



Guidelines

Management of severe traumatic brain injury (first 24 hours)^{☆,☆☆}

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ABSTRACT

The latest French Guidelines for the management in the first 24 hours of patients with severe traumatic brain injury (TBI) were published in 1998. Due to recent changes (intracerebral monitoring, cerebral perfusion pressure management, treatment of raised intracranial pressure), an update was required. Our objective has been to specify the significant developments since 1998. These guidelines were conducted by a group of experts for the French Society of Anesthesia and Intensive Care Medicine (*Société française d'anesthésie et de réanimation* [SFAR]) in partnership with the *Association de neuro-anesthésie-réanimation de langue française* (ANARLF), The French Society of Emergency Medicine (*Société française de médecine d'urgence* (SFMU), the *Société française de neurochirurgie* (SFN), the *Groupe francophone de réanimation et d'urgences pédiatriques* (GFRUP) and the *Association des anesthésistes-réanimateurs pédiatriques d'expression française* (ADARPEF). The method used to elaborate these guidelines was the Grade[®] method. After two Delphi rounds, 32 recommendations were formally developed by the experts focusing on the evaluation the initial severity of traumatic brain injury, the modalities of prehospital management, imaging strategies, indications for neurosurgical interventions, sedation and analgesia, indications and modalities of cerebral monitoring, medical management of raised intracranial pressure, management of multiple trauma with severe traumatic brain injury, detection and prevention of post-traumatic epilepsy, biological homeostasis (osmolality, glycaemia, adrenal axis) and paediatric specificities.

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6. Introduction

The latest French guidelines for the management in the first 24 hours of patients with severe traumatic brain injury (TBI) were published in 1998 [1]. Due to recent changes (intracerebral monitoring, cerebral perfusion pressure management, treatment of intracranial hypertension), an update was required. We would like to highlight the major work done by experts in 1998 and advise readers to refer to it. A large part of the 1998 guidelines remains valid and we present updated recommendations in the present material. These guidelines refer to the early management of severe TBI, i.e. the first 24 hours after injury. Later management (> 24 hrs) and mild and moderate TBI patients have not been taken into consideration.

Guidelines for temperature control were not addressed in this document because of the concomitant publication of French guidelines on targeted temperature management in the ICU with a specific focus on brain-injured patients [2].

7. Methodology

These guidelines were conducted by a group of experts for the French Society of Anaesthesia and Intensive Care Medicine (Société française d'anesthésie et de réanimation [SFAR] in partnership with the Association de neuro-anesthésie-réanimation de langue française [Anarlf], the French Society of Emergency Medicine (Société Française de médecine d'urgence [SFMU]), the Société française de neurochirurgie [SFN], the Groupe francophone de réanimation et d'urgences pédiatriques [GFRUP], and the Association des anesthésistes-réanimateurs pédiatriques d'expression française [Adarpef]). The organising committee defined a list of questions to be addressed and designated experts in charge of each question. The questions were formulated using the PICO (Patient Intervention Comparison Outcome) format.

The method used to elaborate these guidelines was the GRADE[®] method. Following a quantitative literature analysis, this method was used to separately determine the quality of available evidence, i.e. estimation of the confidence needed to analyse the effect of the quantitative intervention, and the level of recommendation. The quality of evidence was rated as follows:

- high-quality evidence: further research is very unlikely to change the confidence in the estimate of the effect;
- moderate-quality evidence: further research is likely to have an impact on the confidence in the estimate of the effect and may change the estimate of the effect itself;
- low-quality evidence: further research is very likely to have an impact on the confidence in the estimate of the effect and is likely to change the estimate of the effect itself;
- very low-quality evidence: any estimate of the effect is very unlikely.

The level of recommendation was binary (either positive or negative), and strong or weak:

- strong recommendation: we recommend or we do not recommend (Grade 1+ or 1–);
- weak recommendation: we suggest or we do not suggest (Grade 2+ or 2–).

The strength of the recommendations was determined according to key factors and validated by the experts after a vote, using

the Delphi and Grade Grid method that encompasses the following criteria:

- the estimate of the effect;
- the global level of evidence: the higher the level of evidence, the stronger the recommendation;
- the balance between desirable and undesirable effects: the more favourable the balance, the stronger the recommendation;
- values and preferences: in case of uncertainty or large variability, the level of evidence of the recommendation is probably weak, and values and preferences must be more clearly obtained from the affected persons (patient, physician and decision-maker);
- cost: the greater the costs or the use of resources, the weaker the recommendation.

The elaboration of a recommendation requires that at least 50% of voting participants have an opinion and that less than 20% of participants vote for the opposite proposition. The elaboration of a strong agreement requires the agreement of at least 70% of voting participants.

The guidelines on the management at the early phase of severe TBI were analysed by 32 experts according to 11 topics:

- how to describe and evaluate the initial severity of traumatic brain injury patients?
- what are the modalities of prehospital management for severe traumatic brain injury patients?
- imaging strategies in severe traumatic brain injury patients;
- indications for neurosurgical interventions (cerebral monitoring excluded);
- sedation and analgesia;
- indications and modalities of cerebral monitoring in severe traumatic brain injury patients;
- medical management of raised intracranial pressure;
- management of multiple trauma with severe traumatic brain injury;
- detection and prevention of post-traumatic seizures;
- biological homeostasis (osmolarity, glycaemia, adrenal axis);
- paediatric specificities of severe traumatic brain injury.

The PubMed and Cochrane databases were searched for full articles written in English or French, and published after 1998. A specific analysis was performed for TBI in paediatric patients.

The level of evidence of the literature focused on TBI is globally associated with a weak level of methodology. The analysis of the literature led to three situations:

- in the presence of clinical trials or meta-analyses with an acceptable methodological quality, the GRADE[®] method was applicable;
- when no meta-analysis was available, a qualitative analysis by the experts following the GRADE[®] method was performed;
- in the absence of recent studies, no recommendation was made.

