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Traumatic brain injury: assessment, resuscitation and early management

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This review examines the evidence base for the early management of head-injured patients. Traumatic brain injury (TBI) is common, carries a high morbidity and mortality, and has no specific treatment. The pathology of head injury is increasingly well understood. Mechanical forces result in shearing and compression of neuronal and vascular tissue at the time of impact. A series of pathological events may then ensue leading to further brain injury. This secondary injury may be amenable to intervention and is worsened by secondary physiological insults. Various risk factors for poor outcome after TBI have been identified. Most of these are fixed at the time of injury such as age, gender, mechanism of injury, and presenting signs (Glasgow Coma Scale and pupillary signs), but some such as hypotension and hypoxia are potential areas for medical intervention. There is very little evidence positively in favour of any treatments or packages of early care; however, prompt, specialist neurocritical care is associated with improved outcome. Various drugs that target specific pathways in the pathophysiology of brain injury have been the subject of animal and human research, but, to date, none has been proved to be successful in improving outcome.

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This review addresses the resuscitation and early management of patients with traumatic brain injury (TBI). The management from injury to arrival in a definitive care environment will be discussed; intensive care management is dealt with elsewhere.[50]

TBI is common, and when severe, has a poor outcome.[11] The incidence of TBI is difficult to ascertain with certainty, but has been reported at 400 per 100 000 patients per year (range 88–1967)[65 153 154 178] or around 1.4 million patients per year in the UK.[58] TBI is the leading cause of death among adults younger than 45 yr[65] and in children (1–15 yr).[136] The majority of TBI is classified as mild, and around 8–10% is classified as moderate or severe.[156 178] Patients with mild TBI have a good prognosis providing treatable complications are not missed. Overall mortality in this group is around 0.1% and is associated predominantly with missed intra-cranial haemorrhage.[73] Although many patients may return to work after mild TBI,[162] around 50% of survivors have moderate or severe disability as assessed by the Glasgow Outcome Scale (GOS) or the disability outcome scale;[156 162 171] this represents significant morbidity. For the minority of patients presenting with more severe TBI, the prognosis is much worse. Approximately 30% of patients admitted to hospital with Glasgow Coma Scale (GCS) score <13 will ultimately die;[156] mortality for those with GCS ≤ 8 after resuscitation may be as high as 50%.[16 61 67 105 107] Of those admitted to hospital with GCS ≤ 12, around 8% will die within the first 6 h, 2% within the first hour.[113] Long-term outcome among survivors of severe TBI is worse than in those with mild TBI; only around 20% will make a good recovery on the GOS (Table 1).[156]

Classically, TBI has been divided into two distinct periods: primary and secondary brain injury. The primary injury is the result of the initial, mechanical forces, resulting in shearing and compression of neuronal, glial, and vascular tissue. Axonal tissue is more susceptible to the injury than vascular tissue. Thus, focal injuries are usually superimposed upon more diffuse neuronal injury. The consequences of the initial injury include physical disruption of cell membranes and infrastructure, and disturbance of ionic homeostasis[143] secondary to increased membrane permeability. This in turn may lead to astrocytic and neuronal swelling, relative hypoperfusion,[12 13 92] and a cascade of neurotoxic events because of increased intracellular calcium.[121 176] The secondary injury is described as the consequence of further physiological insults, such as

Table 1 Outcome at 1 yr after TBI.[156] Outcome is described using the Glasgow Outcome Scale. GCS, Glasgow Coma Scale

Initial severity	Initial GCS	Outcome (%)			
		Dead or vegetative	Severe disability	Moderate disability	Good recovery
Mild	13–15	8	20	28	45
Moderate	9–12	16	22	24	38
Severe	3–8	38	29	19	14

ischaemia,[12 13 92] re-perfusion and hypoxia, to areas of 'at risk' brain in the period after the initial injury. This demarcation of periods of injury is now viewed as excessively simplistic.[121] There is experimental evidence that the extent of 'primary injury' may be modulated by subsequent management, and the 'secondary injury' may start at the time of initial mechanical insult. Although diffuse axonal injury results in axotomy, this process occurs immediately in only the most damaged areas. Most axotomy probably occurs 12–24 h after the initial insult.[98 121] One-third of patients who die after TBI will talk or obey commands before their death, suggesting that the initial injury *per se* is not lethal, even with diffuse axonal injury,[10 119 121] but the consequences are.[2 47 70] The early management of TBI is therefore directed towards minimizing progression of injury in the at risk brain.[121] Although it has not been subjected to randomized, controlled trials, prompt specialist medical and surgical management of patients with TBI is associated with improved outcome.[20 53 85 99 112 132] Prompt and appropriate resuscitation and early management is therefore viewed as an essential part of the supportive care provided for these patients. To this end various groups have produced evidence-based[15 16 36 109 171] or expert consensus-based[87] guidelines on management of TBI.

