelastic-based treatment algorithms

Global haemostatic assays, such as viscoelastic assays (ROTEM and TEG), might be superior to CCAs for the assessment of real-time haemostasis and prediction of outcomes; attributes that might be expected to increase their clinical relevance with future research.[190–192] A recent Cochrane review suggested that the use of viscoelastic assays might result in a survival benefit, a reduction in the need for allogeneic blood-product transfusion, and fewer patients with dialysis-dependent renal failure compared with transfusion guided by any method in adults or children with bleeding,[192] even though a previous Cochrane review less than a year before had suggested that their use in trauma should be restricted to research.[193]

Viscoelastic testing has been incorporated into guidelines and vertical algorithms for diagnosis and to guide use of haemostatic therapies in high-risk patients with active haemorrhage including trauma,[33,125,126,194] but thresholds for treatment according to these measures and for all coagulation laboratory parameters are not well defined and require further investigation. Current recommendations for viscoelastic thresholds that could prompt the initiation of specific and targeted treatments with haemostatic agents and blood products are based on expert opinion (figure 3).[109–111,125,195] Although these thresholds have been introduced for the general trauma population they could also hold potential for patients with TBI with coagulopathy to better target and individualise therapies. This is of particular relevance given the complexity of TBI-associated coagulopathy with the potential coexistence of hypocoagulability and hypercoagulability in these patients.

Thrombosis prophylaxis after TBI

TBI itself is considered an independent risk factor for VTE,[196–198] and progressive and delayed hypercoagulable states have been observed even days after initial TBI.[66] Additionally, some of the treatments mentioned above to reverse hypocoagulable states could carry a risk for thrombosis and thromboembolic complications. With active surveillance and in the absence of prophylaxis, the incidence of deep venous thrombosis (DVT) is substantial, and has been reported to be as high as 54% in patients with severe TBI.[199] Despite these findings, there is considerable practice variation and clinical uncertainty about the safety, choice, and timing of thrombosis prophylaxis for preventing VTE in TBI.[198,200] After TBI, there is understandable concern that thrombosis prophylaxis might result in the expansion of intracranial haematomas; in patients not taking anticoagulants and in whom ongoing haematoma expansion has not been excluded, the risks of continued haemorrhagic progression can be up to 13 times higher than in patients not given thrombosis prophylaxis.[201]

Various types of external compression devices are available for DVT prophylaxis in immobilised patients, including graduated compression stockings, pneumatic compression devices, and foot pumps. Although the institution of mechanical prophylaxis might be associated with a residual DVT rate of 31% and a pulmonary embolism rate of 3%,[197] most studies in trauma

	Strong recommendation with moderate to high quality evidence	Conditional recommendation with low to moderate quality evidence
VKAs	Vitamin K; three-factor or four-factor PCC	Fresh frozen plasma if PCC is contraindicated or not available
Direct factor Xa inhibitors	..	Four-factor PCC or aPCC; activated charcoal within 2 h of drug ingestion for intubated patients with enteral access or low risk of aspiration
DTIs	Idarucizumab for ICH associated with dabigatran	Four-factor PCC or aPCC if idarucizumab is not available or for ICH associated with DTIs other than dabigatran; haemodialysis if idarucizumab is not available or in cases of dabigatran overdose; activated charcoal within 2 h of drug ingestion for intubated patients with enteral access or low risk of aspiration
Unfractionated heparin	Protamine sulfate	..
LMWH	Protamine sulfate	Recombinant factor VIIa for ICH associated with danaparoid or if protamine sulfate is contraindicated
Pentasaccharides	..	aPCC; recombinant factor VIIa if aPCC is contraindicated or not available
Thrombolytic agents (plasminogen activators)	..	Cryoprecipitate; antifibrinolytic agent (tranexamic acid or e-aminocaproic acid) if cryoprecipitate is contraindicated or not available
Antiplatelet agents	..	Desmopressin for ICH associated with aspirin, cyclooxygenase-1 inhibitors, or ADP receptor inhibitors; platelet concentrate for ICH associated with aspirin or ADP receptor inhibitors in cases of neurosurgical intervention

For detailed clinical recommendations and dosing see Frontera and colleagues.[154] The recommendations are in agreement with the guidance document for novel oral anticoagulants from the International Society of Thrombosis and Hemostasis.[188] Levels of recommendation according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[189] All antithrombotics (VKAs, direct factor Xa inhibitors, DTIs, heparins [unfractionated heparin and LMWH], pentasaccharides, thrombolytic agents, and antiplatelet agents) should be discontinued when ICH is present or suspected.[154] ..=Data not available. VKAs=vitamin K antagonists. DTIs=direct thrombin inhibitors. LMWH=low-molecular-weight heparin. PCC=prothrombin complex concentrate. ICH=intracranial haemorrhage. aPCC=activated PCC. ADP=adenosine diphosphate.

Table 3: **Summary of options and current recommendations for the reversal of antithrombotic agents in adult patients with intracranial haemorrhage in the context of traumatic brain injury**

patients indicate that heparin chemoprophylaxis mitigates this risk,[202–205] with a probable benefit of LMWH over unfractionated heparin.[200] Only isolated reports[196] suggest that increased risk of VTE is unaffected by heparin prophylaxis. It should be acknowledged that studies make use of different methods to report thrombotic events, from active surveillance to only clinically overt VTE.

There are clear risks of both withholding and using unfractionated heparin or LMWH for VTE prophylaxis in patients with TBI. The current literature[206,207] suggests that careful consideration of risk factors could support the rational stratification of patients with TBI into high-risk and low-risk groups for thrombosis prophylaxis, which forms the basis of an individualised approach. However, high-quality data to inform comparisons of different approaches and outcomes including the optimal timing of initiation are scarce.[198,200]

Postponing heparin prophylaxis to 24 h after injury and restricting this treatment to patients with low risk of haemorrhagic progression results in risk of haematoma expansion similar to that in untreated patients.[208] Risk factors that might lead to withholding heparin include recent use of anticoagulant or antiplatelet therapy, existing haemostatic defects, active bleeding, or the presence of a haemorrhagic lesion on the initial cranial CT scan. In patients with haemorrhagic lesions, VTE chemoprophylaxis can be initiated at 24–72 h with no increased risk of haemorrhage if repeated neuroimaging shows no evidence of haematoma progression.[209,210] A recently updated systematic review of 23 studies confirmed that pharmacological thrombosis prophylaxis appears to be safe in patients with TBI with stabilised haemorrhagic patterns.[198] In patients with severe TBI and no evidence of haemorrhagic worsening, the initiation of prophylactic heparin within 3 days of injury was not associated with neurological deterioration[211,212] and might result in less injury progression and possibly also neuroprotection.[211] In patients who do show evidence of lesion progression, VTE prophylaxis can be delayed since the risks of haemorrhagic progression clearly outweigh the increased risk of VTE.[213] Retrospective data indicate