After the implementation of the GRADE[®] method, 32 recommendations were formally developed by the organising committee: 10 were strong (Grade 1±), 18 were weak (Grade 2±), and 4 were expert opinions because GRADE[®] methodology was not applicable.

All recommendations were submitted to a reviewing group for a Delphi method assessment. After 2 rounds of voting and evaluation and after various amendments, a strong agreement was reached for 32 (100%) recommendations.

8. How to describe and evaluate the initial severity of traumatic brain injury patients?

R1.1 – We recommend assessing the severity of traumatic brain injury using the Glasgow coma scale, specifically the motor response, as well as pupillary size and reactivity.

Grade 1+, Strong agreement

Argument:

The initial clinical evaluation of severe TBI has not significantly changed since the 1998 French Guidelines [1].

Age, initial Glasgow coma scale, and pupillary size and reactivity are key issues of the neurological outcome at 6 months, even in the recent studies [3–10]. The IMPACT [11] and CRASH [12] studies, including respectively 6681 and 8509 patients, have validated these criteria.

The Glasgow coma scale must be described according to each of the 3 components, according to the original description, *i.e.* Eye-Verbal-Motor response [13,14].

However, the correlation between the Glasgow coma score and outcome has become less evident in recent studies [6]. The extensive use of sedation and tracheal intubation on scene has disabled the assessment of eye and verbal responses. The motor component remains robust in sedated patients and it is well correlated with the severity of head trauma. A simplified assessment of TBI patients based on the motor response has been proposed [11,15–23].

In order to detect secondary neurological aggravation, clinical examination has to be repeated during the initial management of the patient [24–26]. The rhythm of this recurrent examination is left at the discretion of the in-charge physician, but it must be continued after the hospital admission [5,24].

Moderate TBI patients, *i.e.*, with a Glasgow coma score between 9 and 13, have a significant risk of secondary neurological degradation [5]. In this situation, the rhythm of neurological examination can be planned every hour in Australia [27]; every 30 min for the first 2 hours and then every hour during the 4 following hours in the United Kingdom [28]; or every 15 min during the first 2 hours and then every hour for the following 12 hours in Scandinavia [29]. The occurrence of a secondary neurological deficit or a decrease of at least two points in the Glasgow coma score should lead to a second CT scan [27–30].

R1.2 – We recommend investigating and correcting systemic factors of secondary cerebral insults.

Grade 1+, Strong agreement

Argument:

Arterial hypotension at the initial phase of TBI is a key issue associated with a poor prognosis at 6 months [11,31]. The Traumatic Coma Data Bank showed that the occurrence of episodes of arterial hypotension (systolic blood pressure < 90 mmHg) for at least 5 minutes was associated with a significant increase in neurological morbidity and mortality [32]. Prehospital and intrahospital arterial hypotension is associated with an increased mortality [33–35]. The 2014 French Guidelines on haemorrhagic shock recommended maintaining a mean arterial pressure \geq 80 mmHg in severe TBI patients.

Hypoxemia occurs in approximately 20% of patients with traumatic brain injury [35]. It is associated with increased mortality and aggravated neurological outcome. The IMPACT study found that the presence of hypoxia was significantly associated with poor neurological outcome at 6 months [11]. Furthermore, the duration of hypoxemic episodes ($\text{SaO}_2 \leq 90\%$) is an important predictor of mortality [36].

The association of arterial hypotension and hypoxemia appears to be particularly deleterious with a 75% mortality rate [37].

Protocols on the detection and correction of these secondary insults are associated with an improvement of the outcome of

brain-injured patients [1,38]. A retrospective study comparing before-after implementation of protocols focused on intracranial pressure monitoring and the prevention of secondary insults found a significant reduction in mortality after such implementation [39].

R1.3 – We recommend assessing the initial severity of traumatic brain injury on clinical and radiological criteria (CT scan).

Grade 1+, Strong agreement

Argument:

Brain and cervical CT scans should be performed systematically and without delay in any severe (Glasgow coma scale \leq 8), or moderate (Glasgow coma scale 9–13) TBI.

Patients with mild TBI (Glasgow coma scale 14–15) should have a brain CT scan if they meet the followings: signs of fracture of the basal skull (rhinorrhoea, otorrhea, haemotympan, retroauricular haematoma, periorbital haematoma), displaced skull fracture, post-traumatic epilepsy, focal neurological deficit, coagulation disorders, anticoagulant therapy [25,28–30].

R1.4 – We suggest using transcranial Doppler to assess the severity of traumatic brain injury.

Grade 2+, Strong agreement

Argument:

In TBI patients, cerebral perfusion pressure (CPP) may be estimated by the calculation of Pulsatility Index (PI), a parameter derived from the measurement of diastolic, systolic and mean blood flow velocities [40]. Transcranial Doppler (TCD) has gained interest to estimate brain haemodynamics in the intensive care unit. However, there are limited data on the use of TCD in patients with traumatic brain injury upon their arrival at the hospital. These studies found an association between higher mortality rate and a mean blood flow velocity (Vm) below 28 cm/s [41] or a combination of a low Vm and high PI [42]. In 36 children, a diastolic blood flow velocity (Vd) of less than 25 cm/s or a PI greater than 1.3 was associated with poor outcome [43]. After moderate or mild TBI patients (Glasgow coma score 9–14), PI value on admission was higher in patients with a secondary neurological degradation within the first week post-trauma [44]. In a subsequent study, thresholds for predicting secondary neurological degradation in this population were 25 cm/s for Vd and 1.25 for PI [45]. In severe TBI patients (Glasgow score < 9), a strategy based on TCD measurements on admission to the emergency room was described [46]: if the patient had Vd < 20 cm/s and PI > 1.4, therapeutic measures were taken to improve brain perfusion.

Using TCD on arrival at the hospital should be part of the initial assessment of multiple trauma patients, and be included in the Focused assessment with sonography for trauma (FAST).

R1.5 – We do not suggest using biomarkers in clinical routine to assess the initial severity of traumatic brain injury patients.

