

## Trauma Surgery 1

# Early management of severe traumatic brain injury

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This is the first in a *Series* of three papers about trauma surgery

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For more on the *Glasgow Outcome Scale* see <http://tbims.org/combi/gos/>

See *Online* for appendix

For *The Global Evidence Mapping Initiative* see <http://www.ntri.org.au/knowledge-hub>

For *ERABI* see <http://www.abiebr.com/>

for the *International Clinical Trials Registry Platform* see <http://www.who.int/ictrp/en/>

Severe traumatic brain injury remains a major health-care problem worldwide. Although major progress has been made in understanding of the pathophysiology of this injury, this has not yet led to substantial improvements in outcome. In this report, we address present knowledge and its limitations, research innovations, and clinical implications. Improved outcomes for patients with severe traumatic brain injury could result from progress in pharmacological and other treatments, neural repair and regeneration, optimisation of surgical indications and techniques, and combination and individually targeted treatments. Expanded classification of traumatic brain injury and innovations in research design will underpin these advances. We are optimistic that further gains in outcome for patients with severe traumatic brain injury will be achieved in the next decade.

### Introduction

Traumatic brain injury is a major global health problem. Country-based estimates of incidence range from 108 to 332 new cases admitted to hospital per 100 000 population per year.<sup>1</sup> On average, 39% of patients with severe traumatic brain injury die from their injury, and 60% have an unfavourable outcome on the Glasgow Outcome Scale (appendix p 2). The incidence of traumatic brain injury is rising in low-income and middle-income countries because of increased transport-related injuries,<sup>2</sup> and young men (who are over-represented in transport, work, and recreational injuries) are particularly affected. In most countries, ageing populations have given rise to a new cohort—elderly people—who sustain substantial traumatic brain injuries from fairly low-impact falls.<sup>1</sup> Furthermore, blast injury to the brain, which has

distinctive pathological changes, treatment, and prognosis, is common in civilians and military personnel who are exposed to improvised explosive devices and suicide terrorist attacks.<sup>3</sup>

Survivors of severe traumatic brain injury have a low life expectancy, dying 3·2 times faster than the general population.<sup>4</sup> Furthermore, survivors face prolonged care and rehabilitation, and have consequent long-term physical, cognitive, and psychological disorders that affect their independence, relationships, and employment. In 2007, a conservative estimate of lifetime costs per case of severe traumatic brain injury was US\$396 331, with costs for disability and lost productivity (\$330 827) outweighing those for medical care and rehabilitation (\$65 504).<sup>5</sup>

### Key messages

- Incidence of traumatic brain injury is increasing worldwide and overall mortality rates have only slightly improved since 1990. The weighted average mortality for severe traumatic brain injury is 39%, and for unfavourable outcome on the Glasgow Outcome Scale is 60%.
- The randomised trial of early decompressive craniectomy for diffuse brain injury noted worse outcomes after surgery than with medical treatment. Further trials are needed. Steroids are not indicated after traumatic brain injury, except in cases of anterior pituitary insufficiency. Induced hypothermia and hyperoxia need further assessment in clinical trials.
- Promising drug candidates are erythropoietin, statins, ciclosporin-A, tranexamic acid, and progesterone.
- Multimodal monitoring, including cerebral oximetry and microdialysis, needs further assessment to determine if it leads to improved outcomes.
- The IMPACT and MRC-CRASH online prediction models are valuable for clinical practice and research. Promising new biomarkers are glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1.

### Search strategy and selection criteria

We searched Medline, evidence-based medicine reviews, Cochrane Central Register of Controlled Trials, CENTRAL, and Embase from Jan 1, 2006, to Nov 28, 2011, using the core terms “brain injuries”, “craniocerebral trauma” and “traumatic brain injury” and keywords for the following topics: monitoring, decompressive craniectomy, haematoma evacuation, steroids, antifibrinolytics, therapeutic hypothermia, hyperoxia, stem cells, outcomes, predictors of outcome, and novel predictors of outcome. All searches were limited to English language studies in human beings. The appendix (pp 8–12) shows the full search strategies used in Medline. Reference lists of relevant publications and reviews were scanned to identify further relevant citations. 7293 citations were screened, 462 reviewed in full text, and 273 were relevant. We further identified trials with two neurotrauma evidence databases: The Global Evidence Mapping Initiative and Evidence-Based Review of Acquired Brain Injury (ERABI). To identify continuing trials, we did a separate search of the International Clinical Trials Registry Platform on Jan 31, 2012, for decompressive craniectomy, haematoma evacuation, aminosteroids, tranexamic acid, therapeutic hypothermia, hyperoxia, and stem cells.

Mortality and functional outcomes, and resulting long-term dependence and disability, are determined by the initial injury and subsequent treatment. However, an audit<sup>6</sup> of 774 patients treated at an urban, level 1 trauma centre between 2006 and 2008 showed only 17% compliance with Brain Trauma Foundation guidelines for craniotomy, intracranial pressure monitoring, and reversal of coagulopathy. Adherence to clinical practice guidelines for traumatic brain injury, such as those of the Brain Trauma Foundation, are likely to reduce mortality, optimise clinical outcomes, and create substantial economic savings by reducing costs of medical care, rehabilitation, and lost productivity.<sup>5</sup> Survival after severe traumatic brain injury was three times higher in a regionalised trauma system in which patients with serious head injury were transferred to neurosurgical centres, than in a less organised system in which fewer patients were treated in specialist centres.<sup>7</sup>

In this report, which is aimed especially at surgeons and other clinicians who care for patients with acute traumatic brain injury, we summarise advances in the understanding of severe traumatic brain injury and recovery, and give an update of clinical interventions in the crucial early stages of care.

