Moderate and severe traumatic brain injury in adults

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Traumatic brain injury (TBI) is a major health and socioeconomic problem that affects all societies. In recent years, patterns of injury have been changing, with more injuries, particularly contusions, occurring in older patients. Blast injuries have been identified as a novel entity with specific characteristics. Traditional approaches to the classification of clinical severity are the subject of debate owing to the widespread policy of early sedation and ventilation in more severely injured patients, and are being supplemented with structural and functional neuroimaging. Basic science research has greatly advanced our knowledge of the mechanisms involved in secondary damage, creating opportunities for medical intervention and targeted therapies; however, translating this research into patient benefit remains a challenge. Clinical management has become much more structured and evidence based since the publication of guidelines covering many aspects of care. In this Review, we summarise new developments and current knowledge and controversies, focusing on moderate and severe TBI in adults. Suggestions are provided for the way forward, with an emphasis on epidemiological monitoring, trauma organisation, and approaches to management.

Introduction

Traumatic brain injury (TBI) constitutes a major health and socioeconomic problem throughout the world. It is the leading cause of mortality and disability among young individuals in high-income countries, and globally the incidence of TBI is rising sharply, mainly due to increasing motor-vehicle use in low-income and middle-income countries. WHO has projected that, by 2020, traffic accidents will be the third greatest cause of the global burden of disease and injury. In higher income countries, traffic safety laws and preventive measures have reduced the incidence of TBI due to traffic accidents, whereas the incidence of TBI caused by falls is increasing as the population ages, leading to a rise in the median age of TBI populations (table 1). This has consequences for the type of brain damage currently seen, and contusions (falls in older patients) are becoming more frequent than diffuse injuries (high-velocity traffic accidents in younger patients).

Violence is now reported as the cause of closed head injury in approximately 7–10% of cases, a substantial increase from earlier studies. The incidence of penetrating brain injury is also increasing, particularly in the USA, due to the use of firearms in violence-related injuries. Worldwide, armed conflicts and terrorist activities are causing more brain injuries, often due to improvised explosive devices, to the extent that blast injuries of the brain are now recognised as a specific entity. The changing patterns of injury and treatment approaches have challenged current concepts of classification. Moreover, basic research has greatly advanced our knowledge of what happens in the brain after TBI, offering opportunities to limit processes involved in secondary brain damage. However, translating advances from basic research into clinical benefit has proven complex. Here, we discuss current knowledge and novel insights and controversies in the study of adults with moderate and severe TBI, with the aim of integrating basic science and clinical research to provide guidelines on the epidemiological monitoring of TBI, trauma organisation, and management at the acute stage.

Epidemiology and cost

In the USA, monitoring by the Centers for Disease Control and Prevention shows the annual incidence of emergency department visits and hospital admissions for TBI to be 401 per 100 000 and 85 per 100 000, respectively. Epidemiological data on TBI from the European Union are scarce, but do indicate an annual aggregate incidence of hospitalised and fatal TBI of approximately 235 per 100 000, similar to that found in Australia, although substantial variation exists between European countries. Most patients with TBI have milder injuries, but residual deficits in these patients are not infrequent. Approximately 10–15% of patients with TBI have more serious injuries, requiring specialist care.

TBI is more common in young adults, particularly men (75%), which causes high costs to society because of life years lost due to death and disability. In Europe, TBI accounts for the greatest number of total years lived with disability resulting from trauma, and is among the top three causes of injury-related medical-years lost.
costs. In the USA, the financial burden has been estimated at over US$60 billion per year. These numbers stand in stark contrast to the amount of funding for TBI research, which has one of the highest unmet needs within the already severely underfunded field of brain research.

**Classification**

TBI can be isolated, but is associated with extracranial injuries (limb fractures, thoracic or abdominal injuries) in about 35% of cases, which increases the risk of secondary brain damage due to hypoxia, hypotension, pyrexia, and coagulopathy. The recording of the severity of extracranial injuries should therefore form an integral part of TBI classification (panel).

Traditionally, TBI has been classified by mechanism (closed vs penetrating), by clinical severity (Glasgow coma scale [GCS]), and by assessment of structural damage (neuroimaging; panel). The GCS has evolved into a universal classification system for the severity of TBI, and consists of the sum score (range 3–15) of the three components (eye, motor, and verbal scales). For assessment of severity in individual patients, the three components should be reported separately. A standardised approach to assessment is advocated. If painful stimuli are required to elicit a response, nail-bed pressure and supraorbital pressure (to test for painful stimuli) are recommended. Increasingly, in modern practice, classification of TBI by clinical severity is limited. The level of consciousness might be obscured in the acute setting by confounders such as medical sedation, paralysis, or intoxication.