Grade 2-, Strong agreement

Argument:

In addition to the initial assessment using the Glasgow coma scale (GCS) and brain CT imaging, the use of biomarkers has been proposed to provide more information on the severity of TBI.

An association was found between neurological outcome at 3 and 6 months and the following biomarkers: plasma S100 β [47,48], neuron specific enolase (NSE) [49,50], ubiquitin C-terminal hydrolase-L1 (UCH-L1) [51–53], glial fibrillary protein acid (GFAP) [48,49], myelin-basic protein (MBP) [54,55] and tau protein [56]. Similar findings were observed in the cerebrospinal fluid with S100 β protein [47], UCH-L1, SBDPs [57,58] and

tau protein [59]. However, uncertainties still remain in the performance of these biomarkers, particularly serum biomarkers, to evaluate the initial severity of TBI patients [60].

9. What are the modalities of prehospital management for severe TBI patients?

R2.1 – We recommend managing severe TBI patients by a pre-hospital medicalised team on scene and transferring them as soon as possible to a specialised centre including neurosurgical facilities.

Grade 1+, Strong agreement

Argument:

In trauma injuries, TBI was shown to mostly benefit from admission to specialised centres in terms of survival rates [61–69]. The management of severe TBI patients in a specialised neuro-intensive care was associated with improved outcome [70,71].

In a retrospective study comparing two periods (before/after the creation of a neuro-intensive care unit), the neurological outcome was significantly improved in the latter period, after adjusting for other factors such as Glasgow coma scale, age, or occurrence of arterial hypotension upon arrival [70]. For illnesses with the same severity, the mortality rate was lower in neurosurgical centres compared to non-specialised centres, even for patients who did not require neurosurgical procedure. [68]. This is due to expertise accumulated from large inflows of these patients and to the availability of neurosurgeons. The non-specialised centres should be able to early detect patients who need a transfer to a specialised centre.

R2.2 – In adults, we suggest maintaining a systolic blood pressure > 110 mmHg prior to measuring cerebral perfusion pressure.

Grade 2+, Strong agreement

Argument:

The neurological outcome is undoubtedly worsened after a single episode of hypotension (systolic blood pressure < 90 mmHg) during the early phase of TBI [72–75]. More recently, mortality rate was found markedly raised where systolic blood pressure dropped below 110 mmHg at admission [63,76,77].

Prevention of any episode of arterial hypotension is critical: no hypotensive hypnotic agent to induce sedation, continuous sedation rather than bolus of sedatives, correction of hypovolaemia if needed, mechanical ventilation adjusted to facilitate central venous return [78–80]. Rapid correction of arterial hypotension should include vasopressor drugs such as phenylephrine and norepinephrine. Decreasing doses of sedatives or increasing fluids may have delayed effects on haemodynamics. Catecholamines can be initially infused through an indwelling catheter in a peripheral vein.

R2.3 – We recommend controlling the ventilation of severe traumatic brain injury patients throughout tracheal intubation, mechanical ventilation, and end Tidal CO₂ monitoring even during the pre-hospital period.

Grade 1+, Strong agreement

Argument:

Airway control is a priority and pre-hospital tracheal intubation decreases mortality of trauma patients [81–83]. The arterial partial pressure of CO₂ (PaCO₂) has a strong impact on cerebral circulation. Hypocapnia induces cerebral vasoconstriction, and is a risk factor for brain ischaemia [82,84]. Monitoring of end-tidal CO₂ (EtCO₂) in intubated patients is critical to check the correct placement of tracheal tube, to maintain PaCO₂ within a

normal range and to detect a possible decrease in cardiac output [85–88]. An EtCO₂ between 30–35 mmHg is recommended prior to getting arterial gas samples to adjust mechanical ventilation.

10. Imaging strategies in severe traumatic brain injury patients

R3.1 – We recommend performing a brain and cervical computed tomography (CT) scan without delay in severe traumatic brain injury patients.

Grade 1+, Strong agreement

Argument:

The exploration of the entire brain with nested, inframillimetric sections reconstructed with a thickness of more than one millimetre is the reference CT method in TBI.

The sections should be visualised with double fenestration, i.e., central nervous system and bones.

Due to its availability, the CT scan is the first choice to make the diagnosis of the primary brain lesions [89]. It must be carried out without delay in case of coma or abnormal neurological examination. The initial CT scan can guide neurosurgical procedures and monitoring techniques [90,91].

R3.2 – We suggest performing an early exploration of the supra-aortic and intracranial arteries using CT-angiography in patients with risk factors.

Grade 2+, Strong agreement

Argument:

The risk factors for traumatic dissection of supra-aortic and intracranial arteries are [92]:

- presence of a fracture of the cervical spine;
- focal neurological deficit not explained by brain imaging;
- Claude Bernard-Horner syndrome;
- Lefort II or III type facial fractures;
- fractures of the basal skull;
- soft tissue lesions at the neck.

These risk factors should lead to an exploration of the supra-aortic and intracranial vessels by CT-angiography. Even in the absence of these risk factors, indications of this exam can be extended, especially in the most severe patients in whom the neurological examination may be limited [93,94]. In case of a strong suspicion of arterial dissection, a normal CT-angiography should be completed with a MR-angiography or a digital subtraction angiography [95–97].

11. Indications for neurosurgical interventions (cerebral monitoring excluded)

R4.1 – We suggest performing external ventricular drainage to treat persisting intracranial hypertension despite sedation and correction of secondary brain insults.

Grade 2+, Strong agreement

Argument:

Drainage of cerebrospinal fluid (CSF) from normal or small volume ventricles is a therapeutic option to control intracranial pressure. Although mentioned in studies [98], the efficacy of this procedure lacks strong evidence. Subtraction of a small volume of CSF may reduce markedly the intracranial pressure. External ventricular drain can be inserted using neuronavigation [99].

In addition, after failure of first-line treatment of intracranial hypertension, the removal of brain contusions with mass effect is also an option [100].