## Classification

Although modern approaches to disease classification use anatomical, physiological, metabolic, immunological, and genetic attributes, traumatic brain injury remains largely classified on the basis of clinical signs. With the Glasgow Coma Scale, patients are divided into crude categories of mild, moderate, and severe injury. These categories not only fail to identify the heterogeneity and complexity of severe injuries, but also minimise the real burden of mild traumatic brain injury. This issue was addressed in 2007, at a consensus workshop on classification of traumatic brain injury for targeted treatments,<sup>8</sup> in which participants concluded that a new classification system was needed. This effort would be facilitated by a prospective, multicentre database with uniform collection criteria based on common data elements for traumatic brain injury. With the support of 49 institutes and agencies and global participation, the first generation of these data elements was developed,<sup>9</sup> with their feasibility and use being validated in the multicentre prospective Transforming Research And Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study.<sup>10</sup> This high-quality, standardised dataset is a store of modern knowledge that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers of traumatic brain injury to drive the development of a new classification system. As shown in other diseases, precise classification of traumatic brain injury could revolutionise diagnosis, guide patient-specific treatment, and improve outcome.

## Pathophysiology

Traumatic brain injury has a dynamic pathophysiology that evolves in time (figure). The mechanism consists of

the primary injury, followed by a combination of systemic derangements (hypoxia, hypotension, hypercarbia) and local events, which together cause secondary brain injury. Changes to the cerebral environment involve a complex interplay between cellular and molecular processes, in which glutamate-driven excitotoxic effects, oxidative stress, inflammation, ion imbalance, and metabolic disarray are major components. These pathways induce progressive neuronal loss through necrosis and apoptosis (figure).<sup>11,12,14</sup> Also important are the intracellular changes that are determined by the excessive influx of calcium, which affects mitochondrial integrity, depleting cells of an essential source of energy. The metabolic disarray caused by accumulation of lactate results in cytotoxic swelling of cells, which, together with the increased permeability of the cerebral vasculature, leads to brain oedema, elevated intracranial pressure, and reduced cerebral perfusion. Elucidation of these cascades has paved the way for targeted preclinical studies.

## Interventions

### Pre-hospital

Despite the potential benefits of early intervention, few pre-hospital treatment options have proved effective. In nine randomised controlled trials and one cohort study of pre-hospital fluid treatment in patients with traumatic brain injury,<sup>15</sup> hypertonic crystalloids and colloid solutions were not more effective than was isotonic saline. Results from observational studies<sup>16</sup> of pre-hospital endotracheal intubation have been conflicting. Poor outcomes in intubated patients were probably due to misplaced tubes or excessive hyperventilation once intubated. In the only randomised trial<sup>17</sup> of intubation versus non-invasive ventilation, paramedics received intensive training in airway management and monitored end-tidal carbon dioxide after intubation. In this trial, 51% of patients in the pre-hospital paramedic rapid sequence intubation group had good neurological outcomes (extended Glasgow Outcome Scale score 5–8) at 6 months compared with 39% of those in the hospital intubation group ( $p=0.046$ ). Whether paramedic advanced life support is beneficial overall for severe traumatic brain injury remains uncertain;<sup>18</sup> however, many possibilities exist for expansion of pre-hospital research in traumatic brain injury.