Assessment of structural damage by neuroimaging is not influenced by these confounders. Marshall and colleagues proposed a descriptive system of CT classification, which focuses on the presence or absence of a mass lesion, and differentiates diffuse injuries by signs of increased intracranial pressure (ICP; ie, compression of basal cisterns, midline shift). However, the Marshall classification has limitations, such as the broad differentiation between diffuse injuries and mass lesions, and the lack of specification of the type of mass lesion (eg, epidural vs subdural). Thus, this classification system may mask patients who have diffuse axonal injury (DAI) or signs of raised ICP in addition to a mass lesion, and does not fully use the prognostic information contained in the individual CT characteristics scored.

Furthermore, CT can only capture momentary snapshots of the dynamically evolving process of TBI, and important lesions that occur at the microscopic level, such as DAI and ischaemic damage, cannot be visualised. Therefore, new surrogate markers for these processes are needed. Such markers have revolutionised cardiology (eg, troponin) and AIDS therapy, but have not yet been established for TBI.

An alternative approach is to classify patients by prognostic risk. Although not new, this is an approach under development. Recent, well validated models, developed on large patient samples, have become available to facilitate this approach. Prognostic classification can serve as an objective basis for comparison of different TBI series, form the basis for quality assessment of the delivery of health care, and aid the analysis of clinical trials.

**Types of brain damage**

**Primary damage**

TBI is a heterogeneous disorder with different forms of presentation. The unifying factor is that brain damage results from external forces, as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object (eg, gunshot), or blast waves from an explosion. The nature, intensity, direction, and duration of these forces determine the pattern and extent of damage.

On the macroscopic level, damage includes shearing of white-matter tracts, focal contusions, haematomas
(intracerebral and extracerebral), and diffuse swelling (figure 1). At the cellular level, early neurotrauma events (which can occur minutes to hours after initial injury) include microporation of membranes, leaky ion channels, and stearic conformational changes in proteins. At higher shear rates, blood vessels can be torn, causing (micro)hemorrhages.

DAI is characterised by multiple small lesions in white-matter tracts. Patients with DAI are usually in profound coma as a result of the injury, do not manifest high ICP, and often have a poor outcome. Focal cerebral contusions are the most common traumatic lesion, are more frequent in older patients, and usually arise from contact impact. Traumatic intracranial hematomas occur in 25–35% of patients with severe TBI and in 5–10% of moderate injuries.

In static crush injuries and focal blows, much of the energy is absorbed by the skull; thus, brain damage might remain superficial, often with a depressed skull fracture. Blast injuries have been identified as a novel entity within TBI. The pathological mechanism is much less understood, but the injuries are characterised by severe early brain swelling, subarachnoid hemorrhage, and often prominent vasospasm. Outcome of severe blast injuries, even with aggressive management, is still unknown, but has been encouraging after debridement of wounds and aggressive control of ICP, including decompressive surgery.

Ischaemic brain damage is often superimposed on the primary damage (figure 1), and can be widespread or, more commonly, perilesional. Impaired cerebral perfusion and oxygenation, excitotoxic injury, and focal microvascular occlusion can be contributing factors. Secondary damage

Each type of head injury might initiate different pathophysiological mechanisms, with variable extent and duration (figure 1). These mechanisms (acting concurrently and often with synergising effects) and the intensity of systemic insults determine the extent of secondary brain damage. Secondary processes develop over hours and days, and include neurotransmitter release, free-radical generation, calcium-mediated damage, gene activation, mitochondrial dysfunction, and inflammatory responses.

Glutamate and other excitatory neurotransmitters exacerbate ion-channel leakage, worsen astrocytic swelling, and contribute to brain swelling and raised ICP. Neurotransmitter release continues for many days after TBI in human beings, paralleling the course of high ICP, and, with free-radical and calcium-mediated damage, is a major cause of early necrotic cell death. Early gene activation and release of proapoptotic molecules (eg, caspases) induce apoptotic neuronal loss. A third potential cause of cell death, autophagy, might also play an important part.

Inflammatory response is an important component of TBI, particularly around contusions and (micro)hemorrhages. The maximum response occurs within a few days, but cytokines are released from microglia, astrocytes, and polymorphonuclear cells within hours after TBI, leading to opening of the blood–brain barrier, complement-mediated activation of cell death, and the triggering of apoptosis. Although the inflammatory response can be deleterious in excess, it is necessary in order to clean up cellular debris after injury, and inflammatory signals might also trigger...
regeneration. Hence, inflammation in TBI can be thought of as both helpful and harmful.38

Recent research has raised new insights that challenge existing concepts of pathophysiology. Mitochondrial dysfunction can cause energy failure after TBI, with a decrease in production of ATP and consumption of oxygen by 40–50%. This can trigger opening of the mitochondrial transition pore, setting off an autodestruct phenomenon that induces both apoptosis and necrosis.39 Mitochondrial dysfunction might also lead to axonal disruption. The classical concept that DAI is due to mechanical rupture of axons, incompatible with regeneration or repair, has now been abandoned. Neurons can at least partially regenerate their axonal anatomy. This accords with clinical observations that patients with the hallmark features on CT of DAI can recover with modern neurocritical care. Furthermore, laboratory studies have shown that DAI can take up to 48 hours to become fully established and is thus amenable to therapeutic interventions.40

