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Guidelines

Management of patients suffering from mild traumatic brain injury 2023☆,☆☆

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☆ RECOMMENDATIONS FOR PROFESSIONAL PRACTICE of the Société Française de Médecine d'Urgence (SFMU), in association with the Société Française d'Anesthésie et Réanimation (SFAR), with the participation of the Société Française de Biologie Clinique (SFBC), of the Société Française de Radiologie (SFR), and the Société Française de Médecine Physique et Réadaptation (SOFMER).

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ABSTRACT

Objective: To develop a multidisciplinary French reference that addresses initial pre- and in-hospital management of a mild traumatic brain injury patient.
Design: A panel of 22 experts was formed on request from the French Society of Emergency Medicine (SFMU) and the French Society of Anaesthesiology and Critical Care Medicine (SFAR). A policy of declaration and monitoring of links of interest was applied and respected throughout the process of producing the guidelines. Similarly, no funding was received from any company marketing a health product (drug or medical device). The expert panel had to respect and follow the Grade® (Grading of Recommendations Assessment, Development and Evaluation) methodology to evaluate the quality of the evidence on which the recommendations were based. Given the impossibility of obtaining a high level of evidence for most of the recommendations, it was decided to adopt a "Recommendations for Professional Practice" (RPP) format, rather than a Formalized Expert Recommendation (FER) format, and to formulate the recommendations using the terminology of the SFMU and SFAR Guidelines.
Methods: Three fields were defined: 1) pre-hospital assessment, 2) emergency room management, and 3) emergency room discharge modalities. The group assessed 11 questions related to mild traumatic brain injury. Each question was formulated using a PICO (Patients Intervention Comparison Outcome) format.
Results: The experts' synthesis work and the application of the GRADE® method resulted in the formulation of 14 recommendations. After two rounds of rating, strong agreement was obtained for all recommendations. For one question, no recommendation could be made.
Conclusion: There was strong agreement among the experts on important, transdisciplinary recommendations, the purpose of which is to improve management practices for patients with mild head injury.

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Introduction

Mild traumatic brain injury (mTBI) results from a transfer of mechanical energy into the brain due to head injury caused by external physical forces [1]. This definition includes a direct impact to the head, and events such as rapid acceleration/deceleration (*i.e.*, "whiplash") not causing direct trauma. It occasions physiological perturbation of cerebral functioning.

In Europe, traumatic brain injuries represent more than 2.5 million cases a year, of which approximately 90% are characterized as "mild".

The identification criteria are presented in Table 1. Manifestations must not be due to substances (drug or alcohol intoxication, medication, ...), specific conditions (shock, cerebral nervous system infection, penetrating craniocerebral injury...), or confounding factors (psychological traumatism, language barrier). Consequences of anoxic-ischemic cerebral disease, expansive tumour, or infectious processes are obviously excluded from the above definition.

Since the publication of the most recent (2012) French guidelines drawn up by the *Société Française de Médecine d'Urgence*,

Table 1
Criteria for and definition of mild traumatic brain injury (according to the WHO 2004 definition) [1].

1. One or more of the following manifestations:
- Confusion or disorientation
- <30 min loss of consciousness
- <24 h post-traumatic amnesia
- Other transient neurological abnormalities such as focal lesions, epileptic crisis or intracranial injury not necessitating surgical intervention
2. Glasgow coma scale score of 13–15 at 30 min post-injury (or later, during presentation for treatment)

numerous multicentre and international studies have been conducted; on the other hand, clinical trials have remained scarce.

The scope of application for the present professional practice recommendations pertains to adult patients receiving treatment in an emergency medical service structure during the 24 first hours following non-penetrating traumatic brain injury with an initially assessed Glasgow Coma Scale (GCS) score of 13, 14 or 15.

With these recommendations, the authors have endeavoured to define the main aspects of the treatment of mTBI patients in an emergency medical service structure, from dispatching to discharge from emergency units. As is the case with the guidelines of the French paediatric society [2], the present recommendations are designed to assess the level of risk for intracerebral haemorrhagic lesions for patients addressed to emergency medicine structures following mTBI.

Methodology

These recommendations result from work by a group of experts brought together by the SFMU and the SFAR. Prior to the analysis, each expert filled out a declaration concerning possible competing interests. As a first step, the organizing committee defined the objectives of recommendations and the methodology to be implemented. The different fields of application of our recommendations for professional practice recommendations (RPP) and the questions to be addressed were defined by the organizing committee before being modified and validated by the experts. The questions were formulated in accordance with the PICO (*Patients, Intervention, Comparison, Outcome*) format. The GRADE (*Grade of Recommendation Assessment, Development and Evaluation*) methodology was applied in the analysis of the literature and in the drafting of summary tables recapitulating the data in the literature. A level of evidence was determined for each of the cited bibliographic references according to the type of study. It could subsequently be re-evaluated according to the methodological quality of the study, consistency of the results between the different studies, the direct or indirect nature of evidence, and analysis of the cost and extent of benefit. Notwithstanding a sizable number of studies taking up the different dimensions of initial treatment and management of mild traumatic brain injury, very few of them present a high level of evidence. Their methodological quality has been often weak, and there have been few clinical trials. Because it was impossible to obtain a sufficient level of evidence for a majority of the recommendations, it was decided to adopt a Recommendations for Professional Practices (RPP) rather than a Formalized Expert Recommendations (FER) format and to formulate the recommendations using the terminology of the RPP of the SFMU and the SFAR. That is why the guidelines were written out as follows: "the experts suggest to do" or "the experts suggest not to do". Each recommendation was individually assessed by each expert and individually rated on a scale ranging from 1 (complete disagreement) to 9 (complete agreement). The general or overall rating was determined according to the GRADE grid methodology. In order to validate a recommendation, at least 50% of the experts had to express a generally convergent opinion, while fewer than 20% expressed a divergent opinion. To issue a strong recommendation, at least 70% of the participants had to have a generally convergent opinion. In the absence of strong agreement, the recommendations were reformulated and once again rated, the objective still being to reach a consensus.