Head injury research has suffered from lack of clear definitions, making comparison between studies problematic. Various expert panels have produced definitions of type and severity of injury. These are largely based upon history and clinical findings,[15 16 171] supplemented by the appearance of early X-ray computed tomography (CT).[96] The European Federation of Neurosurgeons (EFNS) has produced a pragmatic grading of head injury (Table 2).[171] Of note, severe TBI usually refers to patients with a consistent history and a summated GCS $\leq$8.[16 171]

Risk factors for poor outcome

Various factors have been associated with poor outcome in mild, moderate, and severe TBI in both the adult and the paediatric population. These factors can be separated into those which are fixed at the time of injury and those amenable to intervention (i.e. secondary insults). The former may provide prognostic information, but cannot be influenced by subsequent care.

Table 2 EFNS definition of head injury severity.[171] GCS, Glasgow Coma Scale; LOC, loss of consciousness; PTA, post-traumatic amnesia

Classification	Admission Glasgow Coma Scale and clinical characteristics
Mild	GCS 13–15
Category 0	GCS 15, No LOC, no PTA, No risk factors
Category 1	GCS=15, LOC <30 min, PTA <1 h, No risk factors
Category 2	GCS=15 and risk factors present
Category 3	GCS=13–14, LOC <30 min, PTA <1 h, with or without risk factors
Moderate	GCS=9–12
Severe	GCS $\leq$8
Critical	GCS 3–4, unreactive pupils and absent/decorticate motor reactions (GCS motor scale 1 or 2)

Fixed risk factors

Mechanism of injury

Penetrating injuries have a worse outcome than blunt trauma, when other factors are taken into account.[32 113] Patients with penetrating injuries are more likely to present with a lower GCS and die early.[113] Non-accidental injury in children <5 yr is associated with worse outcome,[46] which may be in part because of a higher rate of cerebral infarction in this group.[120] Pedestrians[94] and pedal cyclists[144] fare worse than vehicle occupants in motor vehicle accidents, and ejection from the vehicle leads to a higher risk of significant intra-cranial injury.[144]

Age, gender, and genetics

The age of the patient influences both the likelihood of TBI and the prognosis. TBI has a bimodal incidence distribution; young adult males comprise the largest peak because of motor vehicle accidents and alcohol-associated trauma,[72 178] with a second smaller peak in the elderly, consequent to falls (Table 3). For a given severity of injury, women appear to fare less well[110 113] and have more brain swelling and intra-cranial hypertension than men.[37] Age appears to be a continuous risk factor if sufficiently large cohorts are examined.[61 170] Some studies have found stepwise thresholds for risk, particularly with age >65,[11] but this may be an artifact of relatively small samples. Genetic factors play a role; for instance, there is evidence demonstrating that the ε4 allele of apolipoprotein E predisposes to poor outcome after TBI, which is the same gene associated with Alzheimer's disease.[175] This is discussed further in another article in this issue.[102]

Pupillary signs

Pupil size and reactivity can be affected by a variety of mechanisms associated with head injury: eye and optic nerve trauma, third nerve injury at any point in its course, mid-brain, and pontine dysfunction, and drug

Table 3 The effect of age on attendance rates for head injury. Moderate to severe head injury is defined as Glasgow Coma Scale ≤12

Age range (yr)	Attendance rates per 100 000 population			
	Male (USA)[72]	Female (USA)[72]	Male: moderate to severe (UK)[178]	Female: moderate to severe (UK)[178]
0–4	128	94	120	114
5–9	230	145	117	69
10–14	572	333	152	52
15–19	670	418	183	52
20–24	512	312	88	36
25–29			67	43
30–34	273	179	71	29
35–39			52	24
40–44	213	120	67	36
45–49			26	43
50–54	179	120	38	31
55–59			26	31
60–64	282	102	45	12
65–69			12	12
70–74			36	13
75–79	350	120	27	19
80–84			102	55
>85			45	67

administration. If direct trauma to the eye is excluded, then pupillary signs may provide prognostic information.

Pupillary constriction is mediated via a parasympathetic pathway, which requires integrity of the third nerve and its nuclei in the brain, which lie close to areas involved in consciousness. Third nerve palsy initially causes mydriasis followed by loss of reactivity to light. Classically, ipsilateral third nerve palsy has been attributed to compression of the nerve on the free edge of the tentorium. It may also occur because of kinking of the nerve over the clivus or 'buckling' of the brainstem as a result of an increase in supra-tentorial pressure.[80] In the presence of unilateral third nerve palsy, the consensual light reflex (opposite eye constricting in response to bright light) should still be present. Optic nerve injury (more common with frontal injuries) will impair both the direct and indirect responses and may lead to fixed or sluggish pupils, which may display spontaneous fluctuations (hippus).[139]

Bilaterally fixed pupils occur in around 20–30% of patients with severe head injury (GCS ≤8) after resuscitation: 70–90% of these patients will have poor outcome (vegetative or dead) when compared with around 30% with bilaterally reactive pupils.[57 64 66] Unreactive pupils are associated with the presence of hypotension, lower GCS, and closed basal cisterns on CT.[4 14 163] The underlying pathology influences the prognostic value of unreactive pupils: patients with epidural haematoma fare better than those with subdural haematoma.[115 116 123 129] Unilaterally unreactive pupils have an outcome intermediate between bilaterally reactive and unreactive pupils. Pupil asymmetry is associated with an operable mass lesion in around 30% of patients.[18]

