American Journal of Emergency Medicine 89 (2025) 78–84

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

# Pharmacotherapy adjuncts for traumatic brain injury: A narrative review of evidence and considerations in the emergency department

Blake Robbins, PharmD [a,*], Lars Almassalkhi, PharmD, MS[b], Regan Baum, PharmD [a], Matthew Blackburn, PharmD [a], Jason Davis, PharmD [a], Lindsey Edwards, PharmD [a], Garrett Hile, PharmD [a], William Olney, PharmD [a], Kyle Weant, PharmD [c], Elise Metts, PharmD [a]

[a] University of Kentucky HealthCare, 800 Rose Street, Lexington, KY, 40536, USA
[b] Atrium Health Wake Forest Baptist, 1 Medical Center Blvd, Winston-Salem, NC, 27157, USA
[c] University of South Carolina College of Pharmacy, 715 Sumter St, Columbia, SC, 29208, USA

ARTICLE INFO

*Article history:*
Received 12 July 2024
Received in revised form 14 November 2024
Accepted 2 December 2024

*Keywords:*
Traumatic brain injury
Emergency department
Pharmacotherapy
Pharmacology
Therapeutics

ABSTRACT

Traumatic Brain Injury (TBI) remains a significant global health concern with significant impact on morbidity and mortality. This narrative review explores adjunctive pharmacologic agents to be employed by emergency medicine clinicians during Advanced Trauma Life Support (ATLS) in patients presenting with a TBI. Pharmacologic agents are commonly employed for the management of rapid sequence intubation and post-intubation analgosedation, hemodynamics, intracranial pressure, coagulopathy, seizure prophylaxis, and infection. This narrative review discusses current evidence and controversies to optimize adjunct pharmacotherapies during the acute management of TBI within the emergency department.



## 1. Introduction

Traumatic Brain Injury (TBI) remains a significant global health concern with more than 200,000 related hospitalizations and approximately 70,000 deaths annually [1]. To mitigate further brain injury, several adjunctive pharmacologic agents may be employed by emergency medicine clinicians during initial presentation. Current guidelines for the management of severe TBI, published in 2016, give general recommendations on select pharmacotherapy adjuncts during Advanced Trauma Life Support (ATLS) which offers a systemic approach to the immediate management of the injured trauma patient [2]. This narrative review will explore current evidence and considerations for select pharmacotherapy adjuncts during ATLS for patients presenting with TBI to the Emergency Department (ED).

## 2. Rapid sequence intubation and post-intubation management

Patients presenting with moderate to severe TBI may require rapid sequence intubation (RSI) for airway protection. Careful consideration must be placed on safely securing the airway while minimizing increases in intracranial pressure (ICP), preventing hypotension, and allowing for post-intubation neurological assessments. The selection of pre-medication, induction, and paralytic agents is essential to promote optimal intubation conditions while minimizing adverse effects [3,4]. In general, agents should be selected by balancing patient-specific factors and optimizing pharmacokinetic properties. Appropriate dosing based on body weight can improve both the efficacy and safety of pharmacologic agents employed [5].

Pre-medications including lidocaine, fentanyl, and remifentanil have been explored to minimize increased sympathetic stimulation inherent to the process of intubation resulting in increased ICP. The benefits of utilizing a premedication should be weighed against potential adverse effects and time required to elicit benefit [6]. Evidence evaluating lidocaine's ability to blunt the sympathetic stimulation associated with RSI has been conflicting [7-9]. Given the potential lack of efficacy in conjunction with risk of adverse effects including hypotension and arrythmias and resultant delays in intubation, lidocaine is not routinely recommended as a pre-treatment for RSI [5,6]. In contrast, studies have consistently demonstrated that fentanyl and remifentanil effectively attenuate increases in ICP. Based on the limited evidence available in the setting of RSI, a 2–3 μg/kg intravenous (IV) dose of

* Corresponding author.
*E-mail address:* blake.robbins@uky.edu (B. Robbins).

https://doi.org/10.1016/j.ajem.2024.12.004
0735-6757/

fentanyl can be considered in patients with concern for elevated ICP [5,10-12].

