TRAUMATIC BRAIN INJURY

Evidence, Guidelines and Treatment Variation

VICTOR VOLOVICI

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COLOPHON

Cover design:	Design Your Thesis | www.designyourthesis.com
Layout:	Design Your Thesis | www.designyourthesis.com
Print:	Ridderprint | www.ridderprint.nl
ISBN:	978-94-6375-602-0

Traumatic Brain Injury: Evidence, Guidelines and Treatment Variation

Traumatisch schedel – hersenletsel: Bewijs, richtlijnen en praktijkvariatie

P R O E F S C H R I F T

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

dinsdag 03.12.2019 om 13:30 uur

Victor Volovici
geboren te Sibiu, Roemenië

Erasmus University Rotterdam

PROMOTIECOMMISSIE

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Chapter 1

GENERAL INTRODUCTION

TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) is an alteration in cerebral function caused by an external force. Clinically it varies between mild TBI, such as concussion, and severe TBI, leading to coma, which has a mortality of 30-40%[1].

TBI is projected to remain among the most important causes for disability from neurological disease until 2030, with rates exceeding those of Alzheimer's disease and cerebrovascular disorders[2].

TBI is routinely classified into mild, moderate and severe according to the clinical situation of the patient upon arrival in the Emergency Department (consciousness level as assessed by the Glasgow Coma Scale (GCS), with a GCS of 13-15 being mild TBI, GCS 9-13 moderate and 1-8 severe).

TBI is a very complex brain disease, depending on the pattern and the extent of damage inflicted to the brain. Together with the complexity of the brain itself, the individual characteristics of every patient, a broad range of clinical phenotypes may occur.

The external forces that cause TBI may result in direct mechanical injury to brain tissue, shearing of connecting nerve bundles and contusions or intracranial bleeds with mass effect. Secondarily, the brain may swell as a result of inflammatory processes which are subsequent to the primary injury. This swelling causes increased intracranial pressure (ICP) within the rigid skull vault and impaired regional blood flow and oxygenation of various brain areas.

The focus of this thesis will be moderate and severe TBI.

GUIDELINES AND EVIDENCE FOR THE TREATMENT OF SEVERE TBI

The complexity of severe TBI in particular hampers the search for the best treatments, as most studies are underpowered to adjust for all possible confounders and carrying out RCTs is quite difficult. Furthermore, the conceptual difference between the damage inflicted during the primary injury and the secondary damage caused by swelling is essential in determining proper treatment patterns and tailoring them to the context of the patient. New treatments have decreased mortality substantially at the beginning of the 20th century until 1990, but mortality has remained the same after 1990 despite a wealth of new studies[3].

A total of 213 RCTs have been either published or are ongoing in TBI, 191 of which are completed. Although this is a reasonably high number of studies, most of these (72%) are single-center studies with an enrollment of fewer than 100 participants[4]. Moreover, of the 80 systematic reviews (of various interventions) only 16 (20%) were judged as up-to-date, complete and of high quality, most of them also showing no treatment effect[5,6].

Despite the limited evidence on effective treatments, over the past 20 years, several guidelines have been published regarding the treatment of severe TBI, the most popular and most used of which are the Brain Trauma Foundation (BTF) guidelines. There have been four editions published so far, the most recent of which was published in 2016[7-10]. There have been several studies performed to assess the impact of guideline adherence on patient outcomes, but the results are contradictory[11-13].

The variation in the severity of brain damage, systemic responses and interplay of various pathologic and physiologic processes lead to difficulties in the classification of TBI and in establishing best clinical treatment. Nevertheless, one of the backbones of current severe TBI management is ICP-directed therapy.

ICP-DIRECTED THERAPY AND CURRENT EVIDENCE

ICP monitor-directed management of severe TBI has been the cornerstone for the management of severe TBI since the 1970s when it was noticed that aggressive therapy to lower increased ICP, associated with severe TBI, leads to lower mortality[14].

In the first editions of the BTF Guidelines[7,8], a "critical pathway" for the management of raised ICP was the cornerstone of treatment of severe TBI (*Figure 1*). Although it was considered only as class III evidence (expert opinion)[15,16], it did offer the clinician an overview of the most relevant interventions and the order in which they should be carried out, as determined by the panel of experts. The critical pathway was attractive for clinical decision making, and it served as the foundation of many severe TBI treatment protocols in various institutions using the BTF Guidelines. However, the 2007 and 2016 editions abandoned this critical pathway, which is illustrative for the development of guidelines and evidence in severe TBI in the last decades.

ICP monitoring

Recently, the usefulness of ICP monitoring itself has been called into question, with a clinical trial showing noninferiority of a treatment protocol based on imaging and clinical

signs compared to ICP measurement [17]. Although the generalizability of this trial has been called into question, after its publication, the value of ICP-directed management protocols became a topic of debate.

Maintaining Cerebral Perfusion Pressure (CPP)> 70 mm Hg

The first step after the insertion of an ICP monitor was maintaining CPP above 70 mmHg. The latest edition of the Guidelines recommends maintaining CPP between 60 and 70 mmHg and avoiding CPP above 70 mmHg because of the risk of adult respiratory distress syndrome[10].

Ventricular Drainage

In the last edition of the guidelines, CSF drainage is mentioned as a separate topic, but no high-level recommendations could be made on usefulness of ventricular CSF drainage in the ICP treatment protocol[10]. Furthermore, no recommendations were made about using ventricular drainage with or instead of ICP monitoring.

Hyperventilation to PaCO2 30-35 mmHg

The re-appraisal of evidence and elimination of a considerable number of studies from the evidence base leaves the clinician with only one recommendation, avoiding hyperventilation with a PaCO2 lower than 25 mmHg. The proper moment for using hyperventilation in the treatment cascade, duration and effectiveness are unknown[10].

Mannitol 0.25- 1.0 g/kg iv.

Although in earlier versions of the guidelines the use of hyperosmolar therapies played a crucial role, In the latest version of the BTF Guidelines the role and effectiveness of these therapies were no longer supported by the evidence base, and as such no formal recommendations could be made[10].

Second tier therapies – PaCO2< 30 mmHg and advanced monitoring (jugular saturation, brain oxygen)

Because of contradictory evidence published more recently, brain oxygen monitoring is no longer recommended by the Guidelines. Hyperventilation as second-tier therapy is also not formally recommended[10].

Second tier therapies – Barbiturates

The administration of barbiturates, but only as a measure to control elevated ICP refractory to maximum standard medical and surgical treatment is recommended, as a level IIB recommendation (based on low-quality evidence)[10].

Second tier therapies – Decompressive Craniectomy

Even though decompressive craniectomy has been used during the past century to lower intracranial pressure, recent trials have shown that patient outcomes are worse when a bifrontal decompression is used for increases in ICP[18] of short duration, possibly due to iatrogenic injury. A more recent trial that better mirrors the clinical "standard" ICP-monitoring treatment showed that while mortality does decrease with decompressive craniectomy, more patients end up in a vegetative state or with severe disability[19]. However, both these studies included a significant proportion (60% and above) of patients with diffuse injury and massive brain edema. These results would not directly apply to patients with isolated contusions and focal edema that stems from a one-sided lesion. The role and timing of decompressive craniectomy in the ICP-directed treatment of severe TBI are still unclear, as is the appropriate choice of patients that would benefit from it.

Overall, the most recent Guidelines offer less recommendation for the clinician than the previous ones. The evidence base, despite growing in terms of quantity, fails to answer the relevant questions that the clinician is confronted with in daily practice. Moreover, despite the the hundreds of RCTs published, the research does not seem to address the role and timing of "old" therapies used in practice: hyperventilation has only one trial in the evidence base, dating as far back as 1991[20].

An unavoidable consequence of the poor evidence base and the changing guidelines recommendations is a large variation in clinical practice. Clinicians faced with lack of evidence and volatile guidelines will use a more eminence-based approach for treating patients, which leads to patients with similar characteristics being treated very differently in centers with comparable experience. While practice variation might be undesirable, it offers perspective for clinical research.

CENTER-TBI: BACK TO BASICS AND TOWARDS THE FUTURE

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) is a prospective, longitudinal study that aims to revisit and renew all existing and earlier recommended interventions and therapies in a "real world" setting, with more than 60 centers participating in 20 countries. In this collaborative study initiative, a vast number of neurotrauma patients will be included and prospectively followed. All data of the patient, including clinical data, imaging studies, cognitive functioning tests, and blood-derived DNA samples will be collected and stored, with more than 2000 variables collected per patient.

Furthermore, all CENTER-TBI participants will be "profiled" before the beginning of the study in order to determine what the practice variation is in terms of the care of severe TBI patients in the acute phase, from admission to the ICU, but also to determine the extent of guideline adherence.

This set of data and the use of comparative effectiveness research[21] in a practice-based setting that exploits practice variation gives clinicians and researchers the opportunity to revisit the "classic" treatments of severe TBI and generate new evidence. Furthermore, clinician-driven research will ensure that the most important issues in TBI patient care will be prioritized and will also ensure the clinical applicability of the results of the study.

In summary, there is a large body of studies in the evidence base for TBI patient care but very few that show treatment effect. The guidelines are underpinned by poor evidence. There are few effective treatments for severe TBI and the mortality has remained the same over the past 30 years.

The aims of this thesis are:

1. To assess the evolution of the current management guidelines for severe TBI, the change in their methodological assessment and their translation from the available evidence (Chapter 2)
2. To describe the practice variation in the acute treatment of severe TBI patients regarding the various steps in the chain of care (Chapters 3, 4)
3. To evaluate guideline adherence and implementation in clinical practice for some of the most relevant topics in ICP management, which have been the subject of extensive debate and changing recommendations over time (Chapter 5)
4. To assess the effect of ventricular versus intraparenchymal pressure devices for the ICP-directed treatment of severe TBI patients according to contemporary evidence generation methods (Chapters 6 and 7)

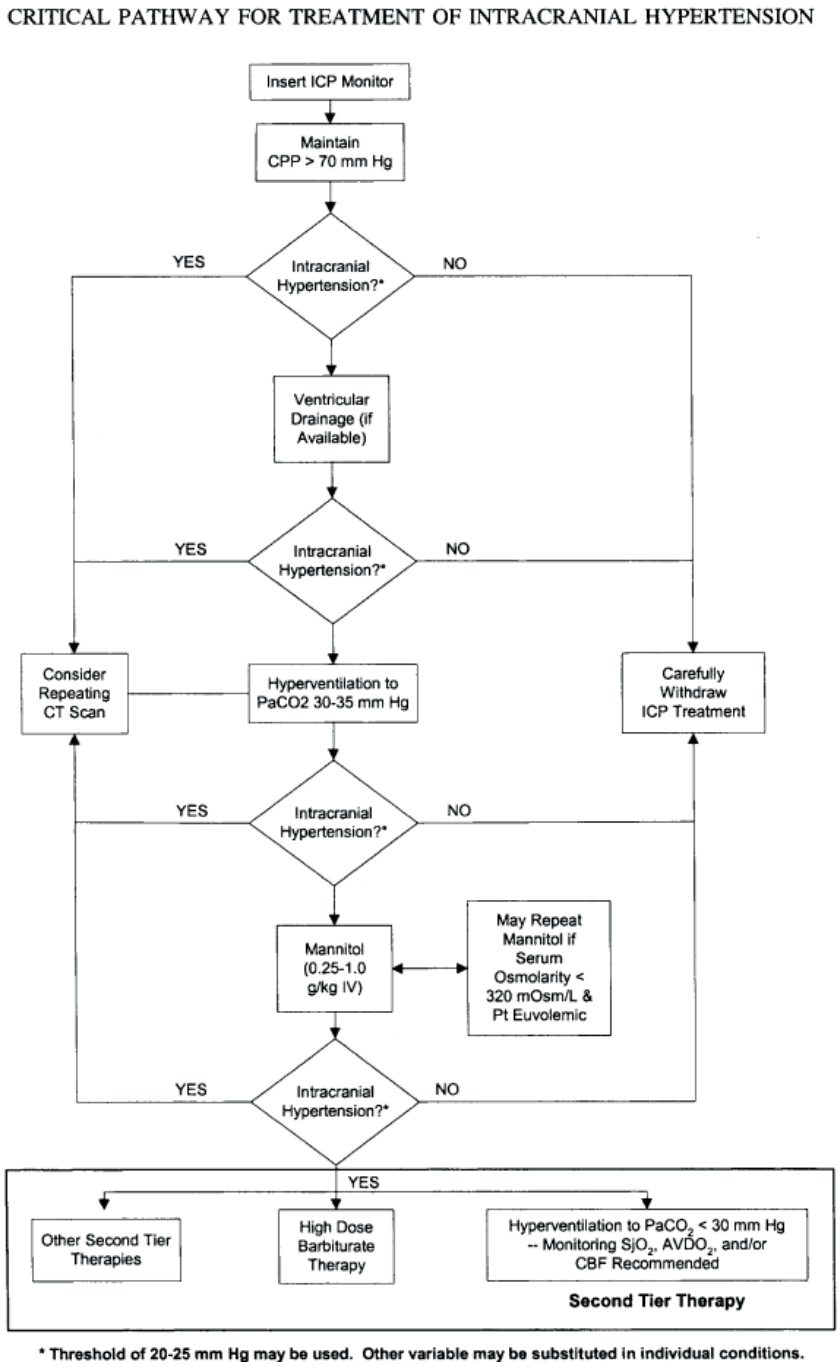

Figure 1. The "Critical Pathway" of ICP treatment from the 1996 and 2000 editions of the BTF Guidelines

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Part 1

EVIDENCE BASE AND TRANSLATION TO GUIDELINES

Chapter 2.1

LETTER: GUIDELINES FOR THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY, FOURTH EDITION

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Neurosurgery. 2017 Aug 1;81(2):E21.
doi: 10.1093/neuros/nyx183. PMID: 28419389

Dear Editor,

We have read the new edition of the Brain Trauma Foundation guidelines[1] with great interest. The group's penchant for instilling methodological purity in an otherwise chaotic field, i.e. evidence in the field of Traumatic Brain Injury(TBI), is highly commendable. The consequence of this methodologic rigor is the disappointing conclusion that only one recommendation can be regarded as Level I: the avoidance of the use of steroids in severe TBI.

In this regard, we are surprised that 2 different papers reporting 2 outcomes (at separate timepoints) of the same trial (CRASH) were viewed as two separate class 1 studies supporting the level I recommendation on avoidance of steroids. The inclusion of the Edwards 2005 paper in the evidence table as a new study seems to imply that there are 2 class 1 evidence studies supporting the recommendation. Even though it was not seen as a separate paper in the overall assessment of the body of evidence, this may still seem reminiscent of "double-dipping".

The issue that plagues guideline generation and applicability in TBI is first and foremost the lack of high-quality methodologically sound studies addressing the key issues clinicians face in the treatment of severe TBI patients. This is highlighted by the fact that when a sound methodological assessment is applied to the existing articles, many fail to be included as evidence to support recommendations on clinical actions. The clinician is left with very little guidance, leading to arbitrariness and variations in clinical practice instead of relative uniformity.

However, variation in clinical practice is not the Gordian knot of TBI. There is no doubt that uniformity of care across (comparable) patients, physicians, hospitals and countries is desirable when an evidence-based approach supports this endeavor. In contrast, when it is unclear what the best treatment is, reducing practice variation through guideline recommendations is undesirable, from two perspectives.

On the one hand, imposing uniformity potentially eliminates any perceived equipoise to perform randomized controlled trials; when certain practices become generally excepted, clinicians will be reluctant to randomize patients. On the other hand, it renders researchers incapable of performing Comparative Effectiveness Research (CER)[2], which exploits existing practice variation by comparing outcomes between centers with different treatment approaches to identify treatments that are superior to others.

It is with deep regret that we observe the failure of the guidelines to provide clinicians with recommendations, but at the same time the failure of the TBI research community to provide the evidence to support guidelines. Fortunately, as the authors observe, current research in TBI shifts towards large-scale observational CER studies, such as TRACK-TBI and CENTER-TBI. Such high quality observational studies may potentially be graded as very good class II studies, supporting level IIA recommendations, and should hence not be underestimated as a new source of evidence to support clinical decision making in TBI.

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Chapter 2.2

EVOLUTION OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR THE MEDICAL MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY

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J Neurotrauma. 2019 Jul 6. doi:10.1089/neu.2019.6474. PMID: 31280663

ABSTRACT

Brain Trauma Foundation (BTF) Guidelines for medical management of severe Traumatic Brain Injury (TBI) have become a global standard for the treatment of TBI patients. We aim to explore the evolution of the guidelines for the management of severe TBI.

We reviewed the four editions of the BTF guidelines published over the past 20 years. The 1996 and 2000 editions were merged because of minimal differences and referred to as 1996. We described changes in topics and recommendations over time and analyzed predictors of survival of recommendations with logistic regression.

The guidelines contained 27 recommendations on 18 topics in 2016, 35 recommendations on 15 topics in 2007, and 22 recommendations on 10 topics in 1996. Substantial delays were found between the search for evidence and the guideline publication, ranging from 18 to 34 months. The overall body of evidence comprised 189 studies on 18 topics in 2016, compared to 156 studies on 15 topics in 2007 and 180 studies on 10 topics in 1996. Over time, a total of 175 studies were discarded from the evidence base following more rigorous grading of evidence. A total of 15/23 (65%) of the 1996/2000 recommendations were discarded over time. Out of 12 new recommendations introduced in the 2007 edition, eight (66%) were discarded in 2016. Survival of recommendations varied between 33% and 100% for level I recommendations and 11% and 31% for level II and III recommendations. No predictors of survival of recommendations were found.

Substantial delays exist between literature search and publication, and survival rate of TBI guideline recommendations is poor. These factors may adversely affect currency and adherence to guidelines. The TBI community should take responsibility to improve the quality of the evidence base and to translate this evidence into guidelines that support clinicians in daily clinical practice.

Keywords: Guidelines for severe TBI; BTF Guidelines; Survival of Recommendations; Evidence Base

INTRODUCTION

Purported aims of clinical practice guidelines include the promotion of an evidence-based delivery of healthcare and reduction of inappropriate variations in practice[1]. To date, more than 6800 clinical guidelines have been developed, available via the Guidelines International Network[2]. However, in the early 2000s attention was drawn to the fact that a previous decade of published guidelines reflected poor quality data, poor reporting, and dubious overall methodology[3]. In the next decade quality of guidelines and their underlying evidence came under fierce scrutiny[4, 5]. In response to this, in 2011 the Institute of Medicine (IOM) developed standards to be followed by future guideline development in order to ensure their proper foundation and form[6]. However, a recent critical overview shows that from 18 standards more than half of guidelines follow eight or fewer of these standards [7]. The authors concluded that there have been "two decades of little, if any, progress."

In the field of Traumatic Brain Injury (TBI), the Brain Trauma Foundation (BTF) Guidelines for medical management of severe TBI have become a global standard. The first edition of these guidelines was published in 1996 – over 20 years ago – and highly welcomed. In a recent survey of mostly academic, preponderantly level I trauma centers, 92% of centers that used any guidelines in the management of their patients either used the BTF Guidelines or a modified version[8]. The initial guidelines were first updated in 2000. The evidence base included animal studies, case reports, letters to the editor. Mechanistic proof-of-principle studies were included if it was felt they provided sufficient information on specific topics to be useful for clinical decision-making[9].

The methodology drastically changed in 2007 and 2016. In the 2016 version, the evidence base was critically reviewed, and low-quality studies were discarded. As a result, the latest edition of the guidelines on the management of severe TBI has been praised for its methodological rigor and criticized for its lack of clinical appeal[10, 11].

In this study, we aim to explore the evolution of the BTF guidelines for the management of severe TBI and its supporting body of evidence over the past 20 years.

MATERIALS AND METHODS

Methodology of the guidelines and study extraction

The basis for this study were the 1996, 2000, 2007 and 2016 versions of the BTF Guidelines. The time between running the last literature search and the publication of the version was calculated. Also, we extracted the number of recommendations per topic and the number of articles in the evidence base per recommendation. The number of studies that make up the evidence base as well as their design was extracted in order to map out the evolution of the evidence underpinning the recommendations for every edition of the guidelines, differentiated by classes of evidence.

Recommendations

We extracted the following variables in a database: the number of Randomized Controlled Trials (RCTs) used to underpin each recommendation when it was issued for the first time; the number of Prospective Observational (PO) and Retrospective Observational (RO) studies; the grading of the recommendation (according to levels of evidence) in the 1996, 2000, 2007 and 2016 editions; whether the recommendation was formally restated or downgraded; the number of patients for each study; and the total number of patients per study design (e.g., RCT, PO, RO). Finally, we recorded for each study that underpinned a recommendation how it would be graded according to the 2016 methodology: class 1 and 2 (high-quality studies) or class 3 and discarded from the evidence base (low-quality studies). If an RCT was used to underpin a specific recommendation, but the data used to draw the conclusion stated in the recommendation was not the primary aim of the RCT we considered it a PO study. For analysis, we combined the 1996 and 2000 versions because of their similarity.

If a recommendation was no longer restated or it was downgraded to a lower level in a subsequent version of the guidelines, this was recorded as the outcome of interest, i.e., non-survival. If a recommendation was merged with another one, the level of the newly merged recommendation was used to determine the outcome. Likewise, if a recommendation was split into two different ones, we judged the outcome for each of the split parts (seen as independent recommendations). Three readers (VV, MC, and IH) extracted data independently then assessed whether the recommendation was positive "+" (intervention recommended), negative "-" (intervention should be avoided) or "+/-" neutral (no clear recommendation, the risks were considered equal to the benefit).

Predictors of survival of recommendations

We used logistic regression analysis to test for predictors of survival of a recommendation; namely the number of high or low-quality studies that underpin a particular recommendation, judging the studies using the strictest methodology from 2016.

RESULTS

Evidence Base

The delay between the last search in MEDLINE and the publication date of the guideline edition was between 18 and 34 months (*Figure 1*).

The overall body of evidence comprised 180 studies for 10 topics in 1996, compared to 156 for 15 topics in 2007, and 189 studies for 18 topics in 2016. The 180 studies in 1996 included, among others, case reports, mechanistic and animal studies and letters to the editor. Most RCTs were considered class 1 evidence, and there were 30 class 1 studies in total. All 30 of these class 1 studies were reappraised: some were reclassified as class 3 and others were removed from the evidence base in subsequent editions. The 5 class 1 studies in 2016 are all new evidence. Of the 180 studies in the 1996/2000 evidence base, only 53 remained in the 2016 evidence base (29%), and were mostly classified as class 3 evidence. From the 156 studies in the evidence base in 2007, 98 (63%) remained in the evidence base of 2016. Of the 189 studies in the evidence base of 2016 (*Figure 2*), five were classified as class 1.

Methodologic assessment of evidence base

Methodological changes occurred in 2007 and again in 2016 with the incorporation of a team of methodologists into the guideline committee. The patient population targeted by the guidelines became more clearly defined, animal studies and case series under 25 patients were no longer regarded as evidence, and hence the guidelines became more restricted in scope[12]. Studies were reclassified according to the new methodology: an RCT would be classified as lower evidence (class 2) if it violated one or more criteria for a good quality RCT[12].

This trend towards methodological rigor continued and was augmented in the most recent update, in 2016[13]. To make positive treatment recommendations, the studies in the evidence base needed to show the effectiveness of interventions in terms of mortality or functional outcome of TBI patients. Secondary outcomes were no longer considered proof of effectiveness.

Survival of Recommendations and Predictors of Survival of recommendations

In 1996, the guidelines contained 22 recommendations on 10 topics, of which 3 were graded as level I, 9 as level II and 10 as level III. In 2000, for the same 10 topics, there were 23 recommendations, of which 3 were level I, 9 were level II, and 11 were level III.

Sixteen new recommendations were presented in 2007 (4 for the original topics and 12 for 5 new topics), yielding a total of 35 recommendations (for 15 topics), of which 1 was level I, 15 were level II, and 19 were level III (*Figure 1*).