Whether decreased cerebral blood flow (CBF) after trauma is indicative of ischaemia or is secondary to metabolic depression remains the subject of debate. PET studies have attempted to clarify the effects of hyperventilation, which lowers ICP by reducing CBF. Some investigators have found that oxygen metabolism is preserved,31 whereas others are more concerned that ischaemia could be induced.32 A combined PET and microdialysis study showed an increase in the oxygen extraction fraction in only 1% of cases, whereas lactate increases were seen in 25% of cases.33 These observations are not consistent with the classical concept of ischaemia, and indicate that other mechanisms contribute to derangements of flow and metabolism. Energy failure due to mitochondrial dysfunction and diffusion barriers to oxygen delivery resulting from cytotoxic oedema are likely to be involved. The role of vasospasm is unclear. Although transcranial doppler studies report flow velocity values suggestive of vasospasm in up to 35% of patients,4 they the correlation with CBF is relatively poor.41

Diagnosis

Head injury does not always implicate TBI. A diagnosis of TBI is established on the basis of clinical symptoms: for example, the presence of any documented loss of consciousness and/or amnesia (retrograde or post-traumatic). Additional clinical investigations can be driven by the patient’s level of awareness, presence of risk factors, and mechanisms of injury (figure 2).

CT is the preferred method of assessment on admission to determine structural damage and to detect (developing) intracranial haematomas. Traumatic intracranial lesions occur frequently in severe and moderate injuries, but are also reported in 14% of patients with a GCS of 14.46 The risk of intracranial lesions in patients with a GCS of 15 is generally low, unless risk factors are present. Therefore, current guidelines advocate CT examinations in all TBI patients with a GCS of 14 or lower and in patients with a GCS of 15 in the presence of risk factors.47–49 Some studies have successfully identified risk factors for intracranial lesions, such as vomiting, age, duration of amnesia, injury mechanism, neurological deficit, and anticoagulant therapy.50,51 In the past, much attention was focused on conventional radiographs of the skull to triage indications for CT, but these are no longer thought to be required. Fractures of the skull can be
seen adequately on CT in the bone-window setting, and three-dimensional reconstructions with volume rendering techniques provide a far superior insight into complex fractures.

MRI studies are seldom done in the acute phase of TBI because they are logistically complex and more time consuming, and do not necessarily provide any further information for clinical decisions. However, MRI can be more informative if a penetrating injury with a wooden object is suspected. In the subacute and chronic phases of TBI, MRI is more informative than CT, offering better detection of white-matter lesions in patients with DAI. Neuroimaging techniques are rapidly progressing from purely structural assessments to more functional imaging, offering a potentially better understanding of TBI.

Because TBI is a dynamic process and pathology evolves, follow-up CT is advisable if lesions were present on the initial CT or if indicated by clinical deterioration. New lesions develop in approximately 16% of patients with diffuse injuries, and 25–45% of cerebral contusions will enlarge significantly. Higher occurrences are reported if the initial CT scan is done within 2 hours of injury. Many clinics will usually follow up the patient on the day after admission, but recent studies indicate that CT progression will generally occur within 6–9 hours after injury. Follow-up CT is always indicated if larger lesions are present or if there is clinical deterioration or increasing ICP. Indiscriminate and too frequent use of CT follow-up are thought to be inappropriate. There is growing concern about the cancer risk connected to CT radiation exposure, which is held responsible for 2% of all cancer cases in the USA, where more than 62 million CT scans, including 4 million in children, are done each year. The need for CT follow-up should thus be balanced against awareness of the cancer risk.

Specific injury mechanisms might cause vascular lesions. Arterial dissections (extracranial and intracranial) have been recognised in up to 17% of patients with cervical spine injuries, and in those with skull-base fractures involving the carotid canal. Traumatic aneurysms are seen in about 15% of patients with penetrating TBI. Consequently, in penetrating brain injury, CT angiography is indicated in the presence of an intracranial haematoma, or when a missile tract, for example, crosses a major vessel trajectory.

**Guidelines and individualised management**

Over the past 10 years, much of the treatment of TBI has evolved towards standardised approaches that follow international and national guidelines (table 2). International guidelines for severe head injury are mostly evidence based, and address specific aspects of management. National guidelines focus more on organisational issues, such as admission and referral policy; however, these remain limited to the constraints of existing trauma systems, and clear statements on the best trauma organisation are often avoided.