Table 4 Glasgow Coma Scale

Behaviour	Response	Score
Eyes open	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Orientated	5
	Words	4
	Vocal sounds	3
	Cries	2
	None	1
Best motor response	Obeys orders	6
	Localize pain	5
	Flexion (withdrawal) to pain	4
	Flexion (abnormal) to pain	3
	Extension to pain	2
	None	1

Glasgow coma scale

The GCS was devised by Teasdale and Jennett in 1974 as a practical scale to describe the depth of coma objectively, both to aid communication between healthcare professionals and to improve reporting of head injury research. The original scale had only 14 points; there was no distinction made between normal and abnormal flexion. The summated score was not discussed at that time.[150] Subsequently, the flexion motor response was subdivided and the use of the total score described (Table 4).[149] The GCS has been modified for the paediatric population,[122 140 147] in whom it functions well, within the limits of the immaturity of the paediatric nervous system, though it is less sensitive to changes in conscious level than the adult score (Table 5).[122] The adult GCS can be used for children ≥5 yr. Various modifications (such as the grimace scale[147]) have been made to improve inter-observer reliability though the relationship between these scales and outcome is not known. Inter- and intra-observer reliability using the GCS is reasonable,[100] though it does depend upon level of training and the severity of the painful stimulus used.[151] The original description used nail-bed pressure with a pen or similar, whereas many clinicians now use supra-orbital or trapezius pressure to evoke 'deep' pain.

Although the GCS is by far the most widely used tool for assessment of consciousness, it is not perfect and other methods do exist. Eye opening and verbal responses are influenced by local trauma, swelling, and tracheal intubation. The European Brain Injury Consortium (EBIC) survey found that the full GCS was testable in only 56% of patients with initial GCS ≤12 on admission to the neurosurgical unit.[105] This problem has led to various methods of predicting verbal scores[128] or simply using the six-point motor score as the predictive component.[56] A commonly used approach to the intubated patient is to assign a verbal score of 1. However, this leads to overestimation of injury severity in a significant number of patients.[40] Alternatively, the overall responsiveness of the

Table 5 Paediatric modifications of the Glasgow Coma Scale

			0–6 months	6–12 months	1–2 yr	2–4 yr	>5 yr
Eyes open	Spontaneous	4	+	+	+	+	+
	To speech	3	+	+	+	+	+
	To pain	2	+	+	+	+	+
	None	1	+	+	+	+	+
Best verbal response	Orientated	5	−	−	−	−	+
	Words	4	−	−	+	+	+
	Vocal sounds	3	−	+	+	+	+
	Cries	2	+	+	+	+	+
	None	1	+	+	+	+	+
Best motor response	Obeys orders	5	−	−	−	+	+
	Localize pain	4	−	+	+	+	+
	Flexion to pain	3	+	+	+	+	+
	Extension to pain	2	+	+	+	+	+
	None	1	+	+	+	+	+
Total score obtainable			9	11	12	13	14

patient may be assessed, as suggested by the Swedish Reaction Scale (Table 6).[141] This scale has been compared with the GCS and found to have better inter-rater agreement than the GCS[44 142] and to be easier to use.[69] However, it does not provide better discrimination between severities of injury. Both the Advanced Trauma Life Support[158] and Advanced Paediatric Life Support[49] systems advocate initial assessment using the four-point alert, responding to voice, responding to pain, unresponsive scale. This has not been subjected to validation as a predictive tool, in terms of either need for intervention or outcome, though the categories do correspond to those in the Swedish Reaction Scale.[141] However, it is a quick, reliable method of assessment, which should be supplemented later by full GCS assessment.[49 158]

The timing of GCS assessment determines the scores obtained. Hypotension and pharmacological sedation or paralysis all reduce the GCS, though this may not be properly taken into account by observers.[91] A large cohort study of more than 12 000 patients from the USA[30] found that field GCS and arrival GCS correlated with each other (unsurprisingly), and both were predictive of survival. Field GCS is associated with early, but not late, outcome in children.[97] However, the relationship between field GCS and survival is non-linear, with a steep relationship between GCS 3 and 7, followed by a shallower decline in mortality between GCS 8 and 15.[159] The relationship between field GCS and functional outcome appears to be approximately linear.[158]

Table 6 Swedish Reaction Scale (simplified)[141]

Mentally responsive	
1	Alert, no delay in response
2	Drowsy or confused, responsive to light stimulation (talk or touch)
3	Very drowsy or confused, responsive to strong stimulation (loud talk, shaking, pain)
Mentally unresponsive	
4	Unconscious, localizes but does not ward off pain
5	Unconscious, withdrawing movements on pain stimulation
6	Unconscious, stereotype flexion movements on pain stimulation
7	Unconscious, stereotype extension movements on pain stimulation
8	Unconscious, no response to pain stimulation

Numerous studies have assessed the relationship between post-resuscitation GCS and mortality and functional outcome in generalized TBI[21 22 38 42 94 108] and specific sub-groups.[76 81 113 116] In general, as with field GCS, these studies show a quasi-exponential relationship, with a sharp decrease in mortality as GCS increases from 3 to 8, with a shallower decrease between 8 and 15. The same relationship appears to apply to children.[81] Although the absolute risk varies with pathology, the relationship between GCS and outcome remains for penetrating injury,[113] and epidural[76] and sub-dural haematoma.[116] Of note, one centre has postulated that this link between GCS and outcome may have been eroded by improvements in care of patients with severe TBI.[6]

The change in GCS may also be prognostic,[135] with deterioration in GCS predicting the need for evacuation of traumatic sub-dural haematoma.

