5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 16

Traumatic Brain Injury, stroke and subarachnoid haemorrhage – How to Make an Impact in neurocritical care management and research (Level 2)

Acute management of TBI, including an outlook on forthcoming TBI trials

Ronny Beer
Innsbruck, Austria

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Disclosures – Speaker's *Potential* Conflicts of Interest

Baxter	Meeting attendance *compensation*
Bayer HealthCare	Research support; meeting attendance *compensation*
Boehringer Ingelheim	Speaker's fees; consultant services (*Austrian Advisory Board*)
FRESENIUS KABI	**Contract research**; speaker's fees; meeting attendance *compensation*
Nestlé HealthScience	Meeting attendance *compensation*
Pfizer	Research support; meeting attendance *compensation*
PORTOLA PHARMACEUTICALS	**Contract research**; speaker's fees; consultant services (*European Advisory Board*)
sanitas MEDIZINPRODUKTE INFOTECHNOLOGIE	Speaker's fees
vasopharm	**Contract research**
FWF Der Wissenschaftsfonds.	**Competitive research grant** (KLIF)

tirol kliniken R. Beer 2019

NeuroCritical Care Medical University of Innsbruck

5th Congress of the European Academy of Neurology | Oslo 2019

Neuroinflammation Science. Synergies. Solutions. 5 years ean

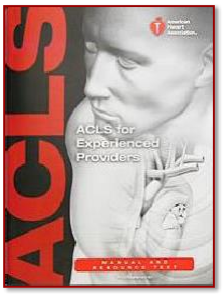
Teaching Course 16:
Traumatic Brain Injury, Stroke and Subarachnoid Hemorrhage –
How to Make an Impact in Neurocritical Care Management and Research

Acute Management of TBI
«Including a Look on TBI Trials»

Ronny Beer, MD
Neurological Intensive Care Unit
Department of Neurology
Medical University of Innsbruck, Austria

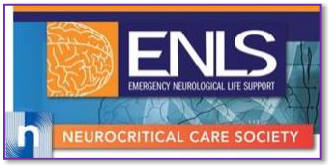
Potential Conflict of Interest: ***Contract Research*** (Principal and National Lead Investigator)
Sposored by ***vasopharm GmbH****, Wuerzburg, Germany*

Emergency Life Support – Emphasis on the «*First* or *Golden Hour*»



Advanced CARDIOVASCULAR Life Support | AHA/ERC

Advanced TRAUMA Life Support | ACS



Emergency *NEUROLOGICAL* Life Support | NCS

- «**Improve brain perfusion** and **thereby outcomes**»
- Addressing **non-neurologic organ dysfunction** as a result of acute brain injury or secondary to brain-specific therapies

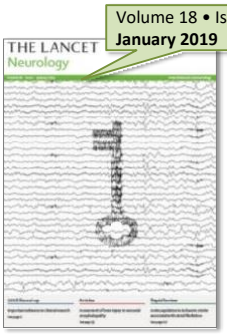
Acute Management of Traumatic Brain Injury (TBI) – Outline

- Starting on **basic knowledge**, the lecture concentrates on the **latest guideline recommendations** and **expert opinions** in each topic of ***TBI management***

- After completion of this **educational activity** the participants should
  - ***Understand*** the **complexity** of the ***disease***
  - Be ***familiar*** with relevant **neuroscores** (i.e., ***GCS*** and ***FOUR Score***)
  - ***Understand*** the **rationale** for (**neuro-**) **monitoring** of **severe TBI**
  - Be ***familiar*** with the **«staircase» approach** to the **management** of **traumatic intracranial hypertension**
  - ***Gain*** some ***insight*** into **contemporary clinical neurotrauma research**

Adapted from Rubiano et al., Nature 2015; 527:S193–S197

TBI – The *Neurological* Perspective



The data to put neurology on top of the public-health agenda

Every January issue of *The Lancet Neurology* includes a special Round Up section. Its pages are a celebration of research achievements over the previous year. Our 2018 Round Up reveals a booming specialty, in which the pace of discovery is accelerating, and for which advocates are needed to raise awareness of this progress and bring in the investment to maintain the pace. But advocacy for brain health research requires good evidence and accurate numbers on its social relevance, and only a few subspecialties within neurology have effectively gathered epidemiological data to support calls for resources and funding. Luckily, this situation is changing.

- But advocay for brain health research **requires good evidence** …
- … ***only few* subspecialities** within neurology have effectively gathered **epidemiological data** to **support calls** for ***resources*** and ***funding***

Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

Implications of all the available evidence
Our estimates suggest that TBI and SCI are severely disabling injuries. The global burden of TBI increased significantly between 1990 and 2016, whereas that of SCI has not changed significantly over time in terms of age-standardised incidence and prevalence.

- … ***TBI*** and **SCI** are **severely disabling injuries**
- … **global burden** of ***TBI increased*** **significantly** …

Adapted from GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, Lancet Neurol 2019; 18: 56–87

TBI – *Collaborative European **NeuroTrauma Effectiveness Research** in TBI*

Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A Prospective Longitudinal Observational Study

CENTER-TBI
Collaborative European NeuroTrauma Effectiveness Research in TBI
European Commission
SEVENTH FRAMEWORK PROGRAMME

TABLE 5. International Initiative on Traumatic Brain Injury Research Studies[a]

Project Title	Project Acronym and Sample Size	Funding Agency
Europe		
Collaborative European NeuroTrauma Effectiveness Research in TBI	CENTER-TBI (n = 5400)	European Commission
Collaborative REsearch on ACute Traumatic brain Injury in IntensiVe care Medicine in Europe	CREACTIVE (n = 7000)	European Commission
United States		
Transforming Research And Clinical Knowledge in Traumatic Brain Injury	TRACK-TBI (n = 2700)	NIH/NINDS
Approaches and Decisions for Acute Pediatric TBI	ADAPT (n = 1000)	NIH/NINDS
Managing severe TBI without ICP monitoring—guidelines development and testing	(n = 780)	NIH/NINDS
Canada		
Predicting and preventing postconcussive problems in paediatrics (5P) study: protocol for a prospective multicentre clinical prediction rule derivation study in children with concussion.	5P (n = 2000)	CIHR/ONF
Improving the diagnosis and treatment of mTBI in children and youth: the power of common data	Common data (n = 1000)	CIHR/FRQS
A longitudinal prospective study of mTBI in youth ice hockey players	Safe to play (n = 1000)	CIHR/HBI
Post-concussion Syndrome in youth: assessing the GABAergic effects of melatonin	PLAYGAME (n = 166)	CIHR
Neurocare: a clinical decision-making tool in youth mTBI	NEUROCARE (n = 1400)	CIHR/OBI

Adapted from Maas et al., Neurosurgery 2015; 76:67–80

TBI – *Collaborative European* ***NeuroTrauma Effectiveness Research*** *in TBI*

Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A Prospective Longitudinal Observational Study

CENTER-TBI
Collaborative European NeuroTrauma Effectiveness Research in TBI
European Commission
SEVENTH FRAMEWORK PROGRAMME

[68]Department of Neurology, Division of Neurocritical Care, Medical University Innsbruck, Innsbruck, Austria.
[79]Trauma Surgery, Medical University Vienna, Vienna, Austria.

FIGURE 1. *Distribution and number of sites per country that will participate in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury.*

BACKGROUND: Current classification of traumatic brain injury (TBI) is suboptimal, and management is based on weak evidence, with little attempt to personalize treatment. A need exists for new precision and stratified management approaches that incorporate emerging technologie

OBJECTIVE: To improve clinical care, using compa

METHODS: This multice countries across Europe tients, presenting within indication for computed imately 20 000 patients will assess generalizability.

EXPECTED OUTCOMES: Collaborative European NeuroTrauma Effectiveness Research in TBI should provide novel multidimensional approaches to TBI characterization and classification, evidence to support treatment recommendations, and benchmarks for quality of care. Data and sample repositories will ensure opportunities for legacy research.

DISCUSSION: Comparative effectiveness research provides an alternative to reductionistic clinical trials in restricted patient populations by exploiting differences in biology, care, and outcome to support optimal personalized patient management.

- Current ***classification*** of TBI is **suboptimal**
- ***Management*** is based on **weak evidence**
- **Need** exists for new ***precision medicine***

Adapted from Maas et al., Neurosurgery 2015; 76: 67–80

TBI – The *Neurological* Perspective

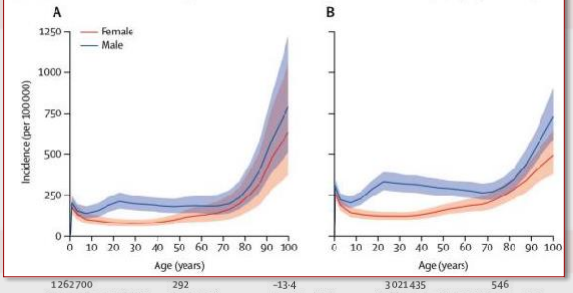
Volume 18 • Issue 1 • January 2019

THE LANCET Neurology

Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

	Incidence			Prevalence		
	2016 counts	2016 age-standardised rates (per 100 000)	Percentage change in age-standardised rates, 1990–2016	2016 counts	2016 age-standardised rates (per 100 000)	Percentage change in age-standardised rates, 1990–2016
Global						8·4 (7·7 to 9·2)
High SDI						−7·9 (−8·7 to −7·1)
High-middle SDI						−5·4 (−6·3 to −4·5)
Middle SDI						32·4 (31·0 to 33·9)
Low-middle SDI						18·7 (17·7 to 20·0)
Low SDI						3·3 (1·9 to 4·8)
High income						−10·2 (−11·0 to −9·2)
Western Europe	1 262 700 (1 042 418 to 1 546 907)	292 (244 to 351)	−13·4 (−17·2 to −9·7)	3 021 435 (2 880 245 to 3 154 517)	546 (519 to 572)	−12·8 (−13·8 to −11·7)
Austria	28 255 (23 166 to 35 170)	322 (266 to 388)	−19·9 (−24·5 to −14·8)	66 670 (63 606 to 69 564)	589 (561 to 616)	−17·7 (−19·4 to −16·2)

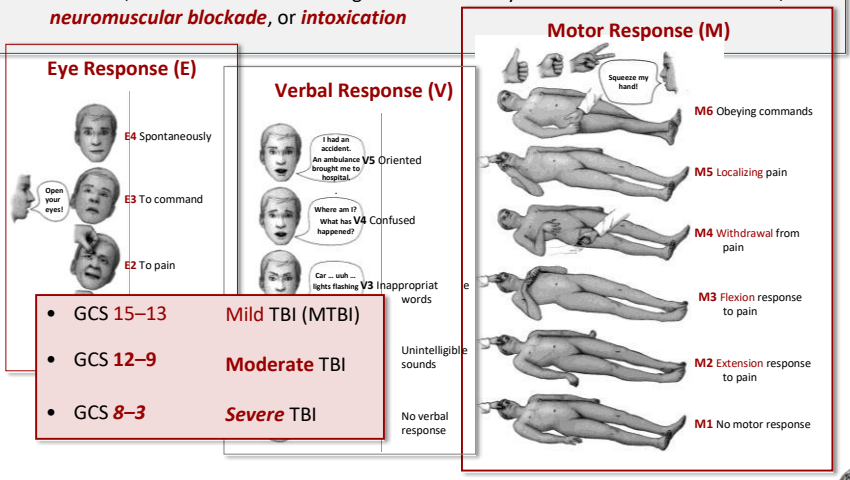
Figure 3: Global incidence of minor (A) and moderate or severe (B) traumatic brain injury, by age and sex, 2016



Adapted from GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, Lancet Neurol 2019; 18: 56–87

TBI – Classification Issues

- Capturing the **severity** of **TBI** based on the ***level of consciousness*** by using **GCS score**
  - **International accepted standard** (AANS, BTF, EBIC, WHO)
  - However, level of consciousness might be obscured by **confounders** such as ***sedation***, ***neuromuscular blockade***, or ***intoxication***



- GCS 15–13 Mild TBI (MTBI)
- GCS **12–9** **Moderate** TBI
- GCS ***8–3*** ***Severe*** TBI

Adapted from Teasdale und Jennett, Lancet 1974; 2: 81–84

Outcome Prediction after TBI – «*IMPACT Database*»

Table 1. Pooled Common Odds Ratios Derived from Proportional Odds Models Adjusting for a Range of Covariates

Variable	Number of studies	Sample size	Adjusted sample size[a]	Reference category	Category	Common odds ratio from proportional odds model: Univariate	Model A	Model B	Model C	Model D
Hypoxia	8	5626	5452	No	Suspected/definite	**2.08**	**1.65**	**1.65**	—	—
Hypotension	9	6595	6420	No	Suspected/definite	**2.67**	**2.06**	**2.06**	—	—
Hypothermia	5	4195	4178	No	Suspected/definite	**2.21**	1.63	**1.62**	1.40	1.36
CT class	7	5209	5192	Diffuse	No visible pathology	**0.45**	**0.47**	—	—	—
					Swelling/shift	**2.62**	**2.23**	—	—	—
					Mass lesion	**2.18**	**1.48**	—	—	—
Cisterns	6	3861	3857	Present	Compressed/absent	**2.45**	**1.83**	**1.68**	**1.64**	**1.63**
Shift	8	4698	4694	No	1–5 mm	**1.36**	**1.31**	1.09	1.10	1.08
					>5 mm	**2.20**	1.38	1.14	1.18	1.21
tSAH	10	7407	7393	No	Yes	**2.64**	**2.01**	**1.90**	—	—
EDH	9	7575	7409	No	Yes	**0.64**	**0.63**	**0.50**	**0.53**	**0.51**
SDH	9	7584	7418	No	Yes	**2.14**	**1.33**	1.17	1.17	1.19
Contusion	8	6656	6639	No	Yes	**1.34**	**1.40**	**1.34**	1.26	1.25
GCS eye score	11	8686	8509	Pain/sound/ spontaneous	None	**2.76**	**1.54**	**1.57**	**1.53**	**1.55**
					Missing/untestable	**1.96**	1.20	1.27	1.23	1.18
GCS verbal score	11	8686	8509	Sounds-orientated	None	**2.62**	**1.51**	**1.53**	**1.50**	**1.51**
					Missing/untestable	**2.60**	**1.42**	**1.44**	**1.33**	**1.33**
GCS motor score	11	8686	8509	Localizes/ obeys	None	**5.30**	—	—	—	—
					Extension	**7.48**	—	—	—	—
					Abnormal flexion	**3.58**	—	—	—	—
					Normal flexion	**1.74**	—	—	—	—
					Missing/untestable	**2.20**	—	—	—	—
Pupil response	9	7282	7126	Both reacting	One reacting	**2.71**	—	—	—	—
					Neither reacting	**7.31**	—	—	—	—
Systolic BP	9	6801	6797	120–150 mm Hg	<120 mm Hg	**1.53**	**1.28**	**1.27**	1.18	1.09
					>150 mm Hg	**1.42**	**1.30**	1.28	**1.33**	**1.33**
Mean arterial BP	9	6647	6643	85–110 mm Hg	<85 mm Hg	**1.30**	1.14	1.14	1.06	1.00
					>110 mm Hg	**1.45**	1.27	1.26	1.29	1.30
Sodium	7	5270	5266	137–142 mmol/L	<137 mmol/L	**1.40**	1.14	1.09	1.07	1.03
					>142 mmol/L	1.14	1.11	1.10	1.05	1.12
Age	11	8509	8509			**2.14**	—	—	—	—