Results

Recommendation fields

The experts voluntarily chose to address only 11 questions, insofar as they seemed to cover the fields having progressed the most and/or having occasioned discussions on patient management.

Recommendations

Following a synthesis of the experts' work and application of the GRADE method, 13 recommendations were formalized. Due to a lack of relevant data in the literature, one of the questions yielded "absence of recommendation". The different recommendations were submitted to the expert group for assessment based on the GRADE Grid method. After two rounds of rating and several amendments, a strong agreement was reached on 100% of the recommendations.

The present PPRs replace the preceding SFMU guidelines for the same field of application [3]. The SFMU and the SFAR strongly urge all emergency physicians to comply with the present guidelines to ensure optimal patient care. However, when they are being applied, each practitioner is called upon to exercise his own judgment, taking into full account his area of expertise and the specificities of his establishment, so as to decide on the means of intervention best suited to the patient of whom he is in charge.

Field 1: Pre-hospital assessment.

Question: During a medical regulation call, which patients with mTBI may not be systematically oriented toward an emergency care structure for evaluation?

Experts: *Damien Viglino (SFMU) — Tobias Gauss (SFAR)*

R1 - The experts suggest that patients with mild traumatic brain injury for whom medical regulation is requested not be systematically referred to an emergency care structure, provided that they can be monitored by a third person in the absence of:

- **Pre-existing coagulation disorder, including anticoagulant treatment;**
- **Age >65 years AND treatment by antiplatelet agent(s);**
- **Intoxication (medicinal, alcoholic, others...);**
- **Symptoms other than headaches (vomiting, loss of consciousness, amnesia >30 min, convulsion, focal neurologic deficit, impairment of awareness);**
- **Sign of trauma (eyelid hematoma, depressed skull fracture, signs of basal skull fracture, mastoid hematoma).**

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

Taking into account the elements in the literature, it is difficult to formulate recommendations applicable to the medical regula-

tory system in France. The overwhelming majority of studies having identified with a high level of evidence the factors predictive of intracranial lesions or the need for neurosurgery have been conducted in contexts without medicalized regulation and in emergency units. Several independent cohort studies have validated criteria for the utilization of a scanner [4], one example being the Canadian CT head rule (CCHR) [5]. The identified factors are as follows: any impairment of awareness (GCS < 15) during management or at 2 h, loss of consciousness, convulsions, sensory-motor deficit, repeated vomiting, open-head injury with depressed skull fracture or signs of basal skull fracture (rhinorrhoea, otorrhea, eyelid or mastoid hematoma), age >65 years, anterograde amnesia. These studies contain reiterated warnings on (a) cases of intoxication or painful lesion that could divert the focus of the patient's attention or perturb the examination or (b) cases of high-kinetic mechanism (pedestrian *versus* vehicle, projection outside a passenger compartment, fall >2 m or 5 stairs). It bears mentioning that the score by far the most widely utilized, the CCHR, excludes patients undergoing anticoagulant treatment, under 16 years old, with GCS < 13 or presenting with a convulsion episode. Application of these criteria in the context of medical regulation in France is a transposition not having been validated in clinical studies.

As a possible option, in the case of a patient under 65 years of age undergoing antiplatelet monotherapy and having suffered minor and asymptomatic head trauma, without open wound, and without any other risk factor for bleeding (anticoagulation, chronic alcoholism, previous intracranial haemorrhage), the experts propose simple home monitoring of symptoms, provided that it can be ensured in good conditions by a third person. Recent studies and a meta-analysis have shown a moderately increased incidence of intracranial haemorrhage under antiplatelet therapy, without increased risk of evolution necessitating neurosurgery or entailing death, and the benefit-risk ratio of systematic imaging has been called into question [6,7].

In other cases, an indication for brain imaging could be retained during the first medical contact. In the absence of a life-threatening situation (neurological, respiratory, hemodynamic or at risk of a functional prognosis necessitating medical intervention), pre-hospital medicalization seems pointless, and non-medicalized transportation to a structure with brain imaging capabilities must be carried out. Initial orientation toward a centre with neurosurgery capabilities should be reserved for severely traumatized patients with neurological impairment, and who do not fall within the scope of mTBI.

Field 2: Emergency room management.

Question: What are the clinical and anamnestic criteria for risk of intracranial lesion after mTBI?

