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ORIGINAL ARTICLE

Treatment of severe traumatic brain injury in German pediatric intensive care units—a survey of current practice

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Abstract

Purpose German pediatric guidelines for severe traumatic brain injury (TBI) management expired in 2011. Thus, divergent evidence-based institutional protocols are predominantly being followed. We performed a survey of current Pediatric Intensive Care Unit (PICU) management of isolated severe TBI in Germany to reveal potential varying practices.

Methods Seventy German PICUs were invited to join an anonymous online survey from February to May 2017. Twenty-nine participants (41.4%) successfully completed the survey (17 university hospitals and 12 district hospitals). The majority of items were polar (yes/no) or scaled (e.g., never - always). Main topics were imaging, neurosurgery, neuromonitoring, adjuvant therapy, and medication. Severity of TBI was defined via Glasgow Coma Scale.

Results The majority of respondents (93.1%) had internal TBI standards, and patients were mainly administered to interdisciplinary trauma units. The use of advanced neuromonitoring techniques, intracranial hypertension management, and drug treatment differed between PICUs. Routine administration of hypertonic saline in TBI-associated cerebral edema was performed by 3.4%, while it was never an option for 31.0% of the participants. Prophylactic anticonvulsive therapy was restrictively performed. If indicated, the main anticonvulsive drugs used were phenobarbital and levetiracetam. Neuroendocrine follow-up was recommended/performed by 58.6% of the PICUs.

Conclusions This survey provides an overview of the current PICU practices of isolated severe TBI management in Germany and demonstrates a wide instrumental and therapeutical range, revealing an unmet need for the revised national guideline and further (international) clinical trials for the treatment of severe TBI in pediatrics.

Keywords ICP · Neuromonitoring · Neuroimaging · Adjuvant therapy

Introduction

Traumatic brain injury (TBI) significantly contributes to mortality and long-term morbidity in children and adolescents [1, 2]. Cases of severe TBI are recorded in the trauma register of the German Society of Trauma Surgery (TraumaRegister® DGU). In 2009, DGU data [3] showed that ~ 290,000 (~ 16%) of ~ 1,800,000 children, aged 0–19 years, were hospitalized after trauma, of those ~ 134.000 (47%) because of TBI. While hospitalization rates decreased in the age group of 5–19 years, an increase of 29% in infants and of 10% in young children (1–4 years) was observed since the beginning of the millennium [3, 4]. In general, TBI was noted in 83.3% (< 1 year), 63.1% (1–4 years), 41.8% (5–14 years), and 33.3% (15–19 years) of all pediatric trauma patients [3]. Fortunately, mortality rates for severe TBI in children are decreasing [5]. However, the overall age-adjusted mortality rate for TBI in

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Germany remains at 8.3 per 100,000 [6] and up to 20.9% in severe TBI in pediatrics [7]. It has been shown that stringent adherence to pediatric guidelines during the first 72 h after TBI significantly improves the survival rate at the time of discharge and increases the chance of favorable neurological outcome [8]. Unfortunately, the last German pediatric guideline for the acute medical management of severe TBI has expired in 2011 and is currently under revision, at least until 2020 [9]. The guideline was created by an expert panel (societies of pediatric critical care medicine/-surgery/-neurology-/radiology and societies of adult neurosurgery/-trauma surgery/-neuroradiology/-anesthesiology/-critical care medicine). In short, the following recommendations for in-hospital treatment were given based on evidence levels II-III [9]: Initial interdisciplinary management should be implemented. Cranial computed tomography (cCT) was suggested as the imaging gold standard, obligatory in cases of coma, prolonged loss of consciousness, focal neurologic deficit, and suspected skull fracture. Further examination with EEG and sonography was recommended, whereas the use of magnet resonance imaging (MRI) was considered optional. Intracranial pressure (ICP) monitoring was perceived as valuable but restricted by the possible side effect of intracerebral hemorrhage [10]. Cerebral perfusion pressure (CPP) was recommended to be above 40 mmHg and below 70 mmHg. In cases of increased ICP osmodiuretics (mannitol), hyperventilation, 30° positioning of upper body, and sedation were recommended. The potential use of hypertonic saline and barbiturates was mentioned, yet remained unrated. A highly restrictive use of adjuvant corticosteroids was suggested [9] based on reports of elevated 14-day mortality [11]. Further, no specific prophylactic anticonvulsive treatment was recommended. Moreover, rehabilitation should be considered in any case [9].