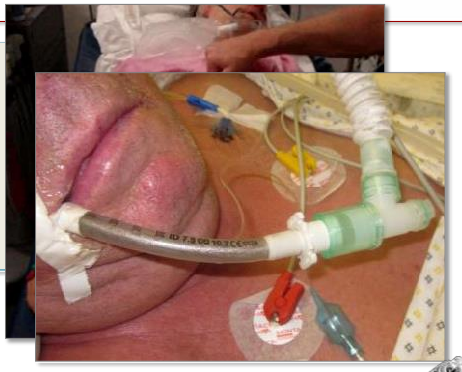
Adapted from Murray et al., J Neurotrauma 2007; 37: 329–337

GCS Score – Practical Considerations

- Consider relevant **limitations** and «***confounders***»
  - **Not only** documentation of **sum score**, it is **important** to **state** the **score** of ***each*** **catergory** (i.e., **E**/**V**/**M**) separately

> Notably, Teasdale and Jennett themselves questioned the validity of the summarized use of the three components of the GCS[5]. The letter unequivocally states that '… the information conveyed by the coma score is less than that contained in the three responses separately. (…) Indeed, in Glasgow, patients under treatment are always described by the three separate responses, and never by the total'[5].

- **Inter-rater reliability**, **validity** and **objectivity**
- Major confounders are **analgesia**, **sedation** and **neuromuscular blockade**
- Other confounding factors are **injury pattern** as well as **therapeutic interventions**



Adapted from Stahel, Br J Surg 2012; 99 Suppl 1:131

GCS Score – Practical Considerations

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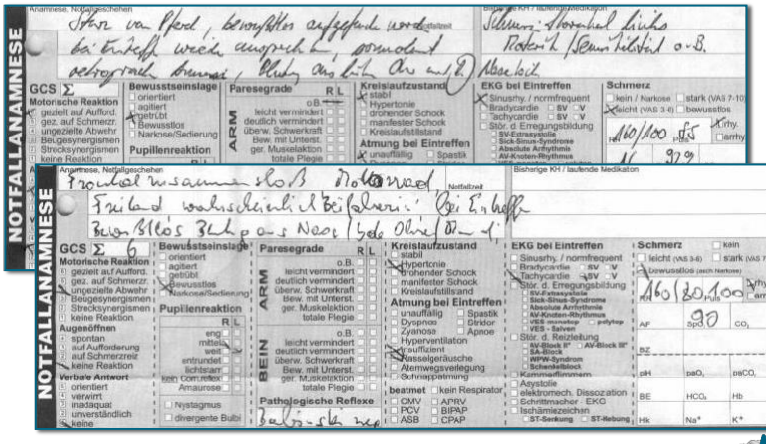
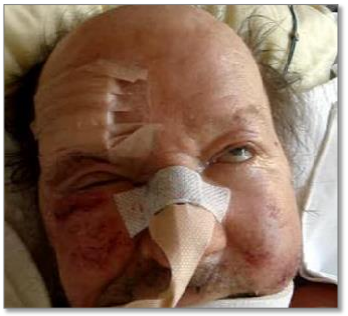


Adapted from Stahel, Br J Surg 2012; 99 Suppl 1:131

GCS Score – Practical Considerations

- Consider relevant **limitations** and «***confounders***»
  - GCS does **not include** relevant clinical indicators that could reflect severity of coma such as **pupil reactivity** and **other brainstem reflexes** (refer to herniation syndromes), changing **breathing patterns**, and **complex** motor responses (of clinical significance)

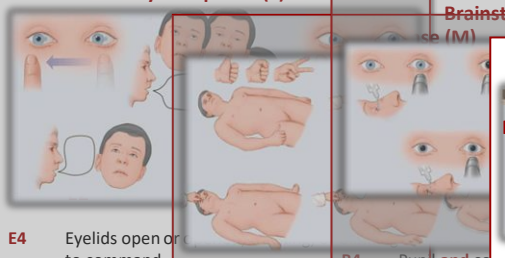


The present study by Hoffmann and colleagues confirms the longstanding notion that the individual motor response component, in conjunction with assessment of pupil reactivity, outweighs the summarized GCS score in predicting outcome in a large cohort of 24 115 patients with TBI from the German Trauma Registry.

Adapted from Stahel, Br J Surg 2012; 99 Suppl 1: 131

Neuroscores – *Full Outline of UnResponsiveness* (*FOUR*) Score

Eye Response (E)



- **E4** Eyelids open or … to command
- **E3** Eyelids open but not tracking
- **E2** Eyelids closed but open to loud voice
- **E1** Eyelids closed but open to pain
- **E0** Eyelids remain closed with pain

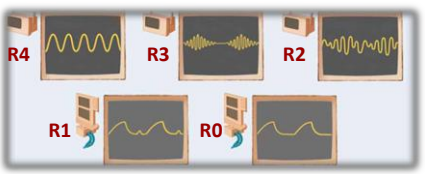
Brainstem Reflexes (B)

- **B4** Pupil **and** co…
- **B3** One pupil w…
- **B2** Pupil ***or*** corn…
- **B1** Pupil ***and*** co…
- **B0** Absent pupil…

Motor Response (M)

- **M4** Obeys commands (e. g., thumbs… peace sign)
- **M3** Localizing to pain
- **M2** Flexion response to pain
- **M1** Extension response to pain
- **M0** No response ~~to pain or generali…~~ **myoclonus status**

Respiration (R)



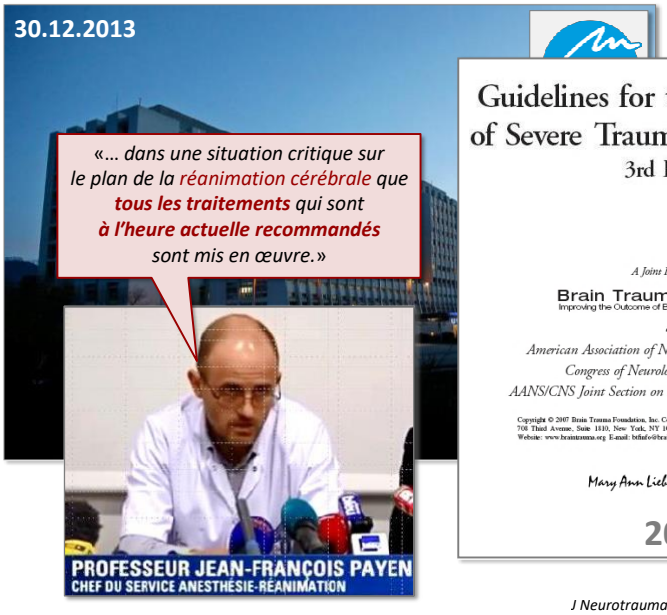
- **R4** Not intubated, regular breathing pattern
- **R3** Not intubated, **Cheyne-Stokes breathing pattern**
- **R2** Not intubated, **irregular** breathing
- **R1** **Intubated**, but **triggering** or breathing above ventilator rate
- **R0** **Apne[a]** or breathing at **ventilator rate**

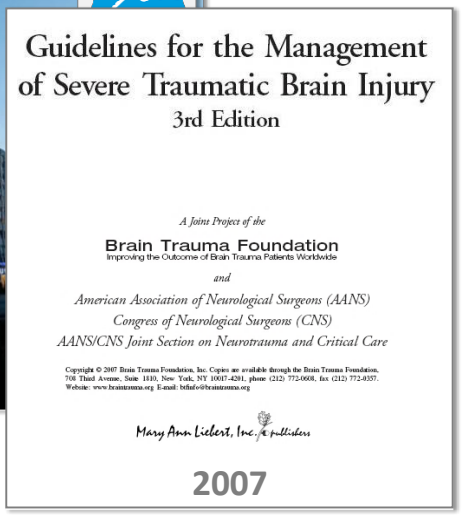
Adapted from Wijdicks et al., Ann Neurol 2005; 58: 585–593

TBI – Media Coverage

Source: https://www.bbc.com/sport/formula1/46734484 (access on 30 June 2019)

TBI – Media Coverage




Guidelines for the Management of Severe Traumatic Brain Injury
3rd Edition

A Joint Project of the

Brain Trauma Foundation
Improving the Outcome of Brain Trauma Patients Worldwide

and

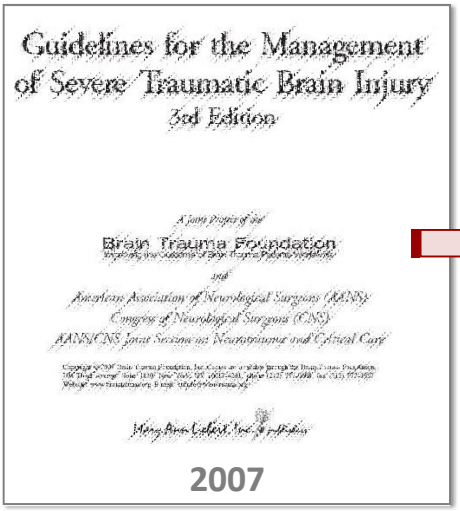
American Association of Neurological Surgeons (AANS)
Congress of Neurological Surgeons (CNS)
AANS/CNS Joint Section on Neurotrauma and Critical Care

Mary Ann Liebert, Inc. / publishers

2007

J Neurotrauma 2007; 24 Suppl 1: S1–S106

TBI – «*Evidence-Based Medicine*»



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2007

J Neurotrauma 2007; 24 Suppl 1: S1–S106

BRAIN TRAUMA FOUNDATION TBI GUIDELINES

Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition

The scope and purpose of this work is 2-fold: to synthesize the available evidence and to translate it into recommendations. This document provides recommendations only when there is evidence to support them. As such, they do not constitute a complete protocol for clinical use. Our intention is that these recommendations be used by others to develop treatment protocols, which necessarily need to incorporate consensus and clinical judgment in areas where current evidence is lacking or insufficient. We think it is important to have evidence-based recommendations to clarify what aspects of practice currently can and cannot be supported by evidence, to encourage use of evidence-based treatments that exist, and to encourage creativity in treatment and research in areas where evidence does not exist. The communities of neurosurgery and neuro-intensive care have been early pioneers and supporters of evidence-based medicine and plan to continue in this endeavor.

Living Guidelines

This Fourth Edition of the Guidelines is transitional. We do not intend to produce a Fifth Edition. Rather, we are moving to a model of continuous monitoring of the literature, rapid updates to the evidence review, and revisions to the recommendations as the evidence warrants. We call this the Living Guidelines model.

2016/2017

Neurosurgery 2017; 80: 6–15
https://www.braintrauma.org/coma/guidelines

TBI – Epidemiology *Update*

Epidemiology of traumatic brain injury in Europe n Europe

Parameter	Place			
	Europe[1]	U.S.[2]	Australia[3]	Asia[4]
Incidence rate[6,7]	235	103	226	344
Prevalence rate[6]	NR	1893	NR	709

Table 5 Comparison with review of Tagliaferri et al. 2006 [38]

	Tagliaferri et al. 2006	This review
Time period of included studies	1980–2003	1990–2014
Number of included studies	23	28 (9[a])
Number of countries	12	16
Average incidence rate per 10^5/year	235	326
Most frequent cause of TBI (number of studies)	RTAs (8)>falls (6)	Falls (14)>RTAs (11)
Sex	Male>female	Male>female
Aver		10, 5

[a] Nin

Nevertheless, changes in epidemiological patterns are found: falls are now the most common cause of TBI, most notably in elderly patients. Improvement of the quality of standardised data collection for TBI is mandatory for reliable monitoring of epidemiological trends and to inform appropriate targeting of prevention campaigns.