From the original 10 topics comprising a total of 23 recommendations (1996/2000 edition), 15 recommendations (65%) were discarded [6 (26%) in 2007 and another 9 (39%) in 2016].

Regarding the 5 new topics added in 2007, 8 of the 12 recommendations (66%) were discarded in 2016.

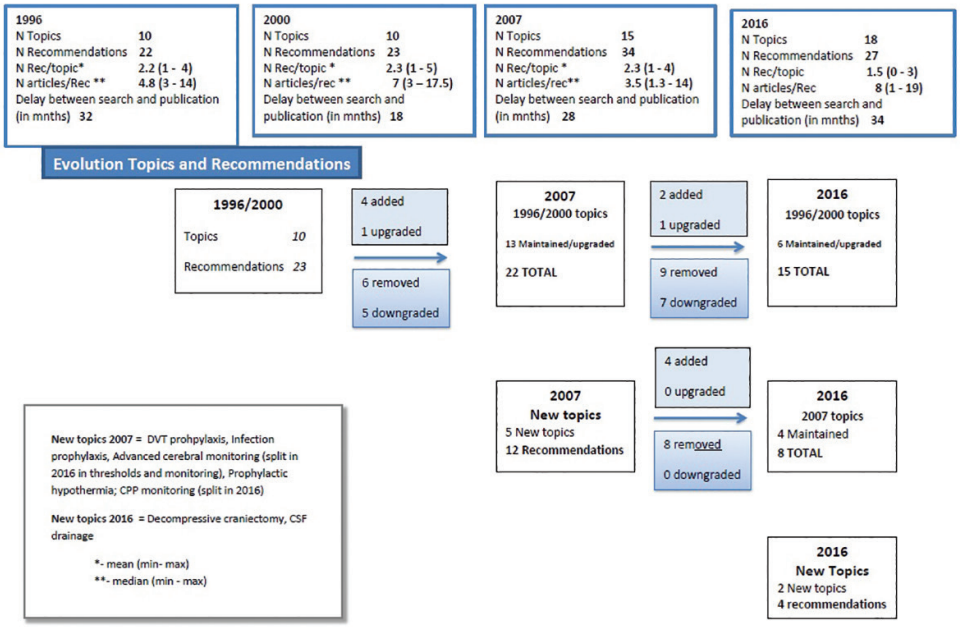

Figure 1. Evolution of the guidelines from one edition to the next. Descriptive data concerning the number of recommendations, as well as the number of recommendations per topic and the numbers of papers/ recommendation for each edition of the guidelines. The 1996/2000 guidelines are pooled together because of minimal differences. The blue rectangles refer to the changes in recommendations.

In total, between the 1996 and 2016 editions, 35 recommendations (70%) were either discarded or downgraded, and only 15 (30%) were kept at the same level or upgraded (*Figure 1*). The survival of recommendations for level II and III recommendations varied between 11 and 33% (*Table 1*).

Of all the recommendations in the various editions of the guidelines, 27 (54%) were not underpinned by an RCT when they were issued, while 18 (36%) were underpinned by at least one class 1 or 2 study, not necessarily an RCT (*Supplementary Appendix 1 and 2*).

We assessed whether the number of high and low-quality studies -as defined by the 2016 methodology- underpinning a recommendation at the moment it was issued were predictors of survival of recommendations. The number of low-quality studies did not predict survival (OR= 1.01, 95% CI= (0.85 to 1.20), p=0.88) but there seemed to be a positive association between the number of high quality studies and survival (OR=1.24, 95% CI= (0.81 to 1.90), p= 0.31) (*Table 2*).

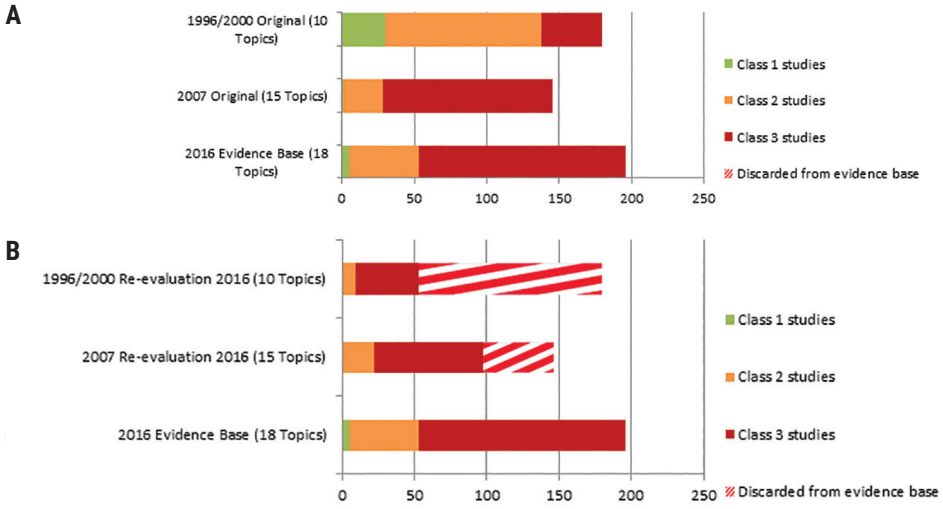

Figure 2. Evolution of the evidence base. The number of articles included in the evidence base, according to the original criteria (A) and the more stringent 2016 methodologic criteria (B). According to the 2016 criteria, class II and III evidence increased substantially between 1996/2000, 2007, and 2016.

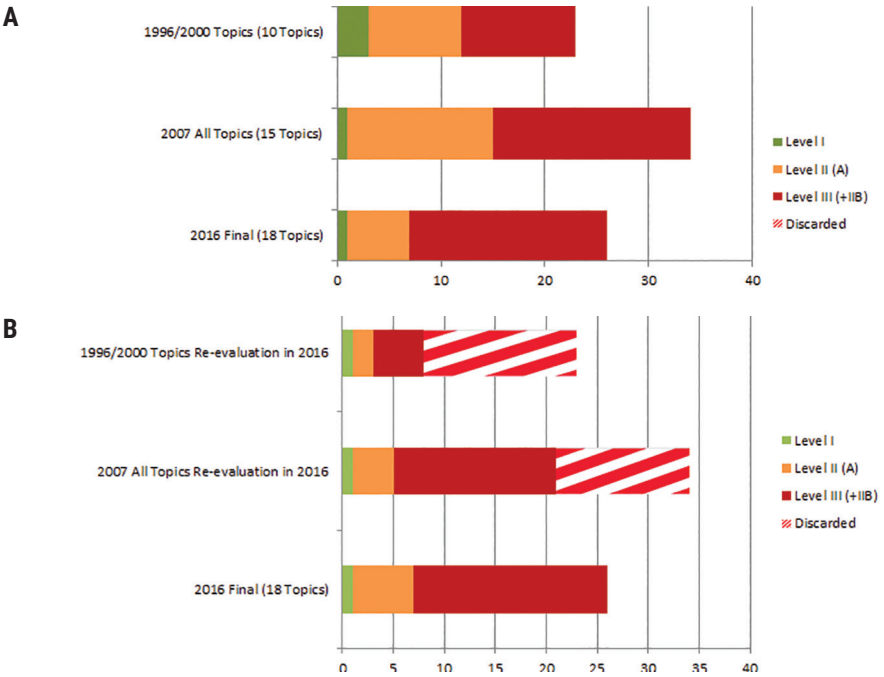

Figure 3. Evolution of the recommendations. The number of recommendations, their level according to the original (A) and 2016 criteria (B), i.e. what happened to the original recommendations in 2016, after introducing the stricter methodologic criteria. The number of topics increases, but not the number of recommendations does not.

Table 1. Survival of recommendations

Edition	Level I	Level II	Level III
1996/2000, survival in 2007	1/3 (33%)	1/9 (11%)	3/11 (27%)
2007, survival in 2016	1/1 (100%)	3/15 (20%)	6/19 (31%)

Number of recommendations that were neither discarded nor downgraded from one edition to the next.

DISCUSSION

Summary of findings

The overall body of evidence comprised 189 studies on 18 topics in 2016, compared to 156 studies on 15 topics in 2007 and 180 studies on 10 topics in 1996. Over time, a total of 175 studies were discarded from the evidence base, following more rigorous grading of evidence. At the same time, the guidelines contained 27 recommendations on 18 topics in 2016, 35 recommendations on 15 topics in 2007 and 22 recommendations on 10 topics in 1996. A total of 15/23 (65%) of the 1996/2000 recommendations were discarded over time. For level II and III recommendations, the likelihood that they would be carried forward and not downgraded in a new edition was between 11% and 33%. When searching for predictors of survival of recommendations, none were found.

Despite a doubling of the evidence base and the addition of new topics, the clinician only has 27 recommendations for 18 topics at his disposal[11], compared to 22 for 10 topics in the first version. Of the 27 recommendations available in 2016, only 8 are based on high and moderate quality evidence, and only one is classified as level I. This is due to the more critical appraisal of the evidence stricter, but the underlying issue is the poor quality and inconsistency of the evidence base.

Evidence base and search updates

Looking at the evidence base of the severe TBI guidelines through the lens of more rigorous methodology (from the 2016 edition), there is consistent growth over the years, especially for class 2 and 3 studies. Moreover, between the last two editions, employing the strictest methodology, the evidence base has increased with 98 studies (52% of the entire current evidence base). Almost half of these, 48 (49%), concerned the seven new topics indicating more research interest in new topics rather than in strengthening the evidence for older recommendations, which was not particularly strong to begin with.

TBI is one of the fields in neurosurgical research where quite a large number of RCTs have been conducted[14, 15]. However, of the 207 RCTs, only 26 across 18 interventions were robust according to a previously conducted overview of research in TBI [14]. In other areas of neurosurgery than TBI, about 1 in 10 trials is considered 'robust'[16] (multi-center, low risk of bias, N > 100 patients). While the evidence base shows significant growth in absolute numbers overall, class 1 evidence remains scarce. Surprisingly, the 5 class 1 and 48 class 2 studies could only be translated into 8 level I and IIA recommendations, of which only three were positive, which denotes treatments with considered proven efficiency which should be used for severe TBI patients.

A substantial and increasing delay was observed between the date of the last literature search and publication of the guidelines. The Cochrane Collaboration[17] recommends that the time between publication and date of the last search should be no more than six months or ideally less than three months. In the 2016 version of the guidelines this was three years, meaning that at the time of publication, the Guidelines are at least three years outdated.

Table 2. Predictors of survival

Covariate	OR and 95% CI	p-value
Number of high quality studies (class 1 and 2)	1.24(0.81 to 1.90)	0.31
Number of low quality studies (class 3 and discarded)	1.01 (0.85 to 1.20)	0.88

Results of the logistic regression analysis for survival of a recommendation based on the number of high (class 1 and 2) and low (class 3 and discarded from the evidence base) quality studies it was issued on, graded according to the 2016 criteria

Survival of recommendations

Compared to other guidelines, severe TBI recommendations have very low survival. According to existing data in the literature, a recommendation underpinned by one or more RCTs would have an 81% chance of surviving in a subsequent version[18]. There were no predictors of survival of recommendations in the analysis we performed when looking either at the number of low of high-quality studies, although there seemed to be a positive assosciation between the number of high-quality studies and survival. The majority of recommendations (77%) were discarded or downgraded due to the change in methodology and reappraisal of existing evidence. The rest were downgraded or discarded due to new evidence. The change in methodology is, therefore, the most likely cause of low survival of recommendations. Nonetheless, the change in methodology was necessary because the 1996/2000 guideline recommendations were improperly classified according to current standards. As such, despite being issued on poor quality evidence, the recommendations were graded higher than they would have been when assessed according to the strictest methodology. This approach might lead to an improperly high degree of confidence in the findings of poor-quality studies. This change in methodology reflects evolving insights into approaches to the grading of evidence and highlights further that many recommendations in the past were based on low-quality studies. According to current insights, many recommendations had received inappropriately high gradings when issued. The final result is a clear reduction in the number of recommendations . The downside of the reduction in number of recommendations is some loss of clinical appeal.

Table 3. Level I and IIA recommendations in the 2016 edition

Positive (Treat with)	**Negative (Do not use)**	**Neutral (Risks and benefits are similar)**
Nutrition	Steroids *(Level I)*	Seizure prophylaxis to treat early PTS
Early tracheostomy	Seizure prophylaxis to treat late posttraumatic seizures (PTS)	
Performing a large rather than a small decompressive craniectomy	Povidine- Iodine use	
	Performing a bifrontal decompressive craniectomy instead of conservative treatment in diffuse injury	

The highest level recommendations that were available to the clinician in 2016, based on high quality studies from the evidence base.

Translation of evidence into guidelines

The challenge of translating the evidence base into clinically appealing guidelines is clearly illustrated in the case of the "Hyperosmolar therapy" topic. Of the 20 original studies included in the evidence base in the 2000 edition, one was still considered evidence in 2016. A total of 6 studies in the evidence base in 2016 could be translated to 0 recommendations. The recommendations in the 2007 edition were re-stated in 2016, but at the same time, a warning was included that they are no longer supported by evidence according to the new methodology. The authors of the BTF Guidelines wanted to retain awareness for the role of hyperosmolar therapies in treating high intracranial pressure (ICP). In the absence of any explicit statement on what the use of hyperosmolar therapies should be, the clinician is left without a formal recommendation. The accompanying text does contain recommendations no longer supported by evidence and a statement that hyperosmolar therapies are indeed important, but no actual guidelines, which leads to confusion.

A similar situation is present in the case of ventilation therapies. For that topic, the evidence base regressed from 28 studies in the 2000 edition to 1 study in 2016, an RCT from 1991. One recommendation remained, and the other three recommendations were re-stated in the text (with the warning that they are no longer "formal" recommendations and that they are no longer supported by evidence meeting current standards).

In contrast to the vague former examples, highly precise recommendations are made about ICP thresholds [13]. The threshold was changed from 20 to 22 mmHg, and this was not well-received by the TBI research community[10], as they argued that this change of 2 mmHg is not clinically relevant and suggests a "cookbook" approach to severe TBI patient care[10].

The most striking change between all 4 editions is the fact that the first editions were focused on lowering ICP as the mainstay treatment for severe TBI[19], while the 2016 version contains no recommendations on lowering ICP except for a large decompressive craniectomy instead of a smaller one and not using a prophylactic bifrontal decompressive craniectomy instead of medical management in diffuse injury.

The best available evidence, graded according to current stringent approaches, leaves the clinician with three positive treatment recommendations, i.e., providing adequate nutrition to decrease mortality; performing an early tracheostomy to reduce mechanical ventilation days (but not to reduce mortality), and to perform a larger rather than a smaller decompressive craniectomy in order to improve outcomes[13]. The rest of the high-quality recommendations advise against the use of steroids (the only level I recommendation available); against the use of povidone-iodine; against the use of seizure prophylaxis for prevention of late posttraumatic seizures. They also advise against the prophylactic use of a bifrontal decompressive craniectomy in diffuse injury[13].

The few treatment recommendations are the reason for critique on the current guidelines. However, in fact, they do justice to the absence of strong evidence. Making treatment recommendations on little evidence carries the risk of recommending treatments that might be redundant or even harmful. Additionally, it might suggest that research into these topics is not needed anymore. On the other hand, it has been argued that it is desirable to standardize care even when a knowledge hiatus exists[18], to create the opportunity to run randomized trials with a uniform control group that represents the current standard of care.

Potential solutions for the future

The challenge is to timely summarize and translate the available evidence into guideline recommendations in the most comprehensive way possible. Being "lost in translation" between clinical studies and clinical practice is not specific to TBI[20] alone.

The first priority is to generate high quality evidence. The TBI research community strongly supports comparative effectiveness research in addition to clinical trials as a way of evidence generation Concerning the outdated searches, solutions have been proposed by the BTF Guidelines authors, among others, in the form of living guidelines, which would be updated online periodically[13]. Living Guidelines, however, do not solve the underlying problem of the poor evidence base, and attention to accurate grading would be essential. As long as the guidelines are properly graded, there is no risk of incorporating potentially harmful treatments based on poor but recent evidence.

One solution for a complete, up-to-date evidence base might be to employ living systematic reviews[21] for individual topics. This solves the problem of outdated guidelines by providing clinicians with a "current" knowledge base on every topic, properly graded according to strict methodology. It would also indicate where a knowledge hiatus exists in order to stimulate the TBI community to perform research in those particular areas. Moreover, the TBI community itself could prioritize these knowledge hiatuses, leading to a more effective collaboration between various groups doing TBI research which might, in turn, lead to the more rapid generation of high-quality evidence. "The Guideline Committee would then use the methodologically sound up-to-date evidence base generated using the living systematic reviews to inform clinically relevant "practice recommendations," developed using the GRADE criteria and branded with a clear level of confidence. This will avoid both the situation of 1996/2000 when recommendations were graded too high while relying on poor quality evidence, as well as the situation of the "hyperosmolar therapies" topic outlined above. A balance needs to be met between evidence base charting and classification (accomplished by the living systematic reviews) and the generation of recommendations. The latter needs to be accomplished by the Guideline Committee that "translates" the results presented in the evidence base synthesis into clinically applicable recommendations, taking into account timing, target population, generalizability, pathophysiology and chains of care. It is critical, however, to grade the recommendations properly according to the level of confidence provided by the evidence base.

In this way, sound methodology and making useful treatment recommendations can be reconciled.

CONCLUSION

Despite considerable interest in TBI research, the evidence for the management of severe TBI remains limited, with few robust studies and even fewer studies showing benefit of a particular intervention. However, there are more high-quality studies in the 2016 version of the Guidelines than in the 1996/2000 versions. Thus, the evidence base is improving slowly, but the TBI research community should take responsibility to generate more high-quality evidence. The underlying evidence base needs to be responsibly translated into clinically applicable, accurately graded recommendations in order to help clinicians treat severe TBI patients. These two efforts should be complementary and stem from a unified vision on evidence, guidelines, and implementation for the benefit of the patient.

Acknowledgments

This work was supported by the European Union Framework 7 program (grant 602150) – CENTER TBI. The funder had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

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Part 2

VARIATIONS IN PROCESSES OF CARE

Chapter 3

INTENSIVE CARE ADMISSION CRITERIA FOR TRAUMATIC BRAIN INJURY PATIENTS ACROSS EUROPE

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J Crit Care. 2019 Feb;49:158-161. doi:10.1016/j.jcrc.2018.11.002. Epub 2018 Nov 8. PMID: 30447560

ABSTRACT

Within a prospective, observational, multi-center cohort study 68 hospitals (of which 66 responded), mostly academic (n=60, 91%) level I trauma centers (n=44, 67%) in 20 countries were asked to complete questionnaires regarding the "standard of care" for severe neurotrauma patients in their hospitals. From the questionnaire pertaining to ICU management, 12 questions related to admission criteria were selected for this analysis.

The questionnaires were completed by 66 centers. The median number of TBI patients admitted to the ICU was 92 [interquartile range (IQR): 52-160] annually. Admission policy varied; in 45 (68%) centers, patients with a Glasgow Come Score (GCS) between 13-15 without CT abnormalities but with other risk factors would be admitted to the ICU while the rest indicated that they would not admit these patients routinely to the ICU.

We found no association between ICU admission policy and the presence of a dedicated neuro ICU, the discipline in charge of rounds, the presence of step down beds or geographic location (North- Western Europe vs. South – Eastern Europe and Israel).

Variation in admission policy, primarily of mild TBI patients to ICU exists, even among high-volume academic centers and seems to be largely independent of other center characteristics. The observed variation suggests a role for comparative effectiveness research to investigate the potential benefit and cost-effectiveness of a liberal versus more restrictive admission policies.

INTRODUCTION

Intensive care unit (ICU) beds are a costly and limited resource. Admission is clearly justified for more severely injured patients needing acute life-sustaining physiological support. For the less severely injured, ICU admission could be justified by the notion that a proportion of these patients subsequently deteriorate or because of care needs that are still too intense to be adequately provided at the ward. However, accurate and broadly applicable admission criteria for such less severely ill patients are lacking and may be subject to service-configuration, other institutional, or clinician-specific determinants. Admission of patients to the ICU who have a low risk of subsequently requiring physiological support or emergent surgical intervention, as a result of the severity of their traumatic brain injury (TBI) or extra-cranial injuries, is undesirable and may have adverse financial consequences.

In the United States, 20% of patients with mild TBI, defined as those with a Glasgow Coma Scale (GCS) of 13-15, presenting to the Emergency Department are admitted to the ICU [1]. Even though admitting a patient with a 'mild' traumatic brain injury (TBI) to the ICU might be the appropriate decision to ensure proper interventions in the case of secondary neurological worsening, existing data do not support this [2, 3]. In Europe, a recent survey demonstrated large variation in the number of critical care beds across countries. Moreover, no clear central policies to facilitate planning to meet the demand and optimal utilization in the future exist[4].

In this study we aim to describe the variation in policy of European neurotrauma centers regarding admission of TBI patients to the ICU.

MATERIALS AND METHODS

Data

Between 2014 and 2015, 68 centers from 20 European countries, participating in the CENTER-TBI prospective longitudinal observational study [5], were approached to complete a set of questionnaires about structure and process of care: The Provider Profiling (PP) questionnaires. These were developed according to best practice. In the item generation phase we have gathered experts together within the CENTER-TBI team and proceeded with item generation and item reduction in a second phase. The questionnaires were then pre-tested with a group of participating centers and face validity was discussed with the participants and the experts involved in item generation. The pilot testing evaluated flow and time required to complete.[6]

We have measured reliability and concordance rates of the questionnaire. To estimate reliability of the questionnaires, we included 17 (5%) duplicate questions, including all question formats. We equally included structure and process questions in the duplicate questions. Concordance rates were estimated by calculating the percentage of overlap between duplicate questions, and presented as mean, median and range. For open questions (e.g. what is the number of intensivist in your center), a differences that were 10% or less were considered concordant. Questionnaires were disseminated during presentations, workshops and email conversations. More information is available at length in one of our group's previous publications[6, 7].

The questionnaire on ICU care contained 3 items and 7 sub-questions on admission criteria which were selected for this analysis (Appendix A) . In most questions the 'general policy' at each center was requested, which was defined as 'routine policy', i.e. what the standard treatment or policy would be in a particular case. In others, we asked for quantitative estimations, whereby the frequency of a treatment strategy could be indicated (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, always 90-100%). The options 'frequently' and 'always' were interpreted as representing the general policy, in line with previous provider profiling studies.[7]

Statistical analyses

To identify possible factors that are associated with admission policy to the ICU, we compared admission policy between different ICU organizations: dedicated neuro- ICU present (yes/no); high or low volume (according to number of beds and according to number of patients admitted, 'high' designating all centers with a number of beds above the median and 'low' centers the centers with number of beds lower than the median); presence of step-down beds (yes/no); healthcare expenditure as % of Gross Domestic Product (GDP; dichotomized in relatively lower and higher % of expenditure); number of ICU beds per 100,000 inhabitants (dichotomized to countries with relatively high vs low numbers of beds); and health expenditure (countries with a higher % expenditure than the median being classified as relatively high and the others classified as relatively low). For analysis of the geographic location, countries were divided into Northern and Western Europe and Southern and Eastern Europe. Differences were tested with chi-square tests, and if appropriate Fisher's exact test. This approach dichotomized hospitals based on admission of mild TBI patients to the ICU into those with a liberal admission policy, versus those with a more conservative policy. A liberal admission policy was defined as the admission of mild TBI patients to the ICU as 'general policy'.

Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.

RESULTS

General characteristics

Among the 68 eligible centers, 66 (97%) completed the questions regarding ICU admission policy. Sixty (91%) of these centers had an academic affiliation and 44 (67%) were designated as level I trauma centers. Experts that completed these questionnaires were primarily intensivists (n = 35, 53%) and neurosurgeons (n = 23, 35%) but also included administrative staff.