The revised North American *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents from 2012* [12] were based on expert panels, alike, and a great need for pediatric level I and II recommendations became apparent [13]. Compared to the German guideline, additional level II and III recommendations to be considered were (i) treatment of ICP at a threshold of 20 mmHg; (ii) hypertonic saline for the treatment of elevated ICP; (iii) etomidate, thiopental, and high-dose barbiturates in cases of intracranial hypertension; (iv) avoidance of early hypothermia (32–33 °C for 24 h); and (v) prophylactic treatment with phenytoin to reduce the incidence of early post-traumatic seizures (PTS). In the meantime (since 2011/12), international experience and evidence-based recommendations on, e.g., brain edema management [14], neuromonitoring, and anticonvulsive treatment [15, 16], and early surgical interventions [17, 18] have been reported, presumably having a significant impact on current practice in pediatric TBI management. Especially results from the ADAPT trial (approaches and decisions for acute pediatric TBI), an observational cohort study aiming to develop new level II recommendations, addressing intracranial hypertension management, basic aspects of neurocritical care, nutritional support and glucose management, are promising but currently mainly pending [7, 13].

To investigate current pediatric management practices of severe TBI in Germany, a survey-based investigation was conducted to investigate how treatment protocols have evolved 7 years after the establishment of the last guideline.

Materials and methods

Seventy German Pediatric Intensive Care Units (PICUs) were invited to join an anonymous online survey (eQuestionnaire ®, www.equestionnaire.de) from February to May 2017. PICUs were chosen based on their university status and registry at the association of pediatric directors (Verband Leitender Kinder- und Jugendärzte und Kinderchirurgen Deutschland, http://www.vlkkd.de/de/Delegierte/, accessed 01/2017). PICU-associated trauma centers were of mixed levels (I and II), including free-standing children's hospitals and university medical centers. Twenty-nine participants (17 University hospitals and 12 district hospitals) completed the survey successfully (response rate of 41.4%). The majority of items were polar (yes/no) or scaled (e.g. never - always). The following terms were used to summarize findings: marginally (never-rarely), infrequently (rarely-sometimes), occasionally (sometimes-often), and strongly (often-always). Severity of TBI was defined via Glasgow Coma Scale [19], with mild TBI-GCS 13–15, moderate TBI-GCS 9–12, and severe TBI-GCS < 9.

Statistical analysis

Percental distribution of given answers was calculated. Missing data was excluded from analysis. Where percentage values are given in this manuscript, this reflects a proportion of those that actively responded to the question and not of the total number of participants in the survey. Data analysis was performed with MS Office Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and GraphPad Prism (Vers.7 and newer, GraphPad Software Inc., CA, USA).

Results

General aspects and interdisciplinary treatment

Of the participating clinics, 93.1% reported following of internal TBI standards. Pediatric patients with severe TBI were mainly (93.1%) administered to the interdisciplinary trauma unit or in some cases (20.7%) directly to the adjacent PICU, where interdisciplinary bedside rounds were further performed by 100% (69.0% daily) after the initial care.

Neuroimaging

At admission, an obligatory indication for cranial cerebral computed tomography (cCT) of severe TBI (GCS < 9) was seen by 82.8%, while only by 37.9% and 0.0% in moderate (GCS 9–12) and mild TBI (GCS 13–15), respectively. However, cCT was uniformly performed in children with prolonged loss of consciousness (55.2%) and focal neurologic deficits (65.5%) such as paresthesia, cranial nerve damage, and convulsions (data not shown). Indication for re-cCT was strongly based on patient dynamics (neurological findings, ICP dynamics) or surgical decision-making and never automatically implemented (Fig. 1a).