- … **falls** are now the *most common cause* of TBI, most notably in ***elderly* patients**

Modifiziert nach Peeters et al., Acta Neurochir 2015; 157: 1683–1696

TBI – A *Complex Disease* Entity

«*Traumatic Brain Injury* – the *Most Complex Injury* to the *Most Complex Organ* of the Body»

Earl F. Ellis, PhD

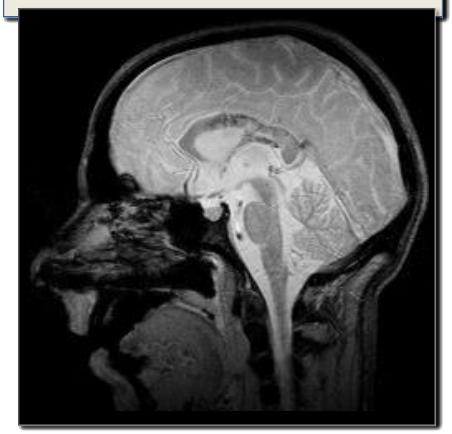
Department of Pharmacology and Toxicology, School of Medicine, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, Virginia, USA

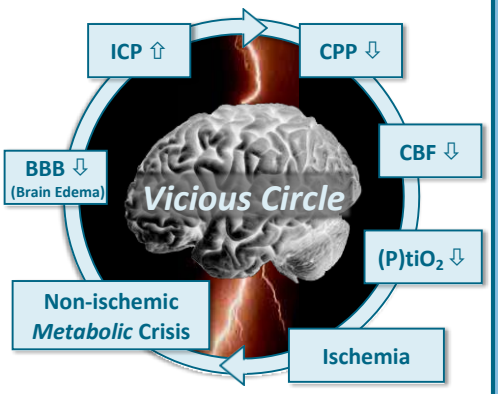
17th Annual Neurotrauma Symposium, October 1999, Miami Beach, Florida, USA

TBI – Heterogeneous Injury & «*Vitious Circle*»

Multiple injury patterns

- ***Brain*** injury | diffuse





TBI – A «*Multisystem*» Disorder

Non-neurologic organ dysfunction in severe traumatic brain injury

- ***Respiratory* failure** 23%
- ***Cardiovascular* failure** 18%
- **Failure of *coagulation system*** 4%

Objective: **To describe the incidence of non-neurologic organ dysfunction and its association with outcome in patients with severe traumatic brain injury admitted to intensive care.**

Patients: **Patients were 209 consecutive patients with severe traumatic brain injury.**

Measurements and Main Results: **Non-neurologic organ dysfunction was measured by the maximum modified multiple organ dysfunction score. Organ system failure was defined as a component score of ≥3 on any day during the patient's intensive care unit stay. One hundred and eighty-five patients (89%) developed dysfunction of at least one non-neurologic organ system. Ninety-six organ system failures were identified in 74 patients (35%). Respiratory failure was the most common non-neurologic organ system failure, occurring in 23% of patients, whereas cardiovascular failure occurred in 18%. Eight patients (4%) had failure of the coagulation system. One patient had renal failure, whereas no patient developed hepatic failure. In a multivariate model, non-neurologic organ dysfunction was independently associated with hospital mortality (odds ratio for hospital mortality, 1.63; 95% confidence interval, 1.34, 1.98 for one maximum modified multiple organ dysfunction score point).**

Table 3. Hospital mortality and neurological outcome by quartile of maximum modified multiple organ dysfunction (mMOD) score

Maximum mMOD Score	0–1	2–3	4–5	6–12
Survivors, *n* (%)	44 (80)	42 (67)	32 (71)	24 (52)
Nonsurvivors, *n* (%)	11 (20)	21 (33)	13 (29)	22 (48)
Favorable, *n* (%)	23 (58)	12 (29)	9 (30)	5 (14)
Nonfavorable, *n* (%)	17 (43)	30 (71)	21 (70)	30 (86)

Table 4. No. of organ system failures and mortality rate

No. of Organ System Failures	Proportion of Patients Not Surviving to Hospital Discharge	No. of Patients
0	0.26	135
1	0.40	55
2	0.47	17
3	1.0	1
4	1.0	1

- **Systemic** (i.e., non-neurologic) **complications** after ***TBI*** are ***common*** and *independent* ***contributors*** to **morbidity** and **mortality**

Adapted from Zygun et al., Crit Care Med 2005; 33: 654–660

TBI – Paroxysmal Sympathetic Hyperactivity

A Review of Paroxysmal Sympathetic Hyperactivity after Acquired Brain Injury

TABLE 1: Features of Paroxysmal Sympathetic Hyperactivity and Mixed Autonomic Hyperactivity

Category	Clinical Features	Paroxysmal Sympathetic Hyperactivity	Mixed Autonomic Hyperactivity
Sympathetic	Increases in HR, RR, BP, temperature, sweating, and pupillary dilation	Yes	Yes
Parasympathetic	Decreases in HR, RR, BP, temperature, and pupillary contraction	No	Yes
Motor features	Decerebrate posturing, decorticate posturing, spasticity, hypertonia and/or dystonia, teeth-grinding, agitation	Yes	Variable
Other	Hiccups, lacrimation, sighing, yawning	No	Yes

TABLE 3: Sample Characteristics of Paroxysmal Sympathetic Hyperactivity Cases

Characteristic	Value
Age, mean yr ± SD	24.2 ± 11.8
Sex, No. (%)	
Male	112 (78)
Female	31 (22)
GCS severe injury [<9], No. (%)	199 (100)
GOS, No. (%)	
1: Death	22 (18)
2: PVS	37 (30)
3: Severe disability	56 (45)
4: Moderate disability	7 (5)
5: Good recovery	3 (2)
Clinical setting, No. (%)	
ICU	139 (45)
Rehabilitation	119 (39)
Combined	48 (16)

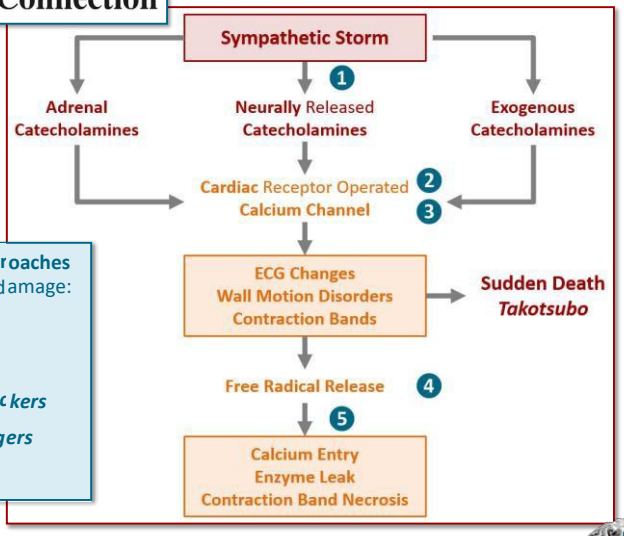
Severe excessive autonomic overactivity occurs in a subgroup of people surviving acquired brain injury, the majority of whom show paroxysmal sympathetic and motor overactivity. Delayed recognition of paroxysmal sympathetic hyperactivity (PSH) after brain injury may increase morbidity and long-term disability.

Adapted from Perkes et al., Ann Neurol 2010; 68: 126–135

TBI – Paroxysmal Sympathetic Hyperactivity

Contemporary Reviews in Cardiovascular Medicine

The Brain–Heart Connection



Possible therapeutic approaches to prevent neurocardiac damage:

1. *GABA Agonists*
2. *Beta-Blockers*
3. *Calcium Channel Blockers*
4. *Free Radical Scavengers*
5. *Anti-Oxidants*

Adapted from Samuels, Circulation 2007; 116: 77–84

TBI – «*Sometimes Size Matters …*»

High-volume trauma centers have better outcomes treating traumatic brain injury

Highest-volume centers demonstrated a
- **9% lower mortality risk**

Lower-volume hospitals discharged
- **Significantly more** patients to **skilled nursing facilities**
- **Fewer** patients to **home** or **rehabilitation**

Survival and discharge status from severe traumatic brain injury (TBI) patients design … onship betw … r for years 2 … Modificatio … Score (ICISS … was de … random effects model controlling for sex, … thnicity, and insurance statu … inpatient mortality and functional recove … ined as discharge to home or rehabilitation versus transfer to … nursing facilities. Hospitals were categorized in … uarterly TBI volume quintiles, using the top quintile (highest-volum … er) as …

After controlling for severity, demographics, and insurance status, highest-volume centers demonstrated a 9% lower mortality risk ($p < 0.001$). Lower-volume hospitals discharged a significantly larger proportion of TBI patients to skilled nursing facilities and fewer patients to home or rehabilitation facilities ($p < 0.01$).

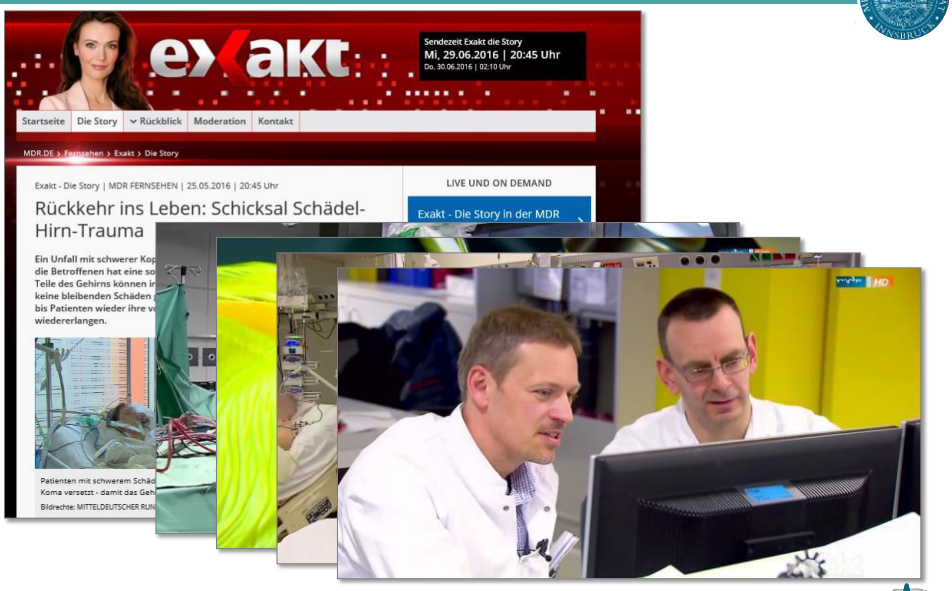
hospitals discharged a significantly larger proportion of TBI patients to skilled nursing facilities and fewer patients to home or rehabilitation facilities ($p < 0.01$).

High volume (>40 patients per quarter) is associated with improved severe TBI patient survival and, probably, improved quality of life. Efforts to identify best practices and implement educational interventions to improve compliance with best-practice standards will benefit patients with severe traumatic brain injury.

- High volume (> **40 patients per *quater***) is associated with **improved severe TBI survival** and, probably, **improved QoL**

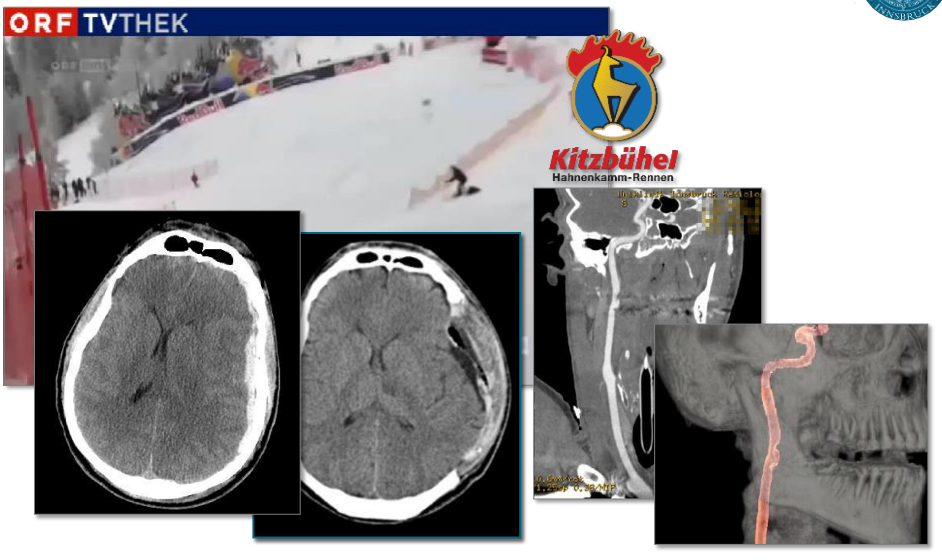
Adapted from Tepas et al., J Trauma Acute Care Surg 2013; 74: 143–148

«*Level1*» Neurotrauma Management – Media Coverage



mdr Exakt – Die Story «Rückkehr ins Leben»; Reportage vom 25.05.2016
http://www.mdr.de/mediathek/fernsehen/a-z/sendung661700_ipgctx-false_zc-ba8902b5_zs-73445a6d.html

«*Level1*» Neurotrauma Management – Media Coverage



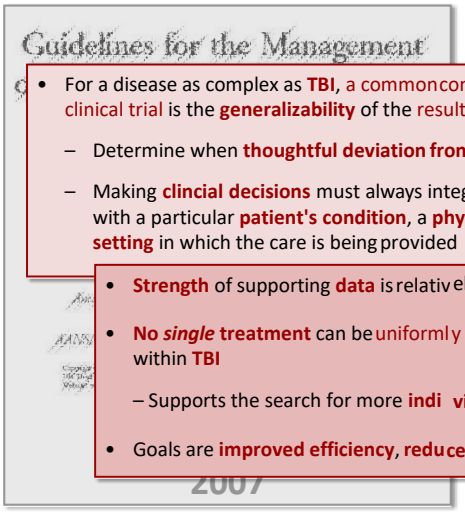
Approved by: Departments of Radiology & Neuroradiology, General & University Hospital, Medical University of Innsbruck

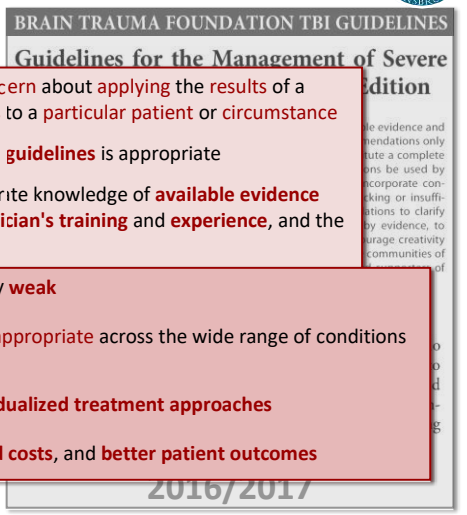
«*Level1*» Neurotrauma Management – Media Coverage

A young woman who suffered a brain injury in an accident retraces the steps of her dramatic recovery and meets other young people adjusting to life after serious brain injuries.