The neurosurgical indications at the early phase of severe TBI patient are:

- removal of a symptomatic extradural haematoma whatever its location,
- removal of a significant acute subdural haematoma (thickness greater than 5 mm with displacement of the median line greater than 5 mm),
- drainage of acute hydrocephalus
- closure of open displaced skull fracture.
- a closed displaced skull fracture with brain compression (thickness > 5 mm, mass effect with displacement of the median line > 5 mm).

R4.2 – We suggest performing a decompressive craniectomy to control intracranial pressure at the early phase of TBI where refractory intracranial hypertension in a multidisciplinary discussion.

Grade 2+, Strong agreement

Argument:

Four clinical trials including more than 1000 patients have investigated the efficacy of decompressive craniectomy after TBI [101–104]. The place of craniectomy in the therapeutic strategy varied across studies, i.e. used as a rescue strategy in refractory intracranial hypertension, or early, in the first 72 hours, before the initiation of therapeutic hypothermia and barbiturates. The most commonly used technique is a large temporal craniectomy (> 100 cm²) with enlarged dura mater plasty. The bifrontal craniectomy, indicated in patients with diffuse lesions, was used in some studies. Aging was an exclusion criterion with a threshold set at 60 years (1 study), 65 years (2 studies) and 70 years (1 study). The decision must be taken on a case-by-case basis. Good outcome, as defined by the Glasgow Outcome Scale (GOS) score of 4 or 5 at 6 months post-trauma, were 28–32% in the control group versus 40–57% after a unilateral craniectomy ($P=0.03$) [102,103]. In the DECRA study, a bifrontal craniectomy was associated with poor outcome: the extended GOS (E-GOS) score of 1–4 (poor outcome) measured at 6 months, was 51% in the control group versus 70% in the intervention group ($P=0.02$) [104]. The RESCUE-ICP study included patients with refractory intracranial hypertension and randomised patients to undergo either decompressive craniectomy (201 patients) or barbiturates coma (188 patients). In the decompressive craniectomy group, the mortality rate was reduced to 26.9% (vs. 48.9% in the medical group), at the expense of more patients with poor neurological outcome (8.5% versus 2.1%). Favourable outcome at 6 months was not different between the two groups: 26.6% in the medical group versus 27.4% in the intervention group [105].

12. Sedation and analgesia

R5.1 – Apart from the treatment of intracranial hypertension and convulsive status epilepticus, the maintenance and cessation of sedation and analgesia in patients with severe TBI should follow the guidelines for non-brain injured patients.

Experts' opinion

Argument:

The current guidelines on sedation and analgesia in the ICU [106] should be extended to stabilised brain-injured patients. Although scarcely studied, the use of clinical scores and the implementation of protocols to manage sedation and analgesia may provide benefits [107,108]. The daily interruption of sedation may be deleterious to cerebral haemodynamics in

patients with low intracranial compliance [109,110]. No evidence was found that one sedative or opioid agent provided more efficacy than another in TBI patients. Arterial hypotension can be observed with barbiturates [111], bolus of midazolam [112] or bolus of opioids [113]. Attention should be paid to the control of systemic haemodynamics in the choice of drugs and their modalities of administration. Insufficient data exist with the use of halogenated agents and dexmedetomidine in TBI patients.

13. Indications and modalities of cerebral monitoring in severe traumatic brain injury patients

R6.1 – We suggest monitoring intracranial pressure (ICP) after severe TBI to detect intracranial hypertension in the following cases:

- signs of high ICP on brain CT scan;
- extracranial surgical procedures (except life-threatening conditions);
- neurological evaluation not feasible.

Grade 2+, Strong Agreement

Argument:

Although the benefit of ICP monitoring on patient outcome has not been clearly demonstrated, this technique has become an integral part of the management of severe TBI patients [114]. Retrospective and observational studies have estimated the risk of intracranial hypertension after severe TBI [115–118]. The incidence of high ICP varies between 17 and 88% [119–122]. An ICP of 20–40 mmHg is associated with a higher risk of 3.95 (95% confidence interval [1.7–7.3]) of mortality and poor neurological outcome [123]. Above an ICP of 40 mmHg, mortality risk is 6.9 times higher (95% confidence interval [3.9–12.4]).

The impact of intracranial hypertension on the outcome requires the use of ICP monitoring in patients whose neurological assessment is not feasible.

When the initial CT-scan is abnormal, more than 50% of patients will present intracranial hypertension [115]. Among the usual CT scan criteria of intracranial hypertension, i.e. the disappearance of cerebral ventricles, brain midline shift over 5 mm, intracerebral haematoma volume over 25 mL [124], the compression of basal cisterns appears to be the best sign to reflect intracranial hypertension [119]. The absence of basal cisterns is associated with an ICP higher than 30 mmHg in more than 70% of cases [125]. However, their visibility cannot exclude intracranial hypertension [126]. The presence of traumatic subarachnoid haemorrhage is associated with a risk of intracranial hypertension [126].

In the case of emergency extracranial surgery, apart from life-threatening surgery, several studies found a high incidence of cerebral hypoperfusion due to arterial hypotension associated with high ICP. A decrease in intraoperative cerebral perfusion pressure below 70 mmHg and 50 mmHg was found in 26–74% of patients [127,128] and in 45% of patients [129], respectively. This reduced perfusion pressure aggravates primary and secondary brain lesions and worsens brain oedema [130–132].

R6.2 – We do not suggest monitoring intracranial pressure if the initial CT-scan is normal with no evidence of clinical severity, and/or transcranial Doppler abnormalities.

Grade 2-, Strong Agreement

Argument:

Although a normal CT-scan cannot exclude the risk of subsequent intracranial hypertension in comatose patients,

the incidence of raised ICP is particularly small when the initial CT-scan is normal (0–8%) [133–135]. Recent advances in CT scan imaging may explain the good performance of CT to rule out intracranial hypertension [136,137].