Decompressive craniectomy and ICP measurement

Almost all of our respondents (25/29) strongly used invasive ICP measurement in severe TBI management mainly via external ventricular drainage and intraventricular/-parenchymal probes. Invasive ICP measurement was initiated by both neurosurgery and PICU. ICP-/CPP-based decision-making was commonly used by participating PICUs who favored intensification of therapy at ICP > 20 mmHg and the use of age-specific CPP ranges (generally > 40 mmHg), with a certain tolerance regarding acuteness of therapy adjustment. The main indication for decompressive craniectomy was therapy-refractory ICP increase, mostly based on current imaging data (Fig. 1b).

Neuromonitoring

With regard to advanced neuromonitoring techniques, a strong use of cerebral (Doppler-) sonography and EEG (conventional multichannel EEG, multichannel aEEG or 2–4 channel cerebral function monitoring, CFM) was reported by 72.4% and 93.1% of participants, respectively (Fig. 2a). EEG was preferably used as a short-term surveillance method, both as multichannel and aEEG setup (data not shown).

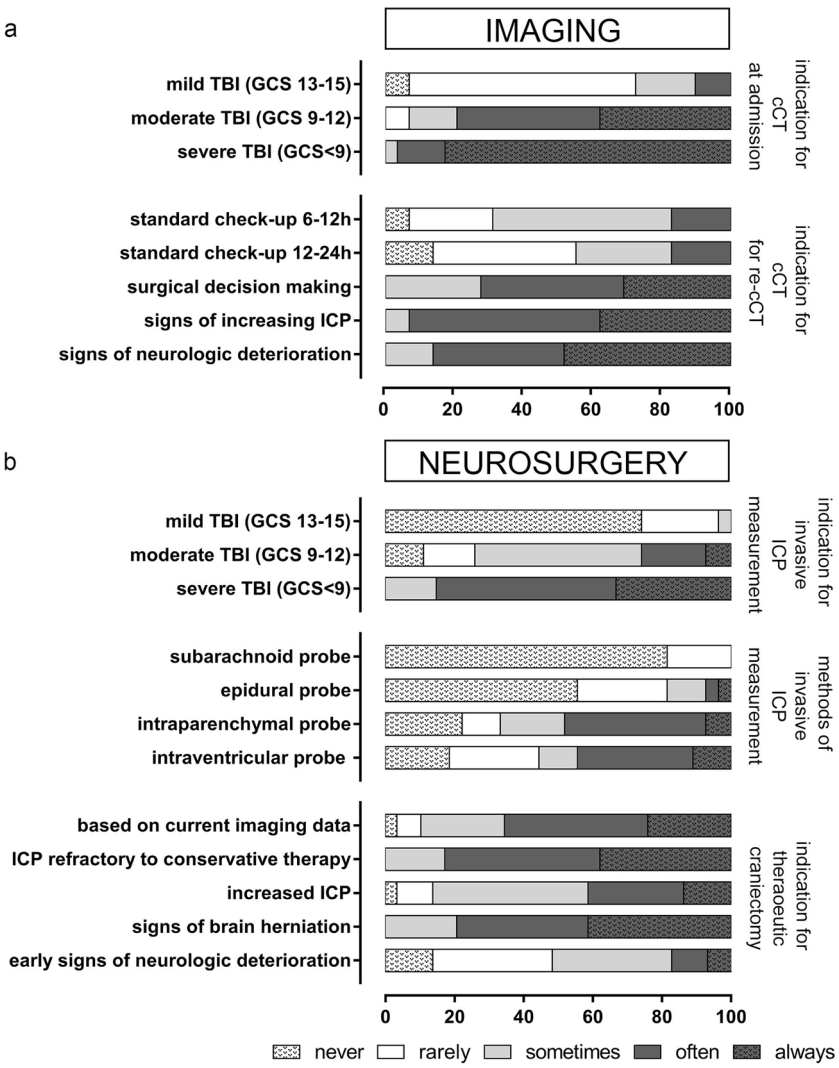

Fig. 1 Survey results regarding imaging and neurosurgery: displayed is the proportional distribution of given answers (never-always) regarding imaging (**a**) and neurosurgical procedures (**b**)