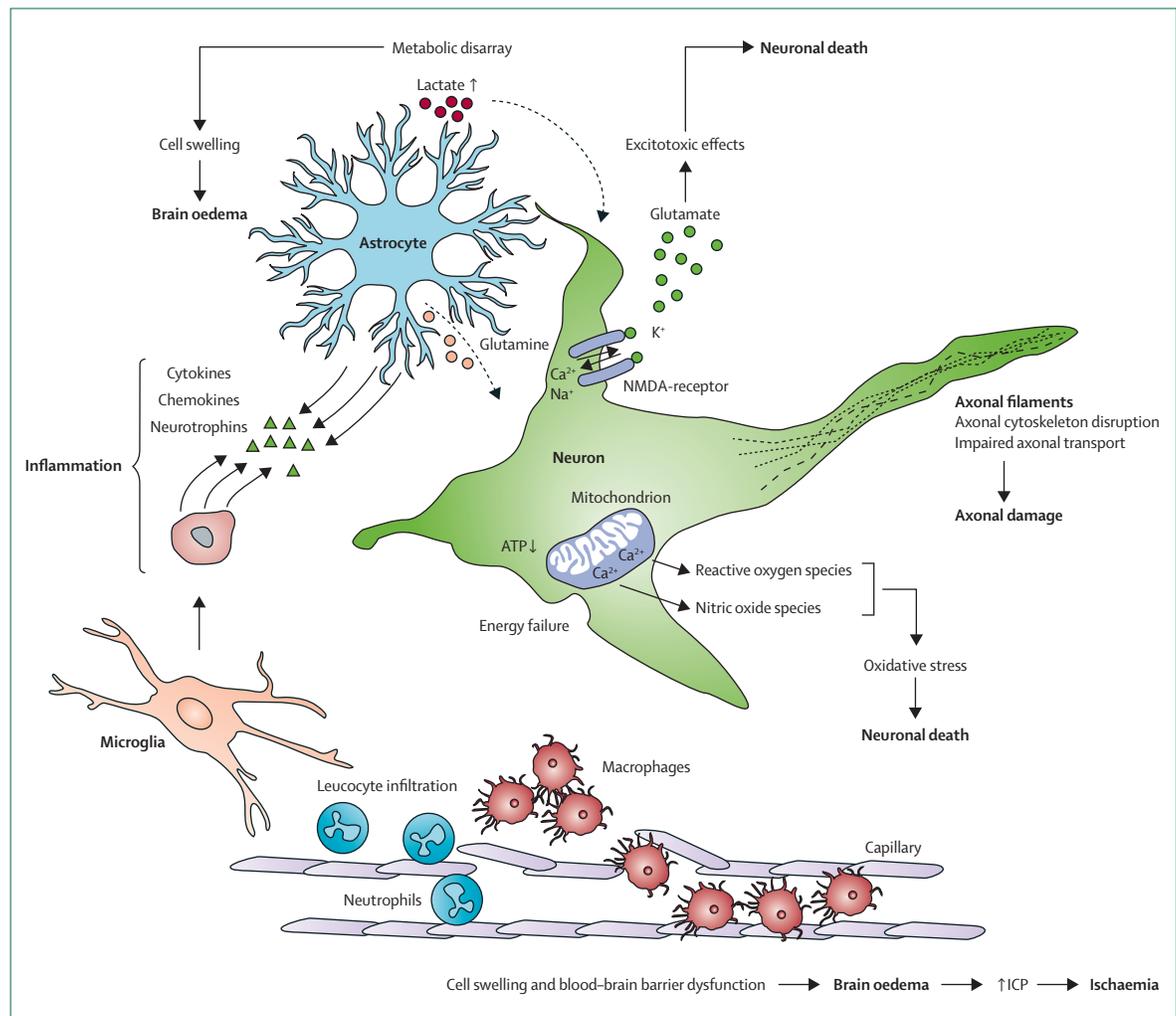
### Non-surgical

The appendix (pp 3–7) summarises randomised trials of non-surgical interventions for early management of traumatic brain injury.

Normobaric and hyperbaric hyperoxia in severe traumatic brain injury aims to improve mitochondrial function in the brain, which increases formation of adenosine triphosphate and the cerebral metabolic rate of oxygen.<sup>19</sup> However, PET scans have not shown clinically significant improvement in brain oxygen metabolism caused by normobaric hyperoxia.<sup>20</sup> This finding might be because once the haemoglobin is fully

saturated, the dissolved plasma oxygen is less than 1% of that transported. Therefore, oxygen delivery is affected much more by correction of anaemia than it is by hyperoxia treatment.<sup>19</sup> Additionally, although the partial pressure of brain oxygen is dependent on cerebral blood flow and the magnitude, timing, and duration of hyperoxia, it might not improve in areas of low cerebral blood flow, which is where the therapeutic effect should be evident.<sup>21</sup>

Hyperoxia has potential toxic effects, including formation of free radicals and pulmonary injury. Furthermore, hyperbaric hyperoxia is difficult to deliver and is not available in most centres. Although normobaric hyperoxia is simple, cheap, and widely available, evidence is insufficient to recommend it for routine clinical use.<sup>22</sup> Bullock<sup>19</sup> has proposed a large phase 3 multicentre randomised trial with 60%  $F_{I}O_2$  normobaric hyperoxia for 48 h; a regimen that seems to be safe for the lungs.



**Figure: Pathophysiology of traumatic brain injury**

The figure simplifies the most characterised pathophysiological molecular pathways. Excitotoxic effects are mediated by an increased concentration of extracellular glutamate resulting from neuronal death and overproduction.<sup>21</sup> Normally glutamate is taken up by astrocytes, which convert it into glutamine and deliver it back to neurons as an alternative energy source. However when excessively produced, astrocytes cannot remove glutamate from the extracellular space. Glutamate binding to neuronal receptors, such as NMDA, induces the influx of Ca<sup>2+</sup> and Na<sup>+</sup> and the efflux of K<sup>+</sup>. This ion imbalance causes depolarisation of the cell membrane and overload of intracellular Ca<sup>2+</sup>, which leads to mitochondrial dysfunction, decreased ATP formation, energy failure, and cell death. Alteration of mitochondrial integrity is followed by release of reactive oxygen species and nitric oxide species, which together cause the oxidative stress that damages membrane lipids, proteins, and DNA. Furthermore, free Ca<sup>2+</sup> activates several enzymes, such as caspases, which contribute to DNA fragmentation and cell apoptosis.<sup>22</sup> Other calcium-activated enzymes (eg, calpains) disrupt the axon's cytoskeletal filaments, thus impairing axonal transport and function.<sup>13</sup> Hypoxia or ischaemia lead to a shift to anaerobic metabolism by astrocytes, producing lactate, which provides an alternative energy source to neurons in a process called coupled lactate metabolism. Neuroinflammation consists of activation of glial cells, the astrocytes, and microglia, which undergo several morphological and molecular changes.<sup>14</sup> Together with fibroblasts, these cells form the glial scar, which impairs axonal regrowth. Microglia accumulate in the injured brain region and phagocytose the debris that originate from dying cells. Glial cells secrete inflammatory cytokines, chemokines (which stimulate the transmigration of activated blood leucocytes into the brain), and reparative factors such as neurotrophins. Infiltrated neutrophils and monocytes sustain the immune response to injury, thus impairing the integrity of the blood-brain barrier, which leads to increased extracellular fluid that, combined with cell swelling, leads to brain oedema and increased ICP. ICP=intracranial pressure.

