

1 Variation in guideline implementation and adherence regarding severe traumatic
2 brain injury treatment: a CENTER-TBI survey study in Europe

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48 **Abstract**

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

52 As part of a prospective, observational, multi-center European cohort study, participants from
53 68 centers in 20 countries were asked to complete 72-item questionnaires regarding their
54 management of severe TBI. Six questions with multiple sub-questions focused on guideline
55 use and implementation.

56 Questionnaires were completed by 65 centers. Of these, 49 (75%) reported use of the Brain
57 Trauma Foundation Guidelines for the medical management of TBI or related institutional
58 protocols, 11 (17%) used no guidelines and 5 used other guidelines (8%). Of 54 centers
59 reporting use of any guidelines, 41 (75%) relied on written guidelines. Four centers of the 54
60 (7%) reported no formal implementation efforts. Structural attention to the guidelines during
61 daily clinical rounds was reported by 21 centers (38%). The most often reported reasons for
62 non-adherence were ‘every patient is unique’ and the presence of extracranial injuries, both
63 for centers that did and did not report the use of guidelines.

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

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68

69 **Introduction**

70 The objective of clinical practice guidelines is to reduce practice variations and improve
71 patient outcomes by synthesizing the best available evidence in clear, concise and easy-to-use
72 documents¹. The Brain Trauma Foundation (BTF) Guidelines for the medical management of
73 severe traumatic brain injury (TBI) are the most widely used for these patients with 4 editions
74 published over the last 20 years². Recent studies show suboptimal and variable adherence
75 rates, which likely relate both to the poor quality of the evidence and the heterogeneity of the
76 TBI patient population, among other reasons³⁻⁶.

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

83

84 **Materials and Methods**

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

93 We have measured reliability and concordance rates of the questionnaire. To estimate
94 reliability of the questionnaires, we included 17 (5%) duplicate questions, including all
95 question formats. We equally included structure and process questions in the duplicate
96 questions. Concordance rates were estimated by calculating the percentage of overlap
97 between duplicate questions, and presented as mean, median and range. Questionnaires were
98 disseminated during presentations, workshops and email conversations. More information is
99 available at length in one of our group's previous publications³.

100 A set of questionnaires designed to measure structure and process of TBI care was developed
101 on the basis of available literature, expert opinion and based on best practice⁷. These
102 questionnaires were comprehensively described in a previous publication³. Pilot testing was
103 undertaken in 16 of the participating centers, and feedback was incorporated into the final
104 questionnaire design.

105 The questionnaire on ICU care contained 6 questions with multiple sub-questions exploring
106 guideline use and implementation. In most questions the "general policy" at each center was

107 surveyed. This was defined as “routine policy”; the standard treatment or policy in a particular
108 case. In others, we asked for quantitative estimations, whereby the frequency of using a
109 treatment strategy could be indicated (never 0-10%, rarely 10-30%, sometimes 30-70%,
110 frequently 70-90%, always 90-100%). The options ‘frequently’ and ‘always’ were interpreted
111 as representing the general policy, in line with previous provider profiling studies⁶. The
112 questions regarding the reasons for guideline-nonadherence also needed to be answered with
113 quantitative estimations as stated above for each individual reason. The reasons given were: ”
114 Lack of knowledge among clinicians”, “Every patient is unique and should be managed by
115 clinical judgment”, “Inadequate time to consult guidelines for urgent decisions”, “Guidelines
116 on TBI do not apply due to extracranial trauma or comorbidity”, “Inadequate resources to
117 apply guidelines (ICU beds, personnel, equipment)” (See *Supplemental Digital Content 1* for
118 more details).

119 We used chi-square and Fisher’s exact tests to compare therapies and monitoring at centers
120 that used BTF or BTF-based guidelines with centers that used other or no guidelines for
121 several recommendations from the two most recent versions of the BTF guidelines (2007 and
122 2016, versions 3 and 4).

123 **Results**

124 Most participants reported use of either BTF Guidelines, or BTF-based institutional
125 guidelines (n = 49; 75%), while 5 centers (8%) used non-BTF-based guidelines. 11 centers
126 (17%) reported that they did not use any guidelines. No regional differences were observed
127 between North – Western Europe (n = 30; 70%, use BTF Guidelines) and South – Eastern
128 Europe (n=19; 83%, use BTF Guidelines).

129 Of the 54 centers that reported to use guidelines, five had no allocation of responsibility to
130 oversee guideline development and maintenance (9%). In other centers, guideline
131 development and maintenance were the responsibility of a multi-disciplinary team (n = 31;
132 56%). However, annual or more frequent audit of guideline adherence was reported in only 4
133 centers (7%), while the remainder (n = 51; 93%) reported either no audits, or only one within
134 the past five years.