The optimal induction agent for RSI should minimize hemodynamic effects to mitigate a decline in mean arterial pressure (MAP) and a subsequent decrease in cerebral perfusion pressure (CPP). Etomidate has readily been employed as an induction agent due to its minimal impact on hemodynamics and has demonstrated cerebral protective properties ideal in the setting of TBI [13]. Ketamine is another commonly utilized induction agent with many advantageous properties including analgesic, dissociative and sympathomimetic effects [14]. The use of ketamine for RSI in TBI has been debated for many years based on early studies in the 1970s reporting harm with its use [15,16]. More contemporary data has demonstrated that ketamine does not increase adverse outcomes in patients with TBI and the use of ketamine is no longer contraindicated for use in head trauma [17,18]. Lastly, propofol is frequently considered as an induction agent due to its relatively rapid onset and offset of action, as well as its common employment in post-intubation sedation. Although not specific to TBI, retrospective data has demonstrated no difference in the hemodynamic effects of etomidate, ketamine, or propofol in trauma patients [19]. Future studies are needed to evaluate the true effect of induction agent selection on clinically significant outcomes surrounding hemodynamics, cerebral perfusion, and neurologic recovery in this patient population.

Commonly employed neuromuscular blocking agents (NMBA) for RSI include the depolarizing NMBA, succinylcholine, and non-depolarizing NMBAs rocuronium and vecuronium. Succinylcholine's short duration of 5–10 min is a desirable pharmacokinetic advantage in patients requiring timely neurologic assessment to help guide further care but has been weighed against a proposed risk of increasing ICP [20,21]. Evidence evaluating the clinical significance of succinylcholine on ICP has been of low quality and has shown mixed results [20,22-26]. Alternative agents include rocuronium and vecuronium, both with longer durations of action ranging from 20 to 80 min depending on agent and dose [21]. The availability of sugammadex, a modified γ-cyclodextrin that selectively and rapidly reverses rocuronium and vecuronium, has been cited to address the primary disadvantage of these NMBAs [27]. Sugammadex is typically dosed at 2–4 mg/kg based on the level of paralysis assessed by twitches following train-of-four stimulation. Unless promptly reversed, rocuronium and vecuronium require timely initiation of sedation to prevent awareness during paralysis [28]. Given the lack of high-quality trials, there is currently insufficient evidence to routinely recommend a preferred neuromuscular blocking agent in the setting of TBI [3].

Following intubation, appropriate sedation should be initiated to minimize any chance of the patient remaining paralyzed while conscious or self-extubating [29]. Propofol is a continuous infusion agent that has long been employed as a first-line option for post-intubation sedation due favorable properties including a short half-life allowing for rapid titration and quick offset, ability to achieve deep sedation when appropriate, and capacity to decrease ICP [30,31]. Midazolam provides a longer duration of activity compared to propofol and also has the ability to achieve amnesia and deep sedation at higher doses [32]. Both agents demonstrate anti-epileptic properties and may be useful in patients displaying post-traumatic seizure activity [30]. Dexmedetomidine possesses amnestic effects but does not provide deep sedation or anti-epileptic properties. It is important to note dexmedetomidine alone should not be utilized in patients who may still be pharmacologically paralyzed [33].

In conjunction with adequate sedation, clinicians should provide appropriate analgesia for patients experiencing TBI. IV push doses of opioids such as hydromorphone, fentanyl, or morphine afford a rapid onset for pain control over short periods. Fentanyl offers pharmacokinetic advantages of a quicker onset and shorter half-life compared to hydromorphone and morphine to optimize neurological assessments [34]. In patients requiring intubation, continuous opioid infusions should be strongly considered during the initial and optimization stage of patient assessment for adequate analgosedation [29].

## 3. Hemodynamic management

The management of blood pressure (BP) in patients with TBI is a delicate balance between maintaining CPP and preventing hematoma expansion. Both extremes in BP complicate care for these patients. Under normal circumstances, a drop in systolic blood pressure (SBP) will result in autoregulation compensation leading to vasodilation to maintain adequate cerebral perfusion, resulting in increased cerebral blood volume, and increased ICP. In the injured brain, cerebral autoregulation may not remain intact. In these cases, cerebral perfusion is dependent on SBP to prevent cerebral ischemia [35]. Hypotension in severe TBI, commonly defined as a SBP <90 mmHg, has been associated with increased mortality and poor functional outcome [36,37]. The resultant hypoperfusion caused by hypotension has also been associated with coagulopathy secondary to tissue factor release [38]. Concomitant polytrauma may also pose challenges to managing BP in TBI as damage control resuscitation is typically employed in early trauma resuscitation. However, given the significant impact that hypotension has on outcomes in severe TBI, guidelines recommend maintaining SBP at or above 100–110 mmHg depending on the age of the patient [2].

Resuscitation of the hypotensive TBI patient, much like other trauma patients, begins with fluid resuscitation. Fluid resuscitation in patients presenting with a TBI involves restoration and/or maintenance of intravascular volume to limit both hypo- and hypervolemia to improve cerebral blood flow (CBF), limit cerebral hypoxia and ischemia, and prevent dangerous elevations in ICP [39]. Hypovolemia and associated hypotension are associated with increased mortality and poor outcomes for patients with TBI [36,40]. At present, there is controversy regarding the optimal administration of IV fluid for patients with TBI.