BBC three Broadcast 20.07.2015
https://www.bbc.co.uk/programmes/b063h17m

TBI – «*Evidence-Based Medicine*»


Guidelines for the Management


BRAIN TRAUMA FOUNDATION TBI GUIDELINES
Guidelines for the Management of Severe

- For a disease as complex as **TBI**, a commonconcern about applying the results of a clinical trial is the **generalizability** of the results to a particular patient or circumstance
  - Determine when **thoughtful deviation from guidelines** is appropriate
  - Making **clincial decisions** must always integrıte knowledge of **available evidence** with a particular **patient's condition**, a **physician's training** and **experience**, and the **setting** in which the care is being provided

- **Strength** of supporting **data** is relativ ely **weak**
- **No *single* treatment** can be uniformly appropriate across the wide range of conditions within **TBI**
  – Supports the search for more **indi vidualized treatment approaches**
- Goals are **improved efficiency, reduced costs**, and **better patient outcomes**

J Neurotrauma 2007; 24 Suppl 1: S1–S106

Neurosurgery 2017; 80: 6–15
https://www.braintrauma.org/coma/guidelines

Managment of TBI – «*Who Cares About Guidelines?*»

Suboptimal compliance with evidence-based guidelines in patients with traumatic brain injuries

POC No.	Process of Care	Definition	Eligibility (no. eligible)	No. Compliant (%)
1	Endotracheal intubation	endotracheal intubation at admission or in the field	all patients (2056)	1890 (92)
2	Resuscitation	transfusion of packed RBCs in 1st 24 hrs if hypotensive & bleeding	SBP on admission ≤90 mm Hg & hematocrit on admission <30 (64)	48 (75)
3	Correction of coagulopathy	transfusion of fresh-frozen plasma in 1st 24 hrs if coagulopathic	admission INR >1.5 (243)	164 (67)
4	ICP monitoring	use of ICP monitor or ventriculostomy to measure ICP	total GCS score ≤8 at 24 hrs & age ≤65 yrs (1569)	818 (52)
5	ICP-directed therapy	maintaining CPP ≥50 cm H_2O on Day 2	all patients w/ ICP monitor or ventriculostomy on Day 2 (978)	742 (76)
6	Physical therapy & rehabilitation after discharge	discharge to rehabilitation w/ persistent deficits at discharge & able to participate in therapy	all patients who survived to discharge & w/ GCS score of 12 or 13 at discharge (111)	71 (64)

Results. The overall compliance rate was 73%, and there was wide variation among centers. Only 3 centers achieve… than av… associa…

- **Despite widespread dissemination** of **EBM guidelines**, patients with ***severe TBI*** continue to receive ***inconsitent care***
- **Barriers** to adoption of EBM need to be ***identified*** and ***mitigated*** to improve outcomes

Adapted from Shafi et al., J Neurosurg 2014; 120: 773–777

TBI – *Brain Trauma Foundation* ***TBI Guidelines, 4th Edition 2016***

Updated Treatment Recommendations[a,b]

Topic	Recommendations
Decompressive craniectomy	Level IIA • Bifrontal … in sever… …asured by the GOS-E score at 6 mo post-injury …s), and with ICP elevation to values >20 mm Hg for more than 15 min within a 1-h period that are refractory to first-tier therapies. However, this procedure …educe ICP and to minimize days in the ICU. …al DC (not less than 12 x 15 cm or 15 cm diameter) is recommended over …l DC for reduced mortality and improved neurologic outcomes in patients *The committee is aware that the results of the RESCUEicp trial[2] were released soon after the completion of these Guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these Guidelines. We intend to update these recommendations if needed. Updates will be available at https://braintrauma.org/coma/guidelines.
Prophylactic hypothermia	Level IIB • Early (w… improv… …ctic hypothermia is not recommended to
Hyperosmolar therapy	Recommendations from the prior (Third) Edition not supported by evidence meeting current standards. Mannitol i… …l hypotension (systolic blood p… Restrict m… …ation or progressive neurologic deterioration not attributable to extracranial causes.
Cerebrospinal fluid drainage	Level III • An EVD … burden… …inage of CSF may be considered to lower ICP • Use of CSF drainage to lower ICP in patients with an initial GCS <6 during the first 12 h after injury may be considered.

- ***Decompressive craniectomy***: **IIA**
- … **results** of the ***RESCUEicp trial*** **released soon *after*** the completion of these Guidelines
- ***Prophylactic hypothermia***: **IIB**
- ***Hyperosmolar therapy***: **Not supported** by evidence
- ***CSF drainage***: **III**

https://www.braintrauma.org/coma/guidelines

TBI – *Brain Trauma Foundation* ***TBI Guidelines, 4th Edition 2016***

Updated Treatment Recommendations[a,b]

Topic	Recommendations
Ventilation therapies	Level IIB
	• Prolonge… m Hg is not recommended.
	Recomme… …y evidence meeting current standards.
	Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP.
	Hyperventilation should be avoided during the first 24 h after injury when CBF often is reduced critically.
	If hyperventilation is used, SjO_2 or $BtpO_2$ measurements are recommended to monitor oxygen delivery.
Anesthetics, analgesics, and sedatives	Level IIB
	• Administ… …sured by EEG as prophylaxis against the develop…
	• High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.
	• Althoug… …t recommended for improvement in mortality or 6-month… …can produce significant morbidity.[3]
Steroids	Level I
	• The use of steroids is not recommended for improving outcome or reducing ICP. In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated.
Nutrition	Level IIA
	• **Feeding patients to attain basal caloric replacement at least by the fifth day and at most by the seventh day post-injury is recommended to decrease mortality.**
	Level IIB
	• **Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.**

- ***Ventilation therapies***: **IIB**
- ***Anesthetics***, ***analgesics***, and ***sedatives***: **IIB**
- ***Steroids***: **I**
- ***Nutrition***: **IIA** & **IIB**

https://www.braintrauma.org/coma/guidelines

TBI – *Brain Trauma Foundation* ***TBI Guidelines, 4th Edition 2016***

Updated Treatment Recommendations[a,b]

Topic	Recommendations
Infection prophylaxis	Level IIA
	• Early trac… …ation days when the overall benefit is thought to outweig… However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.
	• **The use of PI oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.**
	Level III
	• **Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during external ventricular drainage.**
Deep vein thrombosis Prophylaxis	Level III
	• LMWH o… …bination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.
	• In addition to compression stockings, pharmacologic prophylaxis may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage.
	• There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis.
Seizure prophylaxis	Level IIA
	• Prophyla… …d for preventing late PTS.
	• Phenytoi… …S (within 7 d of injury), when the overall benefit is thought to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes.
	• **At the present time there is insufficient evidence to recommend levetiracetam compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.**

- ***Infection prophylaxis***: **IIA** & **III**
- ***DVT prophylaxis***: **III**
- ***Seizure prophylaxis***: **IIA**

https://www.braintrauma.org/coma/guidelines

TBI – *Brain Trauma Foundation* ***TBI Guidelines, 4th Edition 2016***

Updated Monitoring Recommendations[a,b]

Topic	Recommendations
Updated Recommendations: Thresholds[a,b]	
Topic	**Recommendations**
Blood pressure thresholds	Level III • Maintainin… …or at ≥110 mm Hg or above for patients 15 to 49 or … …lity and improve outcomes.
Intracranial pressure thresholds	Level IIB • Treating I… …ove this level are associated with increased mortality Level III • A combination of ICP values and clinical and brain CT findings may be used to make management decisions. *The committee is aware that the results of the RESCUEicp trial[2] were released after the completion of these Guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these Guidelines. We intend to update these recommendations if needed. Updates will be available at https://braintrauma.org/coma/guidelines.
Cerebral perfusion pressure thresholds	Level IIB • The recon… …e outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend upon the autoregulatory status of the patient. Level III • Avoiding aggressive attempts to maintain CPP >70 mm Hg with fluids and pressors may be considered because of the risk of adult respiratory failure.
Advanced cerebral monitoring thresholds	Level III • Jugular ve… …in order to reduce mortality and improve outcomes

- ***BP thresholds***: III
- ***ICP thresholds***: IIB & III
- ***CPP thresholds***: IIB & III
- ***Advanced cerebral monitoring thresholds***: III

https://www.braintrauma.org/coma/guidelines

ICP Monitoring in TBI – «*Damned If I Do Ya, Damned If I Don't*»

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

CONCLUSIONS

For patients with severe traumatic brain injury, care focused on maintaining monitored intracranial pressure at 20 mm Hg or less was not shown to be superior to care based on imaging and clinical examination.

Adapted from Chesnut et al., N Engl J Med 2012; 367: 2471–2481

Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring

Conclusions. In patients with severe TBI treated for intracranial hypertension, the use of an ICP monitor is associated with significantly lower mortality when compared with patients treated without an ICP monitor. Based on these findings, the authors conclude that ICP-directed therapy in patients with severe TBI should be guided by ICP monitoring.

Adapted fromFarahvar et al., J Neurosurg 2012; 117: 729–734

BTF TBI Guidelines, 4th Edition 2016 – «Facts and Myths»

A Trial of Intracranial-Pressure Monitoring

- **Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.**

Recommendations from the prior (Third) Edition not supported by evidence meeting current standards.

ICP should be monitored in all salvageable patients with a TBI (GCS 3-8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns.

ICP monitoring is indicated in patients with severe TBI with a normal CT scan if ≥2 of the following features are noted at admission: age >40 years, unilateral or bilateral motor posturing, or SBP <90 mm Hg.

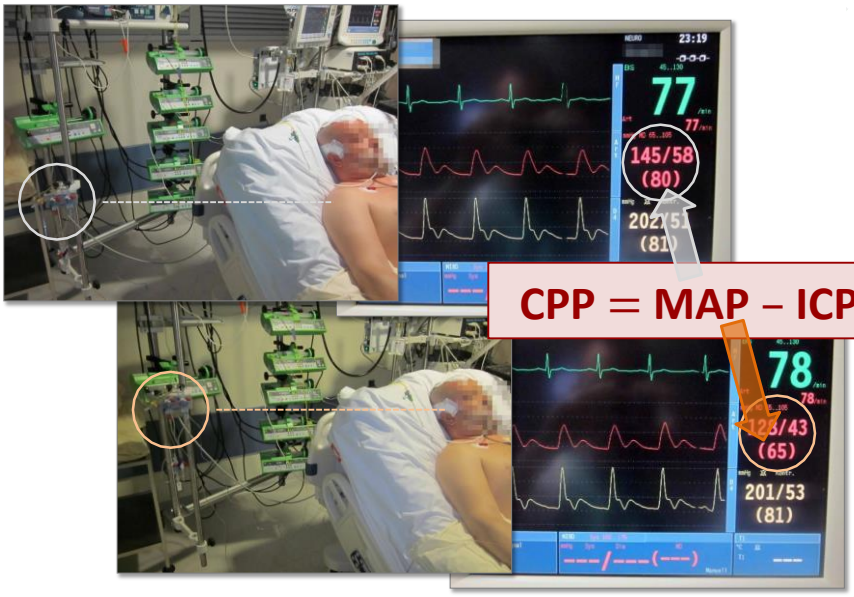
- **Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decrease 2-wk mortality.**

Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring

- **Treating ICP >22 mm Hg is recommended because values above this level are associated with increased mortality.**
- A combination of ICP values and clinical and brain CT findings may be used to make management decisions.
- **The recommended target CPP value for survival and favorable outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend upon the autoregulatory status of the patient.**
- Avoiding aggressive attempts to maintain CPP >70 mm Hg with fluids and pressors may be considered because of the risk of adult respiratory failure.

https://www.braintrauma.org/coma/guidelines

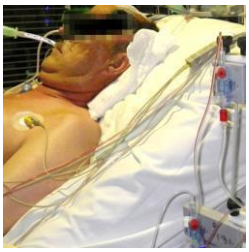
Calculation of CPP– *Where* to Measure Mean Arterial Blood Pressure?



© Neurological Intensive Care Unit, Department of Neurology, General & University Hospital, Medical University of Innsbruck

Calculation of CPP– *Where* to Measure Mean Arterial Blood Pressure?

Calculation of cerebral perfusion pressure in the management of traumatic brain injury: joint position statement by the councils of the Neuroanaesthesia and Critical Care Society of Great Britain and Ireland (NACCS) and the Society of British Neurological Surgeons (SBNS)



Whilst not wishing to dictate local clinical practice, based on the available evidence, the Councils of NACCS and SBNS would recommend that when calculating CPP in TBI the MAP used in the equation CPP=MAP–ICP should be the mean cerebral arterial pressure estimated of the middle cranial fossa, which can b positioning (levelling) the arterial transdu the ear.

They also recommend that the arterial t tioned to remain levelled with the tragus f body elevation or position.

Councils do not endorse positioning (levelling) the arterial transducer at heart level (phlebostatic axis) for CPP-based treatment decisions because there is a requirement for subsequent cerebral MAP to be calculated, which is dependent on the relationship:

$$\text{MAP brain} = \text{MAP heart} - (\text{water column between heart and brain} \times C)$$

where C is a coefficient, always lower than 1, dependent on conditions of both the arterial and the venous elements of the cerebral circulation, which is not reliably predictable and is variable between individuals.

Adapted from Thomas et al., Br J Anaesth 2015; 115: 487–488

Calculation of CPP– *Where* to Measure Mean Arterial Blood Pressure?

A Comparison of Clinical and Research Practices in Measuring Cerebral Perfusion Pressure: A Literature Review and Practitioner Survey

BACKGROUND: Our objective was to determine whether there is variability in the foundational literature and across centers in how mean arterial blood pressure is measured to calculate cerebral perfusion pressure.
METHODS: We reviewed foundational literature and sent an e-mail su Neurocritical Care Society.
RESULTS: Of 32 articles reporting cerebral perfusion pressure data, mean arterial blood pressure was identified in 16: 10 heart and 6 m vey response rate was 14.3%. Responses from 31 of 34 (91%) Unite Subspecialties fellowship-accredited Neurointensive Care Units indica was most often the heart (74%), followed by the midbrain (16%). C received from 10%.
CONCLUSIONS: There is substantive heterogeneity in both resear practice in how mean arterial blood pressure is measured to deter pressure.