Patel and colleagues unequivocally showed a 2-15 times increase in the odds of death (adjusted for case

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<th>Year of publication</th>
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<td>Vos and co-workers</td>
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<td>Newcombe and Merry</td>
<td>1999 Management of acute neurotrauma in rural and remote locations of Australia</td>
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<td>UK National Institute for Health and Clinical Excellence</td>
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"http://www.braintrauma.org/" "http://www.efns.org/" In the NICE guidelines (http://www.nice.org/), the grading scheme for level of recommendations was adapted from the Oxford Centre for Evidence Based Medicine levels of evidence as level A-D; for consistency, we considered grade A as class I, grade B as class II, and grades C and D as class III.
mix) for patients with severe head injury treated in non-neurosurgical centres versus neurosurgical centres. Their report makes a strong case for transferring and treating all patients with severe head injury in a setting with 24-hour neurosurgical facilities. Most neurosurgical centres in the UK are not equipped to receive all patients with TBI because of shortages in human and technical resources, and patients with TBI are referred only for selected surgical indications. In light of these data, we suggest that all treatable patients with TBI should be centralised in large neurotrauma centres that offer surgical therapy and access to specialised neurocritical care. However, this cannot be achieved without profound re-design of national health systems and reallocation of resources. A similar case has been made in the USA: for example, in the state of Florida, which has 20 million inhabitants, five neurotrauma centres have been designated to receive patients with severe TBI and spinal-cord injuries. The concept here is that greater volume (and hence experience) will lead to higher quality services and better outcome.

The evidence-based guidelines show that the strength of supporting data is relatively weak, underscoring the need for more rigorous evidence (table 2). However, for various aspects of care in TBI, such as surgery for epidural haematomas in patients with deteriorating consciousness, randomised controlled trials are unlikely to be considered ethical. Notwithstanding the great benefits of evidence-based approaches, guidelines and practice recommendations should not be made on the basis of the conclusions of literature reviews alone. Furthermore, we should recognise that no single treatment can be uniformly appropriate across the wide range of conditions within TBI, and this vision would support the search for more individualised treatment approaches (ie, determined by monitoring, biomarkers, and possibly genotype).

**Approaches to management**

**Pre-hospital emergency care**

The main goals of prehospital management are to prevent hypoxia and hypotension, because these systemic insults lead to secondary brain damage. When assessed before hospital admission (by ambulance or helicopter crews), oxygen saturation below 90% is found in 44–55% of cases and hypotension in 20–30%. Trauma renders the brain more vulnerable to these insults, and hypoxia and hypotension are strongly associated with poor outcome (hypoxia: odds ratio [OR] 2.1, 95% CI 1.7–2.6; hypotension: OR 2.7, 95% CI 2.1–3.4).

In various settings, the introduction of a pre-hospital system capable of normalising oxygenation and blood pressure has been associated with improved outcome. However, ensuring adequate training of paramedics is vital because intubation by poorly trained paramedics has been associated with worse outcome.

Arterial hypotension is best prevented by early and adequate fluid resuscitation with normotonic crystalloids and colloids. No benefits have yet been shown for hypertonic solutions, or for albumin, which has been associated with worse outcome.

**Admission care**

The primary aims of admission care are stabilisation and diagnostic assessment with prioritisation according to US Advanced Trauma Life Support standards. From a neurosurgical perspective, the immediate priority is rapid detection and treatment of operable lesions. Indications for emergency surgery in closed severe TBI are summarised in the evidence-based surgical guidelines. CT criteria, including volume, thickness, and signs of mass effect (midline shift), are as relevant as signs of neurological deterioration. A shift of emphasis is continuing from the conventional approach of surgery after neurological deterioration to a more pre-emptive approach in which the aim of surgery is to prevent deterioration. In penetrating TBI, a superficial debridement and dural closure is recommended as general standard of care, but in patients with small entry wounds, simple wound closure may be considered. This approach is much more conservative than earlier policies of extensive debridement and repeated surgery for removal of bone fragments with the aim of preventing infection. There is no evidence to support such aggressive approaches, and routine antibiotic treatment is usually effective for infection prevention.

**Intensive care management**

A major focus for neurointensive care is to prevent and limit ongoing brain damage and to provide the best conditions for natural brain recovery by reducing brain swelling and raised ICP. Optimum oxygenation, perfusion, nutrition, glycaemic control, and temperature homoeostasis are indicated, as in general intensive care. However, the concern that the injured brain cannot tolerate hypoglycaemia, which might result as an adverse event from over-enthusiastic glycaemic control, is specific to neurointensive care. Furthermore, the brain must be protected from overt or silent seizures. The benefits of prophylactic antiseizure activity should be balanced against the potential risks. Opinions vary greatly about routine antiseizure prophylaxis, but recommended indications include penetrating brain injury and the presence of a depressed skull fracture in patients with post-traumatic amnesia for more than 24 hours in whom a dural lesion is suspected.