In the pre-hospital and acute setting, hypotonic fluids such lactated ringers (LR) are often less desirable due to a potential increase in cerebral edema. Several studies have compared the administration of 0.9 % sodium chloride (NS), lactated ringer's (LR), and hypertonic solutions. In one study comparing LR to 7.5 % sodium chloride (HTS), there was no difference in 6-month mortality, survival to discharge, or favorable neurological outcomes at 6 months [41]. Similar results were seen in two studies conducted by Vassar et al. comparing 7.5 % HTS with LR and HTS with NS, though the latter study was underpowered [42,43]. In an observational study evaluating the pre-hospital use of LR compared to NS, investigators found LR was associated with increased mortality compared with NS in patients with TBI, warranting the need for prospective randomized trials in this patient population [44]. Additionally, a meta-analysis reviewing twelve pertinent studies of pre-hospital fluid administration in patients with TBI did not find any statistically significant difference in mortality between fluid types [45].

In terms of maintenance fluids and volume status in the post-resuscitative phase of patients with brain injury, the Neurocritical Care Society (NCS) and American Heart Association/American Stroke Association recommend usual maintenance fluid (30 ml/kg/day) and maintaining euvolemia, though the Brain Trauma Foundation (BTF) has no concrete stance or explicit recommendations for this in TBI patients [39]. The lack of clear guidance on fluid management in the TBI population highlights the complicated nature of brain pathophysiology after injury. Changes in the blood-brain barrier (BBB), alterations in neuroendocrine function, endothelial damage, and extracranial injuries can all affect fluid status and CBF. Maintaining appropriate fluid status and avoiding hypotension appears to be best practice to decrease mortality and improve outcomes [2].

If fluid and/or blood product resuscitation does not attain hemodynamic targets, vasoactive agents may be utilized to achieve these goals. While there is no evidence to suggest a single agent is preferred, a study evaluating the use of vasopressors in TBI demonstrated the most utilized agents include norepinephrine, phenylephrine, and

vasopressin [46]. Notably, in this study, the use of any vasopressor was associated with an increased in-hospital mortality and the addition of each additional vasoactive agent demonstrated a stepwise increase in in hospital mortality. Patients who required vasopressors were at baseline determined to have a more severe TBI and overall higher injury burden.

In contrast, many patients with TBI may present hypertensive. The safety and efficacy of acutely and rapidly reducing blood pressure in a hypertensive patient with TBI is less established [47,48]. Hypertension in TBI is caused by the activation of catecholamine release pathways via regional brain injury, resulting in elevated ICP and activation of neuroendocrine pathways. The impact of hypertension is complex and multifactorial, involving blood pressure, cerebral edema, ICP, and cerebral autoregulation [49]. In a study examining the correlation between initial ED SBP and outcomes for patients with moderate to severe blunt TBI found a mortality rate of 21 % when SBP was <120 mmHg, 9 % between 120 mmHg and 140 mmHg, and 19 % with SBP was ≥140 mmHg [50]. Other studies have also demonstrated a U-shaped correlation between mortality and admission hypotension (SBP <90 mmHg) or hypertension (>140–160 mmHg depending on study definitions) [51-54].

Treatment of severe hypertension in patients with TBI may be reasonable on a case-by-case patient basis. No consensus exists regarding the optimal pharmacologic strategy for treating hypertension in TBI. However, similar to sICH, blood pressure variability in the setting of TBI has been associated with poor outcomes [51,55]. Nicardipine administered as a continuous infusion is an attractive option due to its rapid onset and short duration of action allowing for easy titration. Although not evaluated exclusively in the TBI patient population, nicardipine has been shown to achieve quicker BP goal attainment, less variability, and less need for rescue therapy compared to a bolus regimen of labetalol or hydralazine [56-58]. Clevidipine is an alternative continuous infusion agent with a shorter duration of action than nicardipine, offering the advantage of a more rapid titration. Nicardipine and clevidipine have demonstrated similar clinical outcomes including time to blood pressure control, percentage of time in goal, and need for additional antihypertensive agents although data is sparce within the TBI patient population [59]. Lastly, the use of venous vasodilators such as nitroprusside and nitroglycerin should be avoided due to unopposed vasodilation and the possibility of increasing ICP [60,61].

Currently, there are no guideline recommendations on the prevention or treatment of arterial hypertension after severe TBI. Further studies are needed to determine an optimal target for hypertensive TBI patients. In addition, a strategy focused on maintenance of CPP as an endpoint may be a more important variable in early hemodynamic management.