Experts: *Xavier Dubucs (SFMU) — Rémy Bernard (SFAR)*

R2.1 - The experts suggest to stratify the risks of clinical aggravation or intracranial lesion according to the following criteria:

- **High risk**

o **Anamnestic factors:**

■ **Haemostasis disorders: anticoagulants, antiplatelet dual therapy or congenital haemorrhagic disease (haemophilia, Willebrand disease...)**

o **Clinical factors:**

■ **Clinical signs suggesting basilar or cranial skull fracture** (Table 2)

■ **GCS < 15 at two hours from trauma without intoxication**

■ **More than one vomiting episode**

■ **Post-traumatic convulsions**

■ **Focal neurologic deficit**

- **Intermediate risk:**

o **Anamnestic factors:**

■ **Age ≥65 years with mono antiplatelet therapy**

■ **GCS < 15 at 2 h from trauma with intoxication**

■ **High-energy trauma** (Table 3)

o **Clinical factors:**

■ **Amnesia of the facts having occurred more than 30 min after the traumatic event**

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

The one modification to the preceding (2012) guidelines concerns moderation of the place of anticoagulants. Single-agent therapy with aspirin or clopidogrel is no longer considered a risk factor for intracranial haemorrhagic lesions.

All of the risk factors for intracerebral lesion and/or clinical aggravation have been detailed in the numerous studies establishing decision-making rules: CCHR [5] (*Canadian CT Head Rule*), NOC [8] (*New Orleans Criteria*), CHIP [9] (*CT in Head Injury Patients*), NEXUS II [10] (*National Emergency X-ray Utilization Study*), NICE [11] (*National Institute for Health and Care Excellence*), SNC [12] (*Scandinavian Neurotrauma Committee),* NCWFS [13] *(Neurotraumatology Committee of the World Federation of Neurosurgical Societies*). Taken together, they are used to identify patients at low risk of brain damage and who necessitate neither prolonged monitoring in a hospital setting, nor brain CT scan.

None of these rules is perfect; those associating the best performances and the highest number of external validations are the CCHR [7], the NOC [10] and the CHIP [11]. The meta-analysis by Easter *et al.* [14] shows higher specificity of the CCHR as compared to the NOC, while the two present approximately the same sensitivity. The more recent study by Foks *et al.* [15] shows that the CCHR has less sensitivity and specificity than the CHIP decision rule. Lastly, it is interesting to note that to our knowledge, there exists no study demonstrating a lower number of secondary brain scans when the decision rules are applied by doctors. A randomized Canadian cluster trial including 4531 mild traumatic brain injury patients did not highlight any significant difference between the intervention group (education and training of the doctors on the CCHR algorithms) and the non-intervention group ($p = 0.16$) [16]. Approximately 75% of the patients in the two groups underwent CT scanning.

These different factors have led us to establish a list of the criteria synthesizing the knowledge gained through these studies, but without privileging any particular decision rule or score.

Brain scan without injection is the only brain imagery evaluated in all the studies dealing with the above-mentioned risk factors. Brain scan with injection must be performed in the event of clinical signs suggesting carotid artery dissection (*conférence d'actualisation 2013: lésions traumatiques des vaisseaux du cou*): fracture of the

cervical spine, neurological deficit not explained by imagery, Claude Bernard-Horner syndrome, Lefort II or III fracture, basilar skull fracture, soft tissue neck injury.

Notwithstanding sizable heterogeneity, the meta-analysis by Easter *et al.* [14] estimates the prevalence of severe intracerebral lesions at 7.1% [95% CI 6.8–7.4] in mTBI patients. Severe lesions are defined as those necessitating hospital-based surveillance, medical attention or a neurosurgery procedure: subdural hematoma, extradural hematoma, intraventricular haemorrhage, subarachnoid haemorrhage, intraparenchymal haemorrhage, cerebral herniation or depressed skull fracture. The proportion of lesions leading to neurosurgery or death is estimated at only 0.9% [0.8–1.0] of mTBI patients. Low-risk patients (without any of the CCHR factors) have a risk of severe intracerebral lesions estimated at 0.31% [0–4.7]. However, utilization in this study of a composite endpoint leads to assigning the same importance to hospital-based surveillance and neurosurgical procedure.

The study by Foks *et al.* [15], which included 4557 patients with mTBI, found an 8.4% prevalence of intracranial lesions. While potentially surgical lessons were present in mTBI patients, only 0.4% of them were in need of neurosurgery during the 30 days following the trauma. Among the patients without CCHR risk factors, 4% presented with lesions on CT scans, and 0.5% of the lesions were potentially surgical. Among patients without CHIP risk factors, 2.6% presented with lesions on CT scans, and 0.2% of the lesions were potentially surgical.

The prospective study by Probst *et al.* [17] did not reveal a high risk of intracerebral lesions in patients undergoing antiplatelet monotherapy (aspirin or clopidogrel). On the other hand, high risk in elderly patients has been taken into consideration [7], and one study underlines the interest of weighting by age the potential effect of antiplatelet therapy [18]. Included in the Scandinavian guidelines since 2013 [19], weighting by age has been validated by Undén *et al.* [20].

As regards previous ventricular shunt neurosurgery, which was proposed as a risk factor by the NCWFS (*the Neurotraumatology Committee of the World Federation of Neurosurgical Societies*), there exists no literature concerning adults, and the paediatric literature presents discrepant results; that is why it will not be retained for further consideration [21].

Table 2
Clinical signs suggesting basilar or cranial skull fracture.

Skull base	Otorrhea or rhinorrhoea, mastoid ecchymosis, periorbital ecchymosis, hemotympanum or bleeding externalized by the auditory canal
Cranial vault	Palpable cranial vault discontinuity, suspected open or closed depressed skull fracture

Table 3
Anamnestic factors suggesting high-energy trauma.