Sedation and artificial ventilation are used to reduce brain swelling and raised ICP in patients with severe head injuries. In the 1990s, hyperventilation was commonly used, which, although effective in reducing ICP, has the risk of enhancing ischaemia. Arterial
carbon dioxide lower than 30 mm Hg should be avoided, unless facilities exist for more advanced monitoring; osmotherapy is currently preferred as the first agent in the medical management of raised ICP, and interest in early and extensive decompressive craniotomies is increasing.

Osmotherapy
Rapid infusion of mannitol, which creates an osmolar gradient, mobilises water across an intact blood–brain barrier,92 but also improves focal CBF.91 Hypertonic saline infusion creates an analogous, sometimes stronger, osmolar gradient with corresponding improvement in ICP.94–96 When used for medical management of raised ICP, hyperosmolar agents should be administered repeatedly (at least every 4–6 hours) or even continuously, because a rebound phenomenon might otherwise occur after reversal of the osmotic gradients by passing into the extracellular space of the brain. Few studies have compared mannitol with hypertonic saline.44,57 In one study in which short-term administration of equimolar amounts of mannitol and hypertonic saline were compared, hypertonic saline was associated with a larger and more lasting ICP reduction.98

However, use of osmotherapy, particularly for long periods, is associated with electrolyte abnormalities, especially hypernatraemia, cardiac failure, bleeding diathesis, and phlebitis. No benefits of small-volume resuscitation with hypertonic saline have been shown in patients with TBI.46 Consequently, in adults, there is insufficient evidence to support the use of hypertonic saline over mannitol for osmotherapy. We caution against the use of hypertonic saline because of the risks of severe hypernatraemia, and advise particular caution with the combined use of mannitol and hypertonic saline. Careful control of fluid balance, electrolyte status, and serum osmolarity (<320 mMol/L) is mandatory in the use of hypertonic agents.

Decompressive craniectomy
Decompressive craniectomy has been used for more than a century to treat brain swelling and reduce ICP, and a resurgence of interest has recently been seen in this practice, with 240 papers published between 1996 and 2006.11 Despite this renewed enthusiasm, the technique remains controversial. It does not produce improved outcome in all series,101 and has many side-effects, some severe.102 The evidence is also confounded by ambiguous definitions and a lack of focus. A clear distinction should be made between true decompressive craniectomy versus simple removal of a small bone flap, and between procedures done in combination with the evacuation of a mass lesion versus an isolated decompressive craniectomy in diffuse injuries. However, there is consensus that the craniectomy should be large enough (approximately 15 cm×15 cm) and should be done early and with duraplasty.102 Two trials are currently ongoing: the RESCUEicp (Randomised Evaluation of Surgery in Cranietomy for Uncontrollable Elevation of Intracranial Pressure) Study in Europe and the DECRA (Decompressive Cranietomy) Study in Australia.103

Monitoring of the severely injured brain
Many patients develop progressive damage without clear clinical signs; in others, damage develops at an alarming pace, exemplified by the so-called “talk and die” syndrome.104,105 Neuroworsening, defined as a deterioration of the GCS motor score, development of pupillary abnormalities, or development of progressive CT lesions, has been reported in 29–44% of patients.106–108 Clinical monitoring (level of consciousness and pupillary reactivity) remains essential. However, more severely injured patients are universally treated with sedation and artificial ventilation, and advanced monitoring of cerebral variables is required. Besides standard systemic monitoring, ICP and cerebral perfusion pressure monitoring are important. The effectiveness of ICP monitoring in TBI has been questioned,109,110 no monitoring technique can improve outcome unless it can drive an appropriate intervention. Intracranial hypertension develops in up to 77% of cases, and raised ICP is related to poorer outcome.58 ICP monitoring carries a 0.5% risk of haemorrhage and a 2% risk of infection. Intraventricular catheters are preferable, because they are accurate, can be recalibrated, and allow drainage of CSF. Intraparenchymal probes are user friendly and accurate.44 Less accurate data are provided by subdural catheters,64,111 and epidural and intraparenchymal probes are unreliable.112,113 The accuracy of ICP monitoring can be enhanced by use of computer-supported systems.114 Attempts to monitor ICP non-invasively have been unsatisfactory.115,116

More advanced techniques include the monitoring of cerebral oxygenation, CBF measurements, microdialysis, and electrophysiological monitoring. Cerebral oxygenation can be measured focally (brain tissue oxygen tension) or, more globally, by measuring the oxygen content in the cerebral venous outflow. Brain tissue oxygen tension indicates the balance between oxygen delivered to the tissue and its consumption in a specific area, and can indicate regional hypoxia if it falls below 15–20 mm Hg.117,118 The diameter of microvascular vessels and diffusion barriers might also influence recorded values.119,120 Venous oxygen saturation is a more global approach to monitoring oxygenation. Values below 55% indicate an increased oxygen extraction relative to perfusion, and suggest the presence of ischaemia.121,122 Non-randomised studies have indicated benefit of an oxygen-directed therapy protocol.123 Measurements of CBF have shown widespread zones of brain ischaemia in a third of patients with severe
TBI, especially if done within 8 hours of TBI. Microsensor technology has recently been devised to allow continuous blood flow monitoring within the brain by use of thermal diffusion and laser doppler probes.