## 4. Hyperosmolar therapies

Traumatic brain injuries, both the initial insult after a TBI and the subsequent secondary injury, can result in cerebral edema contributing to elevations in ICP. The underlying etiology is currently thought to be secondary to a complex interplay of multiple processes, including both vasogenic and cytotoxic edema [62]. To combat this edema, hyperosmolar therapies may be considered to mobilize this fluid out of the skull cavity by optimizing intravascular osmolality, thereby generating an osmotic gradient within the systemic circulation [63].

Currently, the most utilized osmotic agents in clinical practice are hypertonic (>0.9 %) saline (HTS) and mannitol solutions. The concept behind the utilization of these two agents is founded on the premise both sodium and mannitol molecules are relatively impermeable to a physiologically intact BBB, thereby establishing an osmotic gradient following administration [64]. In the emergent setting, both agents, including up to 23.4 % HTS, have demonstrated safety and efficacy when administered as intermittent IV boluses via peripheral access to rapidly establish an elevated osmotic gradient if central access is unavailable [65,66]. HTS and mannitol are available in a variety of concentrations with the most common being 3 % and 23.4 % for HTS and 20 % for mannitol [67,68]. The dosing of these agents has varied in clinical studies with 3 % HTS recommended to be administered at a dose of 2–5 ml/kg over 5–20 min and 23.4 % is recommended to be administered as 0.5–0.6 ml/kg (maximum of 30 ml) over 10–20 min [66,69]. Mannitol is recommended to be administered at a dose of 0.25–1 g/kg over 5–15 min [66,69,70]. Both of these agents can be readministered as necessary to achieve a targeted reduction in intracranial pressure. Although multiple adverse effects of these agents have been reported with repeated administrations over time, acutely it is important to monitor for IV extravasation, elevations in sodium and osmolality, and electrolyte imbalances. In the acute setting an upper limit of serum sodium from 155 to 160 mEq/L and a serum chloride of 110–115 mEq/L have been suggested as reasonable targets to reduce the incidence of side effects [67].

While multiple guidelines endorse the use of hyperosmolar therapy for the reduction of ICP, it is important to note the quality of evidence remains low due to heterogenous patient populations, low sample size, and inconsistent study designs. Although studies have reported a safe and effective reduction in ICP, hyperosmolar therapy has not been shown to improve clinical outcomes including mortality and neurologic function [66,69,70]. In addition, two meta-analyses have been conducted evaluating the supporting literature behind HTS and mannitol to assess if differences exist between the efficacy of these agents, with neither identifying any differences in clinical outcomes. Guidelines for the acute treatment of cerebral edema put forth by NCS recommend the use of HTS over mannitol for the initial treatment of elevated ICP or cerebral edema in patients with TBI [66]. The underpinnings of this recommendation may lie in the potential advantages of HTS noted in some trials of a faster onset of action and a more substantial and durable reduction in ICP [71]. However, it is important to highlight that the etiology of cerebral edema in this setting is due to a variety of mechanisms involved in cell volume regulation, and it is a gross oversimplification to view this as purely an osmolarity problem [72,73]. The NCS Guidelines echo this concept by stating neither agent should be used with the anticipation of improving neurological outcomes [66].

Hyperosmolar therapies are not without specific risks. Hyperosmolar therapy has been associated with the development of acute kidney injury. Guidelines suggest avoiding HTS in patients with concomitant hypernatremia and hyperchloremia. Mannitol clearance can be reduced in patients with pre-existing renal disease and serum osmolality or osmolar gap should be monitored to minimize adverse kidney effects. Lastly, in patients with extracranial traumatic injuries and a risk of hemorrhage, there is a theoretical concern that mannitol may worsen hypovolemia due to its diuretic effect. Further studies are needed to further establish whether this has clinically significant consequences.

## 5. Management of coagulopathy

Trauma induced coagulopathy is a complex process involving multiple factors preventing hemostasis [74]. One of the proposed mechanisms aiding in the management of the bleeding trauma patient is addressing fibrinolysis. Tranexamic acid (TXA) is an antifibrinolytic agent inhibiting the breakdown of fibrin clots and has been evaluated for its role in the management of trauma induced coagulopathy. Studies conducted in both civilian and military trauma patients have demonstrated a mortality benefit with administration of TXA within 3 h of injury [75,76]. Based on the results of these trials, TXA has been widely accepted as a part of routine care in trauma, but limited data is available to assess the applicability of this therapy to patients with isolated head trauma. It is proposed that increased concentrations of fibrinogen degradation products in the setting of TBI serve as a predictor of worsening hematoma expansion [77]. In a meta-analysis evaluating the use of TXA in TBI, there was a mortality benefit demonstrated but limited information on adverse events or impact on disability prompted the need for