The median number of ICU beds was 33 ([interquartile range (IQR): 22-44], more than half of the centers had a dedicated neuro ICU (n=39, 59%) with a median admission rate of 92 (IQR 52-160) TBI patients annually. The median number of all annual ICU admissions (across all diagnoses) in 2013 was 1214 (IQR 554-1950). TBI admissions therefore represented 7% (IQR 5-8) of all admissions. The majority of these ICUs had a closed organization (the intensivist is primarily responsible for the care of patients), with intensivists that are either physically present 24/7, or can reach the hospital within 30 minutes (n=63, 93%) *(Table 1)*.

Admission criteria

Patients with severe TBI (GCS <= 8) would be admitted to the ICU as a general policy in 65 (98%) of the 66 centers. One center would not admit a patient to the ICU based on GCS score alone, but a only after looking at the patient 'as a whole'.

Moderate TBI patients with GCS of 9-12 and CT abnormalities would be admitted to the ICU as a general policy in 42 (63%) of the centers. The remainder stated that they would admit such patients to the ICU only in the presence of other risk factors. The risk factors were not explicitly indicated in the provider profiling questionnaire.

However, patients with initial GCS of 9-12 and no CT abnormalities would be admitted to the ICU as a general policy only in 17 centers (25%), and in another 43 centers (64%) only if other risk factors were present (*Figure 1*).

Fourteen centers (21%) would admit a mild TBI patient with initial GCS of 13 to 15 to the ICU with prior anticoagulant therapy. Another 53 centers (80%) would admit such a patient to the ICU routinely if there were additional risk factors present. Patients with mild TBI who also had either a small epidural hematoma (EDH) or acute subdural hematoma (ASDH) would be admitted to the ICU as a general policy in 15 (22%) centers. Fourteen (21%) centers would always admit a mild TBI patient to the ICU if he or she had contusional lesions present on the CT Scan.

Table 1. Association between factors that may influence admission policy and centers that have a liberal policy of ICU admission and those that do not.

Factor	Total (% of total respondents)	Centers admitting mild TBI to ICU as a general policy (n = 23)	Centers not admitting mild TBI to ICU as a general policy (n = 43)	p-value
ICU Volume (no of beds)				.53
High-volume	31 (47%)	12 (39%)	19 (61%)	
Low-volume	35 (53%)	11 (31%)	24 (69%)	
ICU Volume according to number of patients admitted				.43
High- volume	31 (47%)	13 (42%)	18 (58%)	
Low- volume	31 (47%)	10 (32%)	21 (68%)	
Dedicated neuro ICU				.45
Available	39 (59%)	15 (38%)	24 (62%)	
Not available	27 (41%)	8 (30%)	19 (70%)	
Following any severe TBI treatment guidelines				.05
Yes	55 (83%)	22 (40%)	33 (60%)	
No	11 (16%)	1 (9%)	10 (91%)	
Having step down beds				.67
Yes	48 (73%)	16 (33%)	32 (67%)	
No	18 (27%)	7 (39%)	11 (61%)	
Discipline in charge of rounds				.72
Neurosurgeons, Neurologists	16 (24%)	5 (31%)	11 (69%)	
Intensivists, Anesthesiologists	50 (76 %)	18 (36%)	32 (64%)	
Geographic location*				.27
North Western Europe	43 (65%)	17 (39%)	26 (61%)	
South Eastern Europe	23 (35%)	6 (26%)	17 (74%)	

Table 1. Continued.

Factor	Total (% of total respondents)	Centers admitting mild TBI to ICU as a general policy (n = 23)	Centers not admitting mild TBI to ICU as a general policy (n = 43)	p-value
Number of ICU beds/100 000 inhabitants				1.0
Relatively low number of beds	25 (47%)	9 (36%)	16 (64%)	
Relatively high number of beds	28 (53%)	11 (39%)	17 (61%)	
Health expenditure as % of GDP				.59
Relatively lower expenditure	25 (43%)	8 (32%)	17 (68%)	
Relatively higher expenditure	33 (57%)	13 (39%)	20 (61%)	
Decision of transfer of TBI patients to the hospital made by intensivists				1.0
Intensivists	8 (12%)	3 (37%)	5 (63%)	
Other specialties	57 (88%)	13 (23%)	20 (77%)	
Decision of transfer of TBI patients to the hospital made by neurosurgeons				.11
Neurosurgeons	41 (62%)	11 (27%)	30 (73%)	
Other specialties	25 (38%)	12 (48%)	13 (52%)	
TBI patients always admitted to the same ICU				.28
Yes	41 (62%)	12 (29%)	29 (71%)	
No	25 (38%)	11 (44%)	14 (56%)	
TBI and polytrauma patients admitted to the same ICU				.25
Yes	47 (71%)	14 (30%)	33 (70%)	
No	19 (29%)	9 (47%)	10 (53%)	

* = The subdivision into geographic location was based on the classification by the United Nations. Austria, Belgium, Denmark, Finland, France, Germany, Lithuania, the Netherlands, Norway, Sweden and the United Kingdom (UK) were subsequently classified as countries from West and North Europe, while all other countries were classified as countries from South and East Europe and Israel, in line with our other publications on this matter

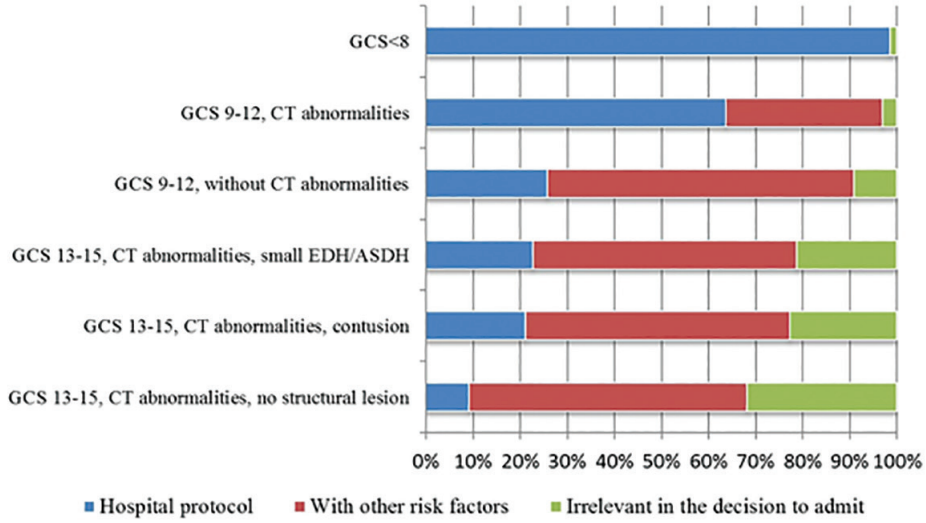

Figure 1. Indications for the admission of patients to the ICU among the interviewed centers (*N*=66). GCS= Glasgow Coma Scale; EDH=epidural hematoma; ASDH= acute subdural hematoma. Irrelevant in the decision to admit designates a criterion that does not influence the decision to admit someone to the ICU or not.

Most centers (*n*=50, or 76%) indicated that they admit TBI patients postoperatively to the ICU as a general policy regardless of their GCS. 64 centers (97%) would admit such patients in the presence of other risk factors. Only 6 centers (9%) would admit a patient with mild TBI and concomitant extracranial injuries to the ICU if these, taken in isolation, would not necessitate ICU observation. This number increases to 60 (91%) if other risk factors were present.

Characteristics of centers with a liberal admission policy

The centers were dichotomized into two categories; those who had responded 'general policy' to any of the questions regarding the admission of GCS 13-15 patients to the ICU (*n*=23, 34.9%) and those who did not (*n*=43, 65.1%). Number of ICU beds per 100 000 inhabitants and healthcare expenditure as % of GDP were not associated with a higher tendency to admit mild TBI patients to the ICU. However, these data were only available for 58 and 55 centers, respectively. The specialist deciding to transfer a TBI patient to the hospital did not influence a more liberal or more conservative approach to patient admission either: when looking at intensivists versus other specialties or neurosurgeons, the majority (n=41; 62%), versus other specialties (*Table 1*).

The only statistically significant difference between these two categories was the fact that ICUs that reported a more liberal admission policy for mild TBI were less likely to follow formal guidelines for severe TBI management ($p = 0.05$). In absolute numbers, 22 of the 55 centers (less than half, 40%) that follow severe TBI guidelines also have a liberal admission policy. Several other center characteristics were compared between these groups but we did not find any clear differences in internal organization of ICUs and hospital, the specialty that oversees patient care, or the geographical region where the center is located. (*Table 1*).

DISCUSSION

Among the 66 centers that responded to our provider profiling questionnaire, mostly academic, level I trauma centers, about a third (*n*=23, 35%) reported that they always admitted mild TBI patients to the ICU in the presence of risk factors. Severe and moderate TBI patients are mostly admitted to the ICU as a general policy, especially in the presence of risk factors. Having a liberal admission policy regarding mild TBI patients did not correlate with other center characteristics except following TBI guidelines, suggesting that the variability is mainly caused by (random) variability of admission policies.

Higher-volume or specialized neuro-ICUs did not appear to be more likely to admit mild TBI patients. Unexpectedly, presence of a step-down unit from ICU did not have an impact in this regard either. This suggests that regardless of the resources available or of the organization, clinicians apply a more liberal or more conservative admission policy according to their personal preference, based on their knowledge and experience. This applies to the presence of step down beds as well, even though our questionnaire did not specifically aim to explore the exact processes of care with regards to the use of these beds and the admission policy surrounding them. Nonetheless, even in centers without step-down beds (n=18), 7 centers (39%) would still admit mild TBI patients to the ICU. Centers that follow severe TBI guidelines are less likely to have a liberal admission policy for mild TBI.

This apparent variation in policy has important implications for both research and processes of care, in two separate areas. ICU admission policy for TBI is ill-supported by high-quality evidence, and from a healthcare expenditure viewpoint, a day in the ICU can incur costs as high as 1597 euro [8]. Given that TBI costs are steeply on the rise [9], avoiding ICU admissions for uncomplicated mild TBI might be a cost-efficient alternative to current policy. Further research is needed to establish whether this alternative is not associated with worse clinical outcomes.

The observed variation provides support for comparative effectiveness research and prognostic modelling, in order to predict neuro-worsening and pinpoint who would indeed benefit from more intensive monitoring. Scarce literature suggests that observation of isolated mild TBI patients on the ICU is seldom necessary [2, 3], but the evidence is of low quality.

Despite the ideal occupancy rate being estimated at 70-75% and higher occupancy rates being linked to more morbidity and mortality[10], many ICUs, especially in academic and larger hospitals routinely operate at far higher occupancy rates[11, 12]. As a result, high opportunity costs arise from admitting patients who may not require ICU level care.

Our study was underpowered to detect subtle associations. Another limitation is that 'risk factors' in the response 'when other risk factors are present' were not specified. In practice, TBI is often associated with extra-cranial lesions (as major bleedings, chest injuries, spinal lesions, limb fractures etc.), other surgical or medical comorbidities, advanced age, mechanism of injury, duration of loss of consciousness, which may, in themselves, be an indication for ICU admission. Our questionnaire was not specifically designed to detect the interplay of these factors in the decision to admit a patient to the ICU. Also, given that the respondents were mostly academic centers and mild TBI is often seen in a non-academic setting, the generalizability of the data is limited. Further research is needed to establish best practice for both academic and non-academic settings.

The issue of cost-efficiency of liberal admission policy for patients with mild TBI to the ICU motivates further investigation to support organizational decision-making and policy making. Moreover, high-quality comparative studies and prognostic models to aid the clinicians in tailoring the admission policy to the needs of the individual patient are necessary.

CONCLUSIONS

There is considerable variation regarding the admission policy of (mild) TBI patients to the ICU in Europe. It is unclear if a liberal admission policy is beneficial for the patients and what the impact is on healthcare costs or whether there is a possible tendency to over-treat at play. Further investigation in this topic is needed, and includes, but is not limited to, on-going large-scale prospective studies, such as CENTER-TBI and TRACK-TBI.

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Chapter 4

VARIATION IN GENERAL SUPPORTIVE AND PREVENTIVE INTENSIVE CARE MANAGEMENT OF TRAUMATIC BRAIN INJURY:

A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study

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Crit Care. 2018 Apr 13;22(1):90. doi: 10.1186/s13054-018-2000-6. PMID: 29650049;

ABSTRACT

Background General supportive and preventive measures in the intensive care management of traumatic brain injury (TBI) aim to prevent or limit secondary brain injury and optimize recovery. The aim of this survey was to assess and quantify variation in perceptions on ICU management of patients with TBI in European neurotrauma centers.

Methods We performed a survey as part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. We analyzed 23 questions focused on 1) circulatory and respiratory management, 2) fever control, 3) use of corticosteroids 4) nutrition and glucose management, and 5) seizure prophylaxis and treatment.

Results The survey was completed predominantly by intensivists (N=33; 50%) and neurosurgeons (N=23; 35%) from 66 centers (97% response rate).

The most common cerebral perfusion pressure (CPP) target was > 60 mmHg (N=39; 60%) and/or an individualized target (N=25; 38%). To support CPP, crystalloid fluid loading (N=60; 91%) was generally preferred over albumin (N=15; 23%), and vasopressors (N=63; 96%) over inotropes (N=29; 44%). The most commonly reported target of partial pressure of carbon dioxide in arterial blood ($PaCO_2$) was 36-40 mmHg (4.8-5.3 kPa) in case of controlled intracranial pressure (ICP < 20mmHg) (N=45; 69%) and $PaCO_2$ target of 30-35 mmHg (4-4.7 kPa) in case of raised ICP (N=40; 62%). Almost all respondents indicated to generally treat fever (N=65; 98%) with paracetamol (N=61; 92%) and/or external cooling (N=49; 74%). Conventional glucose management (N=43; 66%) was preferred over tight glycemic control (N=18; 28%). More than half of the respondents indicated to aim for full caloric replacement within 7 days (N=43; 66%) using enteral nutrition (N=60; 92%). Indications for and duration of seizure prophylaxis varied, and levetiracetam was mostly reported as the agent of choice for both seizure prophylaxis (N=32; 49%) and treatment (N=40; 61%).

Conclusions Practice preferences vary substantially regarding general supportive and preventive measures in TBI patients at ICUs of European neurotrauma centers. These results provide an opportunity for future Comparative Effectiveness Research, since a more evidence-based uniformity in good practices in general ICU management could have a major impact on TBI outcome.

Keywords: intensive care unit; traumatic brain injury; glucose; nutrition; fever; ventilation; blood pressure; seizure; survey; Europe

BACKGROUND

Traumatic brain injury (TBI) is one of the major causes of trauma-related death and hospital admissions in Europe [1]. TBI is recognized as a complex heterogeneous syndrome [2]. The higher vulnerability of this population is reflected by higher mortality rates in patients with TBI compared with non-head injured trauma patients [3]. Therefore, patients with (severe) traumatic brain injury require specialized neuro-intensive care (treatment) at an Intensive Care Unit (ICU) [4].

Case fatality rates in severe TBI are high, ranging from 30% to 40% in unselected observational series [5]. Furthermore, substantial between-country [1] and between center-differences [3, 4, 6] in overall TBI mortality rates exist, which might be partly explained by differences in treatment [7-9].

The key objectives of ICU TBI management are to maintain general physiology and prevent secondary brain injury. A number of brain-specific therapies, such as ICP guided treatment or, less often, brain-metabolic or cerebral vascular autoregulation based goals are employed both clinically or as the subject of clinical research [10]. However, general support of the cardiovascular system, respiratory function, and nutritional or metabolic needs must not be overlooked and could also have a significant impact on outcome [11, 12]. Cerebral metabolic control by seizure or fever management may further contribute to better outcomes [2, 13-15]. At the current time, optimal strategies for general management are only partly established [16, 17]]. This lack of robust evidence may ultimately result in institutional or individual variations in practice which may contribute to variances in outcome.

The aim of this survey study was to assess variation in ICU management perceptions of general supportive and preventive care policies (including for instance circulatory and respiratory management) in patients with TBI in European neurotrauma centers.

METHODS

Participating centers

This study is part of the CENTER-TBI study that collects data on patient characteristics, patient management and outcomes in 68 centers from 20 countries across Europe and Israel [18]. All these centers were asked to complete a 'Provider Profiling Questionnaire' [19]. The questionnaire items, used for this study (treatment at the intensive care), are attached as additional file 1.

Provider Profiling Questionnaire

The provider profiling questionnaire was developed in several stages. First, literature was explored for evidence, including guidelines and available surveys. Second, a pilot study was conducted in 16 participating centers in order to receive feedback, to determine ambiguity and to detect unexpected and missing values. Throughout all stages, experts of various disciplines (neurosurgeons, intensivists, neurologists, emergency department physicians, rehabilitation physicians, medical ethicists, health care economists and epidemiologists) were asked for their advice on the development of the questionnaire. Details on the development, administration and content of the complete provider profiling questionnaires have been published previously [19].

General supportive and preventive management

For the purpose of the current study, we focused on 23 questions specifically aimed at general ICU policies (additional file 1). Specifically, we focused on circulatory and respiratory management, fever control, use of corticosteroids, glucose and nutrition management, and seizure prophylaxis and treatment. Most questions were multiple-choice, except for two questions; the aim for caloric intake in TBI patients and the use of corticosteroids for other conditions. Overall, the general policy of a center rather than the individual treatment preference of the respondent was the premise for completion of the questionnaire. General policy is defined as: 'the way the large majority of patients (>75%) with a certain indication would be treated'.

Statistical analysis

We used descriptive statistics (frequencies and percentages) to present the data. Respondents could indicate how frequently certain management strategies were used (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, and always 90-100%). The combined numbers of respondents that indicated 'frequently' and 'always' were interpreted as representing the general policy of a center, in line with previous reports [20, 21]. To describe center characteristics in more detail we divided centers into higher (Austria, Belgium,

Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland) versus relatively lower income countries (Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia), based on a 2007 report by the European Commission [22]; differences were assessed for statistical significance using the Fisher's exact test without correction for multiple comparisons. We used Statistical Package for Social Sciences (SPSS) version 21 [23] for descriptive analyses.

RESULTS

Participating centers

Of the 68 neurotrauma centers participating in this study, 66 (97%) centers completed the questions on general supportive and preventive ICU management. The questionnaire was predominantly completed by intensivists (N=33; 50%) and neurosurgeons (N=23; 35%). Other professionals that assisted in completion of the questionnaire were administrative staff (N=11; 17%), neurologists (N=5; 8%), anesthesiologists (N=5; 8%) and a trauma surgeon (N=1; 2%).

The majority of centers had an academic affiliation (N = 60, 91%). The majority of centers were designated as level I trauma centers (N= 45; 69%), and a minority as level II (N=4; 6%), level III (N=1; 2%), or no designation (N=15; 23%). More than half of the centers had a dedicated neuroICU (defined as an ICU that is equipped to treat patients with neurological or neurosurgical injury) available (N=39; 59%). The majority of centers adopted a 'closed' ICU organization (the intensivist is primarily responsible for the delivery of care for patients at the ICU) (N= 43; 65%), followed by a 'mixed' ICU organization (the admitting physician, e.g. neurosurgeon is primarily responsible but the care is provided by a intensivist) (N=20; 30%), and a minority adopted an 'open' ICU organization (the admitting physician is primarily responsible for the care at the ICU) (N=3; 5%). Centers indicated to treat a median of 92 (interquartile range 52-160) patients with TBI at their ICU annually. Twenty-eight centers (42%) reported to adhere to the 2007 Brain Trauma Foundation (BTF) guidelines for the management of patients with TBI at their ICU and 21 centers (32%) reported having institutional guidelines that were based on BTF guidelines. The center characteristics and definitions are described in more detail in a previous publication [19].

Circulatory and respiratory management

As part of circulatory management, the most frequently mentioned CPP targets were: > 60 mmHg (N=39; 60%) and/or "individualized" (N=25; 38%). Most centers used crystalloids

(N=60; 91%) and/or vasopressors (N=63; 96%) for CPP support; inotropes (N=29; 44%) were less frequently – but still regularly - employed. Fifteen centers (23%) reported to use albumin containing solutions for volume expansion. (Additional file 2, table 1)

In mechanically ventilated patients with TBI, initial PaO_2 goals of > 75 mmHg (10 kPa) (N=29; 45%) and > 97.5 mmHg (13 kPa) (N=29; 45%) were most commonly cited as a treatment preference, with an initial arterial oxygen saturation goal of >95% (N=56; 86%). In the absence of raised ICP, most centers indicated a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) goal of 36-40 mmHg (4.8-5.3 kPa) (N=45; 69%). In the presence of raised ICP this shifted towards a lower $PaCO_2$ goal of 30-35 mmHg (4.0-4.7 kPa) (N=40; 62%, Figure 1). The timing of tracheostomy in patients with limited or slow neurological recovery varied substantially from within 1 week (N=13, 20%) to between 1 and 2 weeks (N=36, 55%) and more than 2 weeks (N=16, 25%). (Additional file 2, table 1)

Relatively lower income countries more frequently adopted lower oxygen saturation goals (>90%) compared with saturation targets of >95% which were favoured by higher income countries (N=3/11; 27% vs N= 2/55; 4%, p=0.037). (Additional file 3, Table 1)

Fever control

In patients with TBI, the majority of centers indicated that they routinely treat fever (N=65; 98%). One center (2%) reported they would only treat fever "sometimes". The preferred treatments were paracetamol (N=61; 92%) and/or external cooling (N=49; 74%). By contrast, non-steroidal anti-inflammatory drugs (NSAIDs) were less commonly used (N= 29; 44%). Intravascular cooling was also rarely used (N=3; 5%)(Figure 2). (Additional file 2, table 2)

Relatively lower income countries significantly indicated the use of NSAIDs more often than higher income countries (N=11/11; 100% vs N=18/55; 33%, p=0.000). Centers in higher income countries indicated the use of paracetamol significantly more frequently compared with relatively lower income countries (N=53/55; 96% vs N=8/11; 73%, p=0.029). Intravascular cooling was more frequently applied in the lower income group, although this difference did not reach statistical significance. (Additional file 3, Table 2)

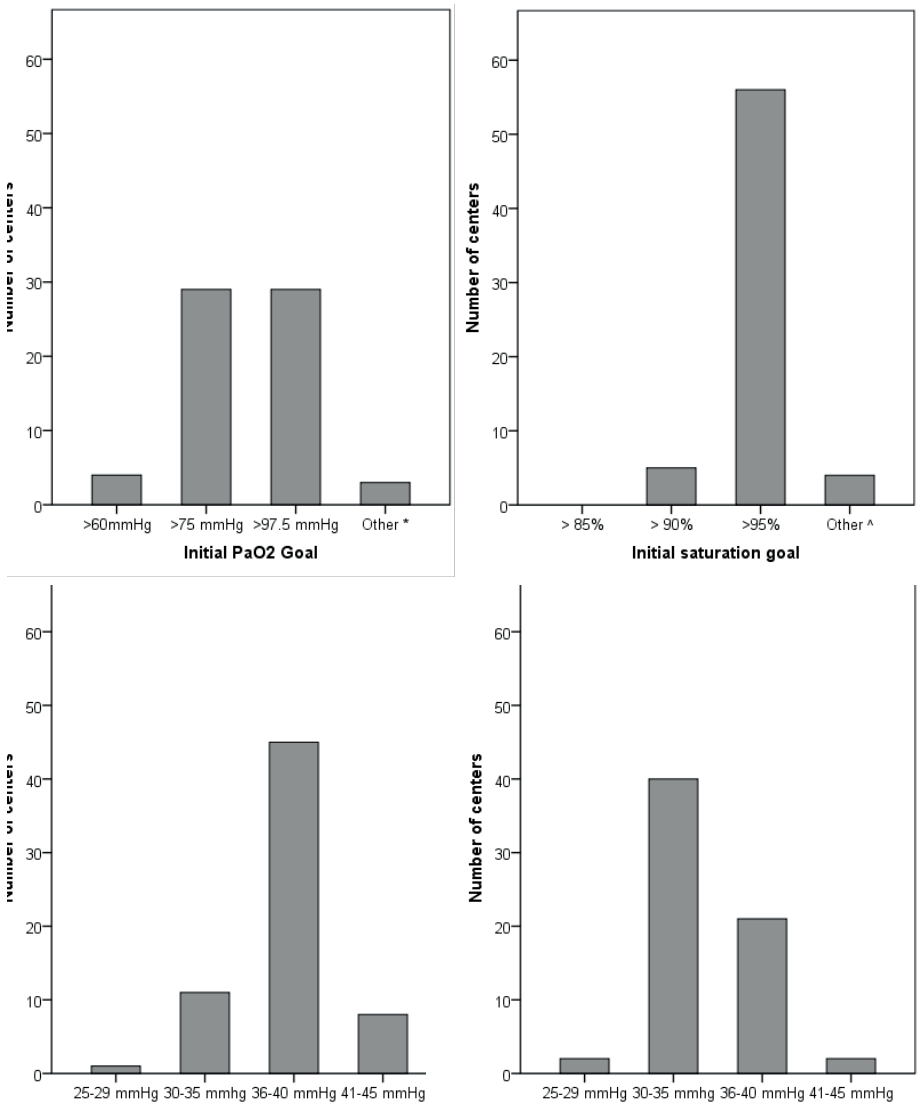

Figure 1. Mechanical ventilation thresholds with corresponding answer frequencies. $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of carbon dioxide in arterial blood, mmHg: milimiters mercury, 25-29 mmHg ≈ 3.3-3.0 kPa (kilopascal), 30-35 mmHg ≈ 4-4.7 kPa, 36-40 mmHg ≈ 4.8-5.3 kPa, 41-45 mmHg ≈ 5.5-6 kPa, 60 mmHg = 8 kPa, 75 mm Hg = 10 kPa, 100 mmHg =13 kPa * No specific goal (N=1), > 90 mmHg (N=2), ^ > 96% (N=2), >97% (N=1), 92-94% (N=1)