Occupant ejected from vehicle,	Pedestrian or cyclist without helmet run over
Overturned vehicle	Fall from a height exceeding five stairs or two meters

Question: What is the role of biomarkers in the evaluation and management of patients admitted to an emergency unit for mTBI?

Experts: *Thomas Geeraerts (SFAR), Yann-Erick Claessens (SFMU), Vincent SAPIN (SFBC).*

R2.2.1 - The experts suggest to use blood-based assay of protein S100B, when it is available, during the three hours following mild traumatic brain injury, in patients at intermediate risk (cf. R2.1), the objective being to limit the number of brain scans.

EXPERT OPINION (STRONG AGREEMENT)

R2.2.2 - The experts suggest to use blood-based assay combining UCH-L1 and GFAP, when they are available, during the 12 h following mild traumatic brain injury, in patients at intermediate risk (cf. R2.1), the objective being to limit the number of brain scans.

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

The S100 Beta protein belongs to the multigene family of low-molecular-weight (9−13 kDa) S100 calcium transporter proteins. It is essentially expressed in the glial cells of the central nervous system, and more specifically in astrocytes. It contributes to the regulation of cellular morphology through interaction with elements of the cytoplasmic cytoskeleton. It is actively secreted by the astrocytes. Its biological half-life approximates 1.5 h, and its peak plasma level is observed two hours after the traumatic event. It can be detected in the cerebrospinal fluid and in the blood.

Two systematic reviews of the literature with meta-analysis [22,23] were recently published. They showed that in a general population with mild or moderate TBI, the plasma concentration of S100 Beta protein inferior to 0.1 μg/L during the three hours after the traumatic event can effectively rule out on CT scan the presence of a significant intracranial lesion (sensitivity 96.4%–100%, NPV 96.9%–100% for Ref. [22] and sensitivity at 87%, 95% CI (81%–92%) for Ref. [23]). Good diagnostic performances have likewise been found for plasma concentration of S100 Beta protein <0.1 μg/L during the three hours following the traumatic event, in patients over 65 years of age having suffered a TBI at intermediate risk of complication [24]. Adaptation of the threshold to patient age could further improve performances, and utilization of S100 Beta protein could also reduce brain scan use (limitation of unnecessary CT, without modification of the prognosis) [25].

On the other hand, the results of these studies do not allow us to conclude that in comparison to clinical criteria alone, S100 Beta protein assay improves the prediction of neurological prognosis in cases of TBI.

It is important to note that S100 Beta protein is also present in other tissues such as adipocytes or chondrocytes. As a result, a high plasma level of S100 Beta protein has been observed after multiple trauma without brain lesions [26], thereby limiting its specificity in the context of TBI associated with musculoskeletal lesions.

Ubiquitin C-Terminal Hydrolase-L-1 (UCH-L1) is a specific marker of neurons due to its abundance in the brain and its characteristic neuronal expression. Its biological half-life approximates eight hours, and its peak plasma level is observed eight hours after the traumatic event.

Glial Fibrillary Acidic Protein (GFAP) represents the main part of the cytoskeleton of the astrocytes and is almost exclusively found in the glial cells of the central nervous system (CNS). It can therefore be considered as a specific marker of CNS pathologies and is implicated in diverse neurological processes such as maintenance of the blood–brain barrier. Its biological half-life approximates 38 h, and its peak plasma level is observed 24 h after the traumatic event. GFAP plasma concentration is not modified by multiple trauma without brain damage.

In the meta-analysis by Amoo *et al.* [23], serum GFA with a threshold of 22 pg/mL detects traumatic brain injury by CT scan with a sensitivity of 93% [73–99] and specificity of 36% [12–68]. In the meta-analysis by Rogan *et al.* [22], the diagnostic accuracy of GFAP in detecting intracranial lesions was assessed in six studies; sensitivity ranged from 67% to 100% and specificity from 0% to 89%, while the negative predictive value (NPV) of GFAP ranged from 72.1% to 100%. For UCH-L1, an analysis of four studies was carried

out, with a sensitivity of 61%–100%, and specificity of 21%–63.7% in detecting intracranial lesions, and its NPV to rule out a lesion by CT scan ranged from 70.7% to 100%.

Carried out during the 12 h following occurrence in an adult of non-penetrating mTBI, a combination of UCH-L1 and GFAP serum, with respective thresholds of 327 pg/mL and 22 pg/mL, satisfactorily rules out the existence of an intracranial lesion (specificity: 36.7% [34.5–39], sensitivity 97.3% [92.4–99.4], NPV 99.5% [98.7–99.9]) [27]. To conclude, using a combination of UCHL1 and GFAP could lead to a reduced number of unnecessary brain CT scans. That said, up until now this couple of biomarkers has been the subject of fewer clinical studies than S100 Beta protein.

Question: What is the optimal time frame for brain scan in view of ruling out intracranial lesion?