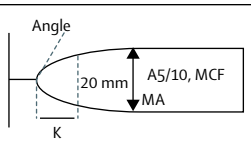
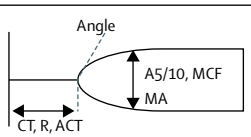
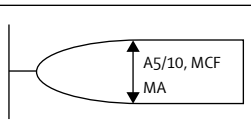
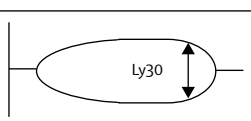
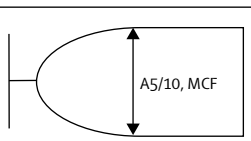
Haemostatic therapy	ROTEM/TEG trace	ROTEM triggers	TEG/rTEG triggers
Consider administering fibrinogen concentrate or cryoprecipitate (FFP*)		EXTEM A10<45 mm (A5<35 mm) or MCF<55 mm **and** FIBTEM A10<10 mm (A5<9 mm) or MCF <12 mm	**TEG:** FF MA<14 mm, cryoprecipitate/fibrinogen/FFP **rTEG:** K>2·5 min or angle <56° (<65°)†, cryoprecipitate/fibrinogen/FFP
Consider administering FFP or PCC		EXTEM CT≥80 s and A10≥45 mm (A5≥35 mm) or MCF≥55 mm **and** normal FIBTEM A10 (A5≥9 mm) or normal MCF	**TEG:** R>10 min, angle <52°, or FF MA<14 mm, FFP **rTEG:** R>1·1 min, FFP and pRBCs; ACT>128 s, FFP and pRBCs
Consider administering platelet concentrate (fibrinogen concentrate, cryoprecipitate*)		EXTEM A10<45 mm (A5<35 mm) or MCF<55 mm **and** normal FIBTEM A10 (A5≥9 mm) or normal MCF	**TEG:** MA<49 mm, platelet concentrate (in patients with normal FF MA) **rTEG:** MA<55 mm, platelet concentrate/fibrinogen/cryoprecipitate
Consider administering antifibrinolytics		Any evidence of hyperfibrinolysis on EXTEM or FIBTEM	**TEG:** Ly30>4%, TXA (if >4% and angle and/or MA↑, TXA contraindicated as considered reactive hyperfibrinolysis) **rTEG:** Ly30>3% (>5%)†, TXA if time since injury <3 h and patient is bleeding
Consider withholding haemostatic therapy and transfusions		Abnormally high A10 or MCF on EXTEM	Recommendation not available

Figure 3: **Algorithm for the use of haemostatic agents and blood products during early care for trauma patients with bleeding based on viscoelastic test results**
Overview of viscoelastic triggers for the differential and targeted use of haemostatic agents and blood products, based on expert opinion, for ROTEM,[111] TEG,[125] and rapid TEG (rTEG).[125,195] If available, specific treatments are given (TEG and rTEG only). The nomenclature for ROTEM and TEG differs slightly and results are not strictly interchangeable,[109,110] because of technical differences and differences in the use of reagents, but the assays are similar in clinical applicability.[110] ROTEM parameters: EXTEM=test for the (extrinsic) haemostasis system. FIBTEM=test for the fibrin part of the clot. CT=clotting time (s). A5/A10=clot amplitude after 5 or 10 min (mm). MCF=maximum clot firmness (mm). TEG parameters: R=reaction time (min). Angle=speed of clot formation (degrees). MA=maximum amplitude (mm). FF MA=functional fibrinogen test maximum amplitude (mm). Ly30=amplitude reduction after 30 min as an indicator of hyperfibrinolysis (%). Additional definitions for rTEG: K=time from end of R until the clot reaches 20 mm amplitude. ACT=activated clotting time. Treatments: FFP=fresh frozen plasma. PCC=prothrombin complex concentrate. pRBCs=packed red blood cells. TXA=tranexamic acid. *Consider alternative treatments if first-line strategies are not available. †Recommended values differ between publications.[125,195]

Search strategy and selection criteria

We searched MEDLINE, Embase, Scopus, and the Cochrane library for English language articles published between Jan 1, 2010, and March 15, 2017, using combinations of the following search terms: "coagulopathy", "traumatic coagulopathy", "blood coagulation", "haemostatic disturbance", "traumatic brain injury", "craniocerebral trauma", "brain injuries", and "isolated head trauma". Reference lists of relevant articles were screened for further studies and key references published before 2010 were also included.

that being over the age of 65 years poses a specific risk for haemorrhagic worsening on repeated CT scans after the initiation of anticoagulation.[212]

The accumulated data have allowed the introduction of rational prophylaxis protocols in neurocritical care, which have been at least partly associated with improved effectiveness.[207,210] Careful stratification is still required to balance the risks and benefits of treatment for individual patients.[198,212] More evidence is needed on the efficacy of pharmacological thrombosis prophylaxis in preventing VTE as well as on appropriate treatments, doses, and timing, but designing and undertaking definitive trials remains a challenging aim.[214] In 2015, the inhibition of factor XI was identified as a new target for VTE prophylaxis.[215] Emerging strategies to better tailor thrombosis prophylaxis should involve consideration of variables such as TBI severity and preinjury anticoagulant treatment, and should include adjusted dosing of unfractionated heparin or LMWH on the basis of viscoelastic test findings.[198,216]

Conclusions and future directions

Altered haemostasis and haemorrhagic progression are substantial and ongoing challenges in the clinical management of TBI. There is a dearth of data on patterns of haemostatic derangements and on the role of targeted haemostatic resuscitation strategies in TBI, which could be distinct from those needed in general trauma. Studies elucidating the various phenotypes and mechanisms underlying the haemostatic abnormalities after TBI, including their clinical manifestations and how they can be rapidly identified with diagnostic devices, are warranted. In particular, the contributions of platelet dysfunction and endothelium abnormalities are gaps in our current knowledge.

Studies are needed to address whether a timely, targeted, and individualised approach to the management of haemostatic abnormalities after TBI protects against secondary injury and improves outcomes compared with empirical transfusion-based therapies with balanced or whole-blood resuscitation. Additionally, the roles of specific treatments such as coagulation factor concentrates, novel blood-derived therapeutics, and bioengineered haemostatic agents need to be investigated. Viscoelastic tests could provide real-time information on the effects of several of the interventions discussed in this Series paper, but thresholds need to be better defined, as is the case for conventional coagulation laboratory parameters. The increasing use of antiplatelet and anticoagulant drugs in the elderly population deserves particular consideration in precision-medicine approaches to the management of TBI.