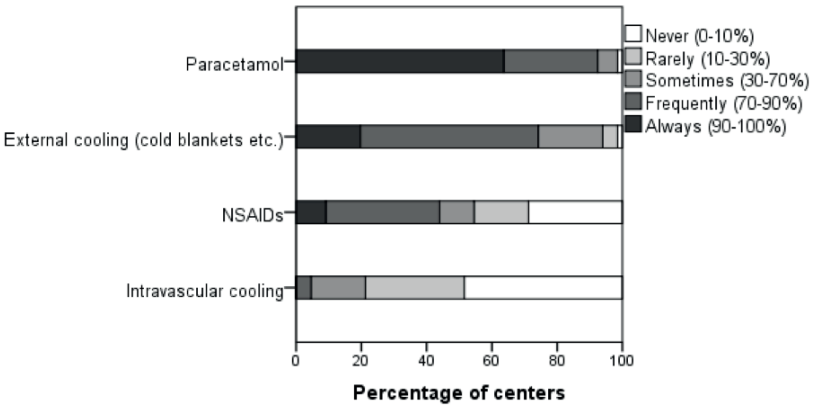

Figure 2. Type of fever treatment and corresponding percentage of centers that indicated to use this type of fever treatment never (in 0-10% of cases), rarely (in 10-30% of cases), sometimes (in 30-70% of cases), frequently (in 70-90% of cases) or always (in 90-100% of cases). NSAIDs: nonsteroidal anti-inflammatory drugs

Use of corticosteroids

Corticosteroids were infrequently used for the primary management of brain injury, although a few respondents indicated that they used them "rarely" (N=5; 8%), "sometimes" (N=2; 3%) or "frequently" (N=1; 2%). However, corticosteroids were used for vasopressor resistant hypotension (N=21; 58%) and, to a lesser extent, sepsis (N=8; 22%) specifically. (Additional file 2, table 3)

Primary use of corticosteroids was significantly more frequently reported by lower income countries compared with higher income countries (N=4/11; 36% vs N=4/55; 7%, p=0.023). (Additional file 3, Table 2)

Glucose and nutrition management

The majority of centers stated that their glucose management was protocolised (N=50; 77%). Most centers reported the correction of hyperglycemia as a primary aim (N=43; 66%), while a smaller number implemented tight glycemic control (N=18; 28%). (Additional file 2, table 4)

Most respondents aimed for full caloric replacement within 7 days post-injury (N=43; 66%.). An open question on the goals for caloric intake showed a high variety in reported strategies as well as metrics used (kcal/day, kcal/kg/day and percentages). The enteral route was preferred (N=60; 92%). The timing of parenteral nutrition was highly variable; centers

were equally distributed between "as soon as possible" (N=13; 20%), "within 24 hours post-injury" (N=13; 20%), "within 72 hours post-injury" (N=10; 15%), "within 7 days post-injury" (N=17; 26%) and "we do not have rules/guidelines for this" (N=12; 19%).

Relatively lower income countries reported using the parenteral route significantly more frequently compared with higher income countries (N=4/11; 36% vs. N=1/55; 2%, p=0.002). (Additional file 3, Table 2)

Seizure prophylaxis and treatment

There was little consensus regarding the use of prophylactic antiepileptic drugs (for all indications). Most centers reported to use levetiracetam as the drug of choice for both seizure prophylaxis and treatment (N=32; 49% and N=40; 61%), followed by phenytoin (N=20; 31% and N=32; 48%) (Figure 3). In general, both the reported duration of anti-seizure prophylaxis, as well as the criteria for initiation of anti-epileptic treatment varied considerably. (Additional file 2, table 5)

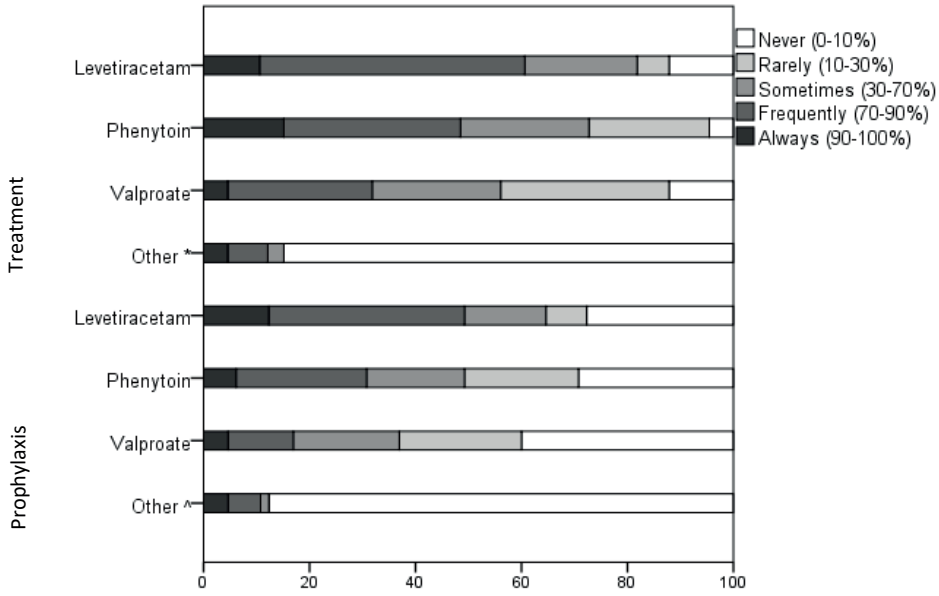

Figure 3- Agents for seizure prophylaxis and treatment with corresponding percentage of centers that indicated to never (in 0-10% of cases), rarely (in 10-30% of cases), sometimes (in 30-70% of cases), frequently (in 70-90% of cases) or always (in 90-100% of cases) use the agent.

* Carbamazepine/ phenobarbital, phenobarbital, benzodiazepines, no prophylaxis used in our hospital, carbamazepine (N=3)

^ Phenobarbital, benzodiazepines, carbamazepine (N=4), midazolam/diazepam, lorazepam

The choice of agent varied with income, with levetiracetam being less commonly used for both seizure prophylaxis (N= 0/11 vs N=32/55; 59%, p=0.000) and treatment (N=1/11; 9% vs N=39/55; 71%, p=0.000) in the lower income group versus higher income countries, respectively. Instead, lower income countries seemed to favour valproate or phenytoin compared with higher income countries (N=7/11; 64% vs N=14/55; 26%, p=0.029). (Additional file 3, Table 2)

DISCUSSION

In this survey, we found varying degrees of consensus between European neurotrauma centers with respect to general supportive and preventive ICU management in patients with TBI. Most variation was found in initial PaO_2 goals for mechanically ventilated patients; CPP targets; the timing of tracheostomy in unconscious patients; nutritional targets; and seizure prophylaxis and treatment.

Large between-center variation was found in topics that are not addressed in the recommendations of the Brain Trauma Foundation (BTF) guidelines (Additional file 4), suggesting the role of guidelines in reducing variances in clinical practice. International guidelines (BTF guidelines and guidelines of the American College of Surgeons) do recommend the use of normalized thresholds (e.g. normoglycemia, -capnia, and -thermia) in patients with TBI, although this is not based on high-level evidence [16, 17]. Indeed, randomized controlled trials (RCTs) on these topics are too limited in number to lead to high-level evidence [10]. Considering CPP targets, the BTF guidelines are unclear whether to use an optimum threshold of >60 or >70 mmHg (and a range of 50 -70 mmHg in the previous BTF guidelines [24]). Despite this ambiguity, a majority of respondents (60%) preferred a target CPP of >60 mmHg. In addition, the current BTF guidelines added that the CPP target might depend on the individual cerebral autoregulatory status, reflected by 38% of respondents who indicated to use an individualized target CPP. The uniformity in reported CPP targets between income groups also suggests that these concepts are widespread. It may be that the willingness to individualize CPP in patients with TBI reflects the growing trend for use of precision medicine [25], where therapies and therapy targets are individualized to patient need, rather than used on a "one size fits all" basis.

Marked variation was also found on topics where consensus was expected based on high-level evidence from RCTs, or the recommendations in the BTF guidelines. The use of steroids for the primary management of TBI was reported by 13% of the respondents (one respondent reported frequent use), but is against the advice of the BTF guidelines and contradicts the prevailing evidence from the CRASH study [26, 27]. However, use in the

majority of centers was for vasopressor dependence and/or sepsis, a use in keeping with current guidelines for the management of sepsis [28]. The use of albumin was reported by 23% of the respondents, while the SAFE study showed that albumin was associated with higher mortality rates in patients with TBI [29]. It is difficult to interpret continued use of albumin for volume expansion as a lack of knowledge of the evidence, since worse outcomes in the albumin treated arm in SAFE-TBI may have been the consequence of a hypotonic carrier causing elevated ICP [30], and well informed clinicians may have used albumin that was isotonic or corrected any accompanying hyponatremia. Finally, the use of tight glycemic control was reported by 28% of respondents, while the NICE-SUGAR and CGAO-REA study recommend using moderate instead of tight glucose control in patients with TBI [31, 32].

On the other hand, we found consensus where variation was expected: a high number of centers indicated to use antipyretic agents for treatment of fever, when there is no consensus on the optimal choice of agent and their potentially deleterious side-effect of CPP lowering is well known[33]. This suggests a strong aversion amongst treating clinicians, however, to allow pyrexia in patients with TBI. The choice of NSAID, despite their well-known potentially harmful systemic side-effect profile, as antipyretics in many centers probably also reflects this, although a continuous intravenous infusion instead of intermittent NSAID dosing might improve fever control (with relatively higher CPP) in neurocritical care [34]. In addition, respondents indicated employing below-normal $PaCO_2$ goals (30-35 mmHg) in the presence of raised ICP in mechanically ventilated TBI patients. This was unexpected given the BTF recommendation to avoid prolonged hyperventilation. Furthermore, even patients in whom intracranial hypertension was not a concern were ventilated to normal carbondioxide (CO_2) tensions showing a reluctance to use permissive ventilatory strategies that have been shown to be effective in reducing mortality in ARDS patients [35].

Our results further suggest that respondents use TBI-specific strategies instead of general strategies (used in general critically ill patients) in the ICU. For example, respondents indicated they frequently or always treat fever, because hyperthermia is associated with worse outcomes in TBI [14, 33] whereas fever is often considered beneficial to some extent in critically ill patients with infections [36].

We found some differences between relatively lower versus higher income countries. It was striking that levetiracetam was significantly more frequently reported by higher income countries as agent of choice for seizure prophylaxis and treatment, while valproate and phenytoin were reported more frequently by lower income countries – although high-level evidence in literature on the agent of choice is lacking [37]. However, there were no clear structural differences in management overall and thus this could not be considered

an explanation for the treatment variation. Indeed, some high cost interventions, such as intravascular cooling and parenteral nutrition, were more commonly used in the lower income countries, suggesting that choice of treatment options are not solely based on cost considerations, but also reflected local clinical culture in different institutions.

Our study has several strengths. To our knowledge, this is the first survey that provides an overview of multiple components of general supportive or preventive ICU management in patients with TBI. The survey was developed in several stages with involvement of clinical experts of various disciplines and the response rate of the survey was high (97%). However, this study also has limitations, as the centers participating in the CENTER-TBI study may still be a biased selection of European centers; with a specialist interest in the topic, or a large engagement in research, or more expertise overall. In a small number of centers, the questionnaire was completed by administrative staff (with no clinical expertise). However, presumably this was in close collaboration with a clinician, considering the high number of clinicians that completed the survey and clinical involvement was encouraged throughout the survey. Other limitations are inherent to surveys: the results are self-reported and are not yet confirmed by independent observations in daily practice and therefore represent what the respondents 'believe' is clinical practice and this may not, in fact, reflect reality. Another limitation is that the survey questions represent generalizations and do not include patient factors (such as demographics, lab results, or imaging), or very specific circumstances, while in clinical practice these details influence clinicians' judgement. In line with this, we did not specify time-frames (for ventilation goals) and lab values (for tight glucose control). Also, we asked about general patients with TBI in the survey and did not specify adult or pediatric TBI.

Overall, the practice variation (and consensus) in general ICU management we found might be explained by a lack of evidence (or incomplete implementation of evidence), by the use of individualized approaches or by a tension between general and TBI-specific strategies. We presume that increased and more evidence-based uniformity in good practices in general ICU management might improve outcome in TBI. In fact, general ICU management is part of daily routine (e.g. temperature measurements, lab results and mechanical ventilation) and deviations are generally easily detected and corrected. It is noteworthy that non-neurological complications are frequent; in one report on TBI patients these were more frequent (around 22%) than neurological complications (around 3%) [29]. Our survey showed that future research on individualized management is needed: a high number of respondents reported individualized practices, that implies a trend towards precision medicine. In addition, the existence of practice variation in general ICU management provides direction to Comparative Effectiveness Research (CER) analyses or RCTs. As RCTs in the field of TBI have been disappointing [10], CER might be a promising approach

to enhance future knowledge on the effectiveness of general ICU management and understanding in what processes variances occur, as we have attempted to do, is a critical starting point. Hence, in the CENTER-TBI study we will evaluate the effect of different ICU management practices on TBI outcome (after case-mix correction), for example, the difference in patients' outcome between the 13 centers that plan tracheostomy within 1 week, the 36 centers that time tracheostomy between 1 and 2 weeks, and the 16 centers that delay tracheostomy longer than 2 weeks.

CONCLUSIONS

This study showed that general supportive and preventive ICU management policies in TBI vary between European neurotrauma centers. These findings stress the need for continued knowledge transfer of existing evidence, further research on optimized individualized management (precision medicine) and (as we propose) comparative effectiveness research.

Declarations:

Funding: European Commission FP7 Framework Program 602150. Data used in preparation of this manuscript were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Commission 7th Framework program (602150). The funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Acknowledgements: The authors would like to thank all clinical and research staff at the CENTER-TBI sites for completing the provider profiling questionnaires.

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SUPPLEMENTARY MATERIAL

Overview of all results

Table 1. Circulatory and respiratory management

Items of the questionnaire	Number completed	N	(%)
Circulatory management			
Target CPP	66*		
>50 mmHg		7	11
>60 mmHg		39	60
>70 mmHg		14	21
Individualized		25	38
IV fluids for treatment CPP	66*		
Crystalloids		60	91
Colloids - starches		10	15
Colloids - albumin		15	23
Other combinations		8	12
Vasoactive drugs to support CPP	66*		
Vasopressors		63	96
Inotropes		29	44
Respiratory management			
Initial PaO_2 goal [1]	65		
> 8 kPa (60 mmHg)		4	6
> 10 kPa (75 mmHg)		29	45
>13 kPa (100 mmHg)		29	45
Other [2]		3	4
Initial arterial oxygen saturation goal	65		
>85%		0	0
>90%		5	8
>95%		56	86
Other [3]		4	6
$PaCO_2$ goal - in the absence of raised ICP	65		
25-29 mmHg (≈ 3.3-3.0 kPa)		1	2
30-35 mmHg (≈ 4-4.7 kPa)		11	17
36-40 mmHg (≈ 4.8-5.3 kPa)		45	69
41-45 mmHg (≈ 5.5-6 kPa)		8	12
$PaCO_2$ goal - in the presence of raised ICP	65		
25-29 mmHg (≈ 3.3-3.0 kPa)		2	3
30-35 mmHg (≈ 4-4.7 kPa)		40	62
36-40 mmHg (≈ 4.8-5.3 kPa)		21	32
41-45 mmHg (≈ 5.5-6 kPa)		2	3
Timing tracheotomy [4]	65		
< 1 week		13	20
1-2 weeks		36	55
>2 weeks		16	25

1) In mechanically ventilated patients, 2) No specific goal (N=1), > 12 kPa (N=2), 3) > 96% (N=2), >97% (N=1), 92-94% (N=1), 4) In patients remaining unconscious

* Multiple answers were possible

CPP: Cerebral Perfusion Pressure, ICP: intracranial pressure, IV: intravenous, mmHg: millimeters of mercury, $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of oxygen in arterial blood

Table 2. Fever control

Items of the questionnaire	Number completed	N	(%)
Fever [1] treated routinely	66		
Never (0-10%)		0	0
Rarely (10-30%)		0	0
Sometimes (30-70%)		1	2
Frequently (70-90%)		21	32
Always (90-100%)		44	66
Type of treatment of fever	66*, **		
Paracetamol		61	92
NSAIDs		29	44
External cooling [2]		49	74
Intravascular cooling		3	5

1) Core temperature above 38 °C 2) Cold blankets etc

* Multiple answers were possible

** Sum of centers that indicated frequently (70-90% of cases) or always (100% of cases)

NSAIDs: nonsteroidal anti-inflammatory drugs

Table 3. Use of corticosteroids

Items of the questionnaire	Number completed	N	(%)
Primary management with corticosteroids	66		
Never (0-10%)		57	87
Rarely (10-30%		5	8
Sometimes (30-70%)		2	3
Frequently (70-90%)		1	2
Always (90-100%)		0	0
Corticosteroids used for other conditions (open question)	36**		
Vasopressor resistant hypotension		21	58
Sepsis		8	22
Other [1]		7	20

1) Adrenal insufficiency, bronchospasm, spinal cord injury, hypopituitarism, hypocortisolism, spinal cord injury, peripheric nerve injury, stress response

* Multiple answers were possible

** Sum of centers that indicated frequently (70-90% of cases) or always (100% of cases)

Table 4. Glucose and nutrition management

Items of the questionnaire	Number completed	N	(%)
Glucose management			
Protocol glucose management	65		
Presence of a protocol		50	77
Absence of a protocol		15	23
Glucose therapy	65		
No specific therapy		2	3
Prophylactic insulin administration[1]		2	3
Insulin administration to correct hyperglycemias		43	66
Tight glycemic control		18	28
Nutrition management			
Aim for full caloric replacement	65		
At 7 days post-injury		12	19
< 7 days post-injury		43	66
>7 days post-injury		10	15
Aim caloric intake (open question)	65		
1900 kcal/day[2]		14	22
27 kcal/kg/day[3]		32	49
Other [4]		10	15
Unknown/no protocol		9	14
Route of nutrition	65		
Parenteral		5	8
Enteral[5]		60	92
Start parenteral nutrition	65		
As soon as possible [6]		13	20
Within 24 hours post-injury		13	20
Within 72 hours post-injury		10	15
Within 7 days post-injury		17	26
We do not have rules/ guidelines for this		12	19

1) Buffered infusion; 2) median 3) median 4) 100%-130%; 80%ee; 100%; 2 kcal/kg/h; for patients with no resp; variable; based on calorimetry; high 5) Including mostly enteral, parenteral on indication 6) Directly after ICU admission

kcal: kilocalories, kg: kilograms

Table 5. Seizure prophylaxis and treatment

Items of the questionnaire	Number completed	N	(%)
General			
Indications for anti-seizure prophylaxis	66* , **		
GCS<10		15	23
Cortical contusion		21	32
Depressed skull fracture		23	35
Subdural hematoma		19	29
Epidural hematoma		12	18
Intracerebral hematoma		19	29
Penetrating brain injury		25	38
Other [1]		5	8
Seizure prophylaxis			
Agents used for seizure prophylaxis	65*, **		
Phenytoin		20	31
Levetiracetam		32	49
Valproate		11	17
Other [2]		7	11
Duration of anti-seizure prophylaxis	66*		
1-3 days		3	5
4-7 days		21	32
> 7 days		6	9
3 weeks		2	3
3 months		5	8
Depending on the patient		22	33
Depending on the physician		12	18
Seizure treatment			
Agents used for seizure treatment	66*, **		
Phenytoin		32	48
Levetiracetam		40	61
Valproate		21	32
Other [3]		8	12
Initiation of anti-epileptic treatment	66**		
A single seizure		44	67
Two or more seizures		61	92

1) Previous seizure, seizure within 24 hours, epileptic fit, ventilated TBI, all severe, EEG confirmed seizures, 2) Carbamazepine/ phenobarbital, phenobarbital, benzodiazepines, no prophylaxis used in our hospital, carbamazepine (N=3), 3) Phenobarbital, benzodiazepines, carbamazepine (N=4), midazolam/diazepam, lorazepam

* Multiple answers were possible

** Sum of centers that indicated frequently (70-90% of cases) or always (100% of cases)

GCS: Glasgow Coma Scale

Variation between higher and lower income countries

Table 1. Thresholds used for circulatory and respiratory management

Items of the questionnaire	Higher income countries (N=55)	Lower income countries (N=11)	P-value
Respiratory management			
Initial PaO_2 goal (in mechanically ventilated patients)			
> 10 kPa (75 mmHg)	25 (50%)	4 (50%)	1.000
>13 kPa (100 mmHg)	25 (50%)	4 (50%)	
Initial arterial oxygen saturation goal			
>90%	2 (4%)	3 (27%)	0.037
>95%	48 (96%)	8 (73%)	
$PaCO_2$ goal - in the absence of raised ICP			
25-35mmHg	8 (15%)	4 (36%)	0.194
36-45 mmHg	46 (85%)	7 (64%)	
$PaCO_2$ goal - in the presence of raised ICP			
25-35 mmHg	35 (65%)	7 (64%)	1.000
36-45 mmHg	19 (35%)	4 (36%)	
Circulatory management			
Target CPP			
>50 mmHg	7 (13%)	0 (0%)	0.591
>60 mmHg	33 (60%)	6 (55%)	0.749
>70 mmHg	13 (24%)	1 (9%)	0.433
Individualized	20 (36%)	5 (45%)	0.735

In order to calculate the Fisher exact test a sufficient number per category (answer option) was needed, therefore categories with low numbers were deleted (for PaO_2 goal and saturation goal) or categories were combined (for $PaCO_2$ goal in the presence and absence of raised ICP)

Higher income: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland; *Relatively low income:* Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia.