Experts: *Pierre Catoire (SFMU), Jean-Yves Gauvrit (SFR), Damien Galanaud (SFR)*

R2.3 - The experts suggest that CT scan of the brain take place as early as possible, so as to identify significant intracranial lesions in patients presenting with mild traumatic brain injury:

- **Ideally, during the hour following admission to emergency structures for patients at high risk of clinical aggravation or intracranial lesion.**
- **At most, during the first eight hours for patients at intermediate risk of clinical aggravation or intracranial lesion.**

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

The expert group defined the optimal time frame for CT brain scan as the lapse of time minimizing the risk of morbi-mortality associated with post-traumatic intracerebral lesions (death, post-traumatic neurological sequels) in patients with indication for emergency imaging. The risk of unduly delayed brain scan is to delay management of lesions accessible to treatment (antagonization of anticoagulation, surgery, advanced neuroprotection...). The risk of unduly early brain scan consists in not being cognizant of bleeding or of an oedema of which the volume would be too small for it to be visible on imaging.

Delayed management of an intracranial lesion accessible to treatment leads to worsened neurological prognosis [28,29]. Among the studies determining the performances of clinical features in prediction of intracranial lesion, none have explicitly considered mTBI patients with lesions necessitating immediate neurosurgical management and justifying immediate brain imagery. As regards severe brain injury patients eligible for surgery, early management (during the three hours following admission) was shown in a retrospective study to reduce mortality [30].

If these clinical criteria for high risk of significant lesion are absent, imagery should enable identification not only of lesions necessitating specific intervention but also of lesions likely to evolve. To our knowledge, there exists no prospective study having assessed a specific risk (based on clinical or radiological criteria) associated with unduly delayed imagery possibly leading to lesion misreading. Geijerstam *et al.* [31] carried out an in-depth review of the literature from 1966 to 2003 and reported eleven cases of significant neurological deterioration in spite of normal initial CT-scan results, but in only three of them, there was documentation on the time elapsed between traumatic event and initial scan. Moreover, numerous factors limit the relevance of these results, particularly the absence of rereading of the initial images and the evolution after 2000 (the three cases date from before 2000) of the quality of CT-scan imaging.

In the absence of robust evidence determinative of a minimal optimal time frame for imagery, the expert group has decided to retain the data from the validation studies [15,32,33] of international recommendations such as the Canadian CT Head [5], New Orleans [8], and NICE [11] rules, which showed that an 8-h time frame enabled identification of lesions in practically all of the patients included in the cohorts. These safety data justify the time frame proposed by the expert group.

It bears mentioning once again that a brain scan with injection must be carried out in the event of clinical signs suggesting carotid artery dissection [34]: fracture of the cervical spine, neurologic deficit not explained by imagery, Claude Bernard-Horner syndrome, Lefort II or III fracture, basilar skull fracture, soft tissue neck trauma.

Question: What is the performance of transcranial Doppler in assessing the risk of neurological aggravation in mTBI patients?

Experts: *Pierre Bouzat (SFAR), Xavier Bobbia (SFMU)*

R2.4 - After abnormal brain scan results, the experts suggest the use of transcranial Doppler for mild traumatic brain injury patients, the objective being to assess the risk of early neurological aggravation.

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

In two prospective cohorts, transcranial Doppler (TCD) ruled out the risk of early neurological aggravation. In a single-centre prospective cohort including patients with light or moderate traumatic brain injury, a pulsatility index (PI) < 1.25 and diastolic blood flow velocity (FVd) > 25 cm/s were associated with an absence of early neurological aggravation [35]. These thresholds were subsequently confirmed in a multicentre prospective observational study including 356 patients with a Glasgow score between 9 and 15. In this study, the negative predictive values of TCD in the prediction of neurological aggravation in mTBI were 98% [96–100] and 100% [97–100] [36]. In these two studies, TCD was carried out after a brain scan without injection, at most 12 h following the traumatic event.

Question: Which patients presenting with a transcranial lesion on initial CT-scan should undergo repeated imaging during the first 48 h?

Experts: *Lionel Velly (SFAR), Sybille Goddet (SFMU), Jean-Yves Gauvrit (SFR), Damien Galanaud (SFR)*

R2.5 - The experts suggest not to carry out repeated imaging in patients presenting with a transcranial lesion on initial CT-scan, except in the following situations:

- **neurological aggravation;**
- **patient >65 years;**
- **haemostasis disorders, unrelated to aspirin intake alone.**

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

The question of repeating imaging recurs in emergency units. The data in the literature concerning clinical monitoring and the need for repeat imaging to find a delayed haemorrhagic lesion

justifying neurosurgical management or surveillance of a patient presenting on initial imagery with a haemorrhagic lesion are contradictory.

Five per cent of patients presenting with mTBI and GCS 15 have abnormal imagery, and they are 30% when GCS ranges from 13 to 15; among them, 1% require neurosurgical management [37]. In 2012, in a study including patients with GCS > 13 and an intracranial haemorrhagic lesion without indication for neurosurgery and not necessitating surveillance in intensive care, it was concluded that in the absence of clinical aggravation, it was not necessary to systematically obtain repeat imagery [38]. A prospective study including patients presenting with an initial haemorrhagic lesion, and who were hospitalized for surveillance, compared the time elapsed for repeat scan at H12 and at H48 and concluded in 2018 that the scan could reasonably be proposed after 48 h in the absence of clinical neurological aggravation [39]. Older studies likewise concluded that in patients presenting with an initial haemorrhagic lesion without indication for surgery and in the absence of neurological aggravation, repeat control generally served no purpose. One study nonetheless mentioned that elderly or coagulopathic patients were at high risk of disease progression [40]. In the presence of traumatic subarachnoid haemorrhage, it seemed useful to conduct repeat imaging after 24–48 h post-TBI [41]. More recently, the CENTER-TBI study observed an increase at D7 of lesions in patients taking antiplatelet agents or anticoagulants (54%), but without impact on the length of hospital stay, number of surgical procedures, mortality rate, or functional disorders at six months [42]. Another study found an increased number of intracerebral lesions in 50% of cases within 24 h [43].