Contributors

MM did the literature search and drafted the manuscript. HS contributed to figure design and revision of the manuscript. SS supported the literature search and contributed to the revision of the manuscript. NM contributed to the writing, revision, and finalisation of the manuscript. TM, HM, and AB contributed to the revision and finalisation of the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of interests

In the past 3 years, MM has received speaker's fees and travel payments from CSL Behring, LFB Biomedicaments France, and TEM International, which is the manufacturer of ROTEM devices and assays. HS has received speaker's fees, travel payments, and honoraria from AOP Orphan, Baxter, CSL Behring, and TEM International. NM has received consultancy fees from Bioartic Inc, and has scientific non-monetary collaboration with Novartis and Lantmännen AS Peptides outside the submitted work. AB has held a key opinion leader contract with and has received speaker's fees and travel payments from Johnson & Johnson Medical, and has received speaker's fees and travel payments from Banyan Biomarkers and DePuy Sythes outside the submitted work. All other authors declare no competing interests.

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Traumatic brain injury 3

Paroxysmal sympathetic hyperactivity: the storm after acute brain injury

Geert Meyfroidt, Ian J Baguley, David K Menon

A substantial minority of patients who survive an acquired brain injury develop a state of sympathetic hyperactivity that can persist for weeks or months, consisting of periodic episodes of increased heart rate and blood pressure, sweating, hyperthermia, and motor posturing, often in response to external stimuli. The unifying term for the syndrome—paroxysmal sympathetic hyperactivity (PSH)—and clear diagnostic criteria defined by expert consensus were only recently established. PSH has predominantly been described after traumatic brain injury (TBI), in which it is associated with worse outcomes. The pathophysiology of the condition is not completely understood, although most researchers consider it to be a disconnection syndrome with paroxysms driven by a loss of inhibitory control over excitatory autonomic centres. Although therapeutic strategies to alleviate sympathetic outbursts have been proposed, their effects on PSH are inconsistent between patients and their influence on outcome is unknown. Combinations of drugs are frequently used and are chosen on the basis of local custom, rather than on objective evidence. New rigorous tools for diagnosis could allow better characterisation of PSH to enable stratification of patients for future therapeutic trials

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This is the third in a Series of four papers about traumatic brain injury

Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium (G Meyfroidt PhD)**; Westmead Hospital, Westmead, NSW, Australia** (I J Baguley PhD)**; and Division of Anaesthesia, University of Cambridge, Cambridge, UK** (Prof D K Menon FMedSci)

Correspondence to:
Prof David K Menon, Box 93, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK
dkm13@cam.ac.uk

Introduction

Excessive sympathetic nervous system activity can develop after severe acquired brain injury, with about 80% of cases occurring after traumatic brain injury (TBI).[1] This condition can have a striking presentation,[2] with paroxysmal tachycardia, arterial hypertension, tachypnoea, hyperthermia, and decerebrate posturing occurring in response to afferent stimulation. Clinical features resembling paroxysmal sympathetic hyperactivity (PSH) were first described after TBI by Wilder Penfield,[3] and his assumption of an epileptic cause gave the syndrome its first name—mesencephalic seizures. In a 2010 review[1] of 349 cases of this syndrome published in the critical care and rehabilitation literature since Penfield's initial description, the same syndrome had over 31 different labels. Some of these labels were descriptive (eg, dysautonomia, autonomic storms, or sympathetic storms), some referred to an assumed epileptic mechanism (eg, autonomic seizures), and some to the site of damage (eg, hypothalamic storms).[1,4–6] The absence of a clear definition or terminology for the syndrome was probably a cause and consequence of the syndrome's under-recognition, despite its relatively high incidence after severe brain damage,[7,8] the well recognised association with morbidity,[9–12] and high healthcare and societal costs.[7] This absence of a clear definition for the syndrome might also explain the slow progress in understanding the pathophysiology of PSH, which was further hindered by a failure to distinguish between mixed parasympathetic and sympathetic hyperactivity[13] and pure sympathetic hyperactivity, with conflation of both into a single diagnosis for many decades.[1] Although conclusive evidence of the absence of parasympathetic involvement is unavailable, the current consensus is that autonomic hyperactivity in this syndrome concerns only the sympathetic nervous system.[1,12,14]

In 2010,[1] the term paroxysmal sympathetic hyperactivity, which was introduced in 2007 by Alejandro Rabinstein,[12] was suggested as the unifying term for this condition. 4 years later, in 2014, 60 years after the first published case, an expert group[15] established a rigorous conceptual definition and diagnostic criteria for the syndrome. These criteria should provide a foundation for more systematic research on this clinical syndrome and its management.

Several classes of drugs, acting on a range of molecular targets, have been used to treat patients with PSH, with varying success. The syndrome is likely to be mechanistically heterogeneous, and identification of the dominant pathophysiological processes responsible for the clinical picture in individual patients could allow more rational matching of patients to therapies and move towards precision-medicine approaches in the treatment of PSH. The recent development of diagnostic criteria for the condition has provided the essential first step for such an exercise, since these criteria can be used to clearly define an initial population of patients for such therapeutic stratification.

The purpose of this Series paper is to provide an overview of the existing literature on PSH, its causes, consequences, pathophysiology, and diagnosis, and to discuss the available evidence to support therapeutic options. Although the dominant underlying cause in PSH is TBI, we also include PSH of other causes since there are substantial commonalities in pathophysiology and therapeutic response.

Definition and diagnostic criteria

Between 1993 and 2008, nine sets of diagnostic criteria for this syndrome were published,[9,10,12,16–21] which differed with regard to timing of diagnosis or assessments relative to occurrence of the injury, the number of clinical

features required, and the degree of deviation from healthy clinical parameters (eg, heart rate, blood pressure, and temperature).[22] An international consensus process in 2014[15] addressed the confusion regarding the nomenclature of the condition, produced diagnostic criteria, developed a diagnostic tool, and reached an agreement on the adoption of the term paroxysmal sympathetic hyperactivity, which was further defined as: "A syndrome, recognized in a subgroup of survivors of severe acquired brain injury, of simultaneous, paroxysmal transient increases in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, sweating) and motor (posturing) activity." [15] The expert consensus group selected 11 of the 16 previously reviewed features[22] to be pathognomonic of PSH (appendix), and proposed a clinical scoring system—the PSH Assessment Measure (PSH-AM; figure 1)—to facilitate diagnostic consistency. The PSH-AM consists of two separate constructs: first, the clinical feature scale, to score the presence and severity of excess adrenergic and motor activity; and second, the diagnosis likelihood tool, to score the likelihood of the presence of PSH. A paediatric adaptation of the clinical feature scale has also been proposed (appendix).[23] Although the PSH-AM is useful, a definition by consensus has limitations, and a clear link with pathophysiological features, the independent contribution of PSH to clinical outcomes, and a more precise definition of the duration of a paroxysm are currently missing.