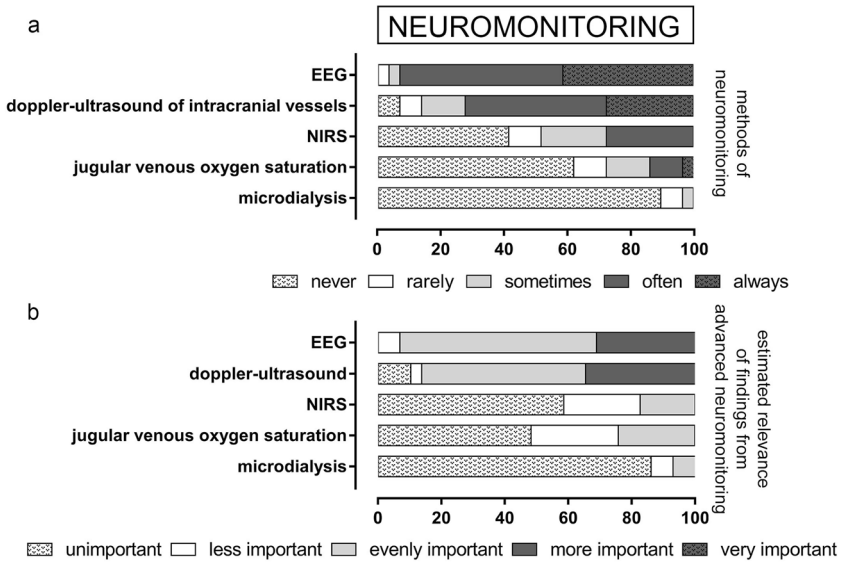

Fig. 2 Survey results regarding neuromonitoring: displayed is the proportional distribution of given answers (never-always) regarding different neuromonitoring methods (**a**) and given answers (unimportant-very important) for the estimated relevance of the methods (**b**)

Commonly (> 90%), the relevance of findings retrieved by these methods was rated as most relevant among all techniques used. In general, only the users of the less common neuromonitoring practices (microdialysis and jugular venous oxygen saturation) rated the respective results as clinically relevant. In line with this finding, (Doppler-) ultrasound findings were rated clinically irrelevant by the minority of participants ($n = 3$) who mostly did not use the technique themselves. There was a dichotomy between the use of noninvasive near-infrared spectroscopy (NIRS) and its estimated diagnostic value. Among the frequent NIRS users (48.3%), 50.0% rated the results of this method as clinically less important or unimportant (Fig. 2b).

Adjuvant ICP therapy

For adjuvant therapy, the majority of respondents strongly (96.6%) used 30-degree positioning of upper body and axially correct positioning. Both techniques were never used by 3.4%. Adjuvant muscle relaxants were infrequently (41.4%) to strongly (48.3%) required. Use of prophylactic hyperventilation was neglected (85.7%), with normocapnia (pCO_2 35-45 mmHg) as the therapeutic goal. Short intermittent hyperventilation was exceptionally used in case of acute ICP increase or therapy-refractory elevation of ICP. The pursued pCO_2 target range was mainly between 35 and 45 mmHg (data not shown). None of the respondents routinely monitored cerebral oxygenation during hyperventilation. Use of hypothermia following severe TBI was never performed by 41.4% of PICUs. The majority (31.0%) of the remaining respondents ($n = 17$) rarely performed hypothermia at variable target temperatures: 17.6% aimed at 32–33 °C, 41.2% at 33–34 °C, and 41.2% at 35–36 °C (Fig. 3).

Management of medication

Results on management of medication indicated that continuous perfusion of muscle relaxants was used more frequently than bolus therapy. The majority favored continuous midazolam treatment for sedation. We observed variable preferences regarding the use and application of clonidine, thiopental, and propofol. All participants reported the use of mannitol to some extend in the therapy of severe pediatric TBI at varying regimens. Routine administration of hypertonic saline was performed by 3.4% while never an option in 31.0% of the participants. Consequently, saline dosage (55.0% applied NaCl 3%, 25.0% NaCl 5.85%, 15.0% NaCl 7–10%, and 5.0% NaCl 20%, respectively) and administration varied largely. Serum osmolarity was recognized as relevant for saline treatment by all participants. However, less than 50% of PICUs reported occasional to routine consideration of this information for their clinical decision-making. Dexamethasone administration was strongly reported in cerebral edema (33.3%) and increasing ICP (33.3%) but not routinely in the treatment regimen of severe TBI (Fig. 4).