CT findings

The incidence of abnormalities on CT increases with severity of head injury. Patients with minor head injuries (GCS= 13–15) have an abnormal CT rate of 2.5–8%[55 144 146] when compared with 68–94% in patients with severe TBI (GCS $\leq$8).[35 38 64 83 108] Various abnormalities on X-ray–CT have been linked to outcome. The most consistent individual abnormalities are mid-line shift,[35 38 133 170] compression of the basal cisterns,[35 133 163] and traumatic sub-arachnoid haemorrhage (SAH),[35 51 71 133 174] all of which are associated with a worse prognosis. The strength of the association between abnormalities and outcome varies with other patient factors, notably age, pupillary signs, and GCS.

Various grading systems have been developed in an attempt to standardize reporting of CT in TBI. The most widely reported is the Marshall system (Table 7) described using data from the Trauma Coma Data Bank (TCDB),[96] which has been shown to predict mortality but not functional recovery both in its original population and in

Table 7 Marshall CT classification of TBI

Category	Definition
Diffuse injury I (no visible pathology)	No visible intra-cranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift <5 mm and/or lesion densities present No high- or mixed-density lesion >25 ml, may include bone fragments and foreign bodies
Diffuse injury III	Cisterns compressed or absent with mid-line shift 0–5 mm No high- or mixed-density lesion >25 ml
Diffuse injury IV	Mid-line shift >5 mm No high- or mixed-density lesion >25 ml
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High- or mixed-density lesion >25 ml, not surgically evacuated

independent studies (Table 8).[64 96 172 174] This classification was derived from 746 patients from the TCDB. All had GCS ≤8; gunshot wounds and patients 'brain dead' on admission were excluded. CT scanning was performed early after injury, 'usually within 4 h'.[96] When the Marshall CT classification is added to age and post-resuscitation GCS motor score to create a three-factor prediction model, the fit of the model to data is excellent, though it should be borne in mind that this is validating the data against the original, not an independent, data set.[96] Despite the widespread use of the Marshall classification, it does have its problems. There may be significant inter-observer variability;[54 64] it does not allow for a 'normal' scan, which may be present in individuals with pathologically mild head injury, but low GCS (as may occur with intoxication); it is a retrospective CT reading since knowledge of clinical course is required to define a mass lesion as evacuated or not; measuring mass volumes on CT is not an exact science;[145] tested on an different population it is not an independent predictor of mortality when clinical features are taken into account.[174] A prospective study of CT predictors in a more general TBI population (patients admitted to a neurosurgical centre with GCS ≤15) has found simpler classifications using the overall appearance of the scan (i.e. massive focal injury, and massive diffuse injury, and traumatic SAH) to be significant predictors in a multivariate analysis, whereas the Marshall classification was not.[174] Other workers have found that specific details such as intra-ventricular haemorrhage and SAH improve the prognostic accuracy of the Marshall classification.[88] Despite these caveats, the Marshall classification is almost always reported in trials, and remains the *de facto* standard for CT classification. Regardless of the CT classification used, it should be borne in mind that other patient factors are important in determining prognosis. The timing of the scan is important. With improved access to scanning facilities, CT is being performed earlier after TBI, which may risk missing operable lesions which develop later in the clinical course. Studies have demonstrated deterioration in 16–43% of later scans, which is associated with worse outcome.[75 134]

Secondary insults

Hypotension

Numerous observational studies have confirmed the association between systemic hypotension occurring at any point after injury and poor outcome.[16] The largest study,[19] a prospective review of more than 700 patients from the American TCDB, found that a single episode of hypotension during the period from injury through resuscitation was associated with an approximate doubling of mortality and a parallel increase in morbidity in survivors. This association persists when age and the presence or absence of hypoxia and extra-cranial injuries are taken into account. Similar associations have been found in other studies. A prospective Australian study[38] found that early (resuscitation) and late (definitive care) hypotension were separately and additively associated with increased mortality. The duration and number of episodes of hypotension are correlated with mortality.[90] The findings in children are similar provided appropriate correction of adequate arterial pressure is made for age.[118] Retrospective data[117] suggest that intra-operative hypotension is also

Table 8 Outcome related to Marshall CT classification. TCDB, Traumatic Coma Data Bank; EBIC, European Brain Injury Consortium. Outcome is defined using the Glasgow Outcome Scale

Category	Outcome[94]		Frequency		
	Unfavourable (dead, vegetative, severe disability)	Favourable (mild disability, good recovery)	TCDB[94]	European Nimodipine trial[64]	EBIC survey[105]
Diffuse injury I (no visible pathlogy)	38	62	7	8	12
Diffuse injury II	65	35	24	33	28
Diffuse injury III	84	16	21	11	10
Diffuse injury IV	94	6	4	4	2
Evacuated mass lesion	77	23	37	38	48
Non-evacuated mass lesion	89	11	5	4	–

important, with a three-fold increase in mortality in those patients experiencing intra-operative hypotension. The precise mechanism for the enhanced susceptibility of the injured brain to hypotension is not clear,[33 143] but up to 90% of head-injured patients have been found to have evidence of ischaemic damage at autopsy.[48]