CPP: Cerebral Perfusion Pressure, ICP: intracranial pressure, IV: intravenous, mmHg: millimeters of mercury, $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of oxygen in arterial blood

Table 2. General treatments at the ICU

Items of the questionnaire	Higher income countries (N=55)	Lower income countries (N=11)	P-value
Respiratory and circulatory management			
IV fluids			
Crystalloids	51 (93%)	9 (82%)	0.260
Colloids- starches	6 (11%)	4 (36%)	0.054
Colloids- albumin	12 (22%)	3 (27%)	0.703
Other combinations	5 (9%)	3 (27%)	0.122
Vasoactive drugs to support CPP			
Vasopressors	52 (95%)	11 (100%)	1.000
Inotropes	24 (44%)	5 (46%)	1.000
Fever control			
Type of treatment of fever (general policy)			
Paracetamol	53 (96%)	8 (73%)	**0.029**
NSAIDs	18 (33%)	11 (100%)	**0.000**
External cooling	40 (73%)	9 (82%)	0.714
Intravascular cooling	1 (2%)	2 (18%)	0.070
Corticosteroid use			
Primary management with corticosteroids			
No	50 (93%)	7 (64%)	**0.023**
Yes	4 (7%)	4 (36%)	
Glucose and nutrition management			
Glucose therapy			
Insulin administration to correct hyperglycemias	36 (69%)	7 (78%)	0.713
Tight glycemic control	16 (31%)	2 (22%)	
Route of nutrition			
Parenteral	1 (2%)	4 (36%)	**0.002**
Enteral	53 (98%)	7 (64%)	
Seizure prophylaxis and treatment			
Agents used for seizure prophylaxis (general policy)			
Phenytoin	16 (29%)	4 (36%)	0.725
Levetiracetam	32 (59%)	0	**0.000**
Valproate	7 (13%)	4 (36%)	0.080
Agents used for seizure treatment (general policy)			
Phenytoin	25 (46%)	7 (64%)	0.333
Levetiracetam	39 (71%)	1 (9%)	**0.000**
Valproate	14 (26%)	7 (64%)	**0.029**

In order to calculate the Fisher exact test a sufficient number per category (answer option) was needed, therefore categories were combined (for the primary management with corticosteroids)

Higher income: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland; *Relatively low income:* Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia.

CPP: cerebral perfusion pressure, IV: intravenous, NSAIDs: nonsteroidal anti-inflammatory drugs

Chapter 5

VARIATION IN GUIDELINE IMPLEMENTATION AND ADHERENCE REGARDING SEVERE TRAUMATIC BRAIN INJURY TREATMENT:

A CENTER-TBI Survey Study in Europe

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World Neurosurg. 2019 Jan 31. pii:S1878-8750(19)30216-5.
doi: 10.1016/j.wneu.2019.01.116. PMID: 30710717

ABSTRACT

Guidelines may reduce practice variation and optimize patient care. We aimed to study differences in guideline use in the management of traumatic brain injury (TBI) patients and analyze reasons for guideline non-adherence.

As part of a prospective, observational, multi-center European cohort study, participants from 68 centers in 20 countries were asked to complete 72-item questionnaires regarding their management of severe TBI. Six questions with multiple sub-questions focused on guideline use and implementation.

Questionnaires were completed by 65 centers. Of these, 49 (75%) reported use of the Brain Trauma Foundation Guidelines for the medical management of TBI or related institutional protocols, 11 (17%) used no guidelines and 5 used other guidelines (8%). Of 54 centers reporting use of any guidelines, 41 (75%) relied on written guidelines. Four centers of the 54 (7%) reported no formal implementation efforts. Structural attention to the guidelines during daily clinical rounds was reported by 21 centers (38%). The most often reported reasons for non-adherence were 'every patient is unique' and the presence of extracranial injuries, both for centers that did and did not report the use of guidelines.

There is substantial variability in the use and implementation of guidelines in neurotrauma centers in Europe. Further research is needed to strengthen the evidence underlying guidelines and to overcome implementation barriers.

INTRODUCTION

The objective of clinical practice guidelines is to reduce practice variations and improve patient outcomes by synthesizing the best available evidence in clear, concise and easy-to-use documents[1]. The Brain Trauma Foundation (BTF) Guidelines for the medical management of severe traumatic brain injury (TBI) are the most widely used for these patients with 4 editions published over the last 20 years[2]. Recent studies show suboptimal and variable adherence rates, which likely relate both to the poor quality of the evidence and the heterogeneity of the TBI patient population, among other reasons[3-6].

Within a prospective, observational study, the Collaborative European NeuroTrauma Effectiveness Research in TBI study (CENTER-TBI; www.center-tbi.eu), we aimed to explore variations in guideline use and implementation strategies for severe TBI in Europe, in particular adherence to the high quality recommendations (levels I and II). We then aimed to detect differences in practice between centers that use BTF guidelines and those that use other guidelines.

MATERIALS AND METHODS

We approached the principal investigators (PIs) of 68 centers from 20 European countries, participating in the CENTER-TBI study between 2014 and 2015. Of these, 65 completed the questionnaires. PIs were asked to complete a set of questionnaires about structure and processes of care. In the item generation phase we have gathered experts together within the CENTER-TBI team and proceeded with item generation and item reduction in a second phase. The questionnaires were then pre-tested with a group of participating centers and face validity was discussed with the participants and the experts involved in item generation. The pilot testing evaluated flow and time required to complete.

We have measured reliability and concordance rates of the questionnaire. To estimate reliability of the questionnaires, we included 17 (5%) duplicate questions, including all question formats. We equally included structure and process questions in the duplicate questions. Concordance rates were estimated by calculating the percentage of overlap between duplicate questions, and presented as mean, median and range. Questionnaires were disseminated during presentations, workshops and email conversations. More information is available at length in one of our group's previous publications[3].

A set of questionnaires designed to measure structure and process of TBI care was developed on the basis of available literature, expert opinion and based on best practice[7].

These questionnaires were comprehensively described in a previous publication[3]. Pilot testing was undertaken in 16 of the participating centers, and feedback was incorporated into the final questionnaire design.

The questionnaire on ICU care contained 6 questions with multiple sub-questions exploring guideline use and implementation. In most questions the "general policy" at each center was surveyed. This was defined as "routine policy"; the standard treatment or policy in a particular case. In others, we asked for quantitative estimations, whereby the frequency of using a treatment strategy could be indicated (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, always 90-100%). The options 'frequently' and 'always' were interpreted as representing the general policy, in line with previous provider profiling studies[6]. The questions regarding the reasons for guideline-nonadherence also needed to be answered with quantitative estimations as stated above for each individual reason. The reasons given were: " Lack of knowledge among clinicians", "Every patient is unique and should be managed by clinical judgment", "Inadequate time to consult guidelines for urgent decisions", "Guidelines on TBI do not apply due to extracranial trauma or comorbidity", "Inadequate resources to apply guidelines (ICU beds, personnel, equipment)" (See *Supplemental Digital Content 1* for more details).

We used chi-square and Fisher's exact tests to compare therapies and monitoring at centers that used BTF or BTF-based guidelines with centers that used other or no guidelines for several recommendations from the two most recent versions of the BTF guidelines (2007 and 2016, versions 3 and 4).

RESULTS

Most participants reported use of either BTF Guidelines, or BTF-based institutional guidelines (n = 49; 75%), while 5 centers (8%) used non-BTF-based guidelines. 11 centers (17%) reported that they did not use any guidelines. No regional differences were observed between North – Western Europe (n = 30; 70%, use BTF Guidelines) and South – Eastern Europe (n=19; 83%, use BTF Guidelines).

Of the 54 centers that reported to use guidelines, five had no allocation of responsibility to oversee guideline development and maintenance (9%). In other centers, guideline development and maintenance were the responsibility of a multi-disciplinary team (n = 31; 56%). However, annual or more frequent audit of guideline adherence was reported in only 4 centers (7%), while the remainder (n = 51; 93%) reported either no audits, or only one within the past five years.

Four of the 54 centers using guidelines (7%) reported no formal implementation process. The majority (n = 41; 75%), had written protocols and algorithms, but less than half paid structural attention to the guidelines during rounds (n = 21; 38%) or organized hospital-led training (n = 20; 36%). Twelve centers of the 55 (22%) had their protocol in a data management system. Five centers (9%) had e-learning modules or used trainings organized by an external organization (n = 3; 4%).

The most often reported reasons for non-adherence were 'every patient is unique' (n = 19; 39%) and the presence of extracranial injuries (n = 8; 16%), for both centers that use and for those that do not use guidelines (*Figure 1*).

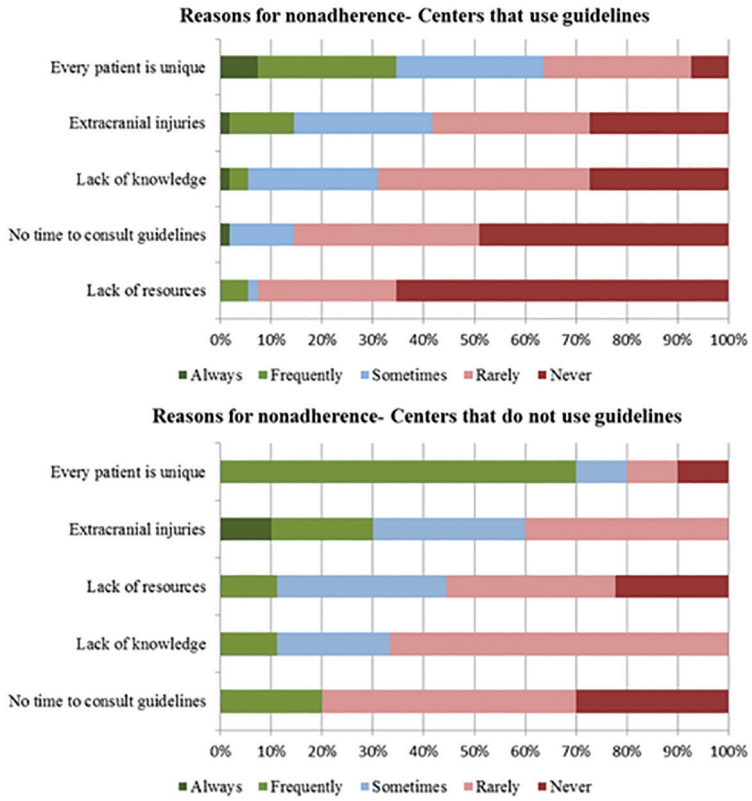

Figure 1. The reasons for nonadherence (and thus implementation barriers) reported by centers that do use guidelines (n=49) and those who do not use guidelines (n=10).

When comparing centers that used BTF Guidelines (n = 49) with those that use other guidelines or none at all (n = 17), the only statistically significant difference in policy was the use of levetiracetam for antiseizure prophylaxis (p = 0.04, *Table 1*).

Overall, the estimated adherence to the medical management recommendations of the centers that use BTF guidelines was "always" (n = 10; 20%), "frequently" (n = 38; 78%) and sometimes (n = 1; 2%).

Regarding ICP monitoring[8] in patients with a Glasgow Coma Scale (GCS) < 9 and CT abnormalities, 44 centers that used BTF guidelines (90%) would monitor ICP as a general policy and 14 (93%) of those that used other guidelines or none at all. Of the 5 centers that used BTF guidelines and would not monitor ICP in such a patient, 4 (8%) reported to "frequently" adhere to medical management recommendations and 1 (2%) reported to "always" adhere to the recommendations.

Corticosteroid use for the primary TBI was reported as "never" in 45 centers that used BTF guidelines (92%), "rarely" in 3 (6%) and "sometimes" in 1 (2%). Of the centers that use other guidelines or no guidelines, 12 "never" use corticosteroids for the primary TBI (75%), 2 "rarely" (13%), 1 "sometimes" (6%) and 1 "frequently" (1%).

Seven (15%) of the centers that used BTF guidelines and 5 (31%) of those who did not use BTF guidelines choose barbiturates as first tier therapy (p = 0.15). The seven centers that used BTF guidelines reported to "frequently" adhere to medical management recommendations.

Five (10%) of the centers that used BTF guidelines and 5 (31%) of centers that do not use BTF Guidelines utilized hyperventilation as a first tier therapy (p=0.10). Of the aforementioned 5 centers that use BTF guidelines, 3 (6%) reported to "always" adhere to the medical management guidelines and 2 (4%) reported to "frequently" adhere to medical management guidelines.

Seventeen (35%) of the centers that used BTF guidelines use phenytoin as the drug of choice for antiseizure prophylaxis and 3 (19%) centers who did not use the BTF guidelines. More than half of the centers that used BTF guidelines, however, used levetiracetam (n = 28; 57%) as the drug of choice. Significantly fewer centers that did not use the BTF guidelines (n = 4; 25%) used levetiracetam as the drug of choice.

DISCUSSION

We found considerable variability in guideline adherence and implementation among neurotrauma centers in Europe. Less than one in three centers reported organized training, paid structural attention to guidelines during daily rounds, or had a protocol in their clinical data management system. However, though such implementation strategies would empirically seem to be useful, there are as yet no data suggesting benefit of any individual implementation or dissemination strategy in different circumstances[9].

With respect to the level II recommendations, several centers, both that use and that do not use BTF guidelines, used barbiturates and hyperventilation as a first – tier therapy, despite the recommendation against this practice[10]. Despite the fact that proportionally more centers that do not use BTF guidelines use barbiturates and hyperventilation as first tier therapies, the difference did not reach statistical significance.

The use of antiseizure prophylaxis was the only statistically significant association with guideline use in our data. The best available evidence supports using phenytoin as the drug of choice to prevent early post-traumatic seizures (PTS). In the 4th edition of the BTF guidelines, published after our questionnaire, the authors conclude that there is insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy in preventing early PTS and toxicity[2]. The fact that significantly more centers that use BTF guidelines use levetiracetam is likely due to its important role in contemporary epilepsy treatment and not the adherence to the recommendations of the BTF guidelines. Moreover, it is easier to use, as there is no need to monitor serum concentrations and is perceived as having a more favorable side effect profile[11-13].

The only level I recommendation, against the use of corticosteroids in primary TBI treatment[2], is adhered to in 92 %.

Both the use of levetiracetam and the approach to corticosteroids reflect more the applicability of the guidelines in a "real world" setting where pragmatic choices take precedence above guidelines recommendations based on the current evidence. Furthermore, the body of evidence against the use of corticosteroids[2,14] for the primary treatment of TBI does not necessarily apply to entities such as late perifocal edema around a contusion. Moreover, the centers participating in this study are well-versed in the treatment of TBI and are involved in international clinical research. As such, the clinical decision making process is nuanced in these centers, and does not follow guidelines unequivocally.

Table 1. The general policies of the centers studied in relation to the type of guideline they use. In most questions we aimed for a reflection of the "general policy" at each center. In others, however, we asked for quantitative estimations, whereby the frequency with which a treatment strategy was used could be indicated (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, always 90-100%). The options 'frequently' and 'always' were interpreted as representing the general policy.

Treatment/Monitoring	Total (% of total respondents)	Centres using BTF guidelines (*n* = 49)	Centres using other guidelines or no guidelines at all (*n* = 16)	*p*-value
Using propofol as first tier therapy				
General policy	54 (83%)	42 (86%)	12 (75%)	.42
Not general policy	11 (17%)	7 (14%)	4 (25%)	
Using barbiturates as first tier therapy				
General policy	12 (19%)	7 (15%)	5 (31%)	.15
Not general policy	52 (81%)	41 (85%)	11 (69%)	
Hypothermia use				
General policy	16 (25%)	12 (25%)	4 (25%)	1.0
Not general policy	49 (75%)	37 (75%)	12 (75%)	
Hyperventilation use as first tier therapy				
General policy	10 (15%)	5 (10%)	5 (31%)	.10
Not general policy	55 (85%)	44 (90%)	11 (69%)	
Use of barbiturates in refractory ICP				
General policy	21 (32%)	15 (31%)	6 (37%)	.75
Not general policy	44 (68%)	34 (69%)	10 (63%)	
Use of transcranial Doppler				
General policy	24 (38%)	18 (38%)	6 (38%)	1.0
Not general policy	40 (62%)	30 (62%)	10 (62%)	
Use of a jugular venous monitor				
General policy	6 (9%)	6 (12%)	0 (0%)	.32
Not general policy	58 (91%)	42 (88%)	16 (100%)	
Antiseizure prophylaxis with phenytoin				
General policy	20 (31%)	17 (35%)	3 (19%)	.35
Not general policy	45 (69%)	32 (65%)	13 (81%)	
Antiseizure prophylaxis with levetiracetam				
General policy	32 (49%)	28 (57%)	4 (25%)	**.04**
Not general policy	33 (51%)	21 (43%)	12 (75%)	
Antiseizure prophylaxis with valproate				
General policy	11 (17%)	8 (16%)	3 (19%)	1.0
Not general policy	54 (83%)	41 (84%)	13 (81%)	

Table 1. Continued.

Treatment/Monitoring	Total (% of total respondents)	Centres using BTF guidelines (n = 49)	Centres using other guidelines or no guidelines at all (n = 16)	p-value
Deep venous thrombosis prophylaxis use				
General policy	62 (94%)	46 (94%)	16 (94%)	1.0
Not general policy	4 (6%)	3 (6%)	1 (6%)	
ICP monitoring in GCS<9 and CT abnormalities				
General policy	58 (91%)	44 (90%)	14 (93%)	1.0
Not general policy	6 (9%)	5 (10%)	1 (7%)	
ICP monitoring in GCS< 9 and no CT abnormalities				
General policy	15 (23%)	12 (25%)	3 (20%)	1.0
Not general policy	49 (77%)	37 (75%)	12 (80%)	
ICP monitoring in GCS 9-12 and CT abnormalities				
General policy	11 (17%)	8 (16%)	3 (20%)	.71
Not general policy	53 (83%)	41 (84%)	12 (80%)	
Mannitol use				
General policy	43 (66%)	34 (69%)	9 (56%)	.37
Not general policy	22 (34%)	15 (31%)	7 (44%)	
Hypertonic saline use				
General policy	44 (68%)	35 (71%)	9 (56%)	.35
Not general policy	21 (32%)	14 (29%)	7 (44%)	
Conjunction of mannitol and hypertonic saline				
General policy	14 (21%)	12 (25%)	2 (12%)	.48
Not general policy	51 (79%)	37 (75%)	14 (88%)	
Administration of mannitol				
Continuous infusion	3 (5%)	1 (2%)	2 (14%)	.14
Boluses	54 (95%)	42 (98%)	12 (86%)	

The reasons for non-adherence include patient heterogeneity and the presence of extracranial injury, which might indeed impose different priorities for care. Resource limitation was also mentioned as a problem in the centers that did not use guidelines. We anticipate that the relatively low adherence also stems from the general poor quality of evidence which underpins current TBI guidelines, although this argument was not specifically queried. Remarkably, we found no clear differences in management policies between centers that report to use or not to use BTF guidelines, save for the more frequent use of levetiracetam in centers adhering to BTF guidelines.

We recognize that the questionnaire format of this study is a limitation in terms of properly auditing guideline use and adherence, together with the relatively low power. However, the centers involved in the CENTER-TBI project are frequently involved in TBI research, with broad exposure to the international TBI community, which might explain the lack of difference between centers that do and those that do not use guidelines in light of the evidence base[14]. Furthermore, the results also need to be interpreted in light of the fact that the questionnaires were filled in before the publication of the 4th edition of the BTF Guidelines.

CONCLUSION

There is substantial variability in reported guideline use, adherence, and implementation strategies and perceived barriers among neurotrauma centers in Europe. Further research first needs to strengthen the evidence base underpinning the guidelines, followed by addressing implementation barriers to develop optimal implementation strategies, in order to optimize clinical practice and potentially improve patient outcomes.

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Part 3

CLINICAL APPLICATIONS

Chapter 6

VENTRICULAR DRAINAGE CATHETERS VERSUS INTRACRANIAL PARENCHYMAL CATHETERS FOR INTRACRANIAL PRESSURE MONITORING-BASED MANAGEMENT OF TRAUMATIC BRAIN INJURY:

A Systematic Review and Meta-Analysis

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J Neurotrauma. 2019 Apr 1;36(7):988-995. doi:10.1089/neu.2018.6086. Epub 2018 Oct 30. PMID: 30251919

ABSTRACT

Intracranial pressure (ICP) monitoring is one of the mainstays in the treatment of severe traumatic brain injury (TBI), but different approaches to monitoring exist. The aim of this systematic review and meta-analysis is to compare the effectiveness and complication rate of ventricular drainage (VD) versus intracranial parenchymal (IP) catheters to monitor and treat raised ICP in patients with TBI.

Pubmed, EMBASE, Web of Science, Google Scholar and the Cochrane Database were searched for articles comparing ICP monitoring-based management with VDs and monitoring with IP monitors until March 2018. Study selection, data extraction and quality assessment were performed independently by two authors. Outcomes assessed were mortality, functional outcome, need for decompressive craniectomy, length of stay, overall complications, such as infections, and hemorrhage. Pooled effect estimates were calculated with random effects models and expressed as relative risk (RR) for dichotomous outcomes and mean difference (MD) for ordinal outcomes, with corresponding 95% confidence intervals (CI).

Six studies were included: 1 randomized controlled trial and 5 observational cohort studies. Three studies reported mortality, functional outcome and the need for a surgical decompression, three only reported complications. Quality of the studies was rated as poor, with critical or serious risk of bias. The pooled analysis did not show a statistically significant difference in mortality (RR=0.90, 95% CI=0.60 to 1.36, p=0.41) or functional outcome (MD=0.23, 95% CI=0.67 to 1.13, p=0.61). The complication rate of VDs was higher (RR=2.56, 95% CI=1.17 to 5.61, p= 0.02) and consisted mainly of infectious complications, i.e. meningitis.

VDs caused more complications, particularly more infections but there was no difference in terms of mortality or functional outcome between the two monitoring modalities. However, the studies had a high risk of bias. A need exists for high quality comparisons of VDs versus IP monitor-based management strategies on patient outcomes.

Keywords: ICP monitoring; Ventricular Catheters; Intraparenchymal monitors; Monitoring Devices; Patient Outcomes; Severe TBI

INTRODUCTION

Intracranial pressure (ICP) monitoring is one of the mainstays of current severe traumatic brain injury (TBI) treatment at the ICU and guidelines recommend using ICP monitoring in order to reduce mortality.[1]

There is a wide range of intracranial pressure sensors. Two types are most commonly used: Ventricular drainage (VD) and intraparenchymal catheters. The IP monitor catheters require a small opening in the skull and their small diameters cause little damage to the brain parenchyma. They have a low risk of infection and other complications, such as intracerebral hemorrhage.[2] The insertion of a ventricular catheter, usually into the frontal horn of the right lateral ventricle, requires a relatively larger opening and is thought to cause more damage to brain tissue than the insertion of a smaller parenchymal sensor.[3] VDs fulfill two objectives: besides monitoring, they permit drainage of CSF, thereby acting as an ICP-lowering intervention. However, this is accomplished at the expense of an increased risk of infections and complications.[2]

Not much is known about the superiority of one method over the other in terms of patient outcomes. In the second Brain Trauma Foundation Guidelines edition of 2000, in which this topic was addressed, no clear recommendation was made and in subsequent editions the topic was no longer addressed due to lack of evidence.[4] However, recently, a randomized controlled trial (RCT) was conducted, the first of its kind, that suggested the superiority of VDs over IP monitors on patient outcomes. Next to this single RCT, several observational studies have been published.

The aim of this study was to review the available evidence on the effectiveness and complication rate of VD versus IP-monitor-guided treatment of raised ICP in patients with TBI.

MATERIALS AND METHODS

A protocol has been published on Prospero.[5]

Search strategy

Searches were not restricted by date, language or publication status. In collaboration with an information specialist from the Erasmus MC library we developed a search strategy (Appendix 1). We performed the search in MEDLINE, EMBASE, ISI Web of Science, Pubmed and Google Scholar, from the first publicly accessible date of a particular database

until March 1st, 2018. Ongoing studies were searched on clinicaltrials.gov. Grey literature was screened using Google Scholar and ISI Web of Science. Reference lists of all relevant trials were hand searched and experts in the field that had previously published on this matter were contacted for unpublished literature on this topic.

Ethical approval and consent

This study did not require ethical approval.