ICP monitoring, particularly with the reference method of intraventricular drain, is associated with complications: catheter placement failure (10%) [115,138], infection (10% for intraventricular drains [139] and 2.5% for intraparenchymal fiberoptic devices [140]), and intracerebral haemorrhage (2–4% for intraventricular drains and 0–1% for intraparenchymal fiberoptic devices [115,141]). Moreover, the benefit of ICP monitoring has not been clearly demonstrated. The randomised controlled study BEST-TRIP (347 patients) found no difference in neurological outcome between ICP monitoring and clinical surveillance with repeated CT-scans [142]. Although the external validity of this study is lacking, the results of that study should be considered. In severe TBI patients with strictly normal initial CT-scan, the risk-benefit balance does not support indication for invasive ICP monitoring. If the neurological surveillance is not feasible and/or if the patient has haemodynamic instability, the risk-benefit balance should be considered on a case-by-case basis. If ICP monitoring is indicated, intraparenchymal probes may be preferred over intraventricular drains (risk-benefit balance).

R6.3 – We suggest monitoring ICP after post-traumatic intracranial haematoma evacuation (subdural, epidural or intraparenchymal) in the case of (only 1 criterion is required):

- preoperative Glasgow Coma Scale motor response inferior or equal to 5;
- preoperative anisocoria or bilateral mydriasis;
- preoperative haemodynamic instability;
- preoperative severity signs on cerebral imaging (compressed basal cisterns, brain midline shift over 5 mm, presence of other intracranial lesions);
- intraoperative cerebral oedema;
- postoperative appearance of new intracranial lesions on cerebral imaging.

Grade 2+, Strong Agreement

Argument:

No randomised study has evaluated the benefit of postoperative ICP monitoring after evacuation of post-traumatic intracranial haematoma (subdural, epidural or intraparenchymal). However, in that situation, the incidence of postoperative intracerebral haematoma ranges between 50% [143] and 70% [144]. More than 40% of these patients will have uncontrollable intracranial hypertension [144,145], following haemodynamic instability [146] or initial neurological signs of severity such as preoperative Glasgow Coma Scale motor response inferior or equal to 5, anisocoria, or haematoma volume greater than 25 mL [147]. An increase in ICP may be due to secondary bleeding after decompression or reperfusion, to a new extra-axial collection, or to an increased brain oedema. Retrospective studies have found benefits of postoperative ICP monitoring after decompressive craniectomy [148,149].

R6.4 – Multimodal monitoring with transcranial Doppler and/or brain tissue oxygenation pressure measurements may be used to optimise cerebral blood flow and oxygenation in severe TBI patients.

Experts' opinion

Argument:

Transcranial Doppler cannot be considered as a non-invasive ICP monitoring. Nevertheless, a weak relationship

between the pulsatility index and cerebral perfusion pressure was found [150–152]. Voulgaris et al. [153] found that the pulsatility index measurement can detect patients at risk of reduced cerebral perfusion pressure. Transcranial Doppler can also exclude the risk of severe intracranial hypertension with a negative predictive value of 88% for a 1.26 cut-off for pulsatility index [154].

Brain tissue oxygenation pressure (PbtO₂) reflects the oxygen supply and diffusion in the interstitial space of brain tissue. The risk for brain ischaemia has been set for PbtO₂ less than 15 mmHg [155]. This risk of ischaemia is also linked to the duration of hypoxic episodes. The time spent under the ischaemic threshold is a determinant factor for irreversible damage. Van den Brink et al. have proposed different ischaemic thresholds: < 5 mmHg for 30 min, < 10 mmHg for 1 hr and 45 min, < 15 mmHg for 4 hrs [156]. PbtO₂ is correlated with local cerebral blood flow, cerebral perfusion pressure, haemoglobin content and PaO₂. A brain tissue response to hyperoxia can be observed. A strong reactivity to oxygen challenge may reflect a loss of cerebral autoregulation [157].

PbtO₂ monitoring is gaining interest to prevent cerebral ischaemia despite normal cerebral perfusion pressure. This monitoring can be used to determine an optimal cerebral perfusion pressure [158]. This strategy might allow optimising treatment during the evolution course of the brain insult. Narotam et al. [159] have retrospectively compared the outcome (survival and neurological outcome at 6 months) after the implementation of a PbtO₂ protocol to maintain PbtO₂ higher than 20 mmHg. An improvement in the outcome was found in this group by comparison with the historical control group managed with intracranial pressure/cerebral perfusion pressure protocol. Similar findings were found by Spiotta et al. [160]. However, the uncontrolled and retrospective nature of these studies cannot allow drawing definitive conclusions on the interest of PbtO₂ in TBI patients.

14. Medical management of raised intracranial pressure

R7.1 – We suggest individualising the objectives of intracranial pressure and cerebral perfusion pressure.

Grade 2+, Strong Agreement

Argument:

The level of ICP associated with poor neurological prognosis is variable in the literature. An ICP higher than 20–25 mmHg is usually admitted as a criterion to initiate therapies. Retrospective and prospective studies have determined ICP values associated with unfavourable outcome [161–168], but effects of ICP monitoring on outcome varied [169–171]. The duration of high ICP is a factor of poor prognosis [172,173], but the direct benefit of ICP monitoring remains controversial [142,174,175]. Moreover, no definite ICP threshold was associated with outcome [176–178]. In this context, recent studies argue in favour of an individualised treatment based on beat-by-beat cerebral autoregulation assessment from the relation between ICP and mean arterial pressure (Pressure Reactivity Index or PRx) [162,163,179–182].

The “optimal” cerebral perfusion pressure (CPP) would correspond to the CPP value for which the autoregulation of cerebral blood flow shows the best vascular response. Recent studies found that the best outcome could be obtained when the actual CPP is close to the optimal calculated CPP [179,180,182,183]. Any deviation from this optimal CPP was associated with poor outcome. These studies support an individualised approach of CPP according to autoregulation status.