However, the results of these studies do not allow us to draw a conclusion on the ideal time frame for repeat imaging in patients with an initial intracerebral lesion without risk factors for aggravation. Repeat imaging must nonetheless be carried out immediately in the event of clinical neurological aggravation.

Question: In patients treated with oral anticoagulant (AOD, AVK), what are the indications and modalities for reversal of these therapies?

Experts: *Anne Godier (SFAR), Geoffroy Rousseau (SFMU)*

R2.6.1 - The experts suggest immediate anti-vitamin K reversal in mild traumatic brain injury patients presenting with an intracranial haemorrhagic lesion identified by imagery, the objective being to limit the risk of neurological aggravation.

EXPERT OPINION (STRONG AGREEMENT)

R 2.6.2 - The experts suggest immediate reversal of direct oral anticoagulants in mild traumatic brain injury patients presenting with an intracranial haemorrhagic lesion identified by imagery, the objective being to limit the risk of neurological aggravation.

EXPERT OPINION (STRONG AGREEMENT)

R2.6.3 - The experts suggest a collegial discussion on the measures to apply for patients with a mechanical heart valve.

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

There exists little literature evaluating the efficacy of anticoagulant (AOD or AVK) reversal with regard to neurological aggravation or mortality in traumatic brain injury (TBI).

AVK treatment increases the risk of intracranial haemorrhage after mTBI [44,45]; the risk is higher in the event of an elevated International Normalized Ratio (INR) [44]. Indeed, INR > 3 at the outset of treatment seems associated with a higher risk of delayed bleeding (RR 14, 95% CI [4–49]) [46]. AVK reversal was assessed in a randomized trial involving cases of spontaneous intracranial haemorrhage, but not in cases of TBI [47]; prothrombin complex concentrates (PCCs) permitted rapid INR correction, reduced hematoma expansion (HE) and lower mortality at D90 (19% *vs.* 35%) compared to fresh frozen plasma administration. In TBI cases, AVK reversal likewise seems to reduce hematoma expansion [48].

While direct oral anticoagulants (DOACs) entail less haemorrhagic risk than AVK, their impact on mTBI prognosis remains insufficiently assessed [44,49,50]. Non-specific reversal of DOACs by PCCs and specific reversal of dabigatran by idarucizumab and direct factor Xa inhibitors by andexanet alfa showed satisfactory results, of which the interpretation was nonetheless limited by the absence of a control group [51–53].

To conclude, the experts propose compliance with the existing guidelines for the management of severe haemorrhage with anticoagulants, with immediate reversal in the event of intracranial haemorrhagic lesion according to the following modalities [54,55]:

- AVK: prothrombin complex concentrate (PCC) non-activated 25 UI/kg + Vitamin K 10 mg IV or orally.
- Apixaban or rivaroxaban: PCC 50 UI/kg (maximum 5000 UI; antidote not available at this time).

Dabigatran: Idarucizumab 5 g IV (PCC 50 UI/kg IV if unavailable).

Question: In patients treated with oral antiplatelet agent, what are the indications and modalities for neutralization of this therapy?

Experts: *Anne Godier (SFAR), Geoffroy Rousseau (SFMU)*

R2.7 - The experts suggest not to neutralize aspirin in a patient with an intracranial haemorrhagic lesion treated by aspirin after mild traumatic brain injury, the objective being to limit the risk of neurological aggravation.

EXPERT OPINION (STRONG AGREEMENT)

Absence of recommendation - In the absence of relevant data, the experts are not in a position to issue a recommendation concerning specific management aimed at limiting the risk of neurological aggravation in patients having presented with an intracranial haemorrhagic lesion following mild traumatic brain injury and treated by an inhibitor of P2Y12 receptors (clopidogrel, prasugrel, ticagrelor).

Argumentation

While the studies evaluating the haemorrhagic risk of aspirin intake following brain trauma are discordant, many of them suggest that aspirin does not aggravate the prognosis. Platelet transfusion in patients presenting with brain injury and treated by aspirin does not seem beneficial in terms of expansion of the hematoma, need for neurosurgical intervention or mortality. In the meta-analysis by Alvikas *et al.*, the absence of platelet transfusion does not seem associated with haemorrhage progression (pooled OR 0.88 [95%CI 0.34–2.28]) [56], and platelet transfusion was not associated with fewer neurosurgical interventions (OR 1.00 [0.53–1.90]) or lower mortality (OR 1.29 [0.76–2.18]). The meta-analysis by de Leong *et al.* yielded similar results concerning mortality (OR 1.17 [1.00–3.13]) [57]. That said, these meta-analyses were based on low-population cohort studies, including patients concomitantly treated by anticoagulants. To our knowledge, there is no randomized study on mTBI patients. A randomized trial including patients with spontaneous intracranial haemorrhage and treated

by aspirin reported that platelet transfusion aggravated their prognosis [58].