See Online for appendix

A Clinical feature scale (CFS) score

	0	1	2	3
Heart rate (beats per min)	<100	100–119	120–139	≥140
Respiratory rate (breaths per min)	<18	18–23	24–29	≥30
Systolic blood pressure (mm Hg)	<140	140–159	160–179	≥180
Temperature (°C)	<37·0	37·0–37·9	38·0–38·9	≥39·0
Sweating	Absent	Mild	Moderate	Severe
Posturing during episodes	Absent	Mild	Moderate	Severe

B Diagnosis likelihood tool (DLT): one point per feature present

Antecedent acquired brain injury
Clinical features occur simultaneously
Episodes are paroxysmal in nature
Sympathetic over-reactivity to normally non-noxious stimuli
Absence of parasympathetic features during episodes
Features persist for >3 consecutive days
Features persist for >2 weeks post-brain injury
Two or more episodes daily
Absence of other presumed causes of features
Features persist despite treatment of alternative differential diagnoses
Medication administered to decrease sympathetic features

C Interpretation of scores

- **CFS subtotal=**
  sum of CFS scores for each of the six features (0–3 points for individual features; maximum subtotal=18);
  CFS subtotal severity scores:
  0=nil; 1–6=mild; 7–12=moderate; ≥13=severe
- **DLT subtotal=**
  sum of points for each feature present (one point per feature; maximum subtotal=11)
- **PSH-AM=**
  CFS subtotal + DLT subtotal;
  PSH-AM score:
  <8=PSH unlikely; 8–16=PSH possible; ≥17=PSH probable

Figure 1: **The PSH Assessment Measure**
The PSH Assessment Measure (PSH-AM; appendix) is calculated using two constructs: (A) the clinical feature scale (CFS), which measures the intensity of the cardinal features identified as crucial to PSH; and (B) the diagnosis likelihood tool (DLT), which is based on the presence of contextual attributes (identified by expert consensus), and indicates the likelihood that the observed features are due to PSH. (C) The PSH-AM score is calculated by combining the CFS and DLT subtotal scores, which gives an estimate of the probability of a diagnosis of PSH. Adapted from Baguley and colleagues,[15] by permission of Mary Ann Liebert, Inc. PSH=paroxysmal sympathetic hyperactivity.

PSH has been described in patients at all stages following brain injury—from early critical care through to the rehabilitation phase. Patients are often sedated acutely to minimise secondary brain injury, and classic features of PSH might not manifest in a patient until sedation has been withdrawn. Nevertheless, it is possible to make a diagnosis as early as within the first week after TBI, even while the patient remains sedated.[24] Although patients can show features of PSH in the absence of provocation, these features are more likely to be provoked by non-noxious stimuli, or present as pathologically persistent physiological responses to noxious stimuli, which in the absence of PSH might result in only short-lived responses in heart rate and blood pressure. The duration of the paroxysmal phase is variable, ranging from less than 2 weeks to many months, after which the syndrome could burn out, leaving residual dystonia and spasticity in many cases.[18] Whether the residual spasticity is truly part of the sequelae of PSH, or is simply a consequence of injury to supraspinal motor tracts that occurs alongside PSH, is unclear, as both are seen commonly after more severe injuries. However, resolution of PSH symptoms can occur without any residual spasticity.

Epidemiology

A review of 349 PSH case reports published before 2010[1] found that about 80% followed TBI, 10% followed anoxic brain injury, 5% followed stroke, and the remaining 5% occurred in association with hydrocephalus, tumours, hypoglycaemia, infections, or unspecified causes. The high prevalence of cases related to TBI is not completely explained by the high incidence of TBI, and could be intrinsically higher when compared with other causes of brain injury. One series of consecutive cases of febrile patients in neurocritical care reported a prevalence of PSH of 33% after TBI, compared with 6% after other causes of brain injury.[12] Regardless of the underlying diagnosis, the reported prevalence of patients with PSH in other studies from various countries ranges from 8% to 33%.[7,9,12,16,25,26] The prevalence of PSH could be changing over time. A retrospective Italian survey[21,27] of 333 patients in vegetative states after massive brain injury described a decreasing incidence of PSH over time, falling from 32% (for TBI) and 16% (for other causes) between 1998 and 2005, to 18% and 7%, respectively, between 2006 and 2010. Further studies are needed to support this trend and to establish its causes. There are few published studies on paediatric

PSH, but the findings are broadly similar to those from studies of adults. In a large paediatric case series (n=249),[4] the prevalence of PSH after TBI was 10%, and 31% after cardiac arrest. In 2015,[28] Pozzi and colleagues published a retrospective analysis of all 407 children who had been admitted to their neurorehabilitation unit after being discharged from an intensive care unit (ICU) following acute brain injury between 2001 and 2011. They identified 26 patients with PSH: 12 had TBI, nine had anoxic brain injury, and five had PSH as a result of other causes. One smaller study (n=220) published in 1997[17] suggested that PSH in children is twice as frequent after severe hypoxic injury compared with TBI. An even higher proportion of 41% was found in a series of 72 children with encephalitis and meningoencephalitis.[29]

This wide range of reported prevalences underlines the difficulties in estimating the true proportion of patients with PSH. Factors that explain the large between-study differences include study design (eg, a subset of patients with severe brain injury *vs* consecutive cases), unit admission criteria, the type and severity of brain injuries, the choice of diagnostic criteria, competing events such as non-survival, and publication bias. In one study[7] the prevalence was affected by the timing of assessment, with 24% of patients meeting the criteria for PSH 7 days after injury, decreasing to 8% after 2 weeks. Furthermore, the perceived prevalence in subacute units is often higher than in ICUs, possibly owing to so-called clustering effects—ie, when patients with more severe injuries are preferentially admitted for rehabilitation. Additionally, stopping the use of powerful analgesics—mainly opioids—upon transfer of a patient from an ICU to a rehabilitation centre might reveal signs of PSH.