Hypoxia

Most,[19 68 93] but not all[90] observational studies in TBI have found an association between observed early hypoxia [Sp_{O_2} <90% or <7.9 kPa (60 mm Hg)] and poor outcome. The association is not as strong as for hypotension, and may be less important in children.[118] Hypoxia may be a marker of the severity of brain or systemic injury, or it may be a secondary insult to the at risk brain. It may also be a surrogate marker for marked hypercapnia, which would be expected to lower cerebral perfusion pressure. Animal work suggests that, in rats, the combination of hypoxia and percussive trauma leads to a small increase in oedema formation when compared with the percussive trauma alone, presumably because of the increasing inability of injured cells to maintain ionic homeostasis.[164]

Hyperglycaemia

Severe head injury leads to a marked sympathetic and hormonal response, with levels of catecholamines inversely related to the severity of injury.[23 127] Hyperglycaemia consequent to this response has been shown to occur within minutes in cats.[127] Hyperglycaemia is common after TBI[68 77 179] and is associated with severity of injury and poor outcome for both early mortality and functional recovery in adults[77 78 179] and children.[24] Approximately 50% of patients present with blood glucose >11.1 mmol l^{-1} (200 mg dl^{-1}), and peak levels greater than this in the first 24 h after admission are associated with a significantly worse mortality[77 179] and functional outcome up to 1 yr post-injury.[179] Patients with a poor outcome after TBI have higher blood glucose than those with a good outcome both on admission (12.1 *vs* 9.3 mmol l^{-1}) and after initial operative management (13.3 *vs* 8.9 mmol l^{-1}).[78] This association is independent of admission and 24 h GCS.[179] Hypoglycaemia is not common as a direct result of TBI in the early period after injury. Hypoglycaemia may, however, be the initial cause of TBI through altered sensorium or behaviour, and the reduced GCS found with persisting hypoglycaemia may mimic severe TBI.[86]

Hypercapnia and hypocapnia

Hypercapnia has long been known to increase cerebral blood volume and flow by cerebral vasodilatation. In situations of reduced intracranial compliance, this would be expected to increase intracranial pressure (ICP) significantly, and hence reduce cerebral perfusion. In situations of reduced cerebral blood flow and oxygen delivery, where intracranial hypertension is not a problem, it is possible that hypercapnia may be of benefit through improvements in cerebral blood flow,[45 52] though this has not been demonstrated directly in humans.[28] Hypercapnia is more likely to occur in the setting of multiple trauma.[101] Arterial carbon dioxide is rarely measured in the field or before tracheal intubation. Physiologically, it is plausible that hypercapnia should be detrimental, and most guidelines mention hypercapnia as a cause of secondary insult, but only a few studies have demonstrated this. A small study from Germany found that hypercapnia had a close negative association with initial GCS,[114] and Miller and colleagues[101] found an association between hypercapnia and poor outcome.

As a consequence of these findings, hyperventilation has previously been used in the initial and ongoing management of TBI. However, cerebral blood flow in the first few hours after injury has been shown to be reduced to less than half of normal (~25 ml 100 g^{-1} min^{-1} *vs* ~50 ml 100 g^{-1} min^{-1})[12 13 92] and various studies have demonstrated both physiological derangements[111 137] and worse outcome[104] if aggressive [Pa_{CO_2} <4 kPa (30 mm Hg)], indiscriminate hyperventilation is used.

Current strategies

General principles

Most clinicians are agreed on the general principles of early management: maintenance of adequate and stable cerebral perfusion, adequate oxygenation, avoidance of hyper- and hypocapnia and avoidance of hyper- and hypoglycaemia, while avoiding iatrogenic injury. The implementation of these principles in clinical practice differs from centre to centre, based largely on historical tradition, local practice, and a lack of clear evidence of benefit of any one therapeutic approach. Guidelines for management from various consortia are available (Table 9).[16 36 87 171]

Arterial pressure maintenance

On the basis of the strong association between hypotension and poor outcome, it is unlikely that there ever will be placebo-controlled trials of the prevention or correction of hypotension in TBI. Although the statistical relationship between arterial pressure and outcome is best described for systolic blood pressure ≤90 mm Hg in the early management and resuscitation phase, evidence from patients with ICP monitoring on ICU would suggest that this is a rather low threshold. Furthermore, although systolic blood pressure is the most easily and accurately measured value in the field, it does not predict mean arterial pressure (MAP) particularly well, which is probably the more

Table 9 Targets for early physiological support. Guidelines from national and international expert panels. EBIC, European Brain Injury Consortium; AAGBI, Association of Anaesthetists of Great Britain and Ireland