In 1959, Lassen[1] defined cerebral perfusion pressure (CPP) based on "arterial blood pressure measured at the level of the head," i.e., the midbrain, using the tragus as an external landmark.

Table 1. Method for Measuring Cerebral Perfusion Pressure (CPP) in Published Literature

Reference	Methods from article or author contact	MAP reference for CPP measurement
Andrews et al., 2002[18]	Author contact	Right atrium
Bouma et al., 1992[17]	Author contact	Tragus
Chambers et al., 2000[19]	Author contact	Right atrium
Chambers et al., 2001[20]	Author contact	Right atrium
Changaris et al., 1987[21]	Author contact	Right atrium
Clifton et al., 2002[22]	Author contact	Right atrium
Contant et al., 2001[12]	Published methods	Tragus
Cremer et al., 2005[23]	Author contact	Right atrium
Howells et al., 2005[24]	Author contact	Right atrium
Robertson et al., 1999[13]	Published methods	Tragus
Schreiber et al., 2002[25]	Author contact	Right atrium
Steiner et al., 2002[14]	Author contact	Tragus
Stiefel et al., 2005[26]	Author contact	Right atrium
Stocchetti et al., 2004[15]	Published methods	Tragus
Struchen et al., 2001[16]	Published methods	Tragus
Tolias et al., 2004[27]	Author contact	Right atrium

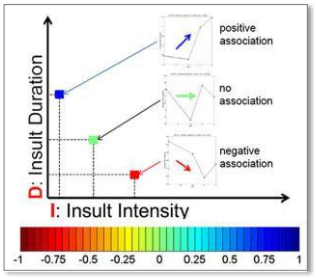
The authors of 16 articles could not be contacted or could not recall how they established methodology.
MAP = mean arterial blood pressure; CPP = cerebral perfusion pressure

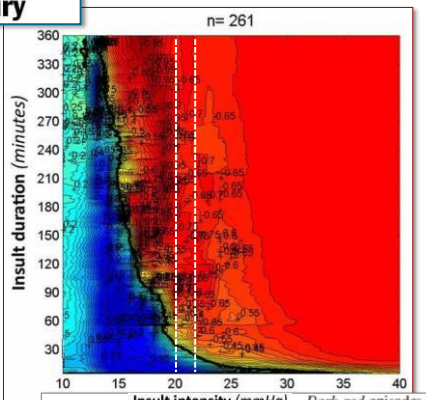
Adapted from Kosty et al., Anesth Analg 2013; 177: 694–698

Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury

Conclusion

An image can be worth a thousand words: the visualizations presented here summarize the complexity and dynamic aspect of secondary insults of raised ICP in TBI, showing that not all TBI patients are equal in their ability to cope with such injury.



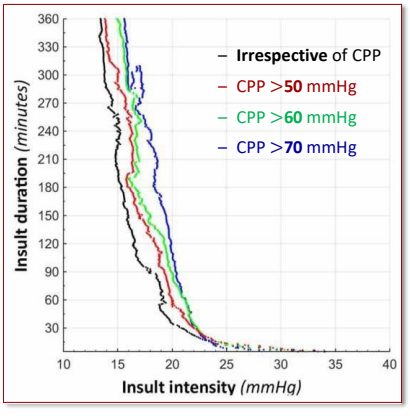


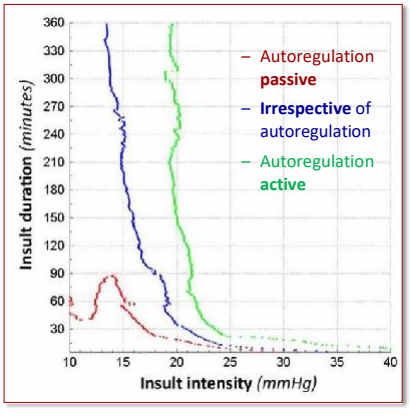
Dark red episodes mean that such ICP insults, on average, are associated with worse outcome (lower GOS categories); *dark blue* episodes mean that such ICP insults, on average, are associated with better outcome (higher GOS categories). The contour of zero correlation is highlighted in *black*, and is called the transition curve

Adapted from Güiza et al., Intensive Care Med 2015; 41: 1067–1076

Traumatic Intracranial Hypertension – «*Definition*» of the Problem

Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury





Adapted from Güiza et al., Intensive Care Med 2015; 41: 1067–1076

tirolkliniken R. Beer 2019
NeuroCritical Care
Medical University of Innsbruck

Note on Neurophysiology – Human Cerebrovascular Autoregulation

Integrative regulation of human brain blood flow

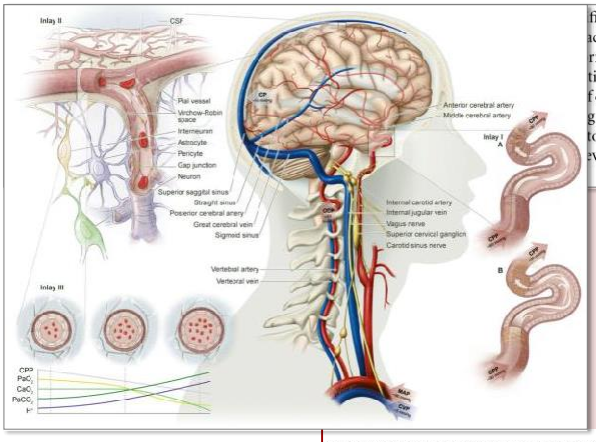


Figure 3. Stylized representation of the classical (left) and contemporary (right) relationships between mean arterial pressure and cerebral blood flow – i.e., autoregulation
Left panel is a stylized representation of the classical view of the relationships between mean arterial pressure (MAP) and cerebral blood flow (CBF), i.e. autoregulation, put forward by Lassen *et al.* (1959) based on the between-subject analysis of patients during various pharmacological interventions or pathologies. Right panel is a schematic diagram based on contemporary data indicating a small plateau region (Tan, 2012) and cerebral autoregulation hysteresis.

Adapted from Willie et al., J Physiol 2014; 592.2: 841–859

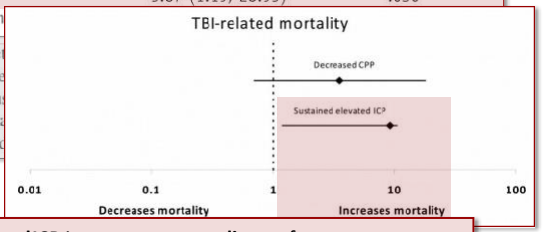
ICP versus CPP – Impact on Outcome

Intracranial pressure versus cerebral perfusion pressure as a marker of outcomes in severe head injury: a prospective evaluation

Independent predictors of all in-hospital mortality in patients with ICP monitoring

Step	Variable	AOR (95% CI)	Adjusted *P* value
1	ISS ≥ 25	24.56 (21.74, 27.75)	<.001
2	Intraparenchymal hemorrhage on CT	9.58 (1.91, 48.06)	.006
3	Age > 55 y	12.84 (1.52, 18.37)	.019
4	Sustained elevated ICP	5.87 (1.19, 28.95)	.030
5	Fixed dilated pupils on adm		

RESULTS: A total of 216 patients met
those, 46.8% (n = 101) were subjecte
increased all in-hospital mortality (adju
P = .031) and death because of cerebr
9.25 [1.19, 10.48], *P* = .035). Decreased



- A **single episode** of **sustained increasedICP** is an **accurate predictor** of ***poor outcomes***
- **Decreased CPP** did ***not*** **affect survival**

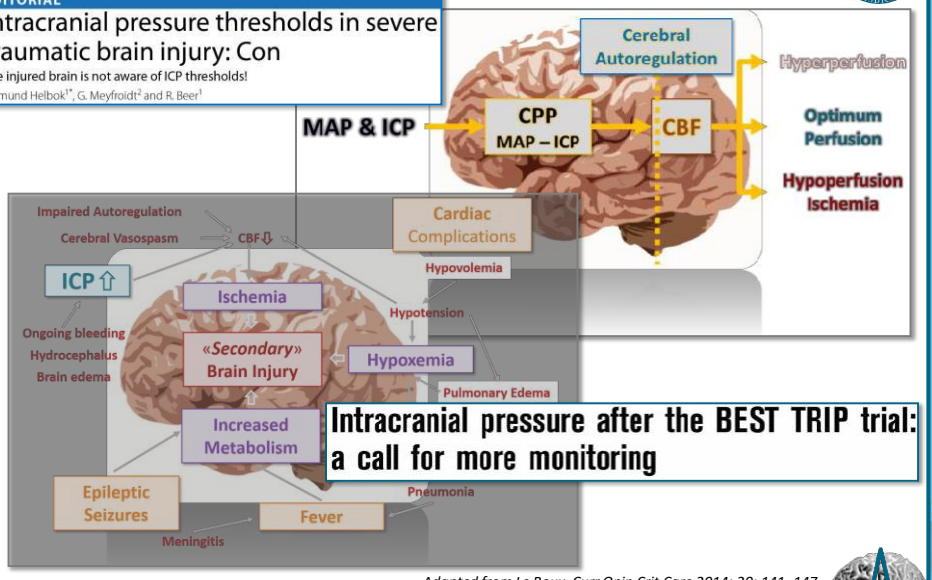
Adapted from Karamanos et al., Am J Surg 2014; 208: 363–371

EDITORIAL

Intracranial pressure thresholds in severe traumatic brain injury: Con

The injured brain is not aware of ICP thresholds!

Raimund Helbok[1*], G. Meyfroidt[2] and R. Beer[1]



Intracranial pressure after the BEST TRIP trial: a call for more monitoring

Adapted from Le Roux, Curr Opin Crit Care 2014; 20: 141–147

Brain multimodality monitoring: an update

Brain multimodality monitoring for the detection and the management of secondary brain injury

Monitoring modality	ICP	$PbtO_2$	Cerebral microdialysis
Secondary brain insult detected	↑ ICP (>20–25 mm Hg); intracranial hypertension	↓ $PbtO_2$ (<15–20 mm Hg); cerebral hypoxia/ischemia	↑ LPR >40; brain energy failure
Clinical utility	Detection of elevated ICP; treatment of intracranial hypertension; CSF drainage (intraventricular ICP); management of CPP	Detection of secondary cerebral hypoxia/ischemia; management of CPP targeted to $PbtO_2$	Monitoring of brain energy supply and detection of energetic dysfunction; Titration of insulin therapy
Relationship with outcome	↑ ICP >20 mmHg is associated with worse outcome [5,6▪▪]	↓ $PbtO_2$ (<15 mm Hg) is associated with worse outcome [20,21]	↑ LPR >40 is associated with worse outcome [42▪▪]
Feasibility, ICU implementation	+++	+−	+
Cost	*	**	***

Adapted from Oddo et al., Curr Opin Crit Care 2012; 18: 111–118

Brain multimodality monitoring: an update

Brain multimodality monitoring for the detection and the management of secondary brain injury

Monitoring modality	ICP	$PbtO_2$	Cerebral microdialysis
	• Jugular bulb monitoring of $AVDO_2$, as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3 and 6 mo post-injury.		
	• Jugular venous saturation of <50% may be a threshold to avoid in order to reduce mortality and improve outcomes.		
	(intraventricular ICP); management of CPP		therapy
Relationship with outcome	↑ ICP >20 mmHg is associated with worse outcome [5,6▪▪]	↓ $PbtO_2$ (<15 mm Hg) is associated with worse outcome [20,21]	↑ LPR >40 is associated with worse outcome [42▪▪]
Feasibility, ICU implementation	+++	+−	+
Cost	*	**	***

https://www.braintrauma.org/coma/guidelines

- Essential (Neuro-)Monitoring Tool: ***Clinical Neurological Examination***

© Neurological Intensive Care Unit, Department of Neurology, General & University Hospital, Medical University of Innsbruck

$PbtO_2$ Monitoring in TBI – Impact on Outcome

Brain tissue oxygen and outcome after severe traumatic brain injury: A systematic review*

13 studies met the initial inclusion criteria and **3** were **included** in the **final outcome analysis**:

- More than 10 patients described
- **Brain hypoxia** defined as ***$PbtO_2$ <10 mmHg*** for ***>15 or 30 min***
- **6-month outcome** data

Table 4. Published safety results of the Licox System (Integra Neurosciences, Plainsboro, NJ) used to measure brain oxygen

Study (Reference)	Number of Patients	Safety Parameters	Adverse Effects
van den Brink et al 2000 (43)	101[a]	Hematoma; infection	None
Dings et al 1998 (33)	101	Hematoma; infection	Two iatrogenic hematomas
van den Brink et al 1998 (20)	82[a]	Hemorrhage; infection	None
van Santbrink et al 1996 (76)	22	Hematoma; infection	None
Meixensberger et al 1998 (39)	22	Bleeding; infection	None
Sarrafzadeh et al 1998 (50)	17	Hematoma; infection	None
Kiening et al 1996 (34)	15	Intracranial bleeding; infection	None
Bruzzone et al 1998 (45)	7	Intracranial bleeding; infection	None
Sarrafzadeh et al 1997 (50)	7	Infection; bleeding	None

Table 1. Study and patient characteristics for the studies selected for analysis

Study (First Author), Location	Number of Patients (Evaluable)	Gender/Age	Duration of Bto_2 Monitoring	Definition of Brain Hypoxia	No. Patients with Brain Hypoxia	Duration of Follow-Up
van den Brink et al 2000 (43), Rotterdam	101 (99)	83M/18F 34 ± 16 years	Average 86 hrs	Bto_2 <10 mm Hg >30 min	43	6 mo
Bardt et al 1998 (32), Berlin	35	28M/7F 33.2 ± 11.3 years	Average 119 hrs	Bto_2 <10 mm Hg >30 min	23	6 mo
Kiening et al 1997 (44), Berlin	23 (16)	19M/4F 26.3 years (15–66 years)	7 days	Bto_2 <10 mm Hg >15 min	5	6 mo