A trial comparing 40% normobaric hyperoxia to 70% normobaric hyperoxia is underway (appendix p 4).

Therapeutic hypothermia resulted in many beneficial effects in animal models of traumatic brain injury, including: reductions in cerebral metabolic disarray, cerebral oedema, apoptosis, formation of free radicals, and concentrations of excitatory neurotransmitters; amelioration of dysfunction at the blood–brain barrier; and improvement in neurobehavioural outcomes.<sup>23–25</sup> Although therapeutic hypothermia can successfully treat refractory intracranial hypertension (appendix p 4), results from trials are conflicting, and whether this treatment is effective remains uncertain.<sup>23,26</sup>

The success of therapeutic hypothermia is probably dependent on the timing of hypothermia onset and duration, temperature targets, rate of rewarming, and avoidance of rebound rises in intracranial pressure.<sup>27</sup> Hypothermia has many possible unwanted effects, including perturbations of clotting, increased infection, cardiac dysrhythmias, and insulin resistance.<sup>28</sup> New technologies, such as automated cooling blankets, provide rapid, accurate, and controlled cooling. Several techniques for selective cooling of the brain have been developed, but await robust assessment.<sup>29</sup>

Clifton and colleagues' hypothermia trial<sup>30</sup> was stopped early for futility; two other hypothermia trials are in progress (appendix p 4): the Eurotherm hypothermia trial, which started in January, 2009, with an initial target of 1800 patients; and the POLAR trial in which pre-hospital cooling is achieved by infusion by trained paramedics of intravenous saline at 4°C to patients with isolated severe traumatic brain injury, and controlled rewarming is done in the intensive-care unit after 48 h.

Questions remain as to whether maintenance of normal body temperature (therapeutic normothermia) by prevention of hyperthermia is beneficial.

### Pharmacological

The appendix (pp 3–7) summarises randomised controlled trials of pharmacological interventions for early management of traumatic brain injury. In the CRASH trial<sup>31</sup> of intravenous corticosteroid in adults with severe traumatic brain injury, risk of death was higher in the treatment group than in the control group (26% vs 22%;  $p=0.0001$ ). Thus, high-dose steroids are not indicated for use in severe traumatic brain injury. However, anterior pituitary insufficiency is an under-recognised problem in patients with severe traumatic brain injury, particularly in elderly people or those who have diffuse axonal injury and skull base fracture. Guidelines have been produced for screening of patients for pituitary insufficiency.<sup>32</sup> Administration of hydrocortisone in physiological doses and endocrine follow-up are indicated.<sup>32,33</sup>

Although treatment with magnesium has been fairly effective in animal models of traumatic brain injury;<sup>34</sup> it had worse outcomes and increased mortality in human beings in Temkin and colleagues' randomised trial.<sup>35</sup>

Statins are inhibitors of cholesterol biosynthesis, suppressing inflammation, rescuing neurons from excitotoxic effects, and reducing apoptosis.<sup>36</sup> Atorvastatin and simvastatin improved spatial learning, reduced neuronal loss, and enhanced neurogenesis in the dentate gyrus in rats, with simvastatin being more therapeutically effective than atorvastatin.<sup>37</sup> Another animal study<sup>38</sup> found that simvastatin inhibits interleukin-1 production and reduces microglia activation and astrogliosis. In a small clinical trial,<sup>39</sup> rosuvastatin reduced amnesia time in moderate traumatic brain injury. Premorbid statin use improves survival and functional outcomes in patients aged 65 years and older with traumatic brain injury.<sup>40</sup>

Different gender responses to traumatic brain injury have stimulated interest in hormone treatments.<sup>41</sup> Progesterone is synthesised by oligodendrocytes and its receptors are expressed on neural cells. The neuroprotective effects of progesterone or its metabolites have been shown in animal studies. Mechanisms include inhibition of glutamate toxic effects, cell death, and inflammation. Additionally, progesterone regulates expression of aquaporin, which might have a role in development of brain oedema.<sup>42</sup> Progesterone has shown some benefits in three randomised trials, with a further two large phase 3 trials (SyNAPSe and ProTECT III) underway (appendix p 5).

Ciclosporin-A is an immunosuppressive drug, which, by stabilising the mitochondrial transition pores, attenuates mitochondrial failure after traumatic brain injury.<sup>43</sup> This drug diminished oxidative stress and lipid peroxidation in mice.<sup>44</sup> A further animal study<sup>45</sup> showed that ciclosporin-A attenuates axonal failure and disconnection after traumatic brain injury. Two trials have shown clinical safety of ciclosporin, with no difference in mortality or clinical outcome (appendix p 6).

Erythropoietin is an endogenous hormone that stimulates haemopoiesis and has neuroprotective and neuroregenerative effects<sup>46</sup> through reduction of apoptosis, inflammation, oxidative stress, and excitotoxic effects. This hormone decreases lesion volume and brain accumulation of leucocytes while promoting angiogenesis and neurogenesis and improving motor and cognitive function.<sup>47</sup> Erythropoietin crosses the blood–brain barrier and binds to receptors on most brain cells.<sup>48</sup> The brain is susceptible to erythropoietin treatment because its receptor is upregulated after injury or hypoxia. Erythropoietin has a long half-life and maintains its effectiveness with delayed administration;<sup>48</sup> however, risk of thrombotic events is increased with this drug. Clinical trials are underway in the USA and Australia (appendix p 3).