further studies [78]. In the largest clinical trial to date, CRASH 3 investigators conducted an international, multi-center, randomized placebo-controlled trial examining the effects of TXA on death and disability in patients with TBI with 3 h of injury [79]. Similar to CRASH 2, TXA was administered as 1 g over 10 min followed by 1 g over 8 h. Overall, investigators found no difference in the primary study outcome of head injury death within 28 days. However, there was a reduction in head injury-related death in patients with a mild-to-moderate head injury (GCS 9–15) who received TXA. No difference was seen in thromboembolic or other adverse events. In a subsequent study published evaluating the use of pre-hospital TXA in patients with moderate to severe TBI (GCS 3–12), no difference was seen in 6-month neurologic outcome. Based on the available data, there is insufficient evidence to support the routine administration of TXA in isolated TBI [80].

Another important aspect of bleeding that can be addressed is the recent use of an anticoagulant. Patients presenting with concern for TBI in the setting of recent anticoagulant use warrant an immediate evaluation to determine if reversal is appropriate. Reversal of an anticoagulant involves careful consideration between the risks of bleeding in the setting of coagulopathy from anticoagulation, thrombosis due to the underlying condition requiring anticoagulation, and thrombosis due to the reversal agent itself. Current guidelines recommend it is best practice to reverse anticoagulants in patients with clinically significant bleeds defined as causing hemodynamic instability, a decrease in hemoglobin >2 g/dL, requirement of ≥2 units of red blood cells, or occurring in a critical site such as the brain [81-83]. Additionally, reversal should be considered when urgent or emergent surgery is required. Clinicians must take into consideration the anticoagulant's time of ingestion, half-life, metabolism, and, when available, the patient's degree of coagulopathy via agent-specific laboratory monitoring [81].

When reversal of anticoagulation is deemed appropriate, clinicians should utilize an evidence-based approach when selecting both the reversal agent and dose. Emergent reversal of vitamin K-dependent oral anticoagulants (e.g., warfarin) with an International Normalized Ratio (INR) ≥1.4 should be completed with prothrombin complex concentrate (PCC), preferably four-factor PCC if available, in conjunction with IV phytonadione [81-86]. Although the FDA approved dosing of PCC for warfarin reversal is based on both INR and weight, lower quality of evidence has demonstrated lower fixed doses may be as effective, more timely, and less costly [87-90]. If PCC is unavailable, fresh frozen plasma (FFP) dosed at 10–15 ml/kg can be utilized but is less effective at reversing warfarin and may exacerbate pre-existing cerebral edema [83]. In all cases, an INR should be repeated 30 min after completion of product administration to guide further dosing [89,90].

In patients presenting with a clinically significant bleed on direct oral anticoagulants (DOAC), apixaban or rivaroxaban, andexanet alfa is recommended by current guidelines for reversal [81,82,91]. If andexanet alfa is not available or if a patient was receiving edoxaban, PCC should be utilized. Although guidelines recommend a weight-based dose of PCC for intracranial hemorrhages, lower quality of evidence also supports lower fixed dosing for DOAC reversal [92,93]. At present, there are no prospective, randomized controlled trials directly comparing the efficacy and safety of andexanet alfa against the previous standard of care, PCC [94-96]. Recently, a RCT demonstrated that andexanet alfa demonstrated better control of hematoma expansion than usual care which included patients receiving PCC with no difference in mortality or neurologic outcomes and an increased rate of thrombotic events [97]. It is important to note anti-Xa activity calibrated to low molecular weight heparin (LMWH) cannot be utilized to determine the degree of coagulopathy caused by a DOAC and should only be utilized as a qualitative method to determine systematic presence. In addition, anti-Xa calibrated to LMWH cannot be reliably utilized to monitor for effectiveness of reversal with andexanet alfa or PCC [81,82].

Patients receiving therapeutic doses of LMWH within 12 h or IV heparin within the proceeding 2–3 h should be reversed using protamine [81-83]. Lastly, idarucizumab has demonstrated complete and immediate reversal of dabigabtran [98]. Of note, a subsequent dose of idarucizumab may be considered if bleeding continues or before an emergent invasive procedure if there is laboratory evidence of persistent dabigatran effect. If idarucizumab is unavailable, FFP may be utilized [81-83].

## 6. Seizure prophylaxis

The rate of post-traumatic seizures (PTS) has been reported as high as 12 % and with subclinical seizures found on electroencephalogram in as many as 25 % of patients [70]. Several anti-seizure medications (ASMs) have been explored to reduce the incidence of early PTS in patients with TBI. Guidelines from both the NCS and the BTF suggest antiseizure medication may be used in hospitalized patients with moderate-severe TBI to prevent early PTS for up to 7 days [69,99]. Selection of alternative ASMs should be based on current available level of evidence, patient-specific factors, and clinical setting.