Effect on outcome

The increased likelihood of patients developing PSH after more severe and more diffuse brain injuries—which have an inherent association with worse hospital or long-term outcomes—makes the assessment of the independent contribution of PSH to such outcomes a challenge. Before 1999, reports on the outcome of patients with PSH were scarce. In one large multicentre study of patients with TBI published in 1993,[16] autonomic hyperactivity was not an independent risk factor for mortality or poor clinical outcome, but a subsequent study[18] reported longer hospital stays and worse clinical outcomes in patients with PSH than in matched controls, which was corroborated by a subsequent case series from the same centre.[7] In two studies[21,27] from a dedicated institute for patients in a vegetative state, a diagnosis of

	Type of brain injury	Number of patients with PSH/total number of patients	Duration of mechanical ventilation	Length of stay			Proportion of patients with tracheostomy	Prevalence of infections	Glasgow Outcome Scale	Functional independence measure
				ICU	Hospital	Rehabilitation centre				
Baguley et al[18]	TBI	35/70	NA	Longer	Longer	Longer	NA	No significant difference	Worse	Worse
Fernandez-Ortega et al[9]	TBI	11/37	Longer	Longer	NA	NA	Higher	Higher	No significant difference	NA
Dolce et al[21]	Vegetative state	87/333	NA	Longer	Longer	NA	NA	NA	Worse	NA
Hendricks et al[30]	TBI	9/76	Longer	NA	NA	NA	NA	Higher	No significant difference	NA
Lv et al[26]	TBI	16/87	No significant difference	Longer	Longer	NA	Higher	Higher	Worse	NA
Fernandez-Ortega et al[8]	TBI	18/179	Longer	Longer	Longer	NA	Higher	Higher	No significant difference	NA
Laxe et al[31]	TBI	13/39	NA	NA	Longer	Longer	NA	NA	No significant difference	No significant difference
Hinson et al[32]	TBI	16/102	NA	No significant difference	NA	NA	NA	NA	No significant difference	NA
Pozzi et al[28]	Mixed paediatric acquired brain injury	26/407	NA	NA	NA	NA	Higher	NA	NA*	NA*
Mathew et al[33]	TBI	29/343	NA	No significant difference	Longer	NA	NA	NA	Worse	NA

Longer refers to a longer duration or length of stay, higher refers to a higher proportion or higher prevalence of patients, and worse refers to a worse score on the scales of measurement when comparing patients with and without PSH after brain injury (see original studies for details regarding the quantitative impact of PSH on specific outcomes). PSH=paroxysmal sympathetic hyperactivity. TBI=traumatic brain injury. NA=not assessed. *Although the paediatric case series by Pozzi et al[28] did not report Glasgow Outcome Scale scores or Functional Independence Measure scores, there was a higher prevalence of permanent vegetative state and higher mortality during follow-up in patients with PSH compared with those without PSH.

Table 1: **Outcomes of patients with brain injury with and without PSH**

dysautonomia was associated with worse Glasgow Outcome Scale scores in patients with and without TBI. A similar association of PSH with protracted hospital stays and worse clinical outcomes was described in a Chinese study.[26] However, findings from other studies have not been consistent with regard to the effects of PSH on outcomes such as the duration of mechanical ventilation or the length of stay in intensive care, hospital, or rehabilitation centres, with no effects on long-term neurological outcomes.[8,9,30,31] The results of outcome studies are summarised in table 1.

Between-study discrepancies might reflect the methodological issues mentioned previously, which are inherent to case series. Additionally, common outcome measures, such as the Glasgow Outcome Scale or Functional Independence Measure, might not be sensitive enough to detect subtle differences in neurological status at the worse end of the outcome scale. Furthermore, PSH outcomes might depend on disease duration, ranging from no effects on neurological outcomes in patients who have the syndrome for a short duration (eg, as a result of sedative and opioid withdrawal), to substantial negative consequences for neurological recovery in those who have persistence of the syndrome.[24] The available data do not allow us to address this theory or establish whether differences in patient management modulate the relationship between the severity of PSH and neurological outcomes. Notwithstanding these uncertainties, the overall clinical impression is that PSH is an independent risk factor for poorer neurological outcomes in patients who have had a brain injury.

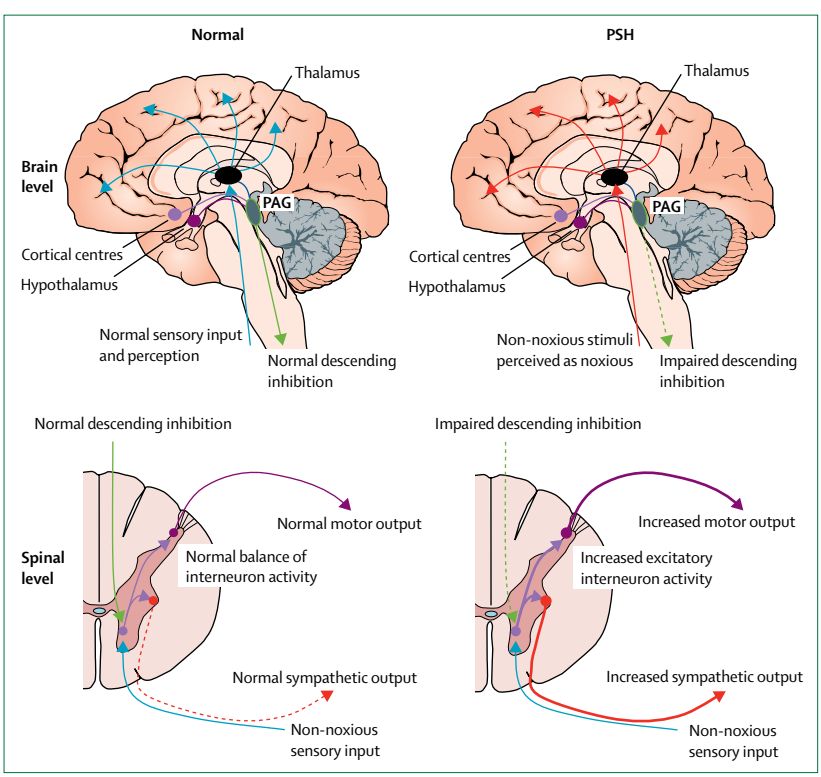

***Figure 2*: Excitatory:inhibitory ratio model of the pathogenesis of PSH**
In normal circumstances, various cortical, hypothalamic, thalamic, and other subcortical inputs modulate activity within brainstem centres—the PAG is shown here as one of the key brainstem hubs in this process. These brainstem nuclei provide inhibitory drive to spinal-reflex arcs, thereby maintaining balance between inhibitory and excitatory interneuron influences on motor and sympathetic efferents, allowing normal sensory stimuli to be perceived as non-noxious. In the excitatory:inhibitory ratio model of PSH, disconnection of descending inhibition produces maladaptive dendritic arborisation and spinal-circuit excitation, with non-noxious stimuli triggering increased motor and sympathetic output (spinally) and potentially becoming perceived as noxious (centrally).[35,36] PAG=periaqueductal grey. PSH=paroxysmal sympathetic hyperactivity.