Inclusion criteria and study selection

Given the expected scarcity of available literature on the topic, we included – next to RCTs - prospective and retrospective observational studies that described a direct comparison between patients with VDs and patients with IP monitoring and that reported either mortality, functional outcomes or complications. Inclusion criteria were: (1) mainly adult population, (2) severe or moderate TBI on admission defined as a Glasgow coma score (GCS) <=12 and (3) closed head injury

Exclusion criteria were (1) penetrating or blast TBI, (2) studies with a predominantly paediatric population, (3) studies without VD and IP comparisons and (4) studies on external lumbar drainage

For studies with mixed populations, including mixed ages (i.e. adults and children) and mixed injury types (i.e. TBI and stroke) we included studies in which the results for our population of interest were presented separately, or in which at least 85% of the participants represented our population of interest.

Considering mixed injury types, one exception was made in the case of the secondary outcomes, i.e. infections, haemorrhage and catheter malfunctions. Since we did not expect any differences between mixed injury types (i.e. ischaemic stroke and severe TBI) in terms of complications when either device was used. We therefore chose to pool all studies that compared complications in patients with an VD and those with an IP monitor in mixed injury types, even if the population represented < 85% severe TBI.

The first phase involved screening the titles and abstracts (Appendix 3). Studies unrelated to the topics of VDs versus IP monitoring or TBI were excluded. In the second phase the remaining abstracts were screened for the inclusion and exclusion criteria.

In the final sifting phase, the full text of the remaining studies was reviewed. Conflicts were resolved by discussion until a final decision was reached.

Data extraction and risk of bias assessment

Each study was assessed by two investigators (VV, IH) and the data was extracted in a matrix consisting of trial details, such as: trial name and date, trial design, author contact information, inclusion and exclusion criteria, adherence to a published protocol, number of patients, duration of intervention, mean age of patients, mean GCS, percentage of severe TBI, male to female ratio, whether the groups were comparable or not and the effect size and confidence intervals for the primary and secondary outcomes individually (Appendix 2). Finally, potential sources of bias and sources of funding were noted.

Quality assessment was performed by two authors independently (VV and JH). For the RCTs we used the Cochrane Collaboration's Risk of Bias Assessment Tool[6] (assessing the risk of bias as high/low or unknown for each domain) tool and for observational trials the ROBINS-I Cochrane tool[7] (assessing the studies as low/moderate/serious or critical risk of bias for each domain and overall) (Appendix 4).

Outcomes

The primary outcomes were mortality and functional outcome at 6 months or final follow-up if earlier, defined by the Glasgow Outcome Scale/Extended (GOS/E).

The secondary outcomes examined were: the need for decompressive craniectomy during ICU stay; the hospital and Intensive Care Unit (ICU) Lengths Of Stay (LOS); monitoring duration; device failure at any time point; all complications; infections, however defined in the paper; intracranial haemorrhage; and the number of episodes of refractory intracranial hypertension (RICH), defined as uncontrollable intracranial hypertension by conventional means requiring an increase in therapy intensity, either medical or surgical.

We anticipated that all outcome data will be dichotomous. As such, for each study, we have extracted the number of participants receiving each device and the number of events (i.e. n/N) or the GOS mean differences.

For the hospital and ICU LOS we calculated the mean difference between groups and the 95% CI.

Statistical analyses

The relative risk (RR) and corresponding 95% Confidence Interval (CI) were extracted for mortality, need for decompressive craniectomy, overall complications (specifically for device failure, infection and haemorrhage), when available and otherwise calculated.

The pooled RR and corresponding 95% CI was then determined using the Mantel-Haenszel approach, and its significance as the true effect estimate was assessed against the null hypothesis RR overall=1 using the z test. Statistical evidence for heterogeneity between studies was assessed using the Q-test and the I^2 index estimated the between-study variability. We used the random effects model for all analyses, as considerable heterogeneity may exist despite the absence of statistical evidence of this, especially in studies with small sample sizes.

For the outcomes reported as mean difference (MD) ± standard deviation (SD), we used the inverse variance method to obtain the pooled MD. In this case we also used the Q-test and I^2 index to estimate statistical heterogeneity between studies. The outcomes were ICU and hospital LOS, mean monitoring duration and mean GOS for each group.

Review Manager (RevMan, Cochrane Collaboration, version 5.3) was used for data synthesis.

RESULTS

Study characteristics

1208 studies underwent abstract screening. Among these, 37 were screened full text (Appendix 3). Six studies were included and characteristics of patients extracted (Appendix 2) with 3968 enrolled patients in total (minimum 122 patients[8], maximum 2562 patients[9]). One of these was an RCT, the rest were retrospective observational cohorts. Three studies included data on mortality, functional outcome, LOS and surgical decompression, the other three reported only complications.

Primary outcome

Three studies with 3013 patients reported mortality rates.[8-10] When the results were aggregated, mortality was not different between VD and IP monitors (RR=0.90, 95% CI=0.60 to 1.36, p=0.63). There was substantial heterogeneity (I^2= 76%, p value of the Q test=0.01) (*Figure 1a*).

In the analysis of studies reporting functional outcome at the end of follow-up, 2 papers involving 451 patients described functional outcome data using the mean GOS difference.[8, 10] When the results were aggregated, mean GOS was not different between the two interventions (Mean Difference (MD) =0.23, 95% CI=-0.67 to 1.13, p=0.61). Heterogeneity was high (Q test p=0.003, I^2=89%) (*Figure 1b*).

We contacted the authors of the Kasotakis et al study[10] in order to obtain the absolute numbers of the functional outcome, but the data on these outcomes were not available anymore.

Aiolfi et al[9] only described the absolute numbers for patients functionally independent at discharge. For the 2562 patients described, there was no difference regarding this number between the two groups patients at discharge (RR= 0.97, 95% CI= 0.83 to 1.13).

Secondary outcomes

Three studies including 3968 patients examined the risk of needing a surgical decompression in both groups.[8-10] There was no difference between the groups (RR= 0.79, 95% CI= 0.56 to 1.10, p=0.16). Heterogeneity was large (Q-test p=0.005; I^2=81%) (*Figure 2a*) .

The mean LOS in the hospital[8-10] did not differ between groups with no heterogeneity (MD= 0.02, 95% CI= -0.42 to 0.46, p=0.93; Q-test p=0.80; I^2=0%). The mean ICU length of stay was shorter in the IP group (MD= 1.09, 95% CI= 0.41 to 1.78, p=0.002).[8-10] Heterogeneity was low (Q-test: p=0.25, I^2= 28%) (*Figure 2b and 2c*).

Two papers including 499 patients reported the mean monitoring duration for both groups.[8, 10] This did not differ when the results were pooled (MD= 1.78, 95% CI= -1.55 to 5.11, p=0.29). there was large statistical heterogeneity (Q-test: p <0.00001, I^2=96%) (*Figure 3e*).

Three studies including 607 patients reported device failures[8, 10, 11] and there was no difference between the two groups in this respect (RR=0.98, 95% CI= 0.35 to 2.69, p=0.96). There was a low level of statistical heterogeneity (Q-test p=0.13, I^2= 52%) (*Figure 3d*).

Six reports including 3968 patients reported overall complications.[2, 8-12] Five reports including 1406 patients reported infections of the device, hemorrhage and 'all complications'.[2, 8, 10-12] With regard to all complications, the VD group fared worse than the IP monitor group (RR=2.56, 95% CI=1.17 to 5.61, p= 0.02). Statistical heterogeneity was high (Q-test p< 0.00001, I^2=91%) (*Figure 3a*). Regarding infections[2, 8, 10-12] in particular, such as meningitis and ventriculitis, VD patients were more at risk (RR=7.09, 95% CI= 2.64 to 19.04, p=0.0001), without evidence of statistical heterogeneity (Q-test p=0.59, I^2= 0%) (*Figure 3b*). The VD group was also more at risk for hemorrhage (RR=2.64, 95% CI= 1.05 to 6.63, p=0.04),[2, 8, 10-12] without evidence of statistical heterogeneity (Q-test , p=0.94, I^2= 0%) (*Figure 3c*).

Episodes of RICH were only reported by one paper[8], and thus did not lend themselves to a pooled analysis. The RR was 0.41, with a 95% CI ranging from 0.24 to 0.70.

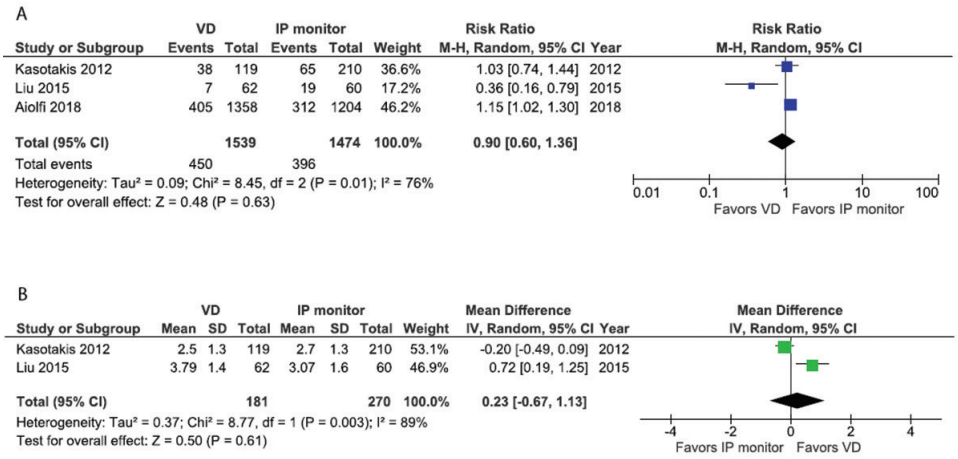

Figure 1. Forest plots of the primary outcomes.. A: Mortality.; B: GOS mean (M-H = Mantel–Haenszel test; IV = Inverse Variance; CI =Confidence Interval)

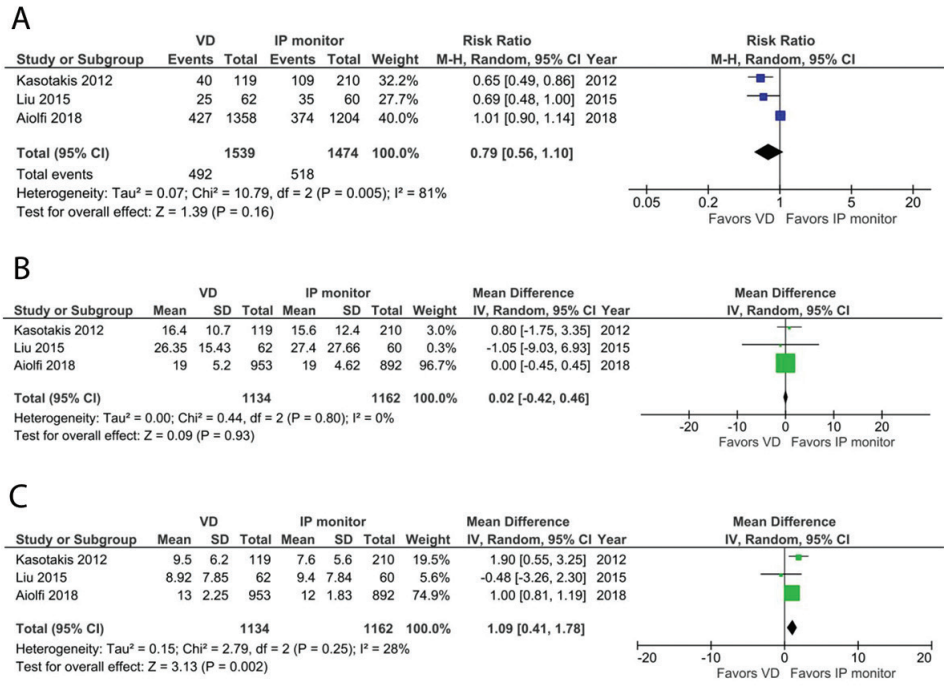

Figure 2. Forest plots of secondary outcomes. A: Need for surgical decompression; B: Hospital length of stay; C: ICU Length of Stay; (M-H = Mantel–Haenszel test; IV = Inverse Variance; CI =Confidence Interval)

Risk of bias

The overall quality of the studies is poor (Appendix 4), with one underpowered RCT (N=122) with high risk of bias with regard to blinding of trial personnel and of the outcome assessors. Of the 5 observational studies, 2 were judged as serious risk of bias and the other 3 were deemed at critical risk of bias according to the methodological assessment.

The risk of bias for the RCT was low on most domains, except blinding of study personnel, which is inherently impossible given the nature of the intervention and the blinding of clinicians to the intervention in the clinical phase. The retrospective observational cohorts were judged as having overall serious[9] and critical risk of bias respectively.[2, 10, 11]

The criterion blinding could not be rated in the Cochrane tool since the monitoring device is identifiable when placed.

DISCUSSION

This is the first systematic review that describes the potential effects of VDs versus IP monitor-guided management on patient outcomes. We found no difference in terms of mortality or functional outcome between the two groups. IP monitors are associated with a shorter ICU stay but not hospital stay and are associated with less complications, in particular less infections. The risk of malfunction is comparable among devices. However, strong inferences on effectiveness of VDs versus IP monitors cannot be made from this analyses given the high risk of bias of the included studies.

The effect of ICP monitoring is the subject of an ongoing debate in the scientific literature.[1, 13-15] General consensus remains that ICP monitoring is recommended in patients with severe TBI who have traumatic abnormalities on the CT scan.[16]

Considerable practice variation exists with respect to the choice of monitoring device. A recent questionnaire-based study carried out by our group in 66 centers in Europe[16] showed that both parenchymal and ventricular monitoring devices were available in more than half of centers (59%). One-third of the participants indicated that they used only parenchymal monitors, whereas one-tenth of the participants indicated that they used only ventricular catheters.[16]

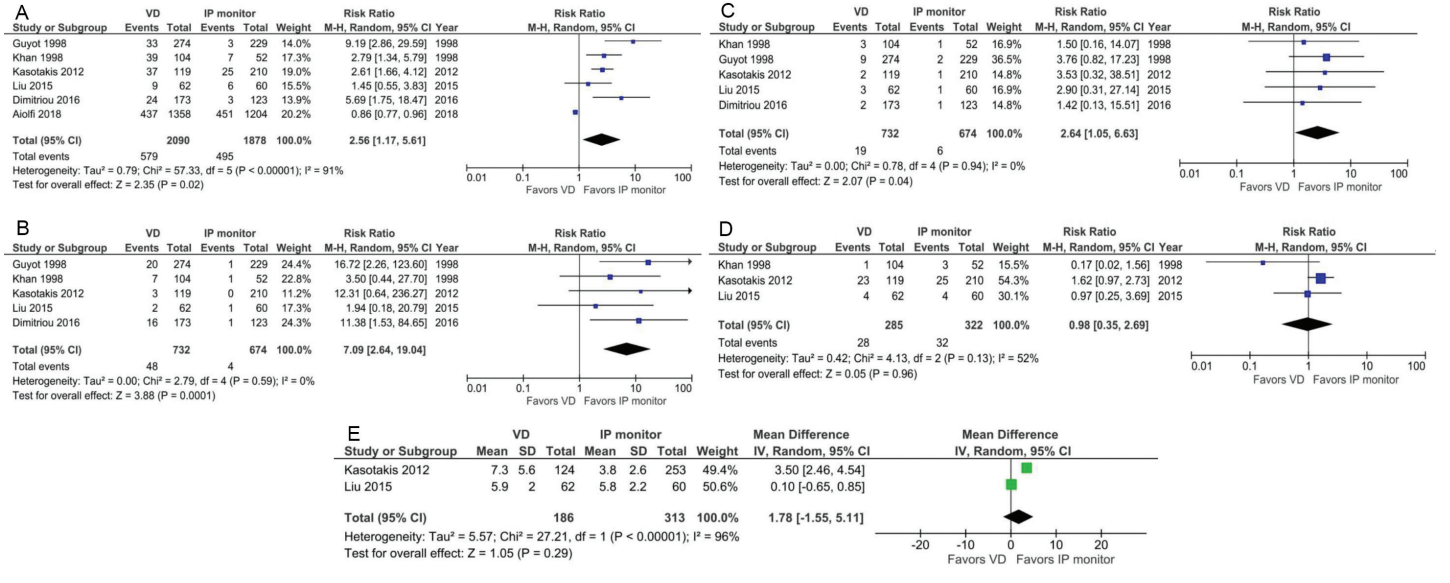

Figure 3. Forest plots of complications and monitoring duration. A: Overall complications; B: Infection; C: Haemorrhage; D: Device malfunction; E: Monitoring duration; (M-H = Mantel–Haenszel test; IV = Inverse Variance; CI =Confidence Interval)

This variation noticed in the study carried out by our group can be explained in light of the limited evidence base for clinical practice. When looking at studies that provide the best quality evidence with a least risk of bias, the only RCT on the topic suggests the superiority of monitoring and treatment using VDs[8] for both mortality and functional outcome, potentially also through a decrease in the number of patients requiring surgical decompression. Our meta-analysis shows no difference between the two groups which likely arises from the pooling of results with lower quality studies. Despite the importance of ICP monitoring and the clinical relevance of the comparison between VDs and IP monitors, we only found 6 papers dealing with this head-to-head comparison. This is perhaps due to the idea that a monitoring device in itself cannot improve outcomes, but guide treatment and because certain imaging characteristics (midline shift, mass lesions, narrow ventricles) might deter clinicians from inserting VD, making RCTs difficult to carry out and less generalizable.

It is essential to distinguish acute craniotomy for the evacuation of life-threatening space-occupying lesions from decompressive craniectomy, a rescue therapy to resolve intracranial hypertension refractory to medical treatment because of the vastly different prognosis.

This was, however, only properly defined as such in the paper by Liu and colleagues.[8] In the other two papers that report this outcome[9, 10], it is unclear whether patients received a decompressive craniectomy or a craniotomy with decompression of the lesion. Kasotakis et al report "surgical decompression" and do not define it[10], whereas Aiolfi et al report in the text "The need for craniectomy" and "Craniotomy/Craniectomy performed within 24 hours" in the table.[9] When the results of Liu et al and Kasotakis et al were pooled, the difference was significant in that the VD group required surgical decompression more often. When the results of the Aiolfi study were added, the difference was no longer significant. Given the major differences in prognosis between a craniotomy with evacuation of a lesion and a craniectomy on patient outcomes, it is likely that confounding was introduced by adding the Aiolfi study to the pooled results, owing in part to the large number of patients included.[9]

The overall complication rate and in particular to the risk of infection and haemorrhage were higher for patients receiving a VD when compared to those receiving an IP monitor.

The infection risk for an VD in the literature ranges between as low as 0%[17] and as high as 22%[17], and this needs to be addressed when VDs are used by the implementation of a strict protocol of insertion, care and maintenance. In this review the calculated infection rate and overall complication rates were higher in the VD groups, ranging from 2%[8] to 9%[12]. The IP monitor group had consistently very low prevalence of infection, usually under 1%.[2, 10]

It is known that a longer duration of monitoring usually leads to a higher infection rate.[12] Only two papers report the mean duration of monitoring and the pooled results show no statistically significant difference between the two groups,[8, 10] but future research on this topic needs to address this potential confounder.

Despite the difference being non-significant in all of the individual studies, the aggregated results show a significantly shorter duration of ICU admission in patients receiving IP monitors. At first glance, it might appear that the lower complication rate leads to a shorter ICU LOS. On average, patients spent one extra day in the ICU. Severe complications would prolong ICU stay for longer than a day and the hospital LOS does not differ significantly. This might, however, be a case of confounding by indication: the insertion of a ventricular probe requires a patent ventricle, and is best accomplished when the ventricular system is not displaced. In case of raised ICP the ventricles become slit and a considerable midline shift may develop, making the surgical insertion of the probe difficult or impossible. There is the risk, therefore, that VDs are used in less severe cases, where its insertion is feasible.

When looking at variables collected in the 6 included papers, we strikingly found no mention of the effect of CSF drainage on therapy intensity level, save for the need for performing a surgical decompression and the ICU LOS and number of episodes of RICH as indications of therapy intensity (the latter only available in the RCT). We feel that this is a necessary addition for future studies, as the beneficial effect of controlling ICP through CSF drainage might be counteracted by the risk of adverse events. It is more likely to assume that VD use decreases treatment intensity and is in this respect beneficial than to assume that it has, as a standalone entity, a direct effect on patient outcomes.

Moreover, except for the only RCT on the topic by Liu and colleagues[8], no other papers report whether CSF was drained intermittently or continuously. Within the aforementioned trial CSF was drained intermittently. So far only small studies suggest a potential benefit of continuous drainage above intermittent.[18] In addition, there was also no information available of crossover patients, i.e. patients that received an VD after receiving an IP monitor and whether there were differences in the readings. This also suggests another possible confounder: the values indicated by VDs during drainage might provide inaccurately low values, not detecting values above the threshold and leading to under-treatment.[19] Furthermore, no mention was made in any of the papers whether antibiotic impregnated catheters were used. These issues need to be dealt with when further research on this topic will be carried out.

In light of the complications, the use of VDs might seem counterintuitive. However, in the pediatric population continuous CSF drainage is a relatively common practice with

evidence to support improvements in both ICP management and injury biomarkers.[20] In the adult population, however, only small studies show a potential benefit of continuous drainage[18]. This statement also figures as a recommendation in the guidelines.[1]

In light of many unanswered questions, a large comparative effectiveness study,[21] such as the ongoing CENTER-TBI and TRACK-TBI cohorts would be needed to address all of the questions regarding the effectiveness, complication rate, and to assess the cost-effectiveness of each device while keeping the risk of bias moderate or low and work around the confounding. The topic of intermittent or continuous drainage also needs to be addressed in a larger dedicated trial, and the focus should also be on the effect of CSF drainage on treatment intensity.

Despite the fact that the only RCT on this topic shows better results for patient outcomes, it did not create a paradigm shift in practice, nor does it figure in the current edition of the guidelines[1]. When all available data was pooled, the results of this RCT are challenged. Further high-quality comparisons are needed to address this issue.

Deviations from the protocol and limitations

We were unable to access absolute values of the GOS(E) in order to dichotomize. The only data available was the mean GOS for the two groups which is a limitation of this study. We would have favored an ordinal approach to data analysis.

We also did not measure the relative risk of receiving an VD when one had received an IP monitor first. We included some studies that did not respect our 85% severe TBI rule, but given that we felt that the risk of infections when these devices are used in other injury types or in mixed injury types are comparable, we avoided the introduction of confounding of our results. VDs used in stroke are usually inserted in cases of intraventricular haemorrhage and kept in until the blood clears, which might lead to a longer monitoring duration in the VD group and consequently more infections. The pooled data available did not suggest a longer monitoring duration with VDs, but only 2 of the 6 papers reported this outcome.

Subgroup analyses were impossible since the studies did not present the required data. Funnel plots could also not be compiled as there were insufficient studies in order to do so.

CONCLUSION

This systematic review suggests that in patients with severe or moderate TBI the use of VDs instead of IP monitors was not associated with less mortality or better functional outcome, but the patients did suffer more complications. Overall, these results need to be interpreted with caution given that the overall body of evidence is poor, consisting of mostly observational studies with serious and critical risk of bias. There remains a need for high quality head-to-head comparisons of VDs and IP monitors.

Acknowledgments

The authors would like to thank Ms. A. Synnot from Cochrane Australia for her invaluable assistance in the preparatory phase of this study and for her help in the protocol stage.

Conflict of interest

All authors report funding from the European Commission, Seventh Framework Programme, grant number 602150.