Clinical microdialysis allows metabolic exploration of the cerebral cortex in vivo. Within the first few hours, most patients with severe TBI have a high lactate:pyruvate ratio, indicating ischaemia or hyperglycolysis. More recently, microdialysis has been used to measure brain penetration of drugs. Microdialysis, oxygen tension catheters, and CBF probes can be used to assess events in a small region, but possibly fail to detect harmful events in other parts of the brain. Conversely, more global approaches (venous oxygen saturation) fail to detect regional abnormalities.

Continuous electroencephalographic monitoring can be used to identify occult seizure activity, which can occur in 15–18% of patients with moderate and severe TBI. In the research setting exists in monitoring cortical spreading depression. Traumatically damaged neurons decrease their firing rates substantially in the early post-injury period. Waves of depolarisation result in ionic flux and loss of resting membrane potential, which worsens neurochemical dysregulation, and places extra metabolic demands on damaged tissue.

Outcome and prognosis
Outcome after head injury is generally assessed at 6 months after injury, representing a compromise between true final outcome and logistic limitations. Experience shows that about 85% of recovery occurs within this time period, but further recovery can occur later. Accurate and consistent outcome determination at a fixed timepoint is a prerequisite for any TBI study. The most frequently used global outcome measure in TBI is the Glasgow outcome scale. More specific tools are required for detailed examination, such as for functional and neuropsychological assessment. These are particularly relevant in the rehabilitation setting. Early and intensive rehabilitation is recommended to achieve the best possible functional outcome and social re-integration. However, the optimum timing and approach to rehabilitation of patients with TBI remains to be determined.

In severe closed head injury, the outcome distribution represents a U-shaped curve, with most patients either dying or recovering to an independent lifestyle. This has promoted dichotomisation of outcomes into unfavourable (death, vegetative state, or severe disability) versus favourable outcome (moderate disability or good recovery). Recent studies using the more detailed 8-point Glasgow outcome scale (extended version), and a structured interview for its assessment, did not find the typical U-shaped outcome distribution. In non-military penetrating head injury, mortality is consistently over 95% in patients with a GCS of 3–5, raising ethical questions of whether active treatment should be initiated, particularly if the cause of injury was a suicide attempt.

The widespread belief that all patients in a vegetative state are awake but not aware has been challenged. Incidental reports on functional MRI studies show that external stimuli can be processed in the human cortex of some vegetative patients, and that even spoken commands might elicit appropriate cortical responses that are indistinguishable from normal human responses. The implications are that caretakers should be aware that the patient might hear, see, and realise a lot more than is commonly thought, and the concept that a vegetative state might be a worse outcome than death has become uncertain.

Few TBI studies have used health-related quality of life measures. Comprehensive disease-specific instruments for such assessment in people after TBI are needed, such as the new disease-specific scale, quality of life in brain injury (QOLIBRI).

Many studies have reported on the univariate association between predictors and outcome after TBI, but few have used multivariate analyses, which adjust for associations between predictors. Extensive work by the IMPACT study group, which analysed individual patient data from over 9000 patients with severe or moderate TBI merged from 11 studies, confirmed age, GCS motor score, pupillary response, and CT class as independent predictors of outcome.

### Table 3: Predictors of outcome in TBI

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<td>None</td>
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<td>5.30 (3.49-8.04)</td>
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<td>Extensor</td>
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<td>Abnormal flexion</td>
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<tr>
<td>One reactive</td>
<td></td>
<td>2.71 (2.36-3.12)</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5661</td>
<td>2.08 (1.69-2.56)</td>
<td>1.65 (1.37-2.00)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6629</td>
<td>2.67 (2.09-3.41)</td>
<td>2.06 (1.64-2.69)</td>
</tr>
<tr>
<td>CT classification</td>
<td>5209</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td></td>
<td>0.45 (0.31-0.67)</td>
<td>0.47 (0.32-0.70)</td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td>2.50 (2.09-3.00)</td>
<td>2.20 (1.54-2.63)</td>
</tr>
<tr>
<td>Class IV</td>
<td></td>
<td>3.03 (2.12-4.25)</td>
<td>2.22 (1.44-3.42)</td>
</tr>
<tr>
<td>Class V/VI</td>
<td></td>
<td>1.18 (0.93-1.61)</td>
<td>1.48 (1.27-1.71)</td>
</tr>
<tr>
<td>Traumatic subarachnoid haemorrhage</td>
<td>7407</td>
<td>2.64 (2.42-2.89)</td>
<td>2.01 (1.83-2.21)</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>4831</td>
<td>1.68 (1.54-1.83)</td>
<td>1.45 (1.36-1.55)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>3872</td>
<td>0.69 (0.60-0.78)</td>
<td>0.76 (0.66-0.88)</td>
</tr>
</tbody>
</table>

Data from Murray et al. 