R7.2 – In adults, we suggest maintaining cerebral perfusion pressure between 60 and 70 mmHg in the absence of multimodal monitoring.**Grade 2+, Strong Agreement****Argument:**

Measurement of ICP allows the determination of cerebral perfusion pressure (CPP) (CPP = MAP-ICP). In the absence of consensus, it is recommended to place the reference point to measure MAP at the external ear tragus [184,185]. A CPP > 70 mmHg is not recommended in routine for all patients. In one randomised controlled trial comparing a strategy maintaining CPP > 70 mmHg versus a strategy maintaining an ICP < 20 mmHg and a CPP > 50 mmHg, the high CPP group had a 5 times higher incidence of respiratory distress syndrome, while no effect was found on the neurological outcome [186]. A CPP < 60 mmHg has been shown to be associated with poor outcome [162,164,165,177,178].

A CPP value higher than 90 mmHg was associated with a worsening of the neurological outcome, due to a possible aggravation of vasogenic cerebral oedema [165].

One study compared two strategies conducted in two centres in Sweden and Scotland. In Sweden, the primary objective was keeping the ICP < 20 mmHg and the CPP around 60 mmHg as a secondary objective (low CPP), while in Scotland, the primary objective aimed at maintaining the CPP > 70 mmHg and PIC < 25 mmHg as a secondary objective (high CPP) [181]. Patients with altered cerebral autoregulation had a better outcome with the ICP-based protocol (low CPP). Patients with preserved autoregulation had a better outcome with the CPP-based protocol. In another retrospective study, CPP < 60 mmHg was associated with a better prognosis when autoregulation was impaired [187].

R7.3 – We recommend using mannitol 20% or hypertonic saline solution, at a dose of 250 mOsm, in infusion of 15–20 minutes to treat threatened intracranial hypertension or signs of brain herniation after controlling secondary brain insults.**Grade 1+, Strong Agreement****Argument:**

Osmotherapy causes a transient increase in the osmolarity of the extracellular space, inducing an osmotic pressure gradient on the blood-brain barrier and a water displacement to the hypertonic environment. Osmotherapy reduces the intracranial pressure (ICP) with a maximum effect observed after 10–15 minutes and for a duration of 2–4 hours, in order to restore cerebral blood flow (CBF). Of the three therapies that decreased ICP, i.e. mannitol, external ventricular drainage, and hyperventilation, mannitol only was associated with improved cerebral oxygenation [188]. Outside the hospital, osmotherapy is the treatment of choice in patients with signs of brain herniation (mydriasis, anisocoria) and/or neurological worsening not attributable to a systemic cause. On the other hand, a prophylactic administration of hypertonic saline solution to patients with no evidence of intracranial hypertension was not superior to crystalloids regarding the outcome [189,190].

At equiosmotic dose (about 250 mOsm), mannitol and hypertonic saline (HS) have comparable efficacy to treat intracranial hypertension [191,192]. Side effects of these osmotic agents should be considered: mannitol induces osmotic diuresis and requires volume compensation while HS exposes to hypernatremia and hyperchloremia. In both cases, monitoring fluid, sodium and chloride balances is necessary.

R7.4 – We do not suggest using prolonged hypocapnia to treat intracranial hypertension.**Grade 2-, Strong Agreement****Argument:**

Hypocapnia was one of the first-line options to treat intracranial hypertension. The only prospective randomised study

that studied the effect of severe and prolonged hypocapnia (25 ± 2 mmHg for 5 days) compared to normocapnia (35 ± 2 mmHg) found worsened neurological outcome in the hypocapnic group [193]. This deleterious effect is due to the exacerbation of secondary ischaemic lesions even for moderate hypocapnia (30 mmHg), decreased cerebral blood flow and increased oxygen extraction, with inconsistent effects on cerebral metabolism [84,194–197]. Thus, prolonged and/or severe hyperventilation to control intracranial hypertension is not recommended in the absence of cerebral oxygen measurement to ensure that cerebral hypoxia is not induced by this procedure.

R7.5 – We do not suggest using 4% albumin solution in severe TBI patients.**Grade 2-, Strong Agreement****Argument:**

The SAFE study [198], that recruited nearly 7000 patients, compared the administration of 0.9% saline serum versus 4% albumin in patients admitted to intensive care. At 28 days, no difference in mortality or organ failure was found between the two groups. However, severe TBI patients who received 4% albumin solution had higher mortality rates than those with 0.9% saline serum (24.5% vs. 15.1%, RR: 1.62, CI 95%: 1.12–2.34, *P* = 0.009). A subgroup analysis conducted by Myburgh et al. [199] with a 2-year follow-up of 460 patients (including 318 severe TBI) found an increased risk of mortality after albumin administration (41.8% vs. 22.2%, respectively; RR: 1.88, 95% CI 1.31–2.7, *P* < 0.001). The hypotonic nature of the 4% albumin infusion may have played a role. If severe TBI is associated with haemorrhagic shock, the use of albumin is not recommended [200]. The European Society of Intensive Care Medicine (ESICM) did not recommend using albumin solution after brain injury [201].

15. Management of multiple trauma with severe traumatic brain injury**R8.1 – In multiple trauma with severe TBI, a whole body CT-scan is considered once haemodynamics and respiratory function are stabilised.****Experts' opinion****Argument:**

In trauma patients with haemodynamic instability, the incidence of neurosurgical lesions is low compared to lesions requiring urgent surgical haemostasis (2.5% vs. 21%) [202]. In unstable patients, haemostasis and haemodynamics should be stabilised prior to considering a whole body CT-scan. Although the benefits of a whole body CT-scan on mortality in severe trauma patients did not reach significance (RR: 0.91, 95% CI: 0.79–1.05) [203], the whole-body CT-scan was found more effective to reduce mortality rate in severe trauma patients compared to segmental CT-scan [204,205].

R8.2 – Apart from life-threatening conditions requiring urgent surgery, haemorrhagic procedure is not recommended in the context of intracranial hypertension.**Experts' opinion****Argument:**

In severe TBI patients, major surgery with haemorrhage, low arterial blood pressure and blood transfusion can contribute to secondary insults to the brain and aggravate the initial injury and cerebral oedema, increase the risk of developing severe lung injury or even multiple organ failure [130,132,206].