Adapted from Maloney-Wilensky et al., Crit Care Med 2009; 37: 2057–2063

$PbtO_2$ Monitoring in TBI – Impact on Outcome

Brain tissue oxygen and outcome after severe traumatic brain injury: A systematic review*

• **Outcome**

Table 2. The association between brain oxygen levels (i.e., brain hypoxia [<10 mm Hg]) and patient outcome at 6 months

Study (First Author), Location	Number of Patients (Evaluable)	Brain Hypoxia (n = 71)		No Brain Hypoxia (n = 79)		Odds Ratio (95% CI)
		Unfavorable Outcome (No. Patients)	Favorable Outcome (No. Patients)	Unfavorable Outcome (No. Patients)	Favorable Outcome (No. Patients)	
van den Brink et al 2000 (43), Rotterdam	101 (99)	29	14	24	32	4.0 (1.9–8.2)
Bardt et al 1998 (32), Berlin	35	18	5	3	9	
Kiening et al 1997 (44), Berlin	23 (16)	5	0	7	4	

Table 3. The association between brain oxygen levels (i.e., brain hypoxia [<10 mm Hg]) and mortality at 6 months

Study (First Author), Location	Number of Patients (Evaluable)	Brain Hypoxia (n = 71)		No Brain Hypoxia (n = 79)		Odds Ratio (95% CI)
		Death (No. Patients)	Survivor (No. Patients)	Death (No. Patients)	Survivor (No. Patients)	
van den Brink et al 2000 (43), Rotterdam	101 (99)	24	19	14	42	4.6 (2.2–9.6)
Bardt et al 1998 (32), Berlin	35	13	10	1	11	
Kiening et al 1997 (44), Berlin	23 (16)	2	3	2	9	

• **Mortality**

Adapted from Maloney-Wilensky et al., Crit Care Med 2009; 37: 2057–2063

tirolkliniken R. Beer 2019
NeuroCritical Care
Medical University of Innsbruck

$PbtO_2$ Monitoring in TBI – *Additional* Benefit Beyond ICP/CPP-Guided Therapy

Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring

Monitored physiological variables among 53 patients who underwent ICP/CPP–based therapy or combined ICP/CCP and brain tissue PO_2–based therapy

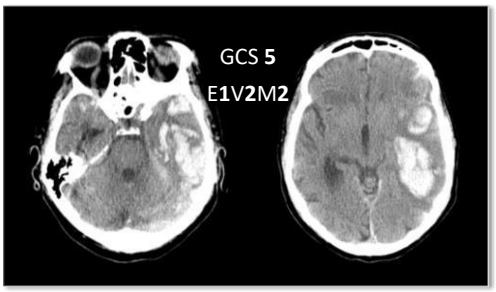
Monitored Variable	Group A	Group B	p Value
ICP monitor (days per patient)	3.73 ± 3.89	5.76 ± 5.08	0.09
mean daily ICP (mm Hg)	15.22 ± 4.21	17.00 ± 7.36	0.34
mean max daily ICP (mm Hg)	21.52 ± 6.9	25.5 ± 9.5	0.16
no. of ICP episodes >20 mm Hg	5.30 ± 7.65	14.05 ± 22.85	0.43
mean daily CPP (mm Hg)	72.93 ± 8.76	72.90 ± 6.19	0.44
mean min daily CPP (mm Hg)	56.3 ± 9.6	57.7 ± 7.1	0.63
no. of CPP episodes <60 mm Hg	3.82 ± 4.97	8.00 ± 13.18	0.46

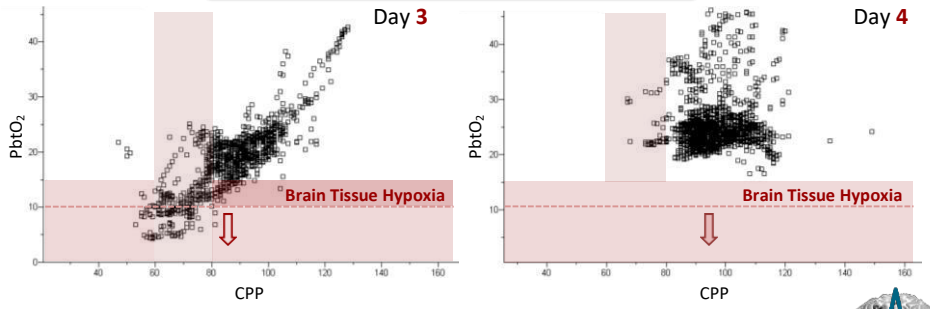
- ***$PbtO_2$ <10 mmHg*** (!) in **Group B**
  - **29%** of episodes when **ICP < 25 mmHg**
  - **27%** of episodes when **CPP > 60 mmHg**
- **App. 30%** of episodes with ***ischemic $PbtO_2$*** (***< 10 mmHg***) ***could not*** be explained by the **ICP/CPP** pathophysiological **concept**
- **Mortality rate**
  - **ICP/CPP** management **44%**
  - Also ***$PbtO_2$*** monitoring ***25%***

The mean daily ICP and CPP levels were similar in each group. The mortality rate in patients treated using conventional ICP and CPP management was 44%. Patients who also underwent brain tissue PO_2 monitoring had a significantly reduced mortality rate of 25% ($p < 0.05$).

Adapted from Stiefel et al., J Neurosurg 2005; 103: 805–811

$PbtO_2$ Monitoring in TBI – *Additional* Benefit Beyond ICP/CPP-Guided Therapy

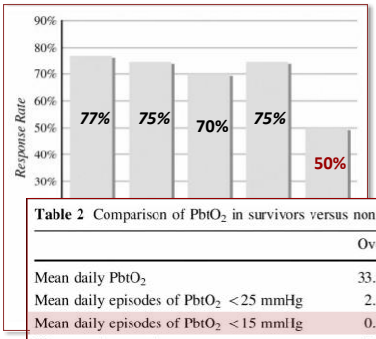




Credits: Dr. M. Kofler, Neurological Intensive Care Unit, Department of Neurology, Medical University of Innsbruck

$PbtO_2$ Monitoring in TBI – Therapeutic Considerations

Medical Management of Compromised Brain Oxygen in Patients with Severe Traumatic Brain Injury



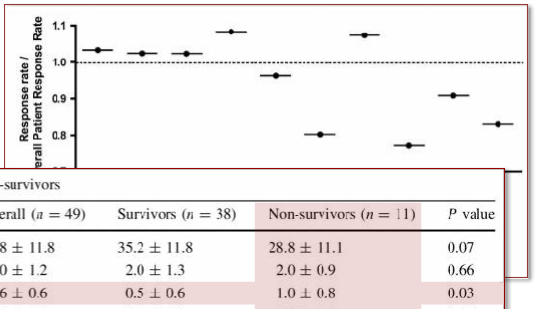


Table 2 Comparison of $PbtO_2$ in survivors versus non-survivors

	Overall ($n = 49$)	Survivors ($n = 38$)	Non-survivors ($n = 11$)	P value
Mean daily $PbtO_2$	33.8 ± 11.8	35.2 ± 11.8	28.8 ± 11.1	0.07
Mean daily episodes of $PbtO_2$ <25 mmHg	2.0 ± 1.2	2.0 ± 1.3	2.0 ± 0.9	0.66
Mean daily episodes of $PbtO_2$ <15 mmHg	0.6 ± 0.6	0.5 ± 0.6	1.0 ± 0.8	0.03
Mean no. interventions	7.7 ± 6.3	8.5 ± 6.6	4.9 ± 2.9	0.15
Mean response rate	0.65 ± 0.34	0.72 ± 0.33	0.44 ± 0.28	0.01
Mean daily minutes of $PbtO_2$ <25 mmHg	295 ± 287	232 ± 234	513 ± 357	0.003
Mean daily minutes of $PbtO_2$ <15 mmHg	102 ± 210	69.9 ± 140	213 ± 351	0.009
Mean length of episodes $PbtO_2$ <25 mmHg	163 ± 171	132 ± 159	273 ± 178	0.002
Mean length of episodes $PbtO_2$ <15 mmHg	106 ± 182	76.3 ± 137	210 ± 273	0.01

Adapted from Bohmann et al., Neurocrit Care 2011; 14: 361–369

Traumatic Intracranial Hypertension – «*Staircase*» Approach

Traumatic Intracranial Hypertension

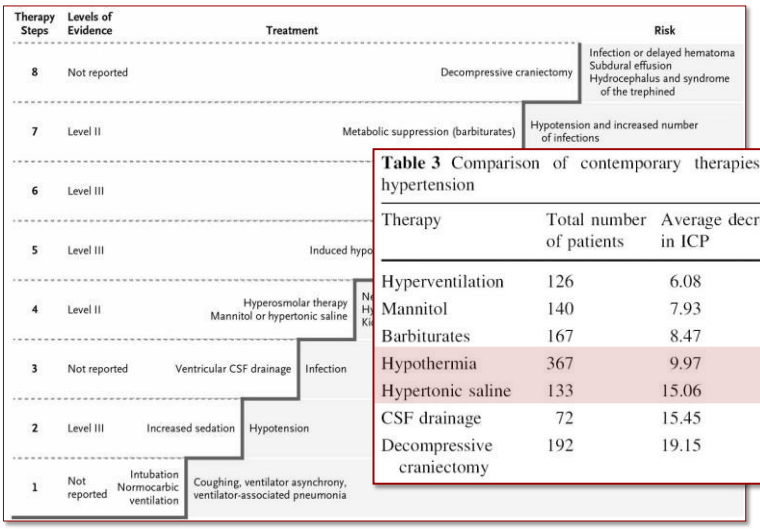


Table 3 Comparison of contemporary therapies for intracranial hypertension

Therapy	Total number of patients	Average decrease in ICP	Standard deviation
Hyperventilation	126	6.08	4.22
Mannitol	140	7.93	5.34
Barbiturates	167	8.47	6.71
Hypothermia	367	9.97	6.66
Hypertonic saline	133	15.06	7.34
CSF drainage	72	15.45	4.67
Decompressive craniectomy	192	19.15	7.70

Adapted from Schrickinger and Marion, Neurocrit Care 2009; 11: 427–436

BTF TBI Guidelines, 4th Edition 2016 – «Facts and Myths»

Comparison of Effects of Equiosmolar Doses of Mannitol and Hypertonic Saline on Cerebral Blood Flow and Metabolism in Traumatic Brain Injury

- **Prospective RCT**
  - **Mannitol 20% 4 ml/kg** vs ***H(T)S 7.5% 2 ml/kg***

Furthermore, considering the impact of HTS on cerebral hemodynamics, the choice of HTS appears to be justified in patients with established cerebral ischemia, especially in the vicinity of focal injuries and intracranial masses or for hemodynamically instable patients.

	Mannitol			*Hypertonic Saline*				
CMRGlc	3.29±2.94	3.17±2.77	3.54±2.52	3.64±4.93	3.41±6.11	3.49±3.29	ns	ns
CMRLtc	−0.29±0.43	−0.21±0.42	−0.32±0.41	−0.19±0.69	−0.14±0.69	−0.13±0.52	ns	ns
Na	141.3±5.1	139.1±4.1†	140.5±4.7†*	144.2±5.1	148.3±5.2†‡	147.3±4.7†*	0.0000	0.0000
Hb	10.5±1.4	10.8±1.6	10.8±1.7	10.1±1.2	10.0±1.2	10.2±1.3	ns	ns
Htc						30.1±3.5	0.0037	0.0001
BUN						11.6±5.4	ns	ns

Recommendations from the prior (Third) Edition not supported by evidence meeting current standards.

Mannitol is effective for control of raised ICP at doses of 0.25 to 1 g/kg body weight. Arterial hypotension (systolic blood pressure <90 mm Hg) should be avoided.

Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.

The present study did not support a definite advantage of HTS over MTL for ICP control whenever given at equiosmolar doses, although it was suggestive of a possible superiority of HTS in diffuse brain injuries.

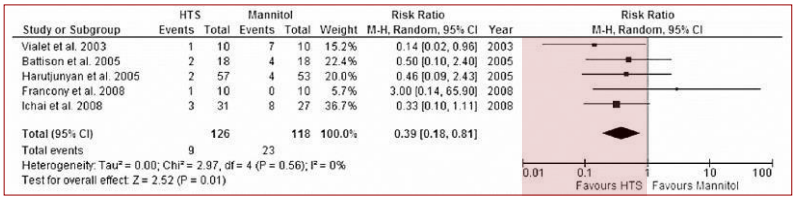
https://www.braintrauma.org/coma/guidelines

Traumatic Intracranial Hypertension – «*Hyperosmolar*» Therapy

A Systematic Review of Randomized Controlled Trials Comparing Hypertonic Sodium Solutions and Mannitol for Traumatic Brain Injury: Implications for Emergency Department Management

- … clinically important **differences** in ***mortality***, ***outcomes***, and ***ICP reduction*** were ***not observed***
- **HTS** appears to lead to ***fewer*** **ICP treatment failures**

Study Selection and Data Extraction: Prosp… …omized trials comparing HTS and mannitol in adults (≥16 years) with severe TBI (Glasgow Coma Scale sco… …elevated ICP were included. ICP elevation, ICP reduction, and treatment failure were defined using study def… **Data Synthesis:** Of 326 articles screened, 7 trials enrolling a total of 191 patients met inclusion criteria. Stud… …e underpowered to detect a significant difference in mortality or neurological outcomes. Due to significant heter… …eity and differences in reporting ICP change from baseline, this outcome was not meta-analyzed. No difference bet… …en HTS and mannitol was observed for mean ICP reduction; however, risk of ICP treatment failure favored HTS (risk …atio [RR] = 0.39; 95% CI = 0.18-0.81). Serious adverse events were not reported. **Conclusions:** Based on limited data, clinically important differences in mortality, neurological outcomes, and ICP reduction were not observed between HTS or mannitol in the management of severe TBI. HTS appears to lead to fewer ICP treatment failures.