Parameter	Brain trauma foundation[15 16]	EBIC[87]	AAGBI[154]
Arterial pressure (mm Hg) (adults)	>90 (Systolic) 'Normal range' or >90 (mean)	>120 (Systolic), >90 (mean)	>80 (mean)
Arterial pressure (mm Hg) (children)	>65 (Systolic) 0–1 yr	–	40–60 (mean) < 3 months
	>75 (Systolic) 2–5 yr	–	45–75 (mean) 3 months–1 yr
		–	50–90 (Mean) 1–5 yr
	>80 (Systolic) 6–12 yr	–	60–90 (mean) 6–11 yr
	>90 (systolic) 13–16 yr	–	65–95 (mean) 12–14 yr
Sa_{O_2} (%)	>90	>95	
Pa_{O_2} (kPa)	>8	>10	>13
Pa_{O_2} (kPa)	>4.6	4.0–4.5	4.5–5.0 (no less than 4.0 if signs of raised ICP)

important determinant of cerebral perfusion pressure. The precise target for systemic arterial pressure (SAP) varies between guidelines. The American pre-hospital management guidlelines[15] advocate maintaining SAP in 'the normal range' and avoidance of hypotension (SAP $\leq$90 mm Hg in adults) while the severe TBI guidance[16] advocates MAP $\geq$90 mm Hg. The European guidelines call for SAP $\geq$120 mm Hg and MAP $\geq$90 mm Hg,[87] and the UK transfer guidelines suggest MAP $\geq$80 mm Hg (Table 9).[155] The study suggesting improved outcome from penetrating torso injuries with hypotensive resuscitation specifically excluded patients with TBI.[9] Although there are theoretical concerns about the administration of large volumes of fluid worsening cerebral oedema or bleeding in patients in whom blood–brain-barrier function is compromised, there is no evidence to support this in clinical practice. There is some evidence suggesting that hypertonic saline may be a useful resuscitation fluid in TBI. Vassar and colleagues[167] have conducted a series of studies investigating the use of hypertonic saline in trauma patients. Hypertonic saline did not increase the rate of bleeding.[167] Logistic regression of a trial of hypertonic saline (7.5%) *vs* Ringer's lactate in heterogeneous trauma patients, including TBI, found improved survival with hypertonic saline.[165] The addition of dextran did not appear to confer benefit or detriment.[168] A subgroup analysis of a further trial including more than 70% of patients with TBI found improved survival with hypertonic saline over Ringer's lactate in patients with GCS $\leq$8.[165] There is insufficient evidence at present to suggest which if any vasoactive agents should be used to support arterial pressure if fluids alone are insufficient.[39]

Mannitol

The Cochrane review could find no evidence to support the use of mannitol in head-injured patients.[173] Various studies have been published suggesting that administration of high dose mannitol (1.4 g kg^{-1}) is associated with improved outcome compared with normal dose (0.7 g kg^{-1}) after traumatic brain injury. However, serious questions have been raised about the conduct of these studies.[125]

Ventilatory support

As with arterial pressure, it has been easier to define what respiratory embarrassments to avoid than what to achieve. The American guidelines suggest $Sa_{O_2} \geq 90\%$ or $Pa_{O_2} \geq$60 mm Hg (8 kPa),[15 16] whereas the European guidance is slightly more aggressive with thresholds of 95% and 10 kPa.[87] The UK transfer guidance is more aggressive still setting a standard of 13 kPa.[155] For patients who are able to maintain their own airway, supplemental oxygen therapy is recommended. For patients unable to maintain oxygenation or their own airway then tracheal intubation may be required.

Hyper- and hypocapnia are both viewed as avoidable secondary insults, though the limits of Pa_{CO_2} vary between guidelines. The American guidance[15 16] suggests a lower limit of around 4.6 kPa, in accord with the UK guidance[155] (4.5–5.0 kPa), whereas the EBIC guidelines[87] suggest a lower Pa_{CO_2} (4.0–5.0 kPa). One study has found that a rather wider range of Pa_{CO_2} on arrival in the emergency department (3.9–6.4 kPa) is associated with improved survival in intubated, but not non-intubated patients (Table 9).[28]

Patients unable to communicate, with a GCS $\leq$8, unable to maintain their own airway, or achieve the respiratory targets are candidates for tracheal intubation and controlled ventilation.[15 16 87 155] There are some studies directly assessing the effect of early tracheal intubation, with conflicting results. One retrospective case–control study of severe TBI patients found that pre-hospital intubation was associated with an absolute reduction in mortality of 10–20%, but not with increased rates of discharge to home.[177] Other studies have found an increase in mortality with pre-hospital intubation.[29 106] One randomized controlled trial of bag-valve-mask ventilation followed by intubation *vs* bag-valve-mask ventilation alone in children with a short transfer time to hospital failed to demonstrate any benefit of tracheal intubation.[41] Time from injury to intubation does not appear to affect mortality or

morbidity.[84] Sub-optimal intubation and ventilation practice is associated with an increase in adverse outcomes. Various reports from the San Diego Paramedic Rapid Sequence Intubation trial highlighted the risks of pre-hospital intubation (by extended-training emergency medical technicians) using neuromuscular block. Tracheal intubation was associated with increased mortality except in the aeromedical transfer groups.[29] This has been attributed to the higher rates of hyperventilation in the ground transport groups and failure to prevent aspiration episodes.[26 27 31] At the time of the studies, most paramedics did not have end-tidal CO_2 monitoring, and patients were ventilated according to set protocols.[27] The introduction of end-tidal CO_2 monitoring reduced the rate of inadvertent hyperventilation.[26] The American guidelines[15 16] do not require end-tidal CO_2 monitoring, whereas the UK transfer guidelines do.[155]