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characteristics as the most powerful independent prognostic variables (table 3).\textsuperscript{138}Other important prognostic factors include hypotension, hypoxia, eye and verbal components of the GCS, and laboratory variables (glucose, platelets, and haemoglobin). Other studies have shown an association between coagulopathy and poorer outcome,\textsuperscript{139,140} indicating that more careful attention to correcting these disturbances might be appropriate.

For clinical application and research, the predictive value of variables can be combined into prognostic models. Many previously developed models had shortcomings in development (in particular, a lack of external validation),\textsuperscript{139,140} but more recently published models have greater validity and generalisability.\textsuperscript{21,26} These models can provide a scientific basis for informing relatives about the likely long-term outcome, facilitate prognostic classification and valid comparisons of outcome between different patient series, and enable the setting of baselines for clinical audits. Furthermore, prognostic models will have an important role in randomised controlled trials for stratification and statistical analyses that explicitly consider prognostic information, such as covariate adjustment.\textsuperscript{141}

### Neuroprotection and clinical trials

The original concept of neuroprotection involved the initiation of treatment before the onset of the event, and was aimed at minimising the intensity of an insult or its immediate effects on the brain by interrupting the harmful cascades of biochemical events. A major new focus of neurobiology now revolves around cell replacement, aimed at promoting neuroplasticity, and regeneration or replacement of lost neuronal and glial cells and neuronal circuits. Over the past 25 years, over 20 agents have been studied in phase III clinical trials of severe TBI (table 4). Other strategies have focused on the use of hypothermia and evaluation of a CBF-targeted approach versus an ICP-directed approach.\textsuperscript{152}

None of the phase III trials have convincingly shown efficacy in the overall study population (table 4).\textsuperscript{153,154} Various factors have contributed to these failures, including uncertainty about validity and robustness of preclinical phase II data, problems in translating results from experimental studies to clinical practice, uncertainty about whether and when the pathophysiological mechanisms targeted are indeed active in individual patients, uncertainty about the therapeutic window, and inadequacies in clinical trial design and analysis. Multidisciplinary efforts are currently ongoing to implement approaches in trial design for dealing with challenges posed by the heterogeneity of TBI populations.\textsuperscript{138} Clinical trials in TBI also pose specific ethical dilemmas that are not always appreciated by policy-making authorities,\textsuperscript{156} and current legislation is often perceived as obstructive bureaucracy.

Patients with TBI are often acutely incapacitated by their injury and cannot always provide informed consent. Proxy consent is generally substituted, but does not serve to protect the patient’s autonomy, might induce selection bias,\textsuperscript{157} and causes substantial delays without offering any real protection to the incapacitated patient, often only providing some legal protection to the incapacitated patient, legislation is often perceived as obstructive bureaucracy.

Future directions

Here, we have illustrated the seriousness and complexity of the problems posed by TBI to patients, relatives, doctors, authorities, and society alike. Great

<table>
<thead>
<tr>
<th>n</th>
<th>Year of study</th>
<th>Start of treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bradykinin inhibition</strong></td>
<td>159</td>
<td>1996</td>
<td>≤12 h</td>
</tr>
<tr>
<td><strong>Calcium-mediated damage</strong></td>
<td>160</td>
<td>1989-1991</td>
<td>12 h of not obeying commands within 24 h of injury</td>
</tr>
<tr>
<td><strong>HIT III nimodipine</strong></td>
<td>161</td>
<td>1994</td>
<td>≤12 h</td>
</tr>
<tr>
<td><strong>Parke Davis/SNX-111</strong></td>
<td>162</td>
<td>1997-1998</td>
<td>≤12 h</td>
</tr>
<tr>
<td><strong>Glutamate excitoxicity</strong></td>
<td>163</td>
<td>1993-1995</td>
<td>≤12 h</td>
</tr>
<tr>
<td><strong>Selfotel</strong></td>
<td>164</td>
<td>1994-1996</td>
<td>≤8 h and within 4 h of admission</td>
</tr>
<tr>
<td><strong>Cerestat/aptiganel</strong></td>
<td>165</td>
<td>1996-1997</td>
<td>≤8 h</td>
</tr>
<tr>
<td><strong>Saphir/D-CPP-ene</strong></td>
<td>166</td>
<td>1995-1997</td>
<td>≤12 h</td>
</tr>
<tr>
<td><strong>Pfizer/CP-101606</strong></td>
<td>167</td>
<td>1997-2000</td>
<td>≤8 h</td>
</tr>
<tr>
<td><strong>Lipid peroxidation/free-radical damage</strong></td>
<td>168</td>
<td>1993-1995</td>
<td>≤8 h</td>
</tr>
<tr>
<td><strong>PEGSD</strong></td>
<td>169</td>
<td>1991-1994</td>
<td>≤4 h</td>
</tr>
<tr>
<td><strong>Tirilazad international trial</strong></td>
<td>170</td>
<td>1992-1994</td>
<td>≤4 h</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>171</td>
<td>1985-1990</td>
<td>≤4 h</td>
</tr>
<tr>
<td><strong>Ultra high-dose dexamethasone</strong></td>
<td>172</td>
<td>1986-1989</td>
<td>&lt;3 h</td>
</tr>
<tr>
<td><strong>CRASH steroid trial</strong></td>
<td>173</td>
<td>2000-2004</td>
<td>≤8 h</td>
</tr>
<tr>
<td><strong>Multiple actions</strong></td>
<td>174</td>
<td>2000-2004</td>
<td>≤6 h</td>
</tr>
<tr>
<td><strong>Magnesium sulphate</strong></td>
<td>175</td>
<td>1998-2004</td>
<td>&lt;8 h</td>
</tr>
</tbody>
</table>