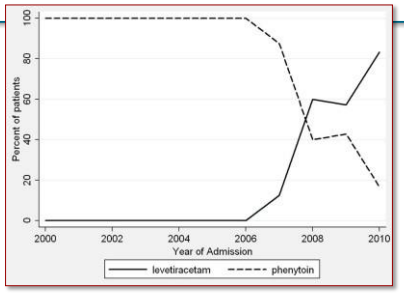


Adapted from Burgess et al., Ann Pharmacother 2016; 50: 291–300

BTF TBI Guidelines, 4th Edition **2016** – «*Facts and Myths*»

- Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS.
- Phenytoin is recommended to decrease the incidence of early PTS (within 7 d of injury), when the overall benefit is thought to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes.
- **At the present time there is insufficient evidence to recommend levetiracetam compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.**

Changing trends in the use of seizure prophylaxis after traumatic brain injury: A shift from phenytoin to levetiracetam



Adapted from Kruer et al., J Crit Care 2013; 28: 883.e9–883e.13

BTF TBI Guidelines, 4th Edition **2016** – «*Facts and Myths*»

- Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS.
- Phenytoin is recommended to decrease the incidence of early PTS (within 7 d of injury), when the overall benefit is thought to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes.
- **At the present time there is insufficient evidence to recommend levetiracetam compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.**

More harm than good: Antiseizure prophylaxis after traumatic brain injury does not decrease seizure rates but may inhibit functional recovery

Outcomes	NP (n = 43)	PP (n = 50)	*p*
Seizure	1 (2%)	2 (4%)	0.50
ICU LOS	17 ± 13	21 ± 10	0.10
Ventilator days	12 ± 12	13 ± 6	0.72
Hospital LOS	25 ± 16	36 ± 31	0.03
GOS score	3.4 ± 1.1	2.9 ± 1.0	0.01
mRS score	2.3 ± 1.7	3.1 ± 1.5	0.02
Disposition			NS
Mortality	3 (7%)	4 (8%)	NS
Rehabilitation center	23 (53%)	30 (60%)	NS
Home	17 (40%)	16 (32%)	NS

- ***Phenytoin* prophylaxis may**
  - ***Not decrease*** early post-traumatic **seizure**
  - ***Suppress* functional outcome**

Adapted from Bhullar et al., J Trauma Acute Care Surg 2014; 76: 54–60

BTF TBI Guidelines, 4th Edition 2016 – «Facts and Myths»

From Villain to Victor:
Ketamine in Acute Neurologic Injury

A recent review describes the potential neuroprotective benefits of ketamine in stroke, neurotrauma, subarachnoid hemorrhage and status epilepticus.[1]

The Ketamine Effect on ICP in Traumatic Brain Injury

Table 2 Ketamine treatment characteristics and ICP response

References	Ketamine dose	Mean duration of ketamine administration (days)	ICP response	Cerebral hemodynamic response	Adverse effects to ketamine	Conclusions
Kolenda et al. [15]	Initial dose: 65 mg/kg/day (adjusted to clinical requirements) Mean dose: 104 mg/kg/day Duration 1–10 days	Continuous infusion	ICP was 2 mmHg higher (statistically significant only at day 8 and 10) in the ketamine group compared to the fentanyl group. Patients under fentanyl had ICP averages of 20 or more on 12 treatment days; and ketamine patients on 19 treatment days. 11 patients had ICP crisis leading to removal from study (6 fentanyl group, 5 ketamine group)	Ketamine group: MABP higher; mean CPP 8 mmHg higher; less bradycardia; less gastric motility issues	None	No difference between ketamine and fentanyl for sedation in terms of ICP control; CPP easier to control with ketamine
Schmittner et al. [16][a]	Initial bolus of 0.5 mg/kg then titrated to Ramsay Sedation Score of 6.	Continuous infusion	Not statistically significant difference between ketamine or fentanyl for ICP or CPP	No difference in depth of sedation, gastric motility, or GOS.	None	No difference between ketamine and fentanyl sedation in terms of ICP control; no elevations in

- **Systematic review** of the literature on the use of ***ketamine*** in **TBI** and its **effects** on **ICP**
  - ***Level IIb***, ***GRADE C*** evidence to **support** that ***ketamine*** does ***not*** **increase ICP** in **severe TBI patients** that are ***sedated*** and ***ventilated***
  - In fact ***ketamine*** may ***lower*** **ICP** in ***selected*** **cases**
  - ***no*** **significant adverse events** related to ***ketamine*** were **recorded** in any of the studies

Adapted from Zeiler et al., Neurocrit Care 2014; 21: 163–173

BTF TBI Guidelines, 4th Edition 2016 – «Facts and Myths»

- Administration of barbiturates to induce burst suppression measured by EEG as prophylaxis against the development of intracranial hypertension is not recommended.
- High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.
- Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity.[3]

- Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is thought to outweigh the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.
- **The use of PI oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.**
- **Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during external ventricular drainage.**

- LMWH or low-dose unfractioned heparin may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.
- In addition to compression stockings, pharmacologic prophylaxis may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage.
- There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis.

https://www.braintrauma.org/coma/guidelines

TBI and Oral Anticoagulant Therapy – Interdisciplinary Consensus Statement

REVIEW Open Access

Diagnostic and therapeutic approach in adult patients with traumatic brain injury receiving oral anticoagulant therapy: an Austrian interdisciplinary consensus statement

Marion Wiegele[1], Herbert Schöchl[2,3*], Alexander Haushofer[4], Martin Ortler[5,6], Johannes Leitgeb[7], Oskar Kwasny[8], Ronny Beer[9], Cihan Ay[10] and Eva Schaden[1]

The task force for perioperative coagulation of the Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine (OEGARI) assembled a national expert committee comprising representatives of the OEGARI, the Austrian Society for Hematology and Medical Oncology (OeGHO), the Austrian Society for Laboratory Medicine and Clinical Chemistry (ÖGLMKC), the Austrian Society of Neurology (ÖGN), the Austrian Society for Neurosurgery (ÖGNC) and the Austrian Society for Traumatology (ÖGU).

Diagnosis

Coagulation tests and **therapeutic target levels**

Reversal of anticoagulants

Note: Only in case of *hemorrhagic TBI!* Perform *interdisciplinary risk-benefit analysis!*

Thromboembolism prophylaxis and **resumption** of **therapeutic anticoagulation**

- **Thrombosis *prophylaxis*:** Clinically and radiographically *stable* TBI (i.e., no progressive hemorrhagic injuries) → start ***LMWH*** SC *at 24 h* at a dose recommended for high risk patients (e.g., *enoxaparin* 4000 IU SC qd; ***note:*** *caution* is required in the presence of *impaired renal function*)
- ***Therapeutic* anticoagulation:** *No* definie recommendation → *case-by-case decision* with expertise from *multidisciplinary team*

Adapted from Wiegele et al., Crit Care 2019; 23:62

Pharmacological Neuroprotection after TBI – Overview of Phase III Trials

Pharmacological interventions in traumatic brain injury: Can we rely on systematic reviews for evidence?

There is **currently *insufficient* evidence** for the **use** of

- ***Magnesium***
- ***Monoaminergic*** and ***dopamine agonists***
- ***Aminosteroids***
- ***Excitatory amino acid inhibitors***
- ***Antifibrinolytic drugs*** in TBI

			Total no. of participants	Conclusion
			17	Limited evidence
			536	No evidence for clinical use
			990	No difference
			127	No reliable evidence
			2287	Insufficient evidence
			480	Insufficient evidence
			20,541	Limited evidence for TBI
Roberts et al. [14]	2011	Sedative agents (prop fentanyl, sufentanil,		
Ma et al. [16]	2012	Progesterone		
Lei et al. [17]	2012	Barbiturates, aminost anti-fibronolytic drug haemostatic drugs, calcium channel blockers, corticosteroid, progesterone, ant-epileptic drugs, excitatory amino acids		
Gu et al. [18]	2014	Propofol and midazolam	4	
Zeiler et al. [15]	2014	Ketamine	7	ICP for sedation

Anticonvulsants are **only** effective in r**educing early seizures** with

- **No significant difference** between ***phenytoin*** and ***levetiracetam***

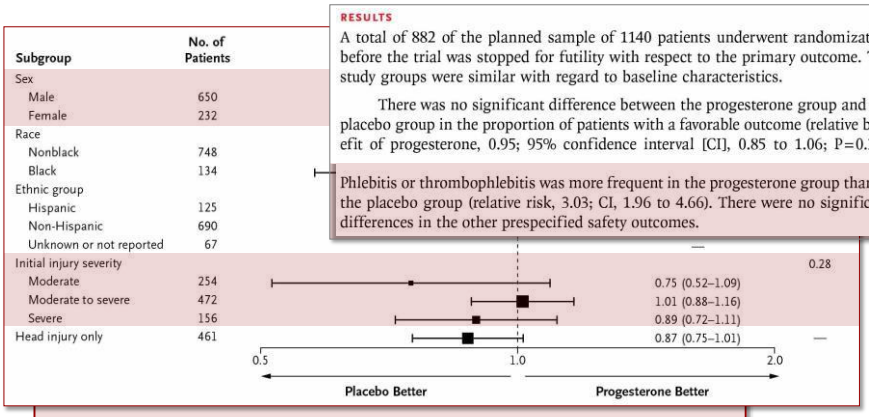
There is ***no* significant difference** between ***propofol*** and ***midazolam*** for sedation in TBI patients

- ***Ketamine*** may ***not*** cause **increased ICP**

Adapted from Gultekin et al., Injury 2016; 47: 516–524

Progesterone for Neuroprotection after TBI – *PROTECT III*

Very Early Administration of Progesterone for Acute Traumatic Brain Injury



Subgroup	No. of Patients	
Sex		
Male	650	
Female	232	
Race		
Nonblack	748	
Black	134	
Ethnic group		
Hispanic	125	
Non-Hispanic	690	
Unknown or not reported	67	
Initial injury severity		0.28
Moderate	254	0.75 (0.52–1.09)
Moderate to severe	472	1.01 (0.88–1.16)
Severe	156	0.89 (0.72–1.11)
Head injury only	461	0.87 (0.75–1.01)

0.5 1.0 2.0

Placebo Better Progesterone Better

RESULTS

A total of 882 of the planned sample of 1140 patients underwent randomization before the trial was stopped for futility with respect to the primary outcome. The study groups were similar with regard to baseline characteristics.

There was no significant difference between the progesterone group and the placebo group in the proportion of patients with a favorable outcome (relative benefit of progesterone, 0.95; 95% confidence interval [CI], 0.85 to 1.06; P=0.35).

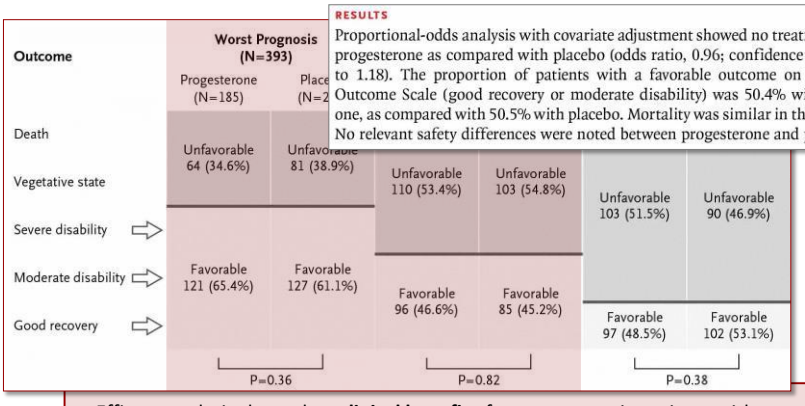
Phlebitis or thrombophlebitis was more frequent in the progesterone group than in the placebo group (relative risk, 3.03; CI, 1.96 to 4.66). There were no significant differences in the other prespecified safety outcomes.

- This clinical trial did ***not*** **show** a **benefit** of ***progesterone*** over placebo in the **improvement** of **outcomes** in patients with acute TBI

Adapted from Wright et al., N Engl J Med 2014; 371: 2457–2466

Progesterone for Neuroprotection after TBI – *SYNAPSE*

A Clinical Trial of Progesterone for Severe Traumatic Brain Injury



RESULTS

Proportional-odds analysis with covariate adjustment showed no treatment effect of progesterone as compared with placebo (odds ratio, 0.96; confidence interval, 0.77 to 1.18). The proportion of patients with a favorable outcome on the Glasgow Outcome Scale (good recovery or moderate disability) was 50.4% with progesterone, as compared with 50.5% with placebo. Mortality was similar in the two groups. No relevant safety differences were noted between progesterone and placebo.

- Efficacy analysis showed ***no*** **clinical benefit** of ***progesterone*** in patients with severe TBI
- These data stand **in contrast** to the **robust preclinical data** and results of **early single-center trials** that provided impetus to initiate phase 3 trials

Adapted from Skolnick et al., N Engl J Med 2014; 371: 2467–2476

Erythropoietin for Neuroprotection after TBI – *EPO-TBI*

Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial

Within 24 h of brain injury, 606 patients were randomly assigned by a concealed web-based computer-generated randomisation schedule to erythropoietin (40 000 units subcutaneously) or placebo (0·9% sodium chloride subcutaneously) once per week for a maximum of three doses. Randomisation was stratified by severity of traumatic brain injury (moderate *vs* severe) and participating site.