Phenytoin historically has the largest body of evidence for PTS prophylaxis with several studies demonstrating its effectiveness at reducing early PTS [100,101]. Current guidelines from the BTF recommend phenytoin to decrease the incidence of early PTS when the overall benefit outweighs possible complications associated with such ASM treatment [70]. Disadvantages of phenytoin include potential adverse-effects (e.g. hypotension, cardiac arrhythmias), medication interactions, and drug level monitoring [102]. Levetiracetam has been increasingly employed over phenytoin in recent years for the prevention of early PTS due to its minimal drug interactions, side effects, and lack of required therapeutic monitoring [103]. Given the increased feasibility of levetiracetam, the more recent NCS guidelines suggest levetiracetam over phenytoin [99].

Several other ASMs have failed to demonstrate a routine place in therapy for the prevention of early PTS. Valproate therapy has been associated with no benefit for prevention of early PTS when compared to phenytoin and failed to prevent late PTS. In addition, a nonsignificant trend toward higher mortality rate was found in the valproate group [104]. These findings suggest against the use of valproate for early or late PTS prophylaxis. Carbamazepine has been demonstrated to reduce the rates of early and late PTS compared to placebo [105]. However, its use has been limited due to the potential for adverse effects, medication interactions, lack IV formulations, and drug level monitoring [102]. Lastly, phenobarbital has been evaluated in two studies involving patients with TBI with wide confidence intervals for early PTS and no effect in reduction late PTS when compared to placebo [106-108]. Due to lack of evidence, adverse-effects, medication interactions, and drug level monitoring, phenobarbital should not be recommended for PTS prophylaxis after TBI [102,109].

## 7. Antibiotic prophylaxis

Patients presenting to the ED with a TBI may often have an accompanying skull fracture. Open skull fractures, such as the case in a penetrating traumatic head injury, exposes the cranial vault to the outside environment. Other traumatic skull fractures, like non-penetrating basilar skull fractures, can expose the central nervous system (CNS) to bacteria from the paranasal sinuses, nasopharynx or middle ear if the dura mater is torn adjacent to the fracture site [110]. Non-penetrating basilar skull fractures account for up to 15.8 % of all skull fractures, with up to 20.8 % those associated with a cerebrospinal fluid (CSF) leak placing patients at increased risk for nosocomial meningitis.

Current guidelines recommend patients with head trauma at increased risk of developing infection are recommended to receive vancomycin plus an anti-pseudomonal beta-lactam able to achieve high CSF penetration (i.e. cefepime, ceftazidime, or meropenem). In patients

having experienced anaphylaxis to beta-lactams and meropenem is contraindicated, guidelines recommend aztreonam or ciprofloxacin as alternative agents. These agents are recommended due to their ability to cover common causative organisms such as *Staphylococcus*, *Streptococcus*, *Enterococcus*, and gram-negative nosocomial organisms like *Pseudomonas* [111].

Despite current guideline recommendations, the efficacy of antimicrobial prophylaxis to prevent post-traumatic meningitis remains controversial due to low quality clinical data. Historical data shows the incidence of CNS infections from penetrating traumatic brain injuries ranged from 8 to 23 % in the civilian population [112]. A multicenter trial evaluating the modern rates of CNS infections in penetrating TBI patients concluded the modern rate of infection was 7 % in those who received appropriate prophylactic antibiotics compared to 6 % for the control group who did not receive prophylactic antibiotics. As a result, there was no statistically significant difference in CNS infection rates between those who did and did not receive prophylactic antibiotic post penetrating TBI [113]. Subsequently, a Cochrane meta-analysis was conducted comparing antibiotics verses placebo or no intervention for basilar skull fractures. Authors found there were no significant differences between antibiotic prophylaxis groups and control groups with respect to decreases in the frequency of meningitis, all-cause mortality, or meningitis related mortality [5]. Lastly, a meta-analysis evaluating antibiotic prophylaxis after basilar skull fractures concluded there is no supporting evidence to recommend prophylactic antibiotics to decrease the risk of meningitis in this patient population [114].

However, patients with evidence of CSF leak (i.e. CSF otorrhea or rhinorrhea, bilateral periorbital ecchymosis, Battle's sign, peripheral facial nerve palsy, hemotympanum or tympanic membrane perforation with blood in the external auditory canal, hearing loss, evidence of vestibular dysfunction and anosmia) are at an increased risk for meningitis. Clinical data suggests patients who present with a CSF leak may benefit from antibiotic prophylaxis. In a study conducted by Yellinek et al. published in 2015, 107 patients with traumatic basilar skull fractures were evaluated with only four patients developing meningitis. All four of these patients had a CSF leak with CSF rhinorrhea [115].