Tranexamic acid is an inexpensive antifibrinolytic drug that could reduce mortality and disability from traumatic brain injury. In the CRASH-2 trial,<sup>49</sup> tranexamic acid reduced mortality in trauma patients. Inconclusive findings from a small substudy<sup>50</sup> of CRASH-2 of intracranial haemorrhage in trauma patients with traumatic brain injury spawned the CRASH-3 study of

tranexamic acid versus placebo in patients with moderate to severe traumatic brain injury (appendix p 3).

### Surgical

Surgery, especially prompt evacuation of intracranial haematomas, has a vital role in improving outcomes in many patients with severe traumatic injury.<sup>51</sup> The Surgical Trial in Traumatic Intracerebral Haemorrhage (STITCH Trauma Trial)<sup>52</sup> is assessing whether surgery makes a difference for patients with traumatic intracerebral haemorrhage and contusion.

Decompressive craniectomy is the removal of skull segments to reduce intracranial pressure. Prophylactic unilateral decompressive craniectomy is frequently undertaken for acute subdural haematoma and for severe contusions and unihemispheric swelling. Decompressive craniectomy has been recommended as a second-tier treatment for intracranial hypertension in severe traumatic brain injury.<sup>51</sup> This technique is standard practice for military blast injury to the brain.<sup>53</sup> Delayed decompressive craniectomy is increasingly used as a salvage procedure for intractable intracranial hypertension in patients with diffuse bilateral swelling.<sup>54</sup> Complications, such as haematoma, subdural hygroma, and hydrocephalus are frequent after decompressive craniectomy.<sup>55</sup>

The decompressive craniectomy (DECRA) trial<sup>56</sup>—a randomised trial of early bifrontotemporoparietal decompressive craniectomy for patients with severe traumatic brain injury with diffuse brain swelling—unexpectedly showed a significantly worse outcome at 6 months in patients in the craniectomy group than in those in the standard-care group ( $p=0.03$ ). This finding has resulted in controversy about the technique, timing, and selection of patients for decompressive craniectomy.<sup>57</sup> The randomised evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure (RESCUEicp) trial<sup>58</sup> is a continuing randomised trial of decompressive craniectomy (table). The trial has a higher intracranial pressure threshold for decompressive craniectomy than did the DECRA trial, and includes patients with mass lesions and unilateral or bilateral decompressive craniectomy.

Transplantation of stem cells and neural precursor cells to repair the injured brain shows potential as a regenerative treatment. The ideal timing for such treatment is unknown. Cells transplanted into the injured brain variably replace lost neurons, reduce inflammation, and produce local trophic effects.<sup>62,63</sup> The few studies in human beings of this therapeutic approach indicate its complexity. Although intravenous infusion of autologous bone marrow-derived cells has been safely done in children<sup>64</sup> and adults<sup>65</sup> after traumatic brain injury, 96% of the cells are sequestered in the lungs and only 0.001% are grafted in the brain.<sup>63</sup> The targeted delivery of cells to the brain by direct transplantation is technically very challenging.

The table describes published and continuing trials of surgical interventions for early management of traumatic brain injury.

### Monitoring of the injured brain

Continuous intensive-care monitoring of patients with severe traumatic brain injury provides information to help prevent and treat secondary cerebral ischaemia. Monitoring of intracranial pressure is standard practice for severe traumatic brain injury in most neurosurgical centres. Guidelines<sup>66</sup> from the Brain Trauma Foundation detail indications for such monitoring alongside supporting evidence. However, the first randomised trial<sup>67</sup> to test the effectiveness of treatment based on intracranial pressure monitoring is being done in six Latin American centres that do not presently monitor intracranial pressure.

Multimodal monitoring of cerebral function is increasingly being used in advanced intensive-care units. Brain tissue oximetry, monitoring of cerebral blood flow, microdialysis, brain temperature monitoring, and continuous electroencephalography<sup>68,69</sup> allow for early detection of potentially correctable physiological derangements, by providing more information than is possible with intracranial pressure monitoring.<sup>68</sup>

Brain tissue oxygen tension independently correlates with outcome,<sup>70</sup> but is poorly predicted by standard monitoring,<sup>71</sup> and intracranial pressure and cerebral perfusion pressure often remain normal after cerebral hypoxia.<sup>72</sup> With brain tissue oximetry, episodes of cerebral hypoxia can be identified and subsequently corrected, but whether clinical outcomes consequently improve is uncertain.<sup>73</sup> Two studies<sup>74,75</sup> showed benefit and one study<sup>76</sup> showed harm from management guided by brain tissue oxygen monitoring. The phase 2 BOOST trial of management based on brain oxygen monitoring is underway.<sup>77</sup> The Brain Trauma Foundation recommends 15 mm Hg brain tissue oxygen tension as a threshold for intervention, on the basis of weak evidence.<sup>78</sup>

Cerebral microdialysis—use of a semipermeable membrane microcatheter to sample metabolites and other small molecules—provides unique insights into neurochemical mechanisms after severe traumatic brain injury. Although microdialysis might become widely available in advanced intensive-care units after technological improvements,<sup>79</sup> this technique is invasive and its use remains experimental.