Anticonvulsive therapy

Prophylactic anticonvulsive therapy (Fig. 2b) was performed "never to infrequently". Antiepileptic drugs were strongly used in patients with suspected seizures associated with pathologic EEG findings (96.6%), clinically diagnosed seizure activity (72.4%), and, to a lesser extent in cases with pathologic EEG without clinical signs of seizure activity (48.2%). Anticonvulsive drugs of choice were phenobarbital (62.1% occasional use, 10.3% always) and levetiracetam (75.9% occasional use, 13.8% always), with lower relevance of phenytoin, diazepam, and clonazepam (Fig. 4).

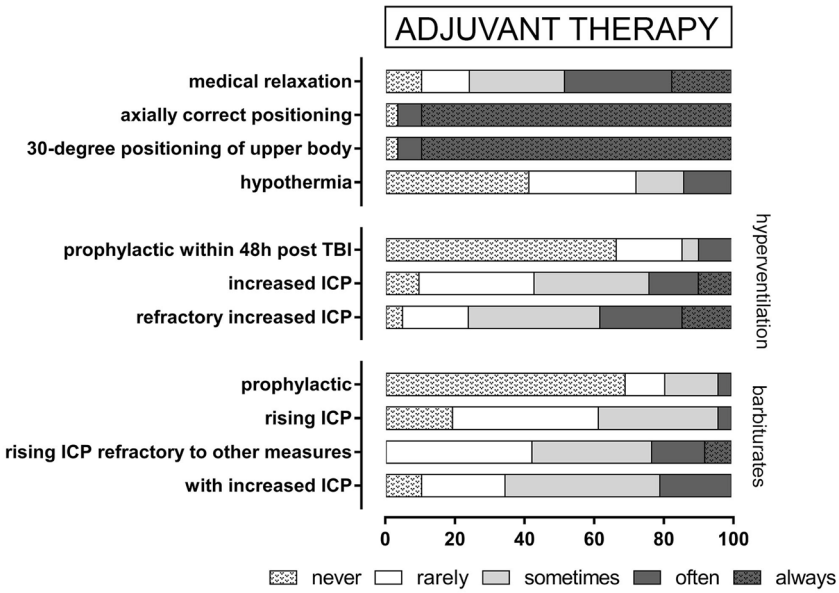

Fig. 3 Survey results regarding adjuvant therapy: displayed is the proportional distribution of given answers (never-always) regarding adjuvant therapy

Aftercare

All participating PICUs were involved in the organization of early rehabilitation and neuropediatric aftercare. Neuroendocrine follow-up was recommended/performed by 58.6% of the PICUs (data not shown).

Discussion

Our survey showed that most of the German PICUs have implemented a local protocol for the treatment of severe TBI (93.1%), conceivably to compensate for the expired German national guideline. However, these individual protocols only partly followed evidence-based regimens and varied largely among each other. Noteworthy, the adherence to evidence-based treatment protocols showed a relation to discharge survival and favorable neurological outcome [8].

While indication for initial cCT in severe TBI was undisputed, routine cCT in mild to moderate TBI was not routinely performed, even with former guideline indications, like skull fracture. In cases of optional indications, like strong headache, cCT was occasionally avoided, most likely for radiation hygiene. This could be of special interest, as the risk of leukemia seems highest for head CTs in children below the age of 5 [20], which also represents the age at which TBI makes up for ~ 50% of all pediatric traumas [3].

Almost all PICUs used invasive ICP measurement in severe TBI management, but also occasionally in mild TBI. A case-related view would have been interesting for a further evaluation of these indications in mild and moderate TBI. Although, no ICP threshold was recommended by the German guidelines, all participants favored a threshold of 20 mmHg. The target CCP ranged from 40 to over 60 mmHg, with a trend to a range of 50–60 mmHg, which is in line with the former German guidelines [9], but exceeds the recommendation of the US guidelines (40–50 mmHg, [12]).