## 8. Conclusion

Various pharmacologic adjuncts may be employed during ATLS in order to improve patient outcomes. While ATLS provides a standardized framework for optimization of care of the TBI patient to help guide the use of these agents, it is important for clinicians to recognize when these agents should be utilized in addition to their risks and benefits.

## CRediT authorship contribution statement

**Blake Robbins:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Conceptualization. **Lars Almassalkhi:** Writing – review & editing, Writing – original draft. **Regan Baum:** Writing – review & editing, Writing – original draft. **Matthew Blackburn:** Writing – review & editing, Writing – original draft. **Jason Davis:** Writing – review & editing, Writing – original draft. **Lindsey Edwards:** Writing – review & editing, Writing – original draft. **Garrett Hile:** Writing – review & editing, Writing – original draft. **William Olney:** Writing – review & editing, Writing – original draft. **Kyle Weant:** Writing – review & editing, Writing – original draft. **Elise Metts:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References


[1] National Center for Health Statistics: Mortality Data on CDC WONDER. Centers for Disease Control and Prevention. Accessed January 3. https://wonder.cdc.gov/mcd.html; 2023.

[2] Carney N, Totten AM, Ullman JS, et al. Guidelines for the Management of Severe Traumatic Brain Injury 4th edition Published online. ; 2016.

[3] Acquisto NM, Mosier JM, Bittner EA, et al. Society of Critical Care Medicine clinical practice guidelines for rapid sequence intubation in the critically ill adult patient. Crit Care Med. 2023;51(10):1411–30. https://doi.org/10.1097/CCM.0000000000006000.

[4] Stollings JL, Diedrich DA, Oyen LJ, Brown DR. Rapid-sequence intubation: a review of the process and considerations when choosing medications. Ann Pharmacother. 2014;48(1):62–76. https://doi.org/10.1177/1060028013510488.

[5] Kramer N, Lebowitz D, Walsh M, Ganti L. Rapid sequence intubation in traumatic brain-injured adults. Cureus. 2018;10(4). https://doi.org/10.7759/CUREUS.2530.

[6] Robinson N, Clancy M. In patients with head injury undergoing rapid sequence intubation, does pretreatment with intravenous lignocaine/lidocaine lead to an improved neurological outcome? A review of the literature. Emerg Med J. 2001;18(6):453–7. https://doi.org/10.1136/EMJ.18.6.453.

[7] Samaha T, Ravussin P, Claquin C, Écoffey C. Prevention de l'augmentation de la pression arterielle et de la pression intracranienne Lors de L'intubation endotracheale en neurochirurgie: esmolol versus lidocaine. Ann Fr Anesth Reanim. 1996;15(1):36–40. https://doi.org/10.1016/0750-7658(96)89400-7.

[8] White PF, Schlobohm RM, Pitts LH, Lindauer JM. A randomized study of drugs for preventing increases in intracranial pressure during endotracheal suctioning. Anesthesiology. 1982;57(3):242–4. https://doi.org/10.1097/00000542-198209000-00019.

[9] Grover VK, Reddy GMSR, Kak VK, Singh S. Intracranial pressure changes with different doses of lignocaine under general anaesthesia. Neurol India. 1999;47(2):118. Accessed December 5, 2023. https://www.neurologyindia.com/article.asp?issn=0028-3886;year=1999;volume=47;issue=2;spage=118;epage=21;aulast=Grover.

[10] Dahlgren N, Messeter K. Treatment of stress response to laryngoscopy and intubation with fentanyl. Anaesthesia. 1981;36(11):1022–6. https://doi.org/10.1111/J.1365-2044.1981.TB08676.X.

[11] Chung KS, Sinatra RS, Halevy JD, Paige D, Silverman DG. A comparison of fentanyl, esmolol, and their combination for blunting the haemodynamic responses during rapid-sequence induction. Can J Anaesth. 1992;39(8):774–9. https://doi.org/10.1007/BF03008287.

[12] Kuzak N, Harrison DW, Zed PJ. Use of lidocaine and fentanyl premedication for neuroprotective rapid sequence intubation in the emergency department. CJEM. 2006;8(2):80–4. https://doi.org/10.1017/S1481803500013518.

[13] Oglesby AJ. Should etomidate be the induction agent of choice for rapid sequence intubation in the emergency department? Emerg Med J. 2004;21(6):655–9. https://doi.org/10.1136/EMJ.2003.009043.

[14] Baekgaard JS, Eskesen TG, Sillesen M, Rasmussen LS, Steinmetz J. Ketamine as a rapid sequence induction agent in the trauma population: a systematic review. Anesth Analg. 2019;128(3):504–10. https://doi.org/10.1213/ANE.0000000000003568.