Pathophysiology

The initially proposed epileptogenic mechanisms[3,13] for PSH are not supported by experimental evidence. Current theories[32,34,35] propose that combinations of diffuse or focal injuries disconnect one or more cerebral centres from caudal excitatory centres. An initial synthesis of this theory suggested that the underlying mechanism is a simple disconnection of cortical inhibitory centres—such as the insula and cingulate cortex—to the hypothalamic, diencephalic, and brainstem centres that are responsible for supraspinal control of sympathetic tone.[34] Although this proposal explained some aspects of PSH (such as dystonia), it failed to provide a complete explanation of all of its features.[34] A more recently proposed model—the excitatory:inhibitory ratio model[32,35]—suggests a two-stage process, with disconnection of descending inhibitory pathways causing spinal circuit excitation; paroxysms then resolve in response to recovery of the inhibitory drivers (figure 2). This model also explains the pathologically increased and extended allodynic responses to stimuli that are either non-nociceptive (movement) or only minimally nociceptive (eg, tracheal suction)—reminiscent of the symptoms of some patients with chronic pain syndromes.[37] The non-PSH literature[36] suggests a putative role for the periaqueductal grey matter as a central inhibitory driver, and implicates midbrain lesions in the functional or structural disconnections that underlie the more severe end of the PSH spectrum. This model also explains some differences in outcomes between patients with PSH, because those with more rapid recovery of supraspinal inhibition are more likely to have shorter duration of PSH and less brainstem involvement than those with slow recovery.

Several attempts have been made to determine the location of the structural lesions that increase the likelihood of a patient developing PSH, but clinical imaging data are ambiguous. In patients with TBI, PSH has sometimes been associated with diffuse axonal injury, younger age,[18] and, less consistently, a greater burden of focal parenchymal lesions on CT imaging.[7,8] Patients with midbrain and pontine lesions are at increased risk of developing PSH,[26] as are those with lesions in the periventricular white matter, corpus callosum, and deep grey nuclei. In 2015, a diffusion-tensor MRI study of 102 patients,[32] 16 of whom had PSH, showed an association between PSH and lesions in the corpus callosum and posterior limb of the internal

capsule. Given that the associations in these studies are all between PSH and markers of more severe or diffuse injury, it is unlikely that any one of these lesions specifically drives the development of PSH, and that instead development of the syndrome is more likely to be associated with the overall burden of injury. These findings support the suggestion[34] that PSH is a complex disconnection syndrome, with learned allodynic hyperresponsiveness having a contributory role, as suggested by the excitatory:inhibitory ratio model (figure 2).

Several central neurotransmitter systems have been implicated in the maladaptive responses that drive PSH, primarily on the basis of efficacy of specific neuromodulatory interventions (see next section). Regardless of these central neurotransmitter changes, good evidence supports an association between PSH and peripheral catecholamine, and possibly corticosteroid, release (figure 3A),[14] which might explain the exaggerated responses to non-noxious or mildly noxious stimuli observed in patients with PSH (figure 3B).[24]

The available data therefore suggest that allodynic hyperresponsiveness in PSH develops as a consequence of impaired control by higher cortical centres, resulting in sympathetic storms. However, maladaptive spinal cord plasticity is also possible, as seen in patients with the well researched and related disorder of autonomic dysreflexia following high spinal cord injury.[38] In patients with PSH, similar spinal cord changes appear to be permanent, or at least persistent, with subclinical allodynic or sympathetic over-responsiveness persisting for at least 5 years after the injury.[39]

Therapeutic options

The three main goals when treating patients with PSH are to avoid the triggers that provoke the paroxysms, to mitigate the excessive sympathetic outflow, and to address the effects of PSH on other organ systems through supportive therapy. The level of evidence supporting these therapeutic options is generally low, consisting of case reports or small case series with efficacy reported in terms of anecdotal decreases in sympathetic hyperactivity. No randomised clinical trials have been done to date, and whether these interventions affect the long-term outcome of patients with severe brain injuries and PSH is unclear.

A range of pharmacological interventions have been used to both prevent and halt paroxysms, with variable efficacy (table 2). Although individual drugs are thought to have a greater or lesser effect on individual components of the syndrome, this differentiation is far from clear, and no drug is universally, or even predictably, effective. In practice, most patients require treatment with multiple drugs with potentially complementary roles—both to target different components of the syndrome and to combine drugs aimed at preventing and treating paroxysms. Individual drugs and drug combinations are typically chosen on the basis of local custom, rather than objective evidence.

In both clinical[8] and experimental settings,[24] the majority (approximately 80%) of paroxysms experienced by patients with PSH occur as allodynic responses to external stimuli such as pain, urinary retention, or movement. When triggers can be identified, or if they are suspected, it makes sense to attempt to treat or avoid them.[46] Opioids, especially morphine, are probably the most frequently used treatment, and are often used as first-line drugs to suppress allodynic responses in these patients.[40] Morphine might also have non-analgesic effects through the modulation of central pathways involved in paroxysms.

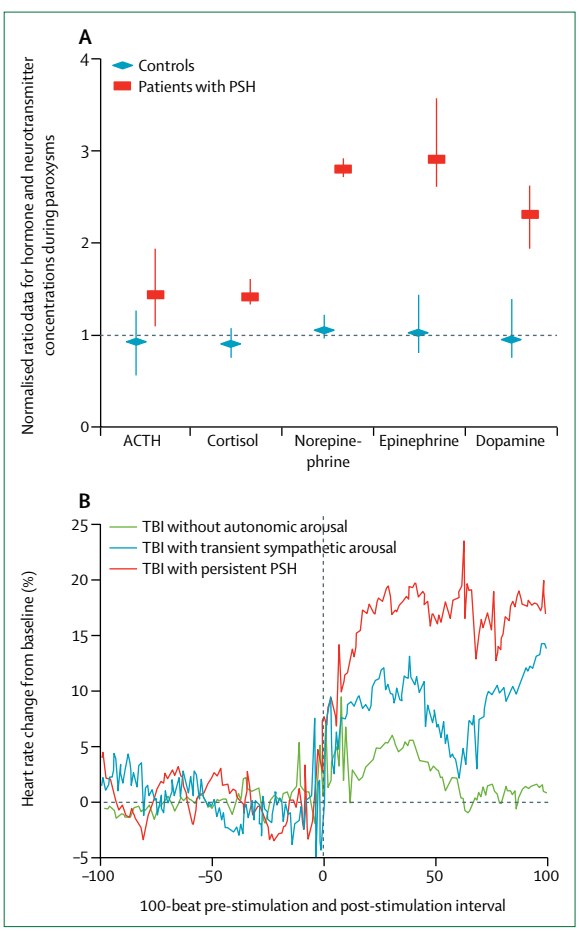

***Figure 3*: Pathophysiology of PSH**

(A) Hormone and neurotransmitter changes in patients with PSH. The median values and IQRs for the normalised ratio of hormone and neurotransmitter concentrations during paroxysms indexed to baseline are shown. Differences between patients with TBI who developed PSH and patients with TBI who did not develop PSH (controls) were significant (p<0·001) for hormone and neurotransmitter concentrations. (B) Heart rate responses following stimulation in patients recovering from TBI. Normalised data are plotted as percentage change from baseline over 100-beat intervals before and after stimulation for groups of patients with normal autonomic responses without arousal, with transient sympathetic arousal responses, and with PSH with persistent, increased sympathetic responses to non-noxious stimuli. Part A adapted from Fernández-Ortega and colleagues,[14] by permission of Mary Ann Liebert, Inc. Part B adapted from Baguley and colleagues,[24] by permission of Elsevier. PSH=paroxysmal sympathetic hyperactivity. ACTH=adrenocorticotropic hormone. TBI=traumatic brain injury.