Glycaemic control

Although hyperglycaemia is common and associated with worse outcome,[24 78 179] none of the major guidelines suggest what, if any, treatment should be instituted.[15 16 87 155] The study by Van den Berghe and colleagues[161] demonstrating mortality benefit with intensive insulin therapy (blood glucose $<6.1\ mmol\ l^{-1}$) in critically ill patients included only a small number of neurosurgical patients. A prospectively planned sub-group analysis demonstrated a small reduction of ICP, less need for vasopressors, a reduction in seizures and diabetes insipidus, and slightly improved long-term outcome in patients with isolated brain injury, not all of whom had TBI.[160] Concerns have been raised about the applicability of this approach to the general TBI population for several reasons.[34] One of the main beneficial effects of insulin therapy is a reduction in sepsis, which is the less common in the TBI population than the general surgical ICU; the brain is not dependent upon insulin for glucose uptake; hypoglycaemia is a cause of brain injury, and the rate of hypoglycaemia (blood glucose $<2.2\ mmol\ l^{-1}$) was five times as high in the intensive therapy group.[160] A microdialysis study by Vespa and colleagues[169] found that intensive insulin therapy (blood glucose $5.0–6.7\ mmol\ l^{-1}$) compared with loose control (blood glucose $6.7–8.3\ mmol\ l^{-1}$) was associated with reduced brain supply of glucose, and increased incidence of microdialysis markers of cellular distress. Mortality and 6-month outcome were similar in both groups. Of note, the loose control group is keeping blood glucose levels just below the range associated with good outcome.[78]

Imaging

CT is the preferred modality for initial assessment of TBI, over skull radiography and magnetic resonance imaging (MRI).[36] Although MRI can demonstrate more subtle lesions, particularly with diffuse injuries, it is largely impractical in the acute setting. CT is more sensitive for SAH, but for all other acute lesions the various sequences of MRI are equally or more sensitive.[43] The risk of finding radiological or clinically significant injuries on CT increases with severity of injury.[35 38 55 64 83 108 144 146] As a consequence of this, various groups have created decision trees to define which patients with minor head injuries should undergo CT scanning.

The two most comprehensive studies gave rise to the New Orleans[55] and Canadian[144] rules (Table 10). They are slightly different (see Table 10) largely based on whether *a priori* conditions were defined as necessitating scanning anyway (such as coagulopathy). In clinical practice, there is little to choose between them. The UK guidance has adopted a slightly modified version of the Canadian rules.[36]

More severe TBI is a clear indication for CT of the head. Furthermore, because these patients do not satisfy the criteria for successful clearance of the cervical spine, if possible spiral CT of the cervical spine should be carried out at the same time.

Other injuries

Head injury is the cause of death in around one-third of patients dying after trauma,[16] and major extra-cranial injuries are found in 50% of patients with severe TBI.[130] Early work suggested that significant extra-cranial injury resulted in significantly higher mortality for patients with TBI.[20] More recent work suggests that this may no longer be the case.[130] The assumption is that improved care of the injured patient after the introduction of Advance Trauma Life Support (ATLS®) and head injury guidelines has lessened the impact of secondary insults as a result of systemic trauma. Hypotension, particularly associated with hypovolaemia, is associated with worse outcome from TBI,[20] so the ATLS® priorities of resuscitation and control of haemorrhage still apply for patients with TBI.

Cervical spine injury is relatively common in patients with TBI. Around 5% of patients with moderate and severe TBI will have cervical spine injury, of whom over half may have cord injury, usually between occiput and C3.[60] The risk of significant spinal injury increases with

Table 10 CT scanning rules for minor head injury. GCS, Glasgow Coma Scale

New Orleans[55]	Canadian[144]
Short-term memory deficits (persistent anterograde amnesia with GCS 15)	Retrograde amnesia ≥30 min
Intoxication	Loss of consciousness ≥5 min
Physical evidence of trauma above the clavicles	Initial GCS 13
Age >60	Age >65
Seizure (suspected or witnessed)	Suspected open or depressed skull fracture
Headache	Sign of basal skull fracture
Vomiting	Vomiting
Coagulopathy	GCS <15 at 2 h after injury

increasing severity of injury.[60] Conversely, around a third of patients with cervical spine injury suffer moderate or severe head injury.[62] Appropriate care of the cervical spine is therefore important for all patients with TBI. The question of how to clear the cervical spine satisfactorily in the obtunded or comatose patient is a vexed one. Traditional three-view series (antero-posterior, lateral, and open mouth odontoid) are inferior to CT, with missed fracture rates of 40–50%, of which over half may be potentially unstable.[1 8 59 82] Most missed fractures occur at the difficult to see, and at risk areas of the craniocervical junction and the cervicothoracic junction.[1 8 59 82] CT may potentially miss soft tissue and cord injury which can be shown by MRI if there are no associated bony injuries. However, MRI has not been shown to make a significant clinical difference to the management of patients with TBI.[59] Because of the practicalities of transferring patients with TBI, and the speed of modern scanners, it is common practice to image the whole of the cervical and upper thoracic spine at the same time as the initial head CT.