[15] Green SM, Andolfatto G, Krauss BS. Ketamine and intracranial pressure: no contraindication except hydrocephalus. Ann Emerg Med. 2015;65(1):52–4. https://doi.org/10.1016/J.ANNEMERGMED.2014.08.025.

[16] Filanovsky Y, Miller P, Kao J. Myth: ketamine should not be used as an induction agent for intubation in patients with head injury. CJEM. 2010;12(2):154–201. https://doi.org/10.1017/S1481803500012197.

[17] Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011;57(5):449–61. https://doi.org/10.1016/J.ANNEMERGMED.2010.11.030.

[18] Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NGW, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. Ann Emerg Med. 2015;65(1):43–51.e2. https://doi.org/10.1016/J.ANNEMERGMED.2014.06.018.

[19] Leede E, Kempema J, Wilson C, et al. A multicenter investigation of the hemodynamic effects of induction agents for trauma rapid sequence intubation. J Trauma Acute Care Surg. 2021;90(6):1009–13. https://doi.org/10.1097/TA.0000000000003132.

[20] Sanfilippo F, Santonocito C, Veenith T, Astuto M, Maybauer MO. The role of neuromuscular blockade in patients with traumatic brain injury: a systematic review. Neurocrit Care. 2015;22(2):325–34. https://doi.org/10.1007/S12028-014-0061-1.

[21] Greenberg SB, Vender J. The use of neuromuscular blocking agents in the ICU: where are we now? Crit Care Med. 2013;41(5):1332–44. https://doi.org/10.1097/CCM.0B013E31828CE07C.

[22] Clancy M, Halford S, Walls R, Murphy M. In patients with head injuries who undergo rapid sequence intubation using succinylcholine, does pretreatment with a competitive neuromuscular blocking agent improve outcome? A literature review. Emerg Med J. 2001;18(5):373–5. https://doi.org/10.1136/EMJ.18.5.373.

[23] Kovarik WD, Mayberg TS, Lam AM, Mathisen TL, Winn HR. Succinylcholine does not change intracranial pressure, cerebral blood flow velocity, or the electroencephalogram in patients with neurologic injury. Anesth Analg. 1994;78(3):469–73. https://doi.org/10.1213/00000539-199403000-00008.

[24] White PF, Schlobohm RM, Pitts LH, Lindauer JM. A randomized study of drugs for preventing increases in intracranial pressure during endotracheal suctioning. Anesthesiology. 1982;57(3):242–4. https://doi.org/10.1097/00000542-198209000-00019.

[25] McLeskey CH, Cullen BF, Kennedy RD, Galindo A. Control of cerebral perfusion pressure during induction of anesthesia in high-risk neurosurgical patients. Anesth Analg. 1974;53(6):985–92. https://doi.org/10.1213/00000539-197453060-00033.
[26] Halldin M, Åk Wåhlin. Effect of succinylcholine on the intraspinal fluid pressure. Acta Anaesthesiol Scand. 1959;3(4):155–61. https://doi.org/10.1111/J.1399-6576.1959.TB00015.X.
[27] Herring WJ, Woo T, Assaid CA, et al. Sugammadex efficacy for reversal of rocuronium- and vecuronium-induced neuromuscular blockade: a pooled analysis of 26 studies. J Clin Anesth. 2017;41:84–91. https://doi.org/10.1016/J.JCLINANE.2017.06.006.
[28] Fuller BM, Pappal RD, Mohr NM, et al. Awareness with paralysis among critically ill emergency department patients: a prospective cohort study. Crit Care Med. 2022;50(10):1449–60. https://doi.org/10.1097/CCM.0000000000005626.
[29] Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306. https://doi.org/10.1097/CCM.0B013E3182783B72.
[30] Oddo M, Crippa IA, Mehta S, et al. Optimizing sedation in patients with acute brain injury. Crit Care. 2016;20(1). https://doi.org/10.1186/S13054-016-1294-5.
[31] Herregods L, Verbeke J, Roily G, Colardyn F. Effect of propofol on elevated intracranial pressure. Preliminary results. Anaesthesia. 1988;43(Suppl):107–9. https://doi.org/10.1111/J.1365-2044.1988.TB09089.X.
[32] Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 2008;182(182):335–60. https://doi.org/10.1007/978-3-540-74806-9_16.
[33] Ruokonen E, Parviainen I, Jakob SM, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med. 2009;35(2):282–90. https://doi.org/10.1007/S00134-008-1296-0.
[34] Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet. 1996;31(4):275–92. https://doi.org/10.2165/00003088-199631040-00004.
[35] Armstead WM. Cerebral blood flow autoregulation and Dysautoregulation. Anesthesiol Clin. 2016;34