Other opioids and routes of administration, such as fentanyl patches, have also been used.[41] In general, the duration of opioid therapy depends on the duration and severity of the PSH symptoms, balanced against the desire to avoid chronic opioid use, but treatment with opioids often extends into the rehabilitation phase. Other sedatives, such as midazolam, have also been used in this context. Although haloperidol has been used in the past to treat patients with PSH, potential adverse effects of this drug on eventual outcome are a concern.[58] Gabapentin, which is often used to treat neuropathic pain, has well documented effects on presynaptic voltage-gated calcium channels in the dorsal horn of spinal cord, and has been found to be clinically useful in patients with PSH who were unresponsive to metoprolol or bromocriptine.[49]

The α2-adrenergic drugs act through central and peripheral suppression of adrenergic outflow. Additionally, they have an imidazole-receptor effect. In patients with PSH, use of clonidine reduces heart rate, blood pressure, and circulating catecholamines, but appears to be less effective in controlling body temperature.[46] The use of clonidine might be less appropriate for patients with paroxysmal symptoms because it could potentiate hypotension and bradycardia between paroxysms, making titration challenging.[46] However, clonidine patches can be effective in controlling sympathetic storms, even at late stages in the course of the condition.[54] Dexmedetomidine has also been reported to be effective in the management of PSH features in the ICU.[47,48]

	Prevention or treatment: dose and route*	Site of action	Clinical features targeted	Evidence of efficacy†	Cautionary notes
Opioids					
Morphine‡[40]	Prevention: intravenous infusion, titrate to effect Treatment: 1–10 mg intravenous bolus	Opioid receptors in brain and spinal cord (and possibly in peripheral tissue)	Most features, particularly hypertension, allodynia, and tachycardia	Consistent	Respiratory depression, tolerance, and need for dose escalation
Fentanyl[41]	Prevention: patch 12–100 μg/h	Opioid receptors in brain and spinal cord (and possibly in peripheral tissue)	Most features, particularly hypertension, allodynia, and tachycardia	Consistent	Respiratory depression, tolerance, and need for dose escalation
Intravenous anaesthetics					
Propofol	Prevention: intravenous infusion; maximum <4 mg/kg per h Treatment: 10–20 mg intravenous bolus	$GABA_A$ receptors in brain	Most features	Consistent	Only if mechanically ventilated, and in acute phase
β-adrenergic blockers					
Propranolol[42–44]	Prevention: 20–60 mg every 4–6 h, orally (rectal administration also described)	Non-selective β adrenoceptors (central, cardiac, and peripheral)	Tachycardia, hypertension, and diaphoresis; might help with dystonia	Consistent	Bradycardia, hypotension, bradyarrhythmia, sleep disturbances, and masked hypoglycaemia, especially with oral antidiabetics
Labetalol[45]	Prevention: 100–200 mg every 12 h, orally	β and α adrenoceptors	Tachycardia, hypertension, and diaphoresis; might help with dystonia	Limited	Bradycardia, hypotension, bradyarrhythmia, sleep disturbances, and masked hypoglycaemia, especially with oral antidiabetics
Metoprolol	Prevention: 25 mg every 8 h, orally	Cardioselective β adrenoceptors	Limited or no impact on any features	Ineffective	Bradycardia, hypotension, bradyarrhythmia, sleep disturbances, and masked hypoglycaemia, especially with oral antidiabetics
α2 agonists					
Clonidine[46]	Prevention: 100 μg every 8–12 h, orally; titrate to a maximum of 1200 μg/day Prevention: intravenous infusion; titrate to effect	α2 adrenoceptors in brain and spinal cord	Hypertension and tachycardia	Intermediate	Hypotension, bradycardia, and sedation; intravenous infusions are not a long-term solution
Dexmedetomidine[47,48]	Prevention: intravenous infusion; titrate to effect Prevention and treatment: 0·2–0·7 μg/kg per h	α2 adrenoceptors in brain and spinal cord	Hypertension and tachycardia	Intermediate	Hypotension, bradycardia, and sedation; intravenous infusions are not a long-term solution
Neuromodulators					
Bromocriptine[34,46]	Prevention: 1·25 mg every 12 h, orally; titrate to a maximum of 40 mg/day	Dopamine D_2 receptors	Temperature and sweating	Intermediate	Confusion, agitation, dyskinesia, nausea, and hypotension
Gabapentin[49]	Prevention: 100 mg every 8 h, orally; titrate to a maximum of 4800 mg/day	α2δ presynaptic voltage-gated Ca^{2+} channels in brain and spinal cord	Spasticity and allodynic responses	Consistent	Well tolerated
Baclofen[50–52]	Prevention: 5 mg every 8 h, orally; titrate to a maximum of 80 mg/day Prevention: intrathecal—specialist use only	$GABA_B$ receptors	Spasticity and dystonia	Orally: limited; intrathecal: consistent	Sedation and withdrawal syndrome

(Table 2 continues on next page)

	Prevention or treatment: dose and route*	Site of action	Clinical features targeted	Evidence of efficacy†	Cautionary notes
(Continued from previous page)					
Benzodiazepines					
Diazepam	Treatment: 1–10 mg intravenous bolus	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Lorazepam	Treatment: 1–4 mg intravenous bolus	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Midazolam	Treatment: 1–2 mg intravenous bolus	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Clonazepam	Prevention: 0·5–8·0 mg/day, orally in divided doses	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Sarcolemmal Ca^{2+} release blockers					
Dantrolene[46]	Treatment: 0·5–2 mg/kg intravenous every 6–12 h; titrate to a maximum of 10 mg/kg per day	Ryanodine receptors in cell membranes of striated muscle fibre cells	Posturing and muscular spasms	Intermediate	Hepatotoxicity and respiratory depression

These data are provided as a record of published reports of drugs used to treat patients with PSH, and not as recommendations for treatment. Drug doses and clinical impressions of efficacy are based on past publications of clinical trials, case series, and case reports,[40–55] and are largely covered in four reviews on the subject.[1,46,56,57] Single case reports and other studies that did not add substantive information were excluded, but drug classes and specific agents that have been commonly used to treat patients with PSH are covered in this table. Combinations of drugs are commonly used in clinical practice—eg, combining interventions for both prevention and treatment of paroxysms, and using drugs in different therapeutic classes with different mechanisms. These drugs and drug combinations are based on local custom, rather than objective evidence. PSH=paroxysmal sympathetic hyperactivity. *Drug administration routes are mainly intravenous or oral, which includes administration through a nasogastric or other feeding tube. The dose ranges listed cover the entire ranges that have been reported in the literature. The dosage and route of administration of drugs used should take into account each patient's individual circumstances and good clinical practice. †Evidence of efficacy is described as consistent when many or most of the publications reviewed showed benefits; intermediate when there was an equivocal impression of benefit in the literature; limited when data were scarce and inconclusive but showed some benefit; or ineffective when the literature showed no benefit. These judgments are subjective because a formal meta-analysis was not possible since the data are very heterogeneous and poorly documented. ‡Or other opioids; doses provided are for morphine.