The cerebral pressure reactivity index is a marker of cerebral autoregulation, which is derived at the bedside and enables identification of the optimum pressure for cerebral perfusion in the individual patient.<sup>80</sup> Targeting of an optimum pressure might prevent episodes of cerebral ischaemia,<sup>81</sup> but no evidence is available to confirm that this technique improves outcomes.<sup>82</sup>

Detection of seizures with continuous electroencephalography is commonly done, but the electroencephalographic signal degrades with sedation. Continuous

electrocorticography, which is started at the time of craniotomy, provides high-fidelity recordings, thus enabling detection of secondary brain insults and ictal discharges that are not readily apparent on electroen-

cephalography.<sup>83</sup> Cortical spreading depressions, which are slow waves of depolarisation, have been noted in half of patients with severe traumatic brain injury at up to 1 week after injury, and are a source of secondary

	Country	Sample	Number of patients	Intervention and comparison	Primary outcomes	Secondary outcomes
Taylor, et al (2001) <sup>59</sup>	Australia (one centre)	Traumatic brain injury, children aged >12 months, intracranial hypertension ( $\geq 20$ mm Hg for 30 min, $\geq 25$ mm Hg for 10 min, $\geq 30$ mm Hg for 1 min) on day 1 or evidence of herniation (dilation of one pupil or bradycardia)	27	Decompressive craniectomy (bitemporal craniotomy) plus conventional medical management vs conventional medical management (control)	Outcome at 6 months (modified Glasgow Outcome Scale, Health State Utility Index) Findings: no significant difference in long-term outcomes at 6 months	Intracranial pressure, length of stay in intensive-care unit or hospital Findings: no significant difference in intracranial pressure, or length of stay in intensive-care unit or hospital between groups
Jiang, et al (2005) <sup>60</sup>	China (five centres)	Traumatic brain injury (Glasgow Coma Score 4–8), age 15–70 years, refractory intracranial hypertension, unilateral cerebral contusion or swelling with midline shift >1 cm on CT, pupillary dilation with poor responsiveness to light <2 h, normal vital signs	486	Standard (unilateral) trauma craniectomy (12×15 cm unilateral bone flap) vs limited craniectomy (6×8 cm unilateral bone flap)	Outcome at 6 months (Glasgow Outcome Scale) Findings: more patients had favourable outcomes in the standard group and more had unfavourable outcomes in the limited group (p<0.05)	Intracranial pressure and complications Findings: mean intracranial pressure fell more rapidly and to a lower level in the standard group (results for significance were unclear); incidence of delayed intracranial haematoma and cerebrospinal fluid fistula were lower in the standard group (p<0.05); no significant differences in other complication rates (including seizure and infection)
Qiu, et al (2009) <sup>61</sup>	China (one centre)	Closed traumatic brain injury (Glasgow Coma Scale score 4–8), age 18–65 years, swollen hemisphere on CT	74	Unilateral decompressive craniectomy (bone window 15 cm diameter) vs unilateral routine temporoparietal craniectomy (bone window 8 cm diameter)	Intracranial pressure (continuous recording for 96 h), Glasgow Outcome Scale at 1 year Findings: mean intracranial pressure significantly lower in 15 cm decompressive craniectomy group, 1 month mortality significantly lower in 15 cm decompressive craniectomy group (p=0.01), rate of good neurological recovery (Glasgow Outcome Scale 4–5) at 1 year was significantly higher in 15 cm decompressive craniectomy group (p=0.035)	Vital signs, arterial oxygen saturation recorded every 12 h for 7 days after craniotomy, Complications recorded every 12 h for 7 days and every 24 h for another 7 days after craniotomy Findings: no significant difference in vital sign abnormalities between groups; incidence of delayed intracranial haematoma (p=0.041) and subdural effusion (p=0.040) higher in 15 cm decompressive craniectomy group
DECRA, Cooper, et al (2011) <sup>66</sup>	Multicentre (15 centres, three countries)	Severe closed traumatic brain injury (Glasgow Coma Scale score 3–8 or Marshall class 3), aged 15–59 years, intracranial pressure >20 mm Hg for >15 min in 1 h refractory to first-line treatment	155	Bifrontotemporoparietal decompressive craniectomy vs standard care in accordance with guidelines from the Brain Trauma Foundation	Original, death or severe disability at 6 months (Extended Glasgow Outcome Scale); final, functional outcome at 6 months (Extended Glasgow Outcome Scale) Findings: Intervention group had worse scores on Extended Glasgow Outcome Scale (odds ratio 1.84, 95% CI 1.05–3.24; p=0.03), and a greater risk of unfavourable outcome (2.21, 1.14–4.26, p=0.02)	Intracranial pressure, intracranial hypertension index, proportion of survivors who scored 2–4 on Extended Glasgow Outcome Scale, number of days in intensive-care unit and hospital, and mortality; in hospital and at 6 months Findings: intervention group had less time with intracranial pressure above threshold (p<0.001), fewer interventions for raised intracranial pressure (p<0.02), and fewer days in intensive-care unit (p<0.001); 6 month mortality was similar between both groups
RESCUEicp, Hutchinson, et al (ongoing) <sup>58</sup>	Multicentre (48 centres, 19 countries)	Traumatic brain injury, aged 10–65 years, abnormal CT, intracranial pressure >25 mm Hg for 1–12 h, refractory to first-line treatment	400	Unilateral or bilateral craniectomy vs medical management, including barbiturate coma	Outcome at discharge or 6 months (Glasgow Outcome Scale, Extended Glasgow Outcome Scale)	Short Form (SF) Health Survey 36 or SF10 for children aged <16 years; assessment of intracranial pressure control, time in intensive-care unit, time to discharge from neurosurgery unit, health economic analysis
STITCH (Trauma), Mendelow, et al (ongoing) <sup>52</sup>	Multicentre (54 centres, 19 countries)	Traumatic intracerebral haemorrhage, aged $\geq 14$ years, <48 h after injury, clinical equipoise regarding the benefits of either treatment	840	Early surgery vs initial conservative treatment	Unfavourable outcome (death or severe disability) with a prognosis-based 8 point Glasgow Outcome Scale and modified Rankin Scale (6-month follow-up)	Rankin scale, euroqol EQ-5D, mortality, survival, major adverse events, quality-adjusted life-years, total health-care costs, social costs (at 6 months and 12 months)