Our study further showed that the relevance of the individual advanced neuromonitoring methods is rated highest by their users. Doppler ultrasound and EEG were the most trusted and most frequently used methods. The application of NIRS in severe pediatric TBI seems indicated as reduced $PbtO_2$ is associated with poor outcome [21, 22]. Interestingly, we found that although NIRS monitoring was frequently applied to pediatric head trauma patients, the clinical relevance of NIRS was somewhat disregarded by a large percentage of its users. This might be due to (i) the limited number of publications regarding the use of $PbtO_2$ in children with TBI, (ii) the spatial limitation of $PbtO_2$ in the assessment of global brain oxygenation [23], (iii) the complex relationship between ICP and $PbtO_2$ [24], and (iv) the paucity of studies on significant effects on outcome parameters. Thus, further studies are needed for clarification.

In addition, a lack of standardized anticonvulsive treatment guidelines (in Germany and the USA) leads to substantial variations in anticonvulsants and continuous EEG monitoring implementation in severe TBI, as recently shown in the *Approaches and Decisions in Acute Pediatric TBI trial* [15]. In our survey, the participating PICUs did not perform routine early anticonvulsive prophylaxis of PTS. Formerly, phenytoin was recommended as medication of choice [9, 12], which was ubiquitously reported to be rarely used by German PICUs of our survey in the management of severe TBI. It is worth mentioning that levetiracetam might serve as a reasonable alternative. Preference of levetiracetam over phenytoin was also

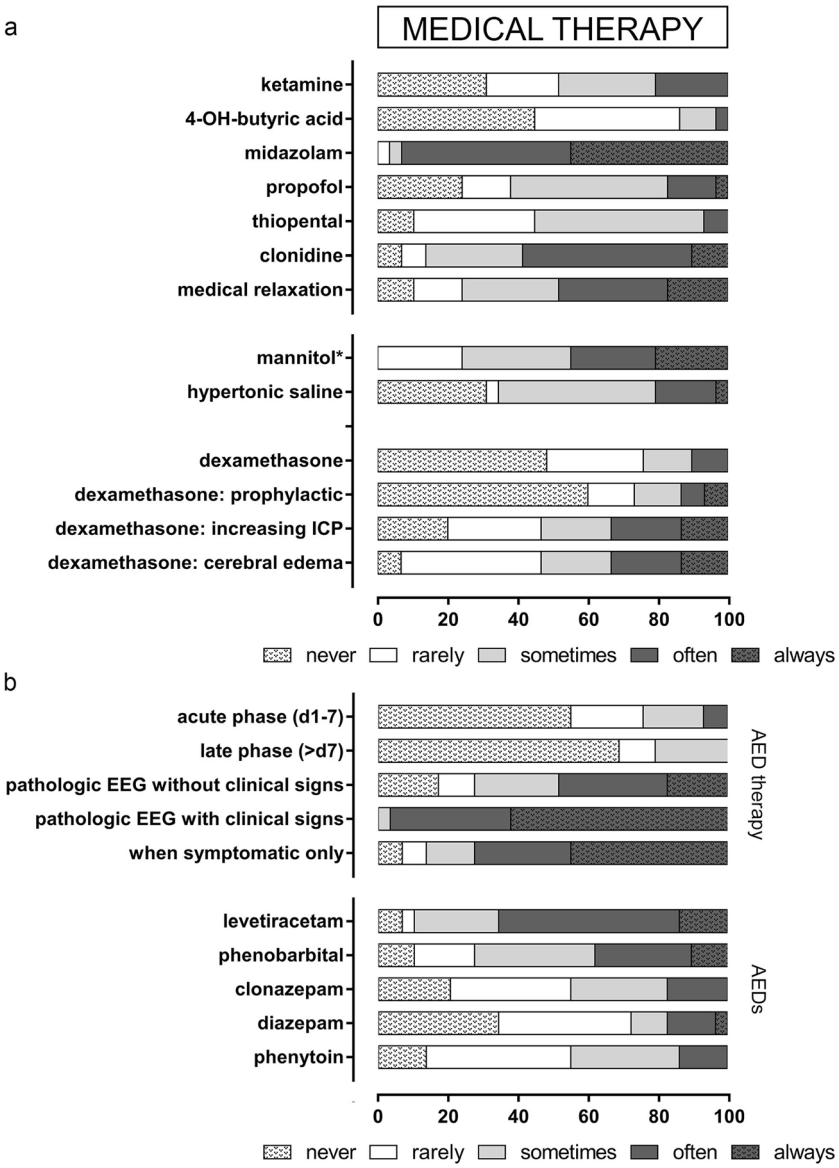

Fig. 4 Survey results regarding medical therapy: AED = antiepileptic drugs, * repeated bolus scheme; Displayed is the proportional distribution of given answers (never-always) regarding general medical therapy (**a**) and anticonvulsive treatment in detail (**b**)