After brain trauma, clopidogrel increased the risk of further bleeding and the need for surgery [59]. While preliminary results suggest that in the event of intracranial bleeding, platelet transfusion could reduce the risk of further bleeding, of the need for neurosurgery, and of mortality [60], they do not suffice to justify a recommendation. Even though prasugrel and ticagrelor are associated with a more intense haemorrhagic risk than clopidogrel, reversal of their effect has not been assessed in brain injury.

Question: What are the criteria justifying consideration of a return home from an emergency structure?

Experts: *Pierre Bouzat (SFAR), Bénédicte Douay (SFMU)*

R2.8 - Even in the presence of anticoagulants or antiplatelet agents, the experts suggest authorisation of a return home from an emergency structure, provided that at least one of the following elements is present:

- **The patient is at low risk of bleeding (cf. R2.1)**
- **Serum biomarker assay is negative (when available)**
- **No brain lesions visible on initial TDM**

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

Following normal cerebral imagery, risks of aggravation may be deemed sufficiently low to justify return home from an emergency unit [61,62]. As for patients taking anticoagulants or platelet aggregation inhibitors, when the clinical elements mentioned below are present, they may be allowed on discharge from in emergency unit to return home [61]. Most studies on the subject have concluded that late intracranial bleeding in these patients is extremely rare and that it does not justify hospitalization [62–65].

The clinical elements permitting return home are: the absence of associated intoxication, absence of repeated vomiting, absence of major and persistent headaches, Glasgow score of 15, absence of neurological deficit, and absence of other factors possibly justifying hospitalization.

Field 3: Emergency room discharge modalities.

Question: Which patients should be oriented toward a post-mTBI care sector?

Experts: *Pierrick Le Borgne (SFMU), Bernard Vigué (SFAR), Bertrand Glize (SOFMER)*

R3.1 - The experts suggest that persistence of symptoms deemed disabling by the patient at seven days after the mild traumatic brain injury should occasion a medical evaluation.

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

Recent works have shown that chronic cognitive complaints (>3 months) are present in 50% of mTBI cases [66], and that cognitive repercussions are disabling in 10% [67]. However, the follow-up of numerous patients appears insufficient. In a large-scale American study, it was found that during their stay in an emergency unit, less than 50% of patients received information on the risk of chronic cognitive disorders and that fewer than 50% were monitored during the ensuing three months [68]. Access to specific healthcare sectors should be provided to mTBI patients, even and especially weeks or months after initial management.

In this context, it is important that several aspects be taken into account:

- On discharge from an emergency unit, patients must have received appropriate information [69], permitting more precise knowledge of their pathology and including a number of elements indispensable not only to immediate follow-up (signs of severity to monitor), but also to continued follow-up in the event of persistent symptoms;
- This information must include recommendations for the resumption of activities (work, study, sports…), indicating a period of exclusion from activities presenting a risk of another trauma, as well as a time of rest, if necessary, followed by progressive resumption of activities entailing a risk of relapse, such as the practice of certain sports [70];
- The patients having presented with highly pronounced symptoms during the initial phase and/or whose symptoms persist for more than seven days must receive active follow-up [71]:
  - Ambulatory care if the symptoms are simple and involve easily identifiable and treatable deficiencies;
  - Management by specialized teams for patients presenting with a highly complex clinical picture or risk factors (neurological or neuropsychological history) [72], or patients with sequelae >4–6 weeks.

Management of cognitive disorders, particularly attentional disorders in the aftermath of brain trauma, is recognized as beneficial. Screening and treatment (if necessary) of mood disorders, anxiety and post-traumatic stress syndrome are of paramount importance [70,73]. Assessment can be carried out in ambulatory care with standardized screening tools, some of them validated for specific pathologies. This type of management involves the identification of partners in a care network providing multidimensional assessment. Persistent symptoms are often due to complex entanglement between the sequelae and a number of biopsychosocial factors. The assessment generally entails the intervention of rehabilitation teams specialized in brain trauma.

The clinical signs justifying active follow-up are: persistent dizziness, sleep disorders, vision impairment, and overall fatigue; these symptoms may in some cases be rapidly treated, whereas in other cases they necessitate specific exploration in search of a differential diagnosis. Conversely, reassuring clinical signs not necessitating active monitoring are as follows: mild symptoms showing improvement in less than 24–48 h [72].

Question: What modalities of information should be delivered to mTBI patents when they are being discharged from an emergency unit?

Experts: *Anthony Chauvin (SFMU), Pierre Bouzat (SFAR)*

R.3.2 - The experts suggest that patients with mild traumatic brain injury necessitating ambulatory treatment, and their next of kin, receive clear standardized written and oral information on the reasons possibly necessitating another consultation in an emergency unit during the 48 h subsequent to the patient's return home.

EXPERT OPINION (STRONG AGREEMENT)

Argumentation

A systematic review and meta-analysis of 51 articles evaluating comprehension and memorization of the instructions given on discharge (*i.e.* diagnosis, treatment, follow-up and instructions for possible return) by mTBI patients was published in 2020 [74]. The

quality of the trials was questionable and their results were highly heterogeneous. While information given in the form of instructional videos seemed to yield optimal retention (66.8%), it was not statistically superior to written (57.8%) or oral (47.0%) instructions.

Notwithstanding these results, the experts agree that any mTBI patient for whom ambulatory treatment has been chosen must imperatively be given clear, complete, written information on (a) the reasons that would justify another emergency consultation and (b) the modalities of implementation (number to call…) (cf. Appendix A). The practitioner should read the information sheet to the patient and make sure that its contents have been adequately understood.