Trials were identified from searching and from those known to the authors. \*Trials are in progress.

**Table: Randomised controlled trials of surgical interventions for early management of traumatic brain injury**

damage.<sup>84</sup> These depressions are predictive of poor outcome,<sup>85</sup> and can be stopped by N-methyl-D-aspartate receptor antagonists, such as ketamine,<sup>86</sup> and by cooling of the brain. Although monitoring of depressions might have a role in future critical-care management, this technique is invasive because it requires craniotomy.

Multimodal monitoring has several limitations: these modalities are mostly focal measures; invasive monitoring can cause morbidity; highly trained staff are needed to manage the equipment and data so that artifacts are not generated and results misinterpreted;<sup>87</sup> so far, little trial-based evidence exists to show that correction of these derangements improves outcome; and the optimum combination of monitoring is not yet identified.<sup>69</sup> The European Society of Intensive Care Medicine has developed recommendations for multimodal monitoring.<sup>87</sup>

Advanced MRI technologies,<sup>88</sup> including volumetric analysis, diffusion tensor imaging, and high-definition fibre tracking, are increasingly being used to define the extent of brain injury and correlate this extent to neurological deficits.<sup>89</sup> These technologies can identify the precise pattern and degree of axonal fibre damage<sup>90</sup> and this information will probably help to track disease process and aid prognostication.<sup>91</sup> However, such imaging is not available until the patient can be safely transported to the imaging facility.

### Outcomes and their prediction

Comparison and prediction of outcomes in traumatic brain injury is challenging because of heterogeneity within the patient population, substantial differences in baseline prognostic risk, and the complexity of outcomes. Seemingly, mortality after traumatic brain injury has decreased and outcome has improved. Mortality rates of 10–15% noted in selected trials are compared with historical cohorts, such as the US Traumatic Coma Databank, which reported a mortality rate of 39% in 1984–87 (appendix p 2). Such conclusions, which are based on data combined from randomised trials and observational studies with no access to individual patient data to adjust for case mix, are flawed. Stein and colleagues' random-effects meta-analysis,<sup>92</sup> which accounted for inter- and intrastudy heterogeneity, showed a steady decline in mortality of about 9% per year in 1970–90, but the rates changed only slightly between 1990 and 2005. Therefore, these findings do not support the perceived continued decline in mortality, and contrast those from previous reports.<sup>93</sup> Furthermore, despite being a so-called hard endpoint, mortality might not be the most appropriate index to assess outcome in traumatic brain injury. Lifelong disability is common and often serious because of cognitive, physical, behavioural, and subjective sequelae. In traumatic brain injury, investigators commonly use the Glasgow Outcome Scale or its extended version to assess functional outcome. In 2006–11, seven studies, each enrolling more than

300 patients with severe traumatic brain injury, reported outcome results according to the Glasgow Outcome Scale. We noted no clear improvement in outcome in time; however, this finding should be interpreted with caution because comparisons of outcome over time are confounded by changes in epidemiology, such as increased injuries in elderly patients (appendix p 2).

Such complexities emphasise the need for high-quality prognostic research in traumatic brain injury. For a long time, predictions were little more than prophecies.<sup>94</sup> The science of clinical decision making, advances in statistical modelling, and availability of large datasets have facilitated evidence-based approaches that regard prognosis in terms of probabilities. Prognostic research has evolved from descriptions of univariate and multivariable associations, to quantifications of added predictive value and development of prognostic models. Most prognostic information is contained in a restricted number of predictors that are available on admission: age, clinical severity, pupillary reactivity, second insults (eg, hypotension, hypoxaemia), computed tomography abnormalities, and laboratory variables (glucose, haemoglobin).<sup>95</sup> However, when combined, these variables explain only about 35% of the variability in outcome.<sup>94</sup>

In the past few years, much interest has focused on biomarkers. Despite initial enthusiasm for the biomarkers S100B and neuron-specific enolase,<sup>96</sup> these biomarkers are not specific to brain injury and, despite some promising results,<sup>97,98</sup> their value beyond that of traditional predictors is still unclear. Novel biomarkers purported to have increased specificity to neuronal-cell or glial-cell damage are being assessed, with encouraging results reported for glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1.<sup>99,100</sup> However, the numbers of patients studied is fairly low, and identification of their specificity and added value compared with other predictors needs further investigation. Results from a moderately small study<sup>101</sup> suggest a possible added predictive value of these biomarkers compared with a model of clinical predictors. Serum ubiquitin carboxy-terminal hydrolase L1 and  $\alpha$  II-spectrin breakdown product 145 kDa have correlated with outcome after severe traumatic brain injury.<sup>102</sup>