observed by others in children [15] and in adults [16], alike. The underlying factors were recently discussed by Kurz et al. [15] and encompass the availability of intravenous application, little side effects, and minimal medication interactions. Moreover, children suffering from severe TBI may have markedly altered protein binding capacity and phenytoin metabolism [25]. However, supporting evidence regarding the efficacy of levetiracetam as a PTS agent is limited [26], with only a limited number of pediatric studies [27]. In addition, the effect of levetiracetam on TBI long-term outcome remains elusive so far, although results from rodent models and small human studies seem promising [28, 29].

Treatment of high ICP mainly followed the expired German guideline using mannitol, sedation, 30° positioning of upper body, restricted hyperventilation, and very restricted hypothermia (see *Cool kids trial*, [30]). Recent pediatric studies [8, 31] indicate that high-dose barbiturates could be beneficial in the absence of hypotension for refractory high ICP treatment. This option was only infrequently used by our respondents, maybe, because of restricted recommendation by the former German guideline. Inexplicably, dexamethasone remains a treatment option for several participants in contrast to present recommendations [9, 11, 12]. The use of decompressive craniectomy is controversially discussed [32, 33] but commonly performed by our participants. To further lower high ICP, mannitol was used more readily, when compared to hypertonic saline. The preference of mannitol over hypertonic saline might be related to the longer experience with the drug [23] and recommendation in the former German national guideline. Furthermore, while the blood-brain barrier is nearly impermeable to both mannitol and sodium,

each medication has its unique advantages [23]. There is no data to support the superiority of one over the other in severe pediatric TBI. Similarly, a recent meta-analysis of the literature showed that there is heterogeneity with regard to which agent is most efficacious in adults [14]. Nonetheless, hypertonic saline has recently been gaining favor for hyperosmolar therapy in pediatric TBI with signs and symptoms of herniation [23] and is already recommended (level II) in the American guideline [12].

All PICUs initiated neurological rehabilitation, a field that has evolved rapidly over the last two decades [34]. Two thirds of the respondents considered (neuro-)endocrine follow-up. Neuroendocrine derangements following TBI, i.e., post-traumatic hypopituitarism, have received increasing recognition in recent years due to their potential contribution to adverse TBI outcome [35]. Alterations of the hypothalamo-pituitary axis have been documented in the acute phase of TBI (mostly transient, gonadotropins > vasopressin > growth hormone > corticotrophin) and post-acute phase (mostly permanent, 25% of TBI survivors, [35]). Thus, acute identification of these TBI-associated dysregulations by PICU physicians and initiation of follow-up could help to minimize long-term adverse consequences of untreated hypopituitarism.

Our study is limited by the low response rate (41.4%), although not uncommon in web-based surveys [36] and German ICU surveys [37]. The transferability of the statements is further limited by the potential differences between survey-reported practices and actual management. It has to be noted that the focus of our study was on isolated severe TBI, while in reality, this entity is strongly associated with other injuries, i.e., part of polytrauma management. However, the present data gives an overview of current (2017) practices in pediatric intensive care management of severe traumatic brain injury in Germany and reveals an unmet need for the revised national guideline for treatment of severe TBI in pediatrics. Further national and international clinical trials (e.g., ADAPT trial) are needed to facilitate the revision of the existing guidelines, especially regarding the medical treatment of cerebral edema (i.e., mannitol versus hypertonic saline), implementation of advanced neuromonitoring techniques, and the role and choice of medical prophylaxis for PTS.

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Compliance with ethical standards

Conflict of interest We declare no competing interests.

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