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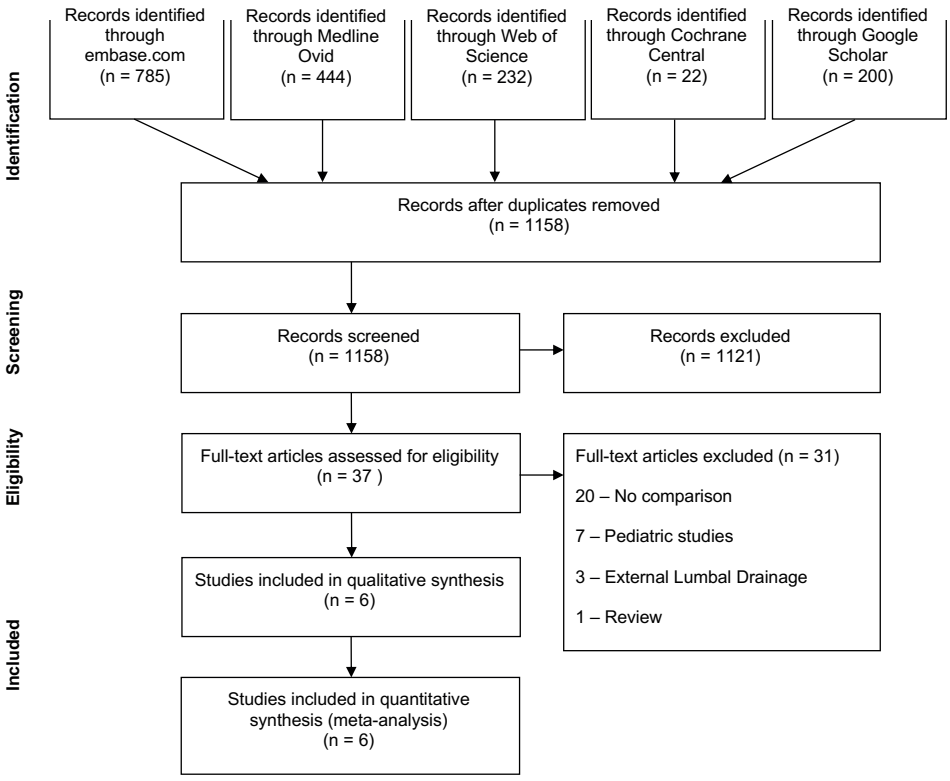
SUPPLEMENTARY MATERIAL



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplementary figure. PRISMA flowchart of included studies

Supplementary table. Risk of Bias of included studies.

Study/Domain	Risk of bias assessment
Liu, 2015	
Random sequence generation	LOW
Allocation concelament	LOW
Blinding	HIGH
Blinding of outcome	UNCLEAR
Incomplete data	LOW
Selective reporting	LOW
Other	LOW
Kasotakis, 2012	
Bias due to confounding	CRITICAL
Bias of selection of participants into the study	SERIOUS
Bias in classification of interventions	SERIOUS
Bias due to deviations from intended intervention	NI
Bias due to missing data	SERIOUS
Bias in measurement of outcomes	NI
Bias in selection of the reported result	NI
Overall	**CRITICAL**
Guyot, 1998	
Bias due to confounding	CRITICAL
Bias of selection of participants into the study	NI
Bias in classification of interventions	SERIOUS
Bias due to deviations from intended intervention	NI
Bias due to missing data	NI
Bias in measurement of outcomes	SERIOUS
Bias in selection of the reported result	LOW
Overall	**CRITICAL**
Khan, 1998	
Bias due to confounding	CRITICAL
Bias of selection of participants into the study	CRITICAL
Bias in classification of interventions	SERIOUS
Bias due to deviations from intended intervention	NI
Bias due to missing data	NI
Bias in measurement of outcomes	SERIOUS
Bias in selection of the reported result	LOW
Overall	**CRITICAL**

Supplementary table. Continued.

Study/Domain	Risk of bias assessment
Dimitriou, 2016	
Bias due to confounding	CRITICAL
Bias of selection of participants into the study	NI
Bias in classification of interventions	SERIOUS
Bias due to deviations from intended intervention	NI
Bias due to missing data	NI
Bias in measurement of outcomes	NI
Bias in selection of the reported result	LOW
Overall	**CRITICAL**
Aiolfi, 2018	
Bias due to confounding	SERIOUS
Bias of selection of participants into the study	SERIOUS
Bias in classification of interventions	LOW
Bias due to deviations from intended intervention	NI
Bias due to missing data	NI
Bias in measurement of outcomes	NI
Bias in selection of the reported result	LOW
Overall	**SERIOUS**

NI= No information

Chapter 8

GENERAL DISCUSSION

SUMMARY OF FINDINGS

The aims of this thesis were to:

1. Assess the evolution of the current management guidelines for severe TBI, the change in their methodological assessment and their translation from the available evidence
    - The current management guidelines have a short lifespan, the methodological assessment has become more stringent and the translation from evidence more nuanced but also more complex

2. Describe the practice variation in the acute treatment of severe TBI patients regarding the various steps in the chain of care
    - There is large practice variation on all levels of TBI care, from admission criteria to surgical choices and adherence to guidelines

3. Evaluate guideline adherence and implementation in clinical practice for some of the most relevant topics in ICP management
    - Adherence is low all around, and even topics supported by high quality evidence are not adhered to 100%

4. Assess the effect of ventricular versus intraparenchymal pressure devices for the ICP-directed treatment of severe TBI patients according to contemporary evidence generation methods
    - There appears to be a trend toward better patient outcomes when using ventricular devices, with less patients requiring a decompressive craniectomy

Over the past 20 years, the main guidelines for the medical treatment of severe TBI (the Brain Trauma Foundation (BTF) Guidelines) have changed fundamentally, with an average survival of recommendations of around 30% between two consecutive editions. We showed that, when applying strict methodology to the evidence base, only less than half of recommendations "survive" from one edition to the next.

The discrepancies between the guidelines, and clinical practice became evident when practice variation was assessed. Among centers participating in a prospective, longitudinal observational study on TBI, considerable variation was present in most aspects of patient care, from intensive care admission criteria (*Chapter 3*) to ICU treatment protocols (*Chapter 4*). The BTF Guidelines are frequently used in clinical practice at any level of care, from

regional hospitals to level I academic trauma centers. However, Practice variations among treatment centers do remain, even on topics which are supported by the best available evidence (*Chapter 5*).

A meta-analysis on the topic of ventricular devices (VDs) versus intraparenchymal (IP) monitors for monitoring and treatment of severe TBI showed that the only available randomized trial suggests the superiority of using VDs in terms of mortality and functional outcome. Moreover, VD patients required less decompressive craniectomies. However, when pooling results from all available literature (*Chapter 6*), there was no benefit in terms of mortality or functional outcome. The only statistically significant results were a longer ICU stay for the VD group and a higher complication rate for the same group. Our analysis of data form the CENTER-TBI study suggests better outcomes in the VD group (*Chapter 7*), with significantly less decompressive craniectomies.

Treating patients: the divide between pathophysiologic (mechanistic) reasoning and clinical reality

Science is thought, up to a certain extent, to be an accumulative, iterative, self-correcting endeavor, where mistakes are a normal short-term side-effect of a long-term process of accumulating evidence[22]. Evidence in medicine relies heavily on RCTs. Philip's paradox[22] states that some of our most effective interventions (insulin for diabetes, defibrillation for ventricular fibrillation, the Heimlich maneuver) will never be the subject of an RCT experiment because of their evident effect. Another obvious example is using the parachute when jumping off a plane[23] to prevent serious morbidity and mortality. The critical question is which interventions in a clinical setting are "parachutes" (and subject to Philip's paradox) and which are not. And even if such interventions show very large effect sizes in observational studies, such that no placebo comparison is deemed necessary, there is still room for potential RCTs. For instance, any new intervention for the same disease (a defibrillating device working in a different manner) would need to be compared to the "old", "proven" intervention using an RCT.

Mechanistic (or pathophysiological) reasoning has, for centuries, formed the basis of clinical reasoning and treatment decisions. However, the history of medicine is also full of examples in which mechanistic reasoning, when tested in patients, failed or proved to be harmful[24]. An (in)famous example is formed by the number of studies testing effectiveness of extracranial-intracranial bypass surgery for restoration of cerebral blood flow. Following the success of coronary bypass surgery, it mechanistically seemed reasonable to perform a bypass on a cerebral vessel distal to a stenosis or occlusion to prevent stroke. Both trials[25,26] that tested this hypothesis versus medical treatment failed, and the most recent one actually showed

significantly more 30-day strokes in the surgical group. This was due in part because the pathophysiological mechanisms were not properly understood[26] (cerebral hemodynamics) and because the intervention[27] (anastomosis) was technically poorly performed.

Another classic example of failure of mechanistic reasoning is the cardiac arrhythmia (CAST) trial[28]. After myocardial infarction, mortality was thought to be due to secondary arrhythmias. The CAST trial randomized people to antiarrhythmic medication versus placebo. However, the trial was terminated early because of futility. The medication group did worse than the placebo group. In retrospect, this medication, which was standard treatment before the trial was initiated, is thought to have killed more people than the Vietnam war.

The problem with mechanistic reasoning and causal inference is illustrated in the image below, by Howick et al, showing a Bayesian problem of probabilities[24]. The probability that an intervention *I* will be causal to an outcome *O* is illustrated in two cases: in the first, if a mechanism consists of five "links" and each have a dependency of 90%, then the overall correlation between *I* and *O* cannot be higher than 59%. In the second example all of the links have a dependency of 99.9% but one link has a dependency of 10%. In this example the probability of the correlation between *I* and *O* remains only 10%, despite all of the other links being strong. For example, antiarrhythmic drugs do not always suppress ventricular extra beats- they work in 90% of patients[24]. The possible problems with mechanistic reasoning are summarized in Table 1.

Table 1. Problems of mechanistic reasoning and examples from clinical practice, partially reproduced from Howick et al 2010[24].

Problem		**Example**
Problems with the mechanism	Mechanism derived from a fanciful theory	Blood - letting
	Mechanism sounds plausible but has no supporting evidence	Extracranial- intracranial bypass for any type of carotid occlusion
	Mechanism is partially supported by evidence, but some factors are ignored	Steroids for the acute phase of severe TBI
Problems with the inference from the mechanism to the conclusion of efficacy	Failure to consider the probabilistic nature of the mechanism	Decompressive craniectomy for TBI
	Failure to consider the complexity of the mechanisms (including failure to consider mechanisms that might produce adverse events)	Hyperventilation for reducing ICP

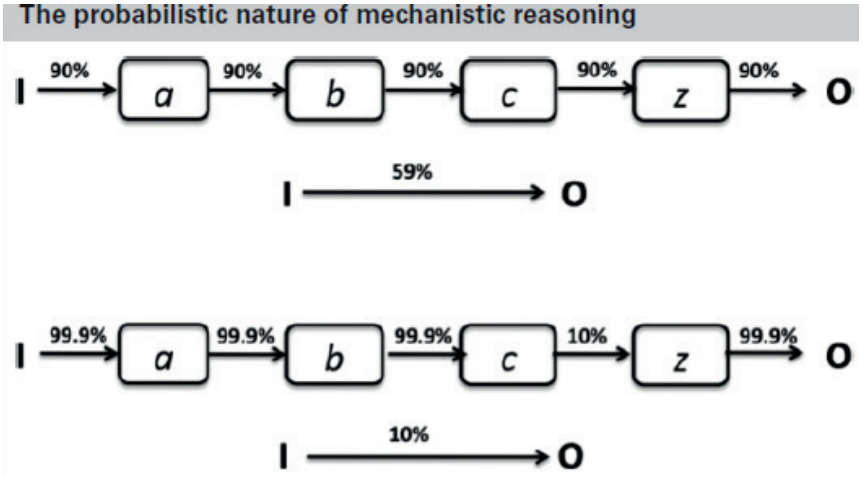


Figure 1. From Howick et al 2010, The probabilistic dependencies between an intervention **(I)** and an outcome **(O)**.

An example from TBI is that although in severe TBI, edema secondary to brain contusions could be safely treated with the most potent anti-inflammatory drugs, steroids, a large RCT on this topic showed that steroids in the acute phase were not only ineffective but they actually caused significantly more mortality[29].

One step further: From mechanistic reasoning to evidence-based medicine

From the early 1990's, the concept of evidence-based medicine[30] started to materialize.

Evidence based medicine (EBM) is the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients. EBM challenged the authoritative "eminence-based" medicine practiced in the years before. Its proponents were taught to have an "enlightened skepticism" attitude towards the application of diagnostic, therapeutic and prognostic technologies in patient care. EBM de-emphasizes intuition, unsystematic clinical experience and pathophysiological rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research[22,30].

The "golden standard" of clinical evidence generation remains to this day the randomized controlled trial (RCT), as opposed to observational studies which suffer from inherent bias[31,32]. However, flawed randomized trials provide less evidence than well-designed ones[33], and poorly designed RCTs may even provide less evidence than well-designed observational studies. This can be due to, for example, biases regarding the funding body[34],

issues regarding generalizability[35] and biases regarding the definition of the intervention (dose, timing, operative technique). The GRADE collaboration published more nuanced criteria for grading studies and trials as evidence, in which RCTs for instance can be downgraded when major flaws are present and observational studies can be upgraded when the effect size is very large[36].

Because of the complexity of the disease, evidence generation in TBI faces different challenges altogether.

The issue of evidence generation in severe TBI

Evidence generation in severe TBI is hampered by the high number of variables that may interact with outcome result, the complex nature of pathophysiological processes that are initiated after brain injury, the wide range of phenotypes of brain injury, the lack of a clear relation between imaging parameters and clinical outcome, and many other uncertainties. Severe TBI also does not lend itself easily to evidence generation through the use of RCTs, because of the difficulty of defining abovementioned variables and because of the long time that passes between the intervention and the outcome (with a myriad of other interventions and potential confounders happening along the way). In the modern era of practicing evidence-based medicine it will be the task of physicians treating patients with severe TBI to collect data that may help answer questions about effectiveness of treatments and in such a way to help define guidelines, in a "medicine-based evidence" approach that compliments EBM (*Chapter 2*).

As mentioned above, the "golden standard" of evidence generation is the randomized controlled trial[31]. Randomization minimizes the risk of confounding and can therefore give a proper effect size estimate when the right sample study population is chosen and the interventions are properly defined. The evaluation of an intervention is usually made in comparing it with the current "standard of care" or with placebo. However, TBI is a field in which no real "standard of care" exists. Indeed, as we show in *Chapters 3, 4 and 5,* considerable variation exists in treatment of severe TBI patients. This, along with a heterogeneous population, makes the assessment of any individual intervention very difficult from a trial design standpoint. Furthermore, carrying out a clinical trial may disrupt the usual care given to the patients.

Guidelines: Lost in translation of (poor) evidence

Studies providing evidence are currently graded into classes of quality, usually 1 through 3, class 1 providing the highest level of evidence, and thus the strongest level of "certainty" about the treatment effect and its size[10]. The impact and conclusion of an individual study is not only taken by itself, rather it is interpreted together with results of other studies on the

same topic. According to the GRADE criteria[36] studies should be valued on consistency (the extent of which the results or conclusions are similar among studies), directness (or external validity of studies) and precision (the degree of certainty surrounding the effect estimate for a given outcome). This leads to a recommendation, which have similar gradings depicted by roman numeral, so they may be level I (high degree of certainty), IIA or IIB (moderate level of certainty) or level III (low degree of certainty).

Over the course of the past 20 years, the Brain Trauma Foundation Guidelines have served as the most widely used guidelines for the management of severe TBI[7,8,10], as shown in *Chapter 5*. Their evolution is both parallel to the evolution of evidence-based medicine, as to the evolution of the evidence base for the treatment of severe TBI. A PubMed search on the term "severe traumatic brain injury" results in 111 articles in 1996 and 806 in 2016, an almost 8-fold increase. This can also be seen in the evolution of the evidence base, as we show in *Chapter 2* it increases steadily despite a stricter methodology of evidence evaluation. With this evolution, recommendations do not become stronger and actually regress in number. Moreover, "classical" topics in the treatment of severe TBI, such as hyperosmolar therapies and hyperventilation did not survive scrutiny[10]. For the latter we see 20 years later only one study in the evidence base (from 1991!) and for the former 6 studies in the evidence base that could not result in any formal recommendation on this topic.

The major differences between the 1996/2000 TBI Guidelines and the Guidelines 20 years later are the evaluation of evidence and the elimination of very poor-quality studies, which were considered evidence in the first editions of the Guidelines. The quality of the evidence is better nowadays, but class 1 and 2 studies are still scarce.

This may disappoint and confuse clinicians, but it also draws attention to a couple of aspects in the treatment of severe TBI: there are 219 RCTs[4], but very few qualify as evidence, which leads to widespread practice variation (the subject of our investigation in *Chapters 3, 4 and 5*). The TBI research community does not prioritize the "older" topics (50% of new studies in the evidence base are on topics added in newer versions). The second aspect lies in the difficulty of generating clinically applicable evidence in severe TBI (or patient-oriented evidence that matters (POEM)[37,38]). This endeavor is very difficult, because of the heterogeneity of the population and of the interventions and not least of all, because of the distance between applying the intervention within a cluster of other interventions (each affecting others) and the outcome itself. This will be discussed in relation to *Chapters 6 and 7*.

The practical (and to a certain extent ethical) question that arises is whether we should make guidelines at all if the evidence is poor to begin with and where there is scarcity of

POEMs. On one hand, the large amount of papers with low quality treatment evidence being published in severe TBI, and the reviews offering clinicians an overview of the most important information in an easy-to-digest manner is a worthy undertaking. On the other hand, if the guidelines based on uncertain evidence are being used for "quality control" of patient care, ineffective and even potentially harmful treatments might end up being widely used with possible nefarious consequences for patients. Ethically the question that rises is whether in the absence of strong evidence, but with the widespread use of guidelines, uniformity in patient care should be sought. This search for uniformity may deter clinicians from applying other new treatments.

Another valid question that arises in this context is whether making guidelines based on poor quality evidence is a worthy endeavor. When there is no confidence in the results of scientific studies, perhaps there should be no guidelines and caregivers need to decide for themselves what the best course of action is for their patients However, because of the complexity of the disease, the multitude of possible treatments and the heterogeneity of the TBI population there is a need to have summaries of the current evidence at hand. The BTF guidelines became very popular, clinicians both inexperienced and highly experienced appreciated the guidance and the overview. However, doubts about the quality of the evidence together with the complexity of the disease make that practice variation in TBI treatment is still very prominent.

Practice variation in the treatment of severe TBI patients: irresponsible or inevitable?

Prohibiting unintended variation is an objective of industrial quality management methods, based, among others, on the theoretical work of Walter Shewhart[39]. The practice of medicine however, has not always the same goals as an industrial undertaking. Applying industrial effectiveness by minimizing variation to health care systems may limit health-care professionals because this can hamper independent clinical reasoning due to the "one-fits-all" standardized approach induced by the use of guidelines.

In the treatment of severe TBI, as we show in *Chapters 3, 4 and 5*, there is large practice variation. From the decision in which care level to admit the patient (*Chapter 3*), to the decision in which order to use the guidelines (*Chapter 5*). In general, severe TBI patients are admitted to the ICU. However, as shown in *Chapter 3,* in quite a considerable number of centers (mostly academic, level I trauma centers, interested in TBI research) patients with only mild TBI and in good clinical condition may also be admitted to the ICU for observation whereas in other centers only patients in bad clinical condition are admitted to the ICU. This difference in treatment among countries was not associated with factors such as Gross Domestic Product or government cost allocation on healthcare, the presence

of a dedicated neuroICU or having step-down beds. Admitting mild TBI patients to the ICU might stem from the idea that TBI, even mild, might deteriorate and intensive observations are required, regardless of cost. However, there is insufficient literature and of insufficient quality reporting the prevalence of patients admitted to the hospital with mild TBI that secondarily deteriorate[40]. Furthermore, among different countries heterogeneous definitions exist of what is seen as ICU care.

Once a patient was admitted to the ICU (*Chapter 4*), there was a large variation in supportive measures for the patients, such as when to treat fever, what the proper cut-off was for the partial pressures of arterial blood gases or oxygen saturation goals. In a broader sense, there was consistent variation regarding which guidelines to use (*Chapter 5*), but even centers that used the guidelines did not always adhere to the recommendations, not even the ones supported by level I or IIA evidence. We also showed that the most important reasons for nonadherence were the concomitant presence of extracranial injuries (which may require different therapies, in contradiction with guideline recommendations), not having enough time to consult guidelines and the reluctance of clinicians to treat patients using a "cookbook" approach.

Lack of adherence to the guidelines has many facets. TBI is a very complex disease and severe TBI even more complex, showing a plethora of possible clinical manifestations[41] and possible natural history outcomes. It is still impossible to accurately predict which patients will suffer from secondary swelling and increased ICP and which would benefit from more aggressive treatment. The current treatments for increased ICP are also complex and do not only affect cerebral edema, but have other systemic effects, such as cardiac or renal effects which may in turn end up increasing ICP through other mechanisms. Interventions that are supported by recommendations based on high-quality evidence (such as not using steroids in the acute phase) are poorly understood from a pathophysiologic point of view. All of these uncertainties taken into consideration, it follows that even in academic centers which are part of the TBI research community, guidelines are not always adhered to and individual patient tailored approaches are attempted. In centers with less trauma care experience physicians may not be up-to-date with guideline recommendations or there may be reluctance to change routine practices. Given these facts, variation in severe TBI care is unlikely to change anytime soon, unless solid, trustworthy and clinically relevant evidence will be generated.

On a more positive note, this practice variation we describe offers opportunities for comparative effectiveness research[42,43]. Instead of turning against variation, a better idea is to take advantage of the "natural randomization" and the various treatment preferences and to use it for better evidence generation.

An illustrative example of the inherent complexity of evidence generation in TBI: Ventricular Drainage vs Intraparenchymal Monitoring

One topic that is matter of heated debate in TBI treatment, is whether or not CSF drainage will be beneficial for outcome, because according to mechanistic reasoning, CSF drainage will lower ICP. For illustration we will discuss the case of draining cerebrospinal fluid (CSF) and measuring intracranial pressure at the same time by a ventricular drainage catheter containing an ICP sensor versus a single intraparenchymal ICP pressure sensor. One RCT[44] of 126 patients shows the superiority of ventricular devices (VDs) over intraparenchymal (IP) monitors in terms of functional outcome and the need for fewer decompressive craniectomies. However, as shown in *Chapter 6*, when the results of all available studies are pooled together, among which an observational study of more than 2000 patients, the effect becomes non-significant and the only conclusion that can be drawn is that VDs are associated with more complications than IPs. In terms of evidence generation, a meta-analysis (preferably of RCTs) has the highest degree of certainty. In this case, even though one RCT recommends the use of VDs over IPs, this could not be translated into a recommendation based on the meta-analysis performed.

This topic illustrates two separate issues: on one hand the difficulty of generating reliable evidence even on interventions that seem logical from a mechanistic perspective: by lowering intracranial volume, the ICP should drop significantly and patients should fare better, but this is not the result of the studies. On the other hand, there is also a difficulty of generating evidence when pooling all available studies. Although the RCT done on this topic had a small sample size and is a potentially not generalizable study, this RCT is the gold standard of evidence generation and it showed a positive effect. But when the meta-analysis is performed, pooling the results potentially introduces confounding, given that all observational studies included are at high risk of bias, have heterogenous definitions of the interventions and outcomes and also have limited generalizability. Our meta-analysis alters the result of the one RCT inasmuch that it is no longer statistically significant.

In conclusion, hypotheses based on pathophysiological reasoning must be tested in studies. In severe TBI, RCTs are difficult to carry out and are to date often underpowered or have limited generalizability. Because of the heterogeneous population and phenotypes of injury, the chance is low that intervention and control groups are matched in terms of all relevant covariates, whereas observational studies may carry high risk of bias. However, evidence generation is essential for clinically relevant topics. Therefore, prospective observational data generation and CER as used in the CENTER-TBI study, may be the only possible way of gathering evidence for best treatment strategies.

CENTER -TBI and future directions of research

Within a large, prospective, observational study (CENTER-TBI[45]), we included a total of 745 patients (*Chapter 7*). There were unfortunately only 109 VD patients we could analyze in the entire cohort, even though we expected more based on the provider profiling performed before the start of the study.

When using a CER approach to test the hypothesis that the use of VD is superior to that of IP monitors in terms of mortality and functional outcome in *Chapter 7*, we noticed a trend toward better outcomes in the VD group and significantly less need for decompressive craniectomies. The clinical outcomes, despite the trends, did not reach statistical significance.