Although various predictive models have been developed for use in traumatic brain injury, substantial limitations have been identified in the development of many of these models.<sup>103,104</sup> Specific issues relate to overfitting and scarcity of external validation. To be of clinical use, a prognostic model should be robust and widely applicable with large generalisability. The prediction models of the International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury (IMPACT) study group, and the Medical Research Council Corticosteroid Randomisation After Significant Head injury (CRASH) trial collaborators, which were developed on large numbers, meet these criteria.<sup>104,105</sup> These models are similar and show that the

greatest prognostic information is contained in a core set of three predictors: age, Glasgow Coma Scale (particularly Glasgow Coma Scale motor score), and pupillary reactivity. Various studies<sup>106,107</sup> show high generalisability of the IMPACT model in other settings and populations. Furthermore, these models create new opportunities in clinical decision making and research. These models have great potential in assessing the quality of health-care delivery and comparing predictive and actual outcomes.

### Implications for research

Disappointingly, discoveries in the laboratory have translated into few new treatments for traumatic brain injury in human beings. Strategies for addressing this failure have been identified,<sup>108</sup> including more research in larger animals, such as pigs and sheep with gyriform brains, rather than in rodents, whose brains are small and lissencephalic.<sup>108</sup> CNS drugs take about 18 years to go from the laboratory bench to the patient, and spend on average 8.1 years in human testing.<sup>109</sup> The cost of development of new CNS drugs is one of the highest in any therapeutic area, and many drug companies are eschewing such investment.<sup>109</sup> A recently formed consortium of research groups will hopefully accelerate the process of finding new therapeutic drugs and biomarkers for brain injury.<sup>110</sup>

Clinical trials of traumatic brain injury are challenging to design and undertake because of patient heterogeneity, the absence of early mechanistic endpoints, and the moderate insensitivity of outcome measures. The IMPACT study group provided three recommendations to overcome patient heterogeneity, which could increase statistical power by up to 50%: enrolment criteria should be as broad as is compatible with understanding of the mechanism of action; covariate adjustment should be used in the analysis phase to mitigate effects of heterogeneity; and an ordinal approach to the analysis of treatment effects should be used, on the basis of either sliding dichotomy or proportional odds methodology.<sup>111</sup>

Diffusion tensor imaging, proteomic biomarkers, and multimodal monitoring might offer new methods for tracking of disease processes and enable more mechanistic assessments than are presently possible. Previous trials have unsuccessfully targeted discrete disease mechanisms in the hope of finding a magic bullet; investigators might therefore do better to think in terms of therapeutic strategies or combination treatments.<sup>112</sup>

Outcome in traumatic brain injury is complex and a multidimensional approach to outcome assessment and classification is needed. Although randomised trials are the gold standard for proving effectiveness of new treatments, they are costly, may have restricted generalisability, and importantly, are unlikely to ever be sufficiently powered to address all the existing uncertainties in clinical management of traumatic brain injury. In a workshop<sup>108</sup> jointly organised by the European Commission and the US National Institute of

Neurological Disorders and Stroke, a strong plea was made for comparative effectiveness research in traumatic brain injury. Heterogeneity in the traumatic brain injury population, and the variability in treatment, makes this injury particularly suitable for comparative effectiveness research, whereby differences in processes and patients can be related to outcome. This research goes beyond the aim of classic randomised trials, which aim to establish effectiveness in carefully controlled settings, to provide real-world answers to questions about clinical management by measurement of benefits and risks of systems of care and interventions in ordinary settings and broad populations. Comparative effectiveness research in traumatic brain injury would necessitate a large-scale contemporary prospective dataset of high quality. As such, the International Initiative for Traumatic Brain Injury Research has been developed for collaboration between international funding agencies. This initiative signals the strong desire of researchers, clinicians, and funding agencies to work together within international collaborations to improve care for patients with traumatic brain injury.

### Conclusion

The outcome of severe traumatic brain injury is dependent on delivery of high-quality care by a well-integrated multidisciplinary team of health professionals. Further improvements will probably result from precise classification, innovations in trial design, implementation of comparative effectiveness research, selection of patients who are likely to benefit from particular interventions, and individualised treatment in intensive-care units based on multimodal monitoring. Preclinical laboratory research in traumatic brain injury will remain a fundamental means for generation of new treatments and biomarkers, and for elucidation of pathophysiology. The findings from RESCUEicp will further define the indications for decompressive craniectomy, which are presently controversial for diffuse brain swelling with intractable intracranial hypertension. Therapeutic hypothermia and hyperoxia are experimental treatments being investigated in large multicentre trials. Strategies to enhance neural plasticity and brain repair with stem-cell and precursor-cell implants will continue to evolve. We are optimistic that further gains in outcome for patients with severe traumatic brain injury will be achieved in the next decade.

#### Contributors

JVR planned the report and drafted the abstract, interventions, pharmacological, monitoring, implications for research, and conclusion sections, and appendix pp 3–7. AIM drafted the outcomes and implications for research sections, and appendix p 2. PB drafted the abstract, introduction and table, appendix pp 3–12, searched for and selected citations, and coordinated referencing and formatting of the manuscript. MCM-K drafted the pathophysiology and pharmacological sections and the figure. GTM drafted the classification section. RLG planned the report, drafted the abstract, introduction, and appendix pp 3–7, and coordinated the report and the evidence searches. All authors revised and edited the report.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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