***Table 2*: Classes of drugs used for treatment and prevention of PSH**

A third class of drugs used to treat patients with PSH is non-selective β-blocking drugs. Propranolol is probably the most frequently used β blocker for this indication, and has the advantage of lipophilicity, which facilitates blood–brain barrier penetration and central action. Schroeppel and colleagues[42] showed that treatment of patients with propranolol was independently associated with lower mortality than treatment with other β blockers. β blockers also reduce the metabolic rate, which is often elevated in patients with PSH.[43,44] Cardioselective β blockers, such as metoprolol, are probably less effective than non-selective β blockers; the combination of α-adrenergic and β-adrenergic blockades might be better suited to controlling paroxysms.[45] The ongoing double-blind randomised clinical trial Decreasing Adrenergic or Sympathetic Hyperactivity after Traumatic Brain Injury (DASH after TBI) is comparing combination therapy with propranolol and clonidine versus placebo in patients with severe TBI in the ICU, and results should provide some clarity about the efficacy of these drugs in controlling sympathetic hyperactivity in patients with PSH in the ICU setting.[55]

Other modulators of sympathetic paroxysms include the dopaminergic D_2 agonist bromocriptine, which is variably effective in reducing temperature and sweating in patients with PSH.[34,46] Baclofen—a $GABA_B$ receptor agonist that is active at inhibitory interneurons in the spinal cord—has been used to treat patients with refractory PSH, and in three small prospective observational trials[50–52] and a case series with up to 10 years of follow-up,[59] continuous intrathecal baclofen (in mean doses of 100–500 μg/day) alleviated symptoms of PSH.[50–52] Dantrolene, used to treat malignant hyperthermia, might also be effective in patients with PSH, particularly for posturing, by reducing intracellular calcium concentrations.[46] A small case series from China[53] reported the possible effect of hyperbaric oxygen therapy on paroxysms and posturing in patients with early subacute PSH, after little success with medical management.

Supportive therapy to address the longer-term consequences in patients with PSH is very important. Physiotherapy, paying attention to the positioning of patients to prevent contractures, and management of their temperature are crucial. Additionally, nutritional management deserves special attention because pronounced increases in resting energy expenditure—up to three times baseline measurements—have been reported during paroxysms,[11] and some patients with PSH who are admitted to rehabilitation units show substantial weight losses of up to 25–29% following ICU management.[60] Indirect calorimetry can be used to guide calorie intake in proportion to the increased resting energy expenditure. Development of PSH is associated with an increased relative risk of heterotopic ossification (59·6,

95% CI 8·4–422·4),[10] and this diagnosis should therefore be considered in all patients with PSH who have hot or painful joints to enable appropriate management.

Conclusions and research agenda

PSH is an intriguing clinical syndrome that occurs in patients after severe acquired brain injury of multiple causes, but it is most prevalent after TBI and hypoxic brain injury. Initiatives to define PSH with clinical criteria are the first steps in a longer journey to study the causes, consequences, and potential therapies for this condition. Potential therapeutic drugs might suppress manifestations of PSH, but no prospective randomised clinical trials have been published on the potential benefits, risks, or effects on outcome of such interventions.

The advances in clinical methods for the diagnosis and characterisation of PSH are based on a broad clinical consensus, and involved most of the active investigators in the field. However, linking these clinical features to lesion location and severity, and to clear neuropathology of the syndrome, remains challenging, in large part because of the variable pathophysiology and, hence, treatment responses of the patients. Stratification of patients with the syndrome into mechanistically homogeneous subgroups with common pathophysiology, diagnostic features, therapeutic responses, and outcomes is essential if we are to pursue precision-medicine approaches to patient management. However, accumulating the large cohorts of patients necessary to allow such stratification is challenging. Despite the recently compiled diagnostic criteria, patient descriptions seem to be varied and inconsistent between studies, especially in terms of imaging findings, therapies, and outcomes. The use of common data elements to standardise such descriptions, borrowed from acute TBI research and modified if needed, could be one way of addressing this issue. This approach would also allow us to develop assessment methods and determine timings for defining early-stage and late-stage patient outcomes, thus enabling more rigorous epidemiological assessment of the incidence of PSH and its effects on patient outcomes. Finally, pragmatic but well conducted clinical trials of available therapies are needed, to be done either individually or in sequence (in an escalation pattern), to support or refute the putative benefits reported in case series and small trials. Such studies will necessitate multicentre recruitment, which could make use of existing collaborative research networks that focus on PSH.

For more on **common data elements on TBI** see https://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards

Search strategy and selection criteria

We searched MEDLINE for papers published in English between Jan 1, 1946, and June 21, 2017, using the following terms: ("PSH" OR "diencephalic epilepsy" OR "storm" OR "paroxysmal sympathetic hyperactivity" OR "dysautonomia") AND ("diagnosis" OR "definition" OR "treatment" OR "pathophysiology" OR "outcome") AND ("brain injury" OR "stroke" OR "cardiac arrest" OR "head injury" OR "traumatic brain injury" OR "subarachnoid haemorrhage" OR "intracerebral haemorrhage") NOT ("tumors" OR "neoplasms" OR "Parkinson's" OR "familial"). This search yielded 975 papers, the titles of which were manually searched for relevance to our review topic. The abstracts of the resulting 67 manuscripts were reviewed, in addition to 115 manuscripts that had been identified during a literature search in 2010 by the same authors, with considerable overlap between the two searches. The abstracts of these manuscripts and the manuscripts selected for review of the full text by one or more of the authors were assessed for their relevance for inclusion in this review. No attempt was made to undertake a full systematic and inclusive review.

Contributors

All authors contributed to the literature search, writing plan, preparation of the first draft, and subsequent revisions.

Declaration of interests

DKM reports personal fees for consultancy work or as a member of data monitoring committees for Solvay, GlaxoSmithKline, BrainScope, Ornim Medical, Shire Medical, and Neurovive, and honorarium for a lecture at the London Hospital, UK, reimbursed to organisers by GlaxoSmithKline. GM and IJB declare no competing interests.

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