135 Four of the 54 centers using guidelines (7%) reported no formal implementation process. The
136 majority (n = 41; 75%), had written protocols and algorithms, but less than half paid structural
137 attention to the guidelines during rounds (n = 21; 38%) or organized hospital-led training (n =
138 20; 36%). Twelve centers of the 55 (22%) had their protocol in a data management system.
139 Five centers (9%) had e-learning modules or used trainings organized by an external
140 organization (n = 3; 4%).

141 The most often reported reasons for non-adherence were ‘every patient is unique’ (n = 19;
142 39%) and the presence of extracranial injuries (n = 8; 16%), for both centers that use and for
143 those that do not use guidelines (*Figure 1*).

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

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

150 Regarding ICP monitoring⁸ in patients with a Glasgow Coma Scale (GCS) < 9 and CT
151 abnormalities, 44 centers that used BTF guidelines (90%) would monitor ICP as a general
152 policy and 14 (93%) of those that used other guidelines or none at all. Of the 5 centers that
153 used BTF guidelines and would not monitor ICP in such a patient, 4 (8%) reported to
154 “frequently” adhere to medical management recommendations and 1 (2%) reported to
155 “always” adhere to the recommendations.

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

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

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

168 Seventeen (35%) of the centers that used BTF guidelines use phenytoin as the drug of choice
169 for antiseizure prophylaxis and 3 (19%) centers who did not use the BTF guidelines. More
170 than half of the centers that used BTF guidelines, however, used levetiracetam (n = 28; 57%)
171 as the drug of choice. Significantly fewer centers that did not use the BTF guidelines (n = 4;
172 25%) used levetiracetam as the drug of choice.

173 **Discussion**

174 We found considerable variability in guideline adherence and implementation among
175 neurotrauma centers in Europe. Less than one in three centers reported organized training,
176 paid structural attention to guidelines during daily rounds, or had a protocol in their clinical
177 data management system. However, though such implementation strategies would empirically
178 seem to be useful, there are as yet no data suggesting benefit of any individual
179 implementation or dissemination strategy in different circumstances⁹.

180 With respect to the level II recommendations, several centers, both that use and that do not
181 use BTF guidelines, used barbiturates and hyperventilation as a first – tier therapy, despite the

182 recommendation against this practice¹⁰. Despite the fact that proportionally more centers that
183 do not use BTF guidelines use barbiturates and hyperventilation as first tier therapies, the
184 difference did not reach statistical significance.

185 The use of antiseizure prophylaxis was the only statistically significant association with
186 guideline use in our data. The best available evidence supports using phenytoin as the drug of
187 choice to prevent early post-traumatic seizures (PTS). In the 4th edition of the BTF guidelines,
188 published after our questionnaire, the authors conclude that there is insufficient evidence to
189 recommend levetiracetam over phenytoin regarding efficacy in preventing early PTS and
190 toxicity². The fact that significantly more centers that use BTF guidelines use levetiracetam is
191 likely due to its important role in contemporary epilepsy treatment and not the adherence to
192 the recommendations of the BTF guidelines. Moreover, it is easier to use, as there is no need
193 to monitor serum concentrations and is perceived as having a more favorable side effect
194 profile¹¹⁻¹³.

195 The only level I recommendation, against the use of corticosteroids in primary TBI
196 treatment², is adhered to in 92 %.

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

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

213 We recognize that the questionnaire format of this study is a limitation in terms of properly
214 auditing guideline use and adherence, together with the relatively low power. However, the
215 centers involved in the CENTER-TBI project are frequently involved in TBI research, with
216 broad exposure to the international TBI community, which might explain the lack of
217 difference between centers that do and those that do not use guidelines in light of the evidence
218 base¹⁴. Furthermore, the results also need to be interpreted in light of the fact that the
219 questionnaires were filled in before the publication of the 4th edition of the BTF Guidelines.

220 **Conclusion**

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

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265 **Legend to tables and figures**

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

268 **Table 1** - The general policies of the centers studied in relation to the type of guideline they
269 use. In most questions we aimed for a reflection of the “general policy” at each center. In
270 others, however, we asked for quantitative estimations, whereby the frequency with which a
271 treatment strategy was used could be indicated (never 0-10%, rarely 10-30%, sometimes 30-
272 70%, frequently 70-90%, always 90-100%). The options ‘frequently’ and ‘always’ were
273 interpreted as representing the general policy

274

275 **Supplemental Digital Content Legend**

276 **Supplemental Digital Content 1, Methods:** The Provider Profiling ICU Questionnaire
277 regarding treatment policy and guideline use

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%)	
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%)	

278

279 **Table 1 – Comparisons in policy between centers that use Brain Trauma Foundation**
 280 **(BTF) Guidelines and those that use other guidelines or none at all**

281