Non-haemorrhagic surgical procedures, e.g. orthopaedic surgery, can be performed early (less than 24 hours) in stabilised brain-injured patients in the absence of intracranial

hypertension. Of 13 studies including patients with traumatic brain injury, none found increased mortality or poor neurological outcome with early surgical procedures [206,130].

R8.3 – We suggest measuring intracranial pressure during extracranial surgical procedure in severe TBI patients.

Grade 2+, Strong Agreement

Argument:

The neurological monitoring of these patients is essential to limit episodes of decreased cerebral perfusion pressure.

Pietropaoli et al. studied the haemodynamic effects of extracranial surgery in the first 72 hours after severe TBI [207]. Thirty-two percent of patients had episodes of intraoperative arterial hypotension (systolic blood pressure < 90 mmHg). These patients had a mortality of 82%, whereas patients without intraoperative arterial hypotension had a mortality of 32%.

16. Detection and prevention of post-traumatic seizures

R9.1 – We do not suggest using antiepileptic drugs for primary prevention to reduce the incidence of post-traumatic seizures (early and delayed).

Grade 2-, Strong Agreement

Argument:

In the study of Annegers et al. on post-traumatic seizure, the incidence of early clinical seizures (within 7 days after the brain injury) was 2.2%, the incidence of delayed seizures (after 7 days) was 2.1%, but it was 11.9% in the first year for the severe TBI patients [208]. This retrospective study with 4541 minor, moderate and severe TBI did not mention the use of antiepileptic prophylaxis or electroencephalogram recordings. In this study, risk factors for delayed clinical seizures were brain contusion, acute subdural haematoma, skull fracture, initial loss of consciousness or amnesia for more than 24 hours and age over 65 years [208,209]. The occurrence of early seizures did not expose to late seizures in the multivariate analysis. More recently, craniectomy has been identified as a possible risk factor for early post-traumatic seizures [210,211].

The study by Temkin et al. [212] and ancillary studies [213,214] have been integrated in the bibliographic analysis, given their importance.

Eleven clinical trials studied primary prevention of post-traumatic seizures: 2 compared phenytoin versus placebo or no treatment (1101 patients) [215,216], 7 phenytoin versus levetiracetam (1392 patients) [217–223], and 2 valproate versus phenytoin or no treatment (291 patients) [224,225]. Three studies were prospective and 8 retrospective. Three studies included electroencephalogram recordings [217,218,220]. Two meta-analyses have been added [226,227]. Apart from the study by Radic et al. [222], including acute and subacute subdural haematomas, none of these studies specifically assessed aforementioned risk factors for post-traumatic seizure.

All studies had a low level of evidence. Apart from the Cochrane 2015 meta-analysis, which was in favour of phenytoin prevention to early post-traumatic seizures including many studies published before 1998 [227], no significant effect of antiepileptic drugs (AEDs) was found to prevent the occurrence of early or delayed post-traumatic seizures. Moreover, increased side effects of phenytoin were shown [218,219,222,223,227] or even a worsening of the neurological outcome with AEDs [214,216,218].

Overall, prevention of post-traumatic seizures with AEDs cannot be recommended. It can be considered in case of risk factors, e.g. chronic subdural haematoma, or past history of epilepsy. In this case, levetiracetam should be preferred to phenytoin, because of a higher degree of tolerance.

There is no specificity in the treatment of seizures or epileptic status after severe TBI.

17. Biological homeostasis (osmolarity, serum glucose, adrenal axis)

R10.1 – In adults, we do not suggest using prolonged hypernatremia to control intracranial pressure in severe TBI patients.

Grade 2-, Strong Agreement

Argument:

Hypertonic Saline (HS)-induced hypernatremia is derived from the effects of bolus of HS to decrease ICP. A continuous infusion of HS to induce serum hyperosmolarity is postulated as effective to decrease cerebral oedema and ICP, and possibly to improve the outcome. However, there is no trial to validate this hypothesis. In paediatrics, the HS group required fewer interventions to maintain ICP < 15 mmHg than a control group receiving Ringer lactate [228]. However, serum sodium concentrations and osmolarity in the HS group were not reported. There are arguments not in favour of the use of controlled hypernatremia after TBI:

- the theoretical beneficial effect of hypernatremia supposes an intact blood-brain barrier (BBB) to create an osmotic gradient. The perfusion of HS could be deleterious with disrupted BBB by increasing the size of cerebral contusions [229];
- the rapid regulation of the brain cell volume limits the effectiveness of a prolonged hyperosmolarity: intracellular osmoles are synthesised to restore normal cell volume. There is then a risk of a “rebound” of ICP during the correction of hypernatremia;
- the relationship between serum sodium and ICP is weak [230];
- hypernatremia is associated with hyperchloremia hyperchlor, which may be deleterious for the renal function. However, these side effects were not found in a retrospective analysis of 50 TBI patients with controlled hypernatremia [231].

R10.2 – We do not recommend using high-dose glucocorticoids after severe TBI.

Grade 1-, Strong Agreement

Argument:

The CRASH study, with more than 10,000 TBI patients, found a higher mortality rate in the high-dose glucocorticoid group vs. placebo [232].

R10.3 – We recommend the maintenance of serum glucose concentration between 8 mmol/L (1.4 g/L) and 10–11 mmol/L (1.8–2 g/L) in severe TBI patients (adults and children).

Grade 1+, Strong agreement

Argument:

Hyperglycaemia is not uncommon after a severe TBI. This stress-related hyperglycaemia is induced by counter-regulation hormones and/or insulin resistance [233]. Observational studies have clearly shown that hyperglycaemia after a TBI is associated with an increased risk of mortality and poor neuro-

logical outcome [234–241]. Hyperglycaemia with serum glucose > 11 mmol/L (2 g/L) has been identified as an independent risk factor of mortality, infection and prolonged duration in the ICU, after adjustment for age and severity score [234,236]. Hyperglycaemia is considered as a secondary insult to the injured brain tissue.