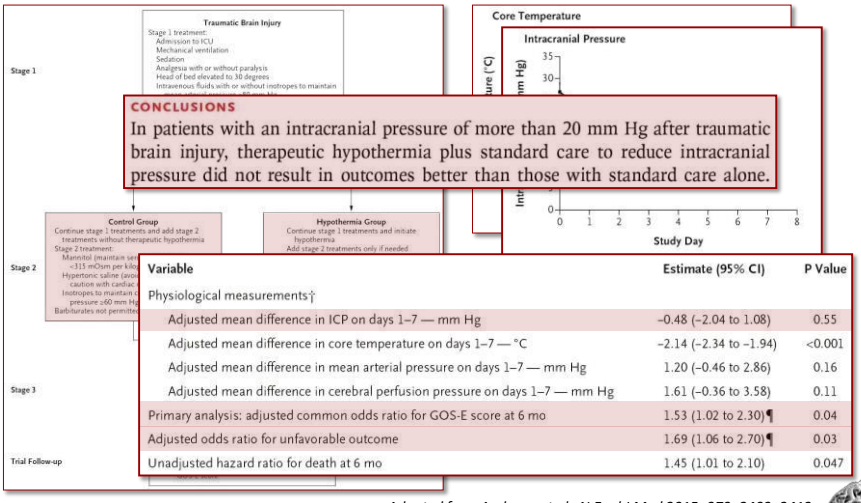
Dead or vegetative (GOS-E 1 or 2)	43/302 (14%)	53/294 (18%)	0·79 (0·55 to 1·14)	−3·8 (−9·7 to 2·1)	0·21
Severe disability (GOS-E 3 or 4)	91/302 (30%)	79/294 (27%)	1·12 (0·87 to 1·45)	3·3 (−4·0 to 10·5)	0·38
GOS-E 5–8	168/302 (56%)	162/294 (55%)	1·01 (0·87 to 1·17)	0·5 (−7·5 to 8·5)	0·90
Moderate recovery (GOS-E 5 or 6)	115/302 (38%)	104/294 (35%)	1·08 (0·87 to 1·33)	2·7 (−5·0 to 10·4)	0·49
Good recovery (GOS-E 7 or 8)	53/302 (18%)	58 (20%)	0·89 (0·64 to 1·24)	−2·2 (−8·4 to 4·1)	0·50
A-priori subgroup analyses					
GOS-E 1–4					
Severe traumatic brain injury (GCS 3–8)	108/220 (49%)	109/219 (50%)	0·99 (0·82 to 1·19)	−0·7 (−10·0 to 8·7)	0·89
Moderate traumatic brain injury (GCS 9–12)	26/82 (32%)	23/75 (31%)	1·03 (0·65 to 1·65)	1·0 (−13·5 to 15·5)	0·89
Intracranial mass lesion*					
Yes	38/63 (60%)	30/60 (50%)	1·21 (0·87 to 1·67)	10·3 (−7·2 to 27·8)	0·25
No	96/239 (40%)	102/234 (44%)	0·92 (0·75 to 1·14)	−3·4 (−12·3 to 5·5)	0·45

- Following **moderate**or **severe TBI**, ***erythropoietin*** did ***not*** **reduce** the number of patients with **severe neurological dysfunction** (**GOS-*E* 1-4**) or increase the *incidence of DVT* of the lower limbs
- The effect of ***erythropoietin*** on **mortality** remains **uncertain**

Adapted from Erythropoietin for Neuroprotection after TBI – EPO-TBI

Therapeutic *Hypo*thermia after TBI – *Eurotherm3235 Trial*

Hypothermia for Intracranial Hypertension after Traumatic Brain Injury



Variable	Estimate (95% CI)	P Value
Physiological measurements†		
Adjusted mean difference in ICP on days 1–7 — mm Hg	−0.48 (−2.04 to 1.08)	0.55
Adjusted mean difference in core temperature on days 1–7 — °C	−2.14 (−2.34 to −1.94)	<0.001
Adjusted mean difference in mean arterial pressure on days 1–7 — mm Hg	1.20 (−0.46 to 2.86)	0.16
Adjusted mean difference in cerebral perfusion pressure on days 1–7 — mm Hg	1.61 (−0.36 to 3.58)	0.11
Primary analysis: adjusted common odds ratio for GOS-E score at 6 mo	1.53 (1.02 to 2.30)¶	0.04
Adjusted odds ratio for unfavorable outcome	1.69 (1.06 to 2.70)¶	0.03
Unadjusted hazard ratio for death at 6 mo	1.45 (1.01 to 2.10)	0.047

Adapted from Andrews et al., N Engl J Med 2015; 373: 2403–2412

VAS203 (*Ronopterin*) for Neuroprotection after TBI – *NOSTRA Phase III*

TBI – *Collaborative European **NeuroTrauma Effectiveness Research** in TBI*

Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A Prospective Longitudinal Observational Study

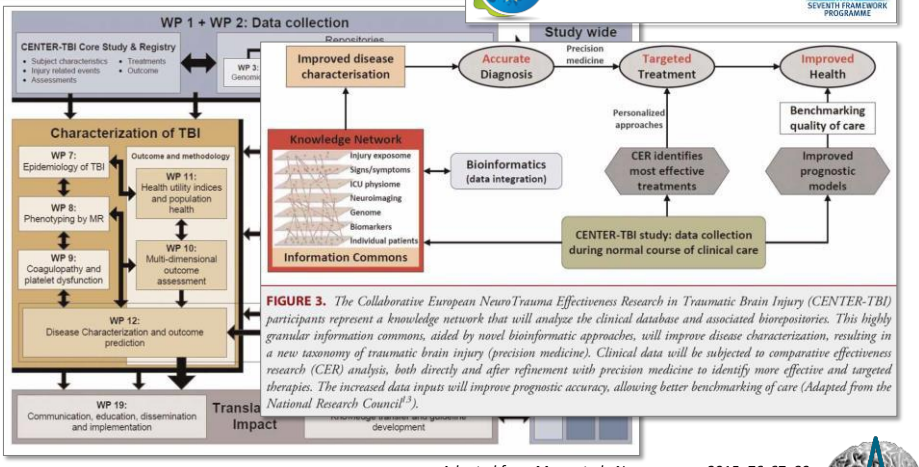


FIGURE 3. *The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) participants represent a knowledge network that will analyze the clinical database and associated biorepositories. This highly granular information commons, aided by novel bioinformatic approaches, will improve disease characterization, resulting in a new taxonomy of traumatic brain injury (precision medicine). Clinical data will be subjected to comparative effectiveness research (CER) analysis, both directly and after refinement with precision medicine to identify more effective and targeted therapies. The increased data inputs will improve prognostic accuracy, allowing better benchmarking of care (Adapted from the National Research Council[13]).*

Adapted from Maas et al., Neurosurgery 2015; 76:67–80

TBI – *Collaborative European **NeuroTrauma Effectiveness Research** in TBI*

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

Methods: A 29-item surve
opinion, and it was pilot-te
in the Collaborative Europ

Results: The survey was c
(*n* = 60, 91%) and designated level I trauma centers (*n* = 44, 67%). The Brain Trauma Foundation guidelines were
used in 49 (749
patients with se
or on peri-insert
ICP. Approximat
treatment (*n* = 3

Conclusions: Su
intracranial hype
centers and pro

ICP threshold	First line (65) Medical management	Second line (58) Decompressive craniectomy
>15 mmHg	N= 3 (5%)	N= 0 (0%)
>20 mmHg	N= 54 (83%)	N= 7 (11%)
>25 mmHg	N= 6 (9%)	N= 32 (50%)
>30 mmHg	N= 0 (0%)	N= 19 (30%)
Individualized	N= 2 (3%)	NA [1] = 6 (9%)

Treatment indications

Target CPP [2] (66)	
> 50 mmHg	N= 7 (11%)
> 60 mmHg	N= 39 (59%)
> 70 mmHg	N= 14 (21%)
Individualized	N= 25 (38%)

Parenchymal monitor

Chosen in the following situations [1] (35)	
- Routine in our department	N= 24 (68%)
- Not routine but small ventricles	N= 10 (29%)
- Failed implantation of catheter	N= 1 (3%)

Start prophylactic antibiotics [2] (61)	N= 26 (43%)
Continue Prophylactic antibiotics [2] (60)	N= 5 (8%)
Assess a **coagulation panel** [2] (65)	N= 50 (77%)

Ventricular catheter

Chosen in the following situations [1] (35)	
- Routine in our department	N= 5 (14%)
- Not routine but enlarged ventricles	N= 8 (23%)
- External CSF drainage	N= 21 (60%)
- Low cost	N= 1 (3%)

Drain is open (38)	N= 19 (50%)
Drain is closed mostly (38) (opened intermittently)	N= 19 (50%)

Start prophylactic antibiotics [2] (58)	N= 32 (55%)
Continue Prophylactic antibiotics [2] (57)	N= 6 (11%)
Assess a **coagulation panel** [2] (65)	N= 50 (77%)

Adapted from Cnossen et al., Crit Care 2017; 21: 233

TBI – *Collaborative European **NeuroTrauma Effectiveness Research** in TBI*

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

Relatively **aggressive** centers (*n* = 32)

Table 1 Factors associated with an aggressive ICP management style

Factor	Relatively aggressive centers (*n* = 32)	Relatively conservative centers (*n* = 34)
Dedicated neurosciences ICU		
Available	19 (49%)	20 (51%)
Not available	13 (48%)	14 (52%)
BTF guidelines used[a]		
Yes	25 (51%)	24 (49%)
No	7 (41%)	10 (59%)
Volume[b]		
High volume	17 (47%)	19 (53%)
Low volume	15 (50%)	15 (50%)
Geographic location[d]		
Northern Europe	4 (44%)	5 (56%)
Western Europe	13 (52%)	15 (48%)
United Kingdom	3 (43%)	4 (57%)
Southern Europe	5 (42%)	7 (58%)
Baltic states	2 (40%)	3 (60%)
Eastern Europe	3 (50%)	3 (50%)
Israel	2 (100%)	0 (0%)

Adapted from Cnossen et al., Crit Care 2017; 21: 233

tirolkliniken R. Beer 2019
NeuroCritical Care
Medical University of Innsbruck

TBI – *Collaborative European **NeuroTrauma Effectiveness Research** in TBI*

The Lancet Neurology Commission

Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research

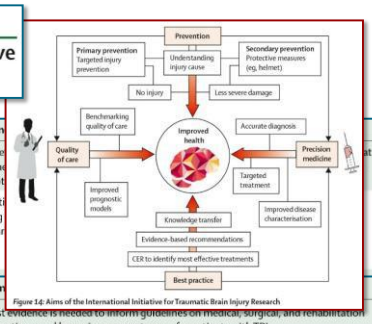


Figure 14: Aims of the International Initiative for Traumatic Brain Injury Research

	Key messages	Recommen
Sections 1, 3, 4, 9	Worldwide, TBI is a leading cause of injury-related death and disability, with a devastating impact on patients and their families	Concerted e reducing the and promot
Sections 1, 4	In low-income and middle-income countries, the incidence of TBI due to traffic incidents is increasing, while in high-income countries, TBI increasingly affects elderly people, mostly due to falls; however, methodological variations confound comparisons of epidemiological patterns of TBI between regions, countries, and continents	An internati monitoring and compar

	Key messages	Recom
Section 5	Evidence underpinning guidelines for medical, surgical, and rehabilitation interventions for TBI is weak	Robust evidence is needed to inform guidelines for medical, surgical, and rehabilitation interventions, and hence improve outcomes for patients with TBI
Section 6	Methods of diagnosis and classification of patients with TBI are insufficient to permit targeting of current and new therapies to the needs of individual patients	Research is needed to improve the precision of diagnosis, classification, and characterisation of TBI using multidomain approaches
Section 7	Trauma disturbs the brain in complex ways, affecting multiple outcome domains	Multidimensional outcome constructs that quantify the overall burden of disability from TBI need to be developed and validated to guide improved clinical management and support high-quality research
Section 8	A validated set of quality indicators is essential for the benchmarking of quality of care, but none exists for TBI	Efforts are needed to develop a set of quality indicators for TBI that includes structure, process, and outcome metrics
Section 9	Substantial between-centre variability in treatment and outcome in TBI offers unique opportunities for comparative effectiveness research to improve the strength of evidence	Comparative effectiveness research should be supported to identify best practices and to improve the level of evidence for systems of care and diagnostic and therapeutic interventions
Section 9	Coordinated research efforts on a global basis are needed to address the growing public health problem of TBI	A commitment of governmental and non-governmental funding bodies, as well as industrial partners, is needed to foster global collaborations and to establish national and international biorepositories and databases that could facilitate future TBI research

Adapted from Maas, Menon et al., Lancet Neurol 2017; 16: 987–1048

Acute Management of Traumatic Brain Injury (TBI) – Synopsis

- Globally, **TBI** is a **leading cause** of injury-related ***death*** and ***disability***
- The **epidemiology** of TBI is **changing** (i.e., number of **elderly people** with **TBI** is **increasing**, mainly due to ***falls***

- **TBI** is **pathophysiologically *heterogeneous*** attributable to the **complexity** of the **brain** as well as to the **pattern** and **extent** of the ***primary injury***
  - **Pathological processes** can **vary *between patients*, *within individual patients over time***, and even ***between different parts of the brain*** at any given time

- Current **management guidelines** emphasize **prevention** of ***secondary insults***, such as ***hypoxia*** and ***hypotension***, and focus on ***control*** of ***ICP***, and ***maintenance*** of ***CPP***
- **Strong evidence** to support treatment guidelines is ***scarce***
  - ***Most* multicenter clinical trials** of **medical** and **surgical interventions** have ***failed*** to show efficacy, despite promising preclinical results

- A number of **neuromonitoring modalities** can be used to **detect** incipient ***secondary injury***, however, there is a **lack** of **certainty** therapies

VIEWPOINT
Precision Medicine in Neurocritical Care

  - Although **population-based targets** for ***ICP*** and ***CPP*** management provide a **useful initial basis** for care, required ***target ranges*** differ between patients and should ***preferably*** be **directed** to the **needs** of ***individual patients***

Adapted from Shrestha, Suarez and Hemphill 3rd, JAMA Neurol 2018; 75: 1463–1464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Thank You for Your Attention!
Questions, comments, wise remarks?
«Time is out of joint. The rest is silence.»
The Tragedy of Hamlet, Prince of Denmark; W. Shakespeare
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