These types of patients are at low risk of secondary complications necessitating a neuro-surgical procedure or surveillance in intensive care. The main complications are chronic neurological and cognitive impairment [75,76]. That is why the experts propose, during the 48 h subsequent to discharge from an emergency unit, monitoring of the following signs: headaches of increasing intensity despite administration of analgesics, repeated vomiting; drowsiness or difficulty waking up; loss of consciousness; behavioural disorders; difficulties seeing, speaking or walking; difficulty moving a limb; exteriorisation of blood or fluid by the nose or the ears.

After this time lapse, the appearance of symptoms should justify a non-urgent medical consultation (*i.e.*, general practitioner or permanent access to care) in order to determine the suitable modalities of follow-up. It would seem important that the patient and his next of kin be informed of the possible occurrence of disabling symptoms formerly known as post-commotional syndrome, during the days or weeks following the traumatic event [77,78].

Declarations of ties of interest

SFMU experts and organizers

Xavier Bobbia declares ties of interest with General Electric Healthcare that are related to the contents of the present RPP, and no ties of interest exterior to the present RPP.

Pierre Catoire has no direct or indirect competing interest with regard to the contents of the present RPP.

Anthony Chauvin has no direct or indirect competing interest with regard to the contents of the present RPP.

Yann-Erick Claessens declares ties of interest with Roche, Biomérieux and Abbott that are related to the contents of the present RPP, and no ties of interest exterior to the present RPP.

Pierre-Géraud Claret declares ties of interest with Roche Diagnostics that are related to the contents of the present RPP, and no ties of interest exterior to the present RPP.

Bénédicte Douay has no direct or indirect competing interest with regard to the contents of the present RPP.

Xavier Dubucs has no direct or indirect competing interest with regard to the contents of the present RPP.

Cédric Gil-Jardiné has no direct or indirect competing interest with regard to the contents of the present RPP.

Sybille Goddet has no direct or indirect competing interest with regard to the contents of the present RPP.

Pierrick Le Borgne has no direct or indirect competing interest with regard to the contents of the present RPP.

Geoffroy Rousseau has no direct or indirect competing interest with regard to the contents of the present RPP.

Damien Viglino has no direct or indirect competing interest with regard to the contents of the present RPP.

SFAR experts and organizers

Rémy Bernard has no direct or indirect competing interest with regard to the contents of the present RPP.

Pierre Bouzat has no direct or indirect competing interest with regard to the contents of the present RPP.

Philippe Cuvillon has no direct or indirect competing interest with regard to the contents of the present RPP.

Denis Frasca has no direct or indirect competing interest with regard to the contents of the present RPP.

Tobias Gauss has no competing interest with regard to the contents of the present RPP, and declares ties of interest with Laboratoire du Biomédicament Français and Cap Gemini Invent, which are unrelated to the present RPP.

Thomas Geeraerts declares ties of interest with Roche that are related to the contents of the present RPP, and no ties of interest exterior to the present RPP.

Anne Godier declares ties of interest with Aguettant, Alexion, Bayer Healthcare, BMS-Pfizer, Boehringer Ingelheim, Sanofi, CSL Behring, LFB, Octapharma that are related to the contents of the present RPP, and no ties of interest exterior to the present RPP.

Jean-François Payen has no direct or indirect competing interest with regard to the contents of the present RPP.

Lionel Velly has no competing interest with regard to the contents of the present RPP, and declares ties of interest with Braintale, Braindex and Baxter, which are unrelated to the present RPP.

Bernard Vigué has no direct or indirect competing interest with regard to the contents of the present RPP.

SFBC expert

Vincent Sapin has no direct or indirect competing interest with regard to the contents of the present RPP.

SFR experts

Damien Galanaud declares ties of interest with Braintale that are related to the contents of the present RPP, and no ties of interest exterior to the present RPP.

Jean-Yves Gauvrit has no direct or indirect competing interest with regard to the contents of the present RPP.

SOFMER expert

Bertrand Glize has no competing interest with regard to the contents of the present RPP, and declares ties of interest with IPSEN, which are unrelated to the present RPP.

Appendix A. Post-discharge recommendation sheet

To whom it may concern,

You or one of your friends or relatives have been treated for apparently benign cranial trauma. It is necessary during the days following the traumatic event to be on the lookout for clinical signs. Surveillance can be carried out by you or by your entourage

If one of the following symptoms (re)appears during the 48 h after discharge, you should urgently seek out medical advice (SAMU 15, in France):

- Loss of consciousness, excessive drowsiness, or lowered alertness
- Behavioural disorders or convulsions
- Difficulties seeing, hearing or speaking
- Difficulty maintaining balance
- Difficulty mobilizing a limb
- Intense headaches resistant to analgesics

- Vomiting or nausea
- Blood or fluids exiting from the nose or ears
- Neck pain

Frequently, some of the symptoms you have presented during the initial phase persist but are likely to disappear within seven days. For example:

- A moderate headache
- Nausea without vomiting
- Dizziness
- Difficulties memorizing or concentrating
- Sleeping disorders or fatigue
- Loss of appetite.

In the event of reasonable doubt or persistence for more than seven days, you can consult your attending physician.

Do not take medicine without any medical prescription or recommendation.

In addition, if you practice an activity or a sport entailing a risk of further brain trauma, it is recommended not to resume for 14 days.

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