Table 4: Overview of phase III randomised clinical trials in TBI
advancements have been achieved over the past 10–15 years, but advances in basic science have not yet led to new treatments of clinically proven benefit, and advanced monitoring has not routinely resulted in individualised management. Current classification systems are no longer sufficient and not all patients have access to the best care. Clinical trials in TBI have had methodological problems posed by the inherent heterogeneity of the TBI population, and we note a disconnection between ethical directives and their validity and applicability in the emergency situation of acutely incapacitated patients with TBI. Therefore, a great deal is still to be accomplished. From the perspective of clinicians, we would suggest that the following topics are prioritised.

First, standardised epidemiological monitoring should be implemented to offer a sound basis for appropriate targeting of prevention. Second, a specific focus should be directed towards trauma organisation with concentration of care for more severely injured patients in specialised centres. The specifics of the best structure might vary with the local setting, but we strongly feel that there is now sufficient evidence to prove the benefits of centralisation. This centralisation should form a continuum from emergency systems through to rehabilitation care. Third, we suggest that further dissemination of existing guidelines should form the basis for standards of care, but recommend an additional strong focus on more individualised treatment, targeting the specific needs of a given patient. This approach will require advanced diagnostics and monitoring, thus allowing identification of pathophysiological alterations. These diagnostic procedures could include the use of biomarkers and genotyping. As in the acute phase, specialised facilities and concentration of care are necessary in the post-acute setting, offering appropriate rehabilitation programmes, and exploring strategies for promoting recovery and regeneration.

These goals cannot be achieved without more basic and clinical research. Multiple mechanisms of TBI have been identified in the experimental setting, but much more needs to be elucidated. From a research perspective, attention might focus on the cerebrovascular interface and mechanisms of energy failure after TBI. Notwithstanding the importance of basic science, clinically oriented research with therapeutic trials is needed, perhaps based more on an integral concept or combined approaches, rather than focusing on the possible benefit of agents that target a single pathophysiological mechanism among the many other processes. The methods used in TBI clinical trials require refinements, including the implementation of approaches to deal with the inherent heterogeneity of TBI populations. Whatever route is taken or priorities chosen, advancing the field further will require great multidisciplinary efforts from researchers and clinicians, facilitated by appropriate funding.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed, by use of the search terms “traumatic brain injury” or “head injury” and other appropriate targets, such as “epidemiology”, “pathophysiology”, and “guidelines”, up to May, 2008. Papers were also identified from the authors’ own files and from references cited in relevant articles. An electronic search of resources, such as international and national guidelines and book chapters, was also done. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Contributors
All authors contributed equally to the preparation of this Review.

Conflicts of interest
The authors are members of the European and American Brain Injury Consortia. AIRM has been a consultant and a member of steering committees for clinical trials in TBI for Pharmos, Solvay, Vasopharm, and Novo Nordisk. NS has been a member of steering committees or safety boards for clinical trials in TBI for Pharmos, Solvay, Vasopharm, and Xytis.

Acknowledgments
We dedicate this Review to the memory of Bryan Jennett (1926–2008), who inspired us to devote a large part of our lives and work to TBI. He was one of the founding leaders of neurotrauma research and a great inspiration to all around him. Many of the concepts and insights developed by him in the 1970s are still in use today. We thank our co-workers and partners in research, both within their own institutes and within the American and European Brain Injury Consortia. We are grateful to Beverly Walters for help in editing the manuscript, to Paul Parizel for advice on neuroradiological items, and to Anne-Claire van Harderwijk for administrative support. AIRM is a recipient of a NIH grant (NS-042691) supporting methodological and clinical research in TBI, and RMB is funded by the US Department of Defense.

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