In general ICU, the initial positive results of strict glycaemic control [242] were not further confirmed [243]. The increased risk of hypoglycaemia associated with intensive insulin therapy cannot be neglected. Using cerebral microdialysis, insulin therapy with a glycaemic control < 6 mmol/L (1.1 g/L) was associated with a decrease in interstitial brain glucose concentration [244–248]. Concomitant elevations of interstitial brain concentrations of lactate, glutamate, and lactate/pyruvate ratio suggested a cerebral energy crisis that may aggravate the initial injury. A randomised, crossover study with 13 TBI patients showed that a strict control of serum glucose (4.4–6.1 mmol/L or 0.8–1.1 g/L) resulted in increased cerebral metabolism and elevation of markers of energy crisis compared to a liberal strategy (6.6–8.3 mmol/L or 1.2–1.5 g/L) [249].

Seven randomised controlled trials have assessed the effects of glycaemic control in TBI patients [242,250–255]. All found that a strict control of serum glucose did not improve the neurological outcome or mortality, while the risk of hypoglycaemia is increased. In 88 severe TBI, a higher incidence of hypoglycaemia was observed in the group with a strict control of serum glucose (4.4–6.1 mmol/L or 0.8–1.1 g/L) [253]. Although no difference in mortality at day 28 or neurological outcome at 6 months was found between 2 targeted concentrations of serum glucose, i.e. 5.9 mmol/L (1.1 g/L) vs 6.5 mmol/L (1.2 g/L), episodes of severe hypoglycaemia were more frequent in the strict control group [255]. Similar conclusions were observed in a post-hoc analysis of TBI patients from the NICE-SUGAR study, [254]. A meta-analysis published in 2012 with 1248 TBI patients [256] found no benefit of a strict glucose control on mortality (RR: 0.99, 95% CI [0.79–1.22]) and a greater risk of hypoglycaemia (RR: 3.1, 95% CI [1.54–6.23], $P=0.002$).

Overall, a targeted serum glucose concentration between 8 mmol/L (1.4 g/L) and 10 mmol/L (1.8 g/L) is recommended for TBI patients. That implies regularly measuring blood glucose concentrations from venous or arterial blood samples.

18. Paediatric specificities of severe traumatic brain injury

R11.1 – We suggest measuring ICP after paediatric severe TBI, including inflicted TBI in infants.

Grade 2+, Strong agreement

Argument:

Recent studies with severe brain-injured children indicated that ICP monitoring might have a positive impact on neurological outcome [257–260] although this effect cannot be separated from the global management of patient. In addition, studies [163,261–276] found that the level of cerebral perfusion pressure was more correlated with the outcome than the isolated value of ICP.

ICP monitoring is less performed in children < 2 years old [258,277,278]. The inflicted trauma represents a prominent cause of TBI in this subgroup [277,278]. This population is however at risk for high ICP and poor outcome [258,279–282]. In TBI children < 2 years old, the incidence of raised ICP was found high and a strong association existed between cerebral perfusion pressure and neurological outcome [283,284]. The ICP-related complication rates in children and infants did not differ from adults [285,286].

R11.2 – We suggest setting the minimum cerebral perfusion pressure value according to the age: 40 mmHg for children of 0 to 5 years old, 50 mmHg for 5 to 11 years old and between 50 and 60 mmHg for children older than 11 years old.

Grade 2+, Strong agreement

Argument:

Children with cerebral perfusion pressure (CPP) below 40 mmHg were at higher risk of poor prognosis, including death or severe disability, considering the time spent below this CPP threshold [163,273,287,288]. Although no study had explored the impact of a guided-strategy maintaining CPP > 40 mmHg, an association was found between favourable outcome and CPP thresholds according to the patient age [266,274,276]. Children of 0–5 years and of 6–11 years with CPP < 30 mmHg and < 35 mmHg, respectively, were 8 times more likely to have a poor outcome than those with CPP > 40 mmHg and > 50 mmHg, respectively [276]. Children of 12–17 years with CPP < 50 mmHg had a 2.35-times higher risk of poor outcome than those with CPP > 60 mmHg [276].

The minimal CPP threshold associated with a reduced risk of death was 55 mmHg and 60 mmHg for children of 8 and 7 years, respectively [264,274]. For 10 years old children, the optimal CPP was 58 mmHg [266]. It should be noted that a minimal CPP value does not mean an optimal CPP, which should be explored for each patient.

The relationship between ICP measurements and outcome in children was explored with therapies initiated if ICP > 20 mmHg. These studies consistently found a strong correlation between ICP ≤ 20 mmHg and favourable outcome based on Glasgow Outcome Scale measurements (no, minor or moderate disability) [261–263,268–270,272,289]. A strong association was observed between ICP > 40 mmHg (or sometimes 35 mmHg) and unfavourable outcome (death, vegetative state, severe disability) [163,261,262,266,268,272,273,290]. Accordingly, the 2012 American Guidelines [291] confirmed that treatment of high ICP in children should be considered if ICP exceeded 20 mmHg. However, some data suggest that this ICP threshold should be lower in young children. Physiologically, ICP and CPP are reduced in proportion to the children age while comparable values to adults are observed after 6–8 years of age [292]. This supports strategies considering age-related ICP values [163,266,273,290]. If the association between ICP values and outcome is dependent on the age, ICP should be maintained below 20 mmHg in the younger group [271]. However, further studies are needed to confirm these data.

R11.3 – We recommend managing severe TBI children in a paediatric trauma centre or in an adult trauma centre with paediatric expertise.

Grade 1+, Strong argument

Argument:

The management of severe trauma children, especially severe TBI, in a paediatric trauma centre or by default in an adult trauma centre with paediatric expertise, was associated with a reduced morbidity and mortality [293–305].

Disclosure of interest

N. Engrand declares he has a conflict of interest with Sophysa.
S. Mirek declares conflicts of interest with Integra Neurosciences, Depuy France Codman Neuro and Sophysa.

The other authors declare that they have no competing interest.

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