Seizures

Seizures are relatively common after TBI with a reported incidence of early (<1 week) seizure of 4–25%. Various factors have been associated with increased seizure risk: GCS <10, cortical contusions, depressed skull fracture, epidural, subdural, or intracranial haematoma, penetrating head wound, or seizure within 24 h of injury.[152] Seizures increase cerebral metabolic rate, enhance neurotransmitter release and are associated with rises in ICP. Meta-analysis of trials of anti-epileptic drugs (phenytoin or carbamazepine) demonstrates efficacy in preventing seizures (relative risk of early seizure, 0.34), but no impact on mortality or incidence of seizures long-term.[131] The American guidelines suggest the use of anti-epileptics as a treatment option to prevent early seizures in high-risk patients.[16] The European guidelines do not mention the subject.[87]

Targeted therapy

On the background of the lack of evidence for benefit of any current management strategy, and a large body of animal TBI research, investigators have searched for novel pharmacological agents that can modify the natural history of TBI. To date, no agent has been shown to have a significant mortality or morbidity benefit in human TBI.

Calcium channel antagonists

Calcium channel antagonists, particularly nimodipine, have been shown to reduce the risk of death after aneurysmal SAH. Oligaemia, vasospasm, and SAH are common after TBI. Therefore, it was a logical step to investigate the use of calcium channel antagonists in TBI.[51 64 148] A dose of 1 mg increasing to 2 mg h^{-1} commenced early after head injury and continued for up to 3 weeks was found to have no significant effect on mortality.[51 64 148] One study found a beneficial effect on the rate of poor outcome (death and severe disability).[51] A Cochrane meta-analysis of relevant trials confirmed the lack of beneficial effect for general TBI.[79] Sub-group analysis suggests that there may be a small beneficial effect for the sub-group of patients with traumatic SAH. (Odds ratio 0.59, 95% CI 0.37–0.94.)[79]

Magnesium

Magnesium acts as calcium channel and *N*-methyl-D-aspartate (NMDA) receptor antagonist, and increases cerebral blood flow. It may therefore be expected to have beneficial effects in TBI. However, no benefit has been shown in Phase III studies.[5 17]

Amino-steroids

TBI causes mitochondrial dysfunction, which in turn produces oxygen free radicals which cause membrane lipid peroxidation, leading on to membrane dysfunction. Lazaroids are steroid derivatives, which inhibit lipid peroxidation but do not have the receptor-dependent steroid side effects. Pre-clinical studies in rats, mice, and cats demonstrated efficacy of tirilazad in reducing mortality and morbidity after head trauma. Human Phase III trials have however been disappointing and there is no evidence of benefit (or harm) from the administration of tirilazad 10 mg kg^{-1} every 6 h for 5 days, to patients with TBI, GCS 3–12 starting within 4 h of injury.[95 124]

Dexanabinol

Dexanabinol is a synthetic cannabinoid anatagonist. It has no psychotropic activity and inhibits glutamate excitotoxicity, inflammation, and free radical damage. Animal studies[138] and a Phase II trial in humans[74] suggested benefits when given after TBI. A large multi-centre placebo-controlled trial of 861 patients with blunt TBI, aged 16–65 yr with GCS motor score 2–5, no eye opening and at least one reactive pupil given a single dose of dexanabinol 150 mg within 6 h of injury found no evidence of benefit for mortality or long-term outcome.[89]

Glucocorticoids

Corticosteroids have been used for the treatment of head injury since the 1960s, since the findings that they reduced cerebral oedema associated with tumours. Methylprednisolone has been shown to be of benefit in acute spinal cord injury. However, meta-analysis of around 2000 patients in various trials found no evidence of benefit.[3] A subsequent large multi-centre trial was stopped early by the data monitoring committee after recruiting

10 000 patients with GCS ≤14, when excess 2-week mortality was found in the steroid group.[126] The cause for increased mortality is unclear and does not appear to have been because of infective or gastrointestinal complications. These results apply to the use of high-dose glucocorticoids. The issue of steroid replacement for critical illness-associated adrenal sufficiency after TBI is under investigation.[7 25]

Glutamate antagonists

Glutamate is an excitotoxin *in vitro* and may play a part in the pathophysiology of cellular injury after TBI. On this basis, various NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonists have been investigated as neuroprotective agents in TBI.[63 103] However, Phase II human trials have either not taken place (AMPA) or have shown no benefit.[63 103 157] Whether this failure is because of inadequate trial design, ineffective drugs, or poorly understood molecular mechanisms is not clear.[63 157]

Summary

In summary, TBI is common, with potentially devastating consequences. Despite decades of research, there are still very few data to define the best practice for managing TBI in its early stages. Hypotension, hypoxia, hyper- and hypocapnia, hyper- and hypoglycaemia all remain potentially avoidable insults, which are associated with worse outcome after TBI. There is no single treatment, which has been, or is likely in the future, to improve dramatically the outcome for patients with TBI. Adherence to national and international guidelines may be associated with improved outcome.

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