Recent trials[18,19] have shown that when patients need a decompressive craniectomy especially for diffuse brain injury, mortality is lower when compared to medical therapy but it results in more patients in a vegetative state or with a severe disability. One of the interpretations of the recent decompressive craniectomy trial[19] is that it is worthwhile to try to prevent through every available measure the rise in ICP and secondary edema, and this might be the explanation for the effect noticed when using VDs. Even in this large cohort, the number of patients we could include was limited, as the use of VDs is much less prevalent as what we had expected at the beginning of the study. Despite the RCT[44] suggesting that ventricular drainage should be the gold standard, the number of centers adopting this policy is still very low.

Despite our CER study, the question still remains up for debate. A more targeted approach would be needed to provide better evidence to support this intervention, such as a study designed for it specifically with more power and subsequently better generalizability.

Nowadays, more clinical data is routinely prospectively collected for research purposes. Despite the fact that, when compared to RCTs, studies based on this data do not always reliably estimate the treatment effect[46,47], there are ways to make studies based on this data more reliable[47] such as falsification end points ,negative controls of known null associations, validation datasets and pre-specified rules when the study hypotheses should be considered confirmed or rejected. Designing studies using a CER approach and the aforementioned routinely collected clinical data would, in the future, improve the evidence base considerably, as long as they are properly graded methodologically. One of the drawbacks of prospectively collecting data would be that clinical indicators such as mortality or readmission rates would be used for quality control purposes. In this case, random noise in clinical data might be misinterpreted as poor care, for example high mortality in hospitals which treat highly complex patients. This may deter clinicians from using clinical data for benchmarking purposes[48]. Also, good and reliable prospective data collection is a very daunting task. It

requires a good protocol and a lot of time, effort and funding in order to be done properly. Such effort demands intense dedication in order to ensure that proper data can be used and analyzed to ensure worthwhile conclusion can be drawn.

The scientific efforts of the CER community need to continue and, as ever, we are learning a lot from the first-ever large-scale research attempts in TBI. CENTER-TBI and TRACK-TBI the sister study will give us a better understanding and better definitions of the study population and treatment clusters[1,45]. The focus will then need to be on establishing a new evidence base for the "old" topics, identifying new ways of using "old" interventions and generating new hypotheses. CENTER-TBI is as much an endeavor of CER and evidence generation as it is an endeavor of hypothesis generation. RCTs will not be replaced by CER, rather they will be complementary to CER. This will allow for a more rational use of resources, while at the same time reflecting clinical practice as it is and minimizing the "observer" effect from quantum mechanics (the presence of an observer during an experiment such as an RCT influences the experiment and the outcomes). Furthermore, CER provides a more "real world" approach to observational study design, as with RCTs there are always exclusion criteria and thus the trial includes a selected population with subsequent generalizability issues. The potential for clinically applicable, "real-world" evidence of CER has been illustrated in recent studies about thrombosis prophylaxis after traumatic injury[49] and the comparison of outcomes for gastric bypass and gastric banding[50]. The number of patients included and the logistics of setting up these RCTs would have been otherwise extremely cumbersome.

Future projects for severe TBI in particular would include CER analyses on old and new topics (Table 2).

Table 2. Future potential projects where CER research could be used for generating evidence in severe TBI.

Intervention	Comparison study
Hyperosmolar therapies	Mannitol versus hypertonic saline and continuous mannitol versus bolus administration
Hyperventilation	Hyperventilation used early versus hyperventilation as second tier therapy
Ventricular drainage	Continuous versus intermittent drainage
Traumatic intracerebral hemorrhage (contusions)	Early evacuation versus medical management
Anesthetics and analgetics	Comparison of various protocols
ICP and CPP	Aggressive versus less aggressive treatment

CONCLUSION

In this thesis we aimed to study the evolution of the guidelines for the management of severe TBI, to evaluate the practice variation regarding various aspects of patient care in severe TBI, and to apply modern evidence-generating methods in order to solve a specific clinical question (VD versus IP use). Evidence generation in severe TBI is complex; we found that the evidence underpinning management of severe TBI patients is weak and the current version of the guidelines provides clinicians with little guidance. We also found that a CER approach can complement the conclusions of RCTs and can serve as a basis for both evidence as well as hypothesis generation. Further research needs to be directed towards broadening the evidence base for the "classical" interventions of severe TBI and better definitions of the various phenotypes of the severe TBI populations to be used in subsequent studies.

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Chapter 9

NEDERLANDSE SAMENVATTING

NEDERLANDSE SAMENVATTING

Traumatisch schedelhersenletsel (TSH) is een heterogene aandoening met een zeer hoge incidentie, morbiditeit en mortaliteit. De behandelingsmogelijkheden zijn, vooral voor ernstige traumata, schaars en voor de meeste behandelingen is bovendien slechts marginaal bewijs in de literatuur terug te vinden. Dit proefschrift legt zich toe op het beschrijven en verbeteren van de totstandkoming van deze bewijslast en richtlijnen voor TSH.

In **hoofdstuk 2** wordt de relatie tussen bewijs, aanbeveling en richtlijn onderzocht. Daarbij wordt een kritische beoordeling en analyse verricht van de belangrijkste en meest gebruikte richtlijnen voor de behandeling van ernstig traumatisch schedelhersenletsel (ETSH). Uit de verrichte analyses blijkt dat het bewijsniveau van de aanbevelingen in het verleden onterecht hoog werd bevonden. Daarnaast blijkt dat de kans dat een aanbeveling van een richtlijn ook aanwezig is in de daaropvolgende richtlijn ("overleving") 30 procent is. Niettemin is er wel een stijgende trend te merken in de kwaliteit van onderzoek naar ETSH, kwalitatief hoogstaand bewijs blijft echter schaars. Dit hoofdstuk laat bovendien zien dat ondanks deze verbeterde bewijslast het aantal aanbevelingen alsnog achteruitgaat.

In hoofdstuk 3, 4 en 5 wordt praktijkvariatie in de behandeling van TSH onderzocht. De slechte bewijslast en zwakke aanbevelingen leiden tot significante verschillen in klinische praktijkvoering, zowel in behandelcentra met veel ervaring in de behandeling van TSH als in behandelcentra waar de ervaring minder is.

Hoofdstuk 3 onderzoekt de opnamecriteria voor patiënten met TSH in 68 centra in twintig Europese landen. Ondanks de schaarste van intensive care (IC) bedden is een groot verschil in indicatiestelling voor opname op IC te zien. Zo bezetten in 68 procent van de centra patiënten met een helder bewustzijn en slechts enkele afwijkingen op beeldvorming een IC-bed en in de overige centra alleen de zeer ernstige patiënten met een verlaagd bewustzijn. Contextuele factoren als de aanwezigheid van een "High Care" unit, het aantal bedden of andere criteria als het percentage van het totale bruto binnenlands product dat wordt besteed aan gezondheidszorg tonen geen correlatie met de indicatiestelling voor IC-opname.

In **hoofdstuk 4** worden de verschillen in IC-behandeling bij ETSH in kaart gebracht binnen Europese centra. Voor slechts enkele behandelingen, zoals het behouden van de cerebrale perfusiedruk middels kristalloïden infusie of het vermijden van hyperthermie, is een grote mate van consensus tussen behandelcentra (90 tot 95 procent overeenkomst in beleid). Desalniettemin is voor de meeste behandelingen weinig overeenkomst in beleid tussen de centra terug te vinden. Tevens wordt in dit hoofdstuk beschreven dat er weinig

overeenkomst tussen de aanbevelingen van de richtlijnen en de daadwerkelijke situatie bestaat, dit is bijvoorbeeld te zien bij de aanbevelingen omtrent het profylactisch geven van anti-epileptica.

Op het verschil in richtlijnaanbevelingen en praktijk wordt verder ingegaan in **hoofdstuk 5**. Er wordt gezien dat sommige centra helemaal geen richtlijnen gebruiken (elf procent) en dat van de centra die wel richtlijnen gebruikten zeven procent geen formele implementatie heeft doorgevoerd. Zelfs klasse één aanbevelingen (bijvoorbeeld het niet gebruiken van steroïden in de acute fase) worden niet integraal gevolgd door alle centra.

Hoofdstukken 6 en 7 onderzoeken vervolgens een belangrijk thema in de behandeling van ETSH, namelijk de keuze voor of een intraventriculaire katheter of een intraparenchymateuze sensor voor intracraniële druk monitoring.

Hoofdstuk 6 is een review van alle artikelen die de resultaten vergelijken van intracraniële drukmonitoring met ventrikel katheters en met intraparenchymateuze sensors. Zes artikelen zijn geïncludeerd, waaronder één randomized controlled trial (RCT). Deze RCT laat zien dat de resultaten voor patiënten die gemonitord worden met een ventrikel katheter significant beter zijn qua morbiditeit en mortaliteit dan de resultaten voor patiënten gemonitord met een intraparenchymateuze sensor. Wanneer echter een meta-analyse wordt verricht van de resultaten van alle artikelen wordt geen verschil gezien in uitkomsten tussen patiënten in beide groepen.

In **hoofdstuk 7** wordt een "comparative effectiveness research" (CER) aanpak gebruikt om de uitkomsten te vergelijken tussen patiënten behandeld met een ventrikel katheter en patiënten behandeld met intraparenchymale sensor. De studie is Europees, prospectief, observationeel en beslaat meerdere centra en 790 patiënten. Patiënten met een ventrikel katheter hebben in deze studie minder decompressieve craniectomiëen nodig en er wordt een trend gezien tot betere uitkomsten binnen deze groep, echter het verschil is niet statistisch significant.

In de discussie van dit proefschrift wordt gereflecteerd over de manier waarop bewijs wordt verkregen en gehanteerd in de geneeskunde en de implicaties hiervan voor toekomstige studies, aanbevelingen en richtlijnen omtrent de behandeling van ETSH. We concluderen dat mechanistisch denken prevalent blijft in de medische wereld en kan leiden tot ongewenste uitkomsten voor patiënten. Derhalve is het essentieel om prospectief data te verzamelen, vooral in relatie tot onderwerpen die zich niet makkelijk lenen voor het uitvoeren van een RCT. Een CER aanpak zou, samen met de prospectieve dataverzameling, gebruikt kunnen worden om kwalitatief hoogstand bewijs te genereren.

Chapter 10

ENGLISH SUMMARY

ENGLISH SUMMARY

Traumatic Brain Injury (TBI) is a heterogeneous disease with a high incidence, morbidity and mortality. Good treatment modalities are, especially for severe traumas, few and for most of them there is little to no evidence available in the literature. This thesis aims to analyze and improve the evidence generation process and its translation to guidelines.

In **chapter 2** the relationship between evidence, recommendation and guidelines is analyzed. We use for illustration a critical appraisal and analysis of the most important and most used guidelines for the medical management of severe TBI. From our analyses we conclude that the recommendations in the past were unjustly highly graded. Moreover, the chance that a certain recommendation still appears in a subsequent edition of the guidelines ("survival") is around 30 percent. However, methodologically sound evidence is being published and the quality of research in TBI is improving, but very high quality evidence to guide care is still lacking. This chapter also shows that despite the improvement in evidence base, the number of recommendation decreases.

Chapter 3, 4 and 5 analyze practice variation in TBI. The poor evidence and recommendations lead to significant differences and in the treatment of patients and the choices of caregivers, in both centers with much experience in the treatment of TBI but also in centers with slightly less experience.

Chapter 3 analyzes the admission criteria for TBI patients in 68 centers from twenty European countries. Despite the general low availability of Intensive Care Unit (ICU) beds, large differences in admission criteria are noted. In 68% of the centers patients without alteration of consciousness but with imaging abnormalities would be admitted to the ICU, whereas in others only patients in a coma would be admitted to the ICU. Contextual factors such as the presence of a High Care step-down bed, the number of beds or even the percentage of spending from the Gross Domestic Product show no correlation with the indication to admit a patient to the ICU.

In **chapter 4** we analyze the differences in the treatment of severe TBI in European centers. For very few supportive measures, such as crystalloid fluid loading to support cerebral perfusion pressure or prevention of hyperthermia there is consensus (90-95%). For the rest of the general and supportive measures, there is limited consensus between centers. In this chapter we also note low guideline adherence for a couple of recommendations, for instance prophylactic use of anti-epileptic drugs.

Regarding the differences between guideline recommendations and actual practice, in **chapter 5** we perform an analysis of treatment variation in European centers. We notice that certain centers do not use guidelines at all (11%) and that from the centers that do use guidelines seven percent have no formal implementation efforts of said guidelines. Even for level I evidence (not using steroids in the acute phase) there is no 100% adherence.

In chapters 6 and 7 we analyze an important theme of severe TBI, the choice for either an intraventricular catheter (VC) or an intraparenchymal monitor (IPM) for the monitoring of intracranial pressure (ICP).

Chapter 6 is a review of all the studies that compare the results of ICP monitoring with VC versus IPM. Six articles were included, among which a randomized controlled trial (RCT). This RCT showed that the results in terms of mortality and functional outcome are significantly better for patients who received a VC compared to those monitored with an IPM. When the results of all the studies are pooled in the meta-analysis, however, the result is no longer significant in neither mortality or functional outcomes.

In **chapter 7** we use a "comparative effective research" (CER) methodology to compare outcomes between patients monitored with a VC and those monitored with an IPM. This study is European, prospective observational and includes 790 patients from 20 centers. Patients with a VC needed less decompressive craniectomies and a trend was observed for better functional outcomes in the VC group, but it did not reach statistical significance.

In the general discussion we reflect on the manner in which evidence is generated in medicine and in TBI and the implications for future studies, recommendations and guidelines for the treatment of severe TBI. We conclude that mechanistic reasoning still prevails in the medical world and this may lead to unwanted outcomes. This makes prospective data collection essential, especially for topics that do not lend themselves easily to evidence generation through RCTs. CER approaches together with this data collection could be used in the future to generate high quality evidence.

Appendix

CURRICULUM VITAE
PHD PORTFOLIO
LIST OF PUBLICATIONS
DANKWOORD

CURRICULUM VITAE

Victor Volovici was born on the 11th of October 1987 in Sibiu, Romania. After graduating from high school in his native city, he moved to Bucharest to attend the "Carol Davila" University of Medicine and Pharmacy. During his medical studies in 2010 he began doing research in the field of microsurgery in the lab of dr. D. Zamfirescu, focusing on microsurgical training but also composite tissue transplantation. During this period (2010-2012) he also travelled to various academic centers in Europe for short term observerships, one of which was Rotterdam, under the supervision of dr. E. J. Delwel and Prof. Dr. C. Dirven. In 2013 he moved to the Netherlands and began his career as a junior resident in the Erasmus MC under supervision of Prof. Dirven. In 2015 he started his PhD as an investigator in the CENTER-TBI traumatic brain injury European project, under the supervision of Prof. Dirven, Prof. E. W. Steyerberg en dr. H. F. Lingsma. In 2018 he began his (AIOS) neurosurgical training under supervision of Prof. Dirven. In 2013 he also began a collaboration with the "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca (Prof. Dr. I. S. Florian) on neurosurgical and microsurgical (Assoc. Prof. G. Dindelegan) research, which continues to this day.

PHD PORTFOLIO

Name PhD Student: Victor Volovici	PhD period: 2015-2019
Erasmus MC Departments of Neurosurgery and Public Health	Research School: NIHES
Promotoren: Prof. Dr. C. M. F. Dirven and Prof. Dr. E. W. Steyerbeg	Copromotor: Dr. H. F. Lingsma

	Year	ECTS
General courses		
NIHES ESP03 Introduction to Data analysis	2015	0,4
NIHES ESP10 Methods of Clinical Research	2015	0,4
Specific courses		
NIHES ESP38 Conceptual Foundation Epidemiologic Study Design	2015	0,4
NIHES ESP62 Markers and Prediction Research	2015	0,4
NIHES ESP40 Case-control Studies	2016	0,4
NIHES ESP48 Causal Inference	2016	0,4
NIHES ESP66 Logistic Regression	2016	0,8
International Congresses		
International Brain Injury Association Congress The Hague	2016	
2 x poster presentations	2016	0,8
1 x oral presentation	2016	0,4
World Congress of Microsurgery Seoul	2017	
2 x oral presentations	2017	1,5
1 x poster presentation	2017	0,5
Didactic activities		
Neurosurgical Masterclass Cluj-Napoca – organizer, faculty		
Topic: Gliomas	2015	2,0
Topic: TBI	2016	2,0
Topic: Benign tumors	2017	2,0
Topic: Skull Base	2018	2,0
Topic: Vascular	2019	2,0
Skull Base Course Rotterdam - Faculty	2017	2,0
	2018	2,0
Comprehensive 7-day Microsurgical Course Cluj-Napoca – Course Director	2017	2,0
	2018	2,0
	2019	2,0
European Association of Neurosurgical Societies Microvascular Course – Course Co-Chairman	2018	3,0
Supervising thesis		
Supervising Master thesis Gavin Bruggeman: Diffuse Axonal Injury	2018	3,0
Total		**32,4**

LIST OF PUBLICATIONS

Publications pertaining to this thesis

- **Volovici V**, Steyerberg EW, Cnossen MC, Haitsma IK, Dirven CMF, Maas AIR, Lingsma HF. Evolution of Evidence and Guideline Recommendations for the Medical Management of Severe Traumatic Brain Injury. J Neurotrauma. 2019 Jul 31
- **Volovici V**, Ercole A, Citerio G, Stocchetti N, Haitsma IK, Huijben JA, Dirven CMF, van der Jagt M, Steyerberg EW, Nelson D, Cnossen MC, Maas AIR, Polinder S, Menon DK, Lingsma HF; CENTER-TBI collaborators. Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe. World Neurosurg. 2019 May;125:e515-e520
- **Volovici V**, Ercole A, Citerio G, Stocchetti N, Haitsma IK, Huijben JA, Dirven CMF, van der Jagt M, Steyerberg EW, Nelson D, Cnossen MC, Maas AIR, Polinder S, Menon DK, Lingsma HF. Intensive care admission criteria for traumatic brain injury patients across Europe. J Crit Care. 2019 Feb;49:158-161
- **Volovici V**, Huijben JA, Ercole A, Stocchetti N, Dirven CMF, van der Jagt M, Steyerberg EW, Lingsma H, Menon D, Maas A, Haitsma I. Ventricular drainage catheters versus intracranial parenchymal catheters for intracranial pressure monitoring-based management of traumatic brain injury: a systematic review and meta-analysis. J Neurotrauma. 2018 Sep 25
- Huijben JA, **Volovici V**, Cnossen MC, Haitsma IK, Stocchetti N, Maas AIR, Menon DK, Ercole A, Citerio G, Nelson D, Polinder S, Steyerberg EW, Lingsma HF, van der Jagt M; CENTER-TBI investigators and participants. Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. Crit Care. 2018 Apr 13;22(1):90
- **Volovici V**, Haitsma IK, Dirven CMF, Steyerberg EW, Lingsma HF, Maas AIR. Letter: Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017 Aug 1;81(2):E21

Other publications

- **Volovici V** – Translating evidence into guidelines (letter to the editor). *JAMA Surgery*, September 2019
- **Volovici, V**, Dammers R, Dirven CMF, Delwel EJ - Conquering the Rock—A Retrospective Single-Center Experience of the Transapical Petrosal Transtentorial (Kawase) Approach: Operative Technique and Impact on Cranial Nerve Function, J Neurol Surg B June 2019, DOI: 10.1055/s-0039-1692485

- **Volovici V**, Dammers R, Lawton MT, Dirven CMF, Ketelaar T, Lanzino G, Zamfirescu DG. The Flower Petal Training System in Microsurgery: Validation of a Training Model Using a Randomized Controlled Trial. Ann Plast Surg. 2019 Jun 19
- **Volovici V***, Holl DC*, Dirven CMF, van Kooten F, Miah IP, Jellema K, Peul WC, van der Gaag NA, Kho KH, den Hertog HM, Dammers R, Lingsma HF. Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis. Acta Neurochir (Wien). 2019 Jun;161(6):1231-1242
- **Volovici V**, van Dijk EJ, van der Lugt A, Koudstaal PJ, Vincent AJ. A modified encephalo-duro-synagiosis technique induced neovascularization in symptomatic atherosclerotic carotid artery occlusion: A Phase 1 trial. World Neurosurg. 2019 Jan 4. pii: S1878-8750(18)32886-9
- Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt N, de Laat K, Koot RW, **Volovici V**, Dirven CMF, van Kooten F, Kho KH, den Hertog HM, van der Naalt J, Jacobs B, Groen RJM, Lingsma HF, Dammers R, Jellema K, van der Gaag NA; Dutch Subdural Hematoma Research Group (DSHR). Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial. Trials. 2018 Oct 20;19(1):575
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- **Volovici V***, Holl DC*, Dirven CMF, Peul WC, van Kooten F, Jellema K, van der Gaag NA, Miah IP, Kho KH, den Hertog HM, Lingsma HF, Dammers R; Dutch Chronic Subdural Hematoma Research Group (DSHR). Pathophysiology and Nonsurgical Treatment of Chronic Subdural Hematoma: From Past to Present to Future. World Neurosurg. 2018 Aug;116:402-411.e2
- Cnossen MC, Huijben JA, van der Jagt M, **Volovici V**, van Essen T, Polinder S, Nelson D, Ercole A, Stocchetti N, Citerio G, Peul WC, Maas AIR, Menon D, Steyerberg EW, Lingsma HF; CENTER-TBI investigators. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. Crit Care. 2017 Sep 6;21(1):233
- **Volovici V**, Dammers R, Kompanje EJ. In Reply: The History of the Kernohan Notch Revisited. Neurosurgery. 2017 Apr 1;80(4):226

- **Volovici V**, Dammers R, Zamfirescu DG. The double stitch everting technique in end-to-side vascular anastomoses. Microsurgery. 2017 Jan;37(1):88-89
- De Hoog, J.; **Volovici, V.**; Dammers, R.- Successful surgical optic nerve decompression in a patient with hypertrophic pachymeningitis due to granulomatous polyangiitis, BMJ Case Rep. 2015 Jan 22;2015
- Verploegh, I.; **Volovici, V**.; Dammers, R; Berghauser Pont LME – Management of Chronic Subdural Hematoma. Part I- Pathogenesis and Diagnosis, Contemporary Neurosurgery, volume 37, Number 2
- Verploegh, I.; **Volovici, V**.; Dammers, R; Berghauser Pont LME – Management of Chronic Subdural Hematoma. Part II- Treatment and Prognosis, Contemporary Neurosurgery, volume 37, Number 3
- Dammers R, **Volovici V**, Kompanje EJ. The History of the Kernohan Notch Revisited. Neurosurgery. 2016 Apr; 78(4):581-4. doi: 10.1227/NEU.0000000000001097.
- **Volovici V***, Verploegh IS*, Haitsma IK, Schouten JW, Dirven CM, Kros JM, Dammers R. Contemporary frameless intracranial biopsy techniques: Might variation in safety and efficacy be expected? Acta Neurochir (Wien). 2015 Nov;157(11):2011-6; discussion 2016. doi: 10.1007/s00701-015-2543-0
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- Dammers R, **Volovici V**, Kompanje EJ. In Reply: The History of the Kernohan Notch Revisited. Neurosurgery. 2016 Oct;79(4):E546-7
- **Volovici, V.**, Dammers R., Berghauser Pont, L.- Letter to the editor. Comment on " What clinical factors predict the incidence of deep venous thrombosis and pulmonary embolism in neurosurgical patients? ", J Neurosurg. 2015 Mar;122(3):721-2. doi: 10.3171/2014.9.JNS142030

Books and book chapters

- Dindelegan, G; **Volovici, V** (editors) – Experimental microsurgical and microvascular techniques (Cluj-Napoca, Manuscript in preparation)
- **Volovici V**, Dammers R, van Veelen MLC "Chapter 16- Tumors of Pineal Cell origin", Chapter in "Pineal Region Lesions: Management Strategies and Controversial Issues", Editor Florian IS

ISBN 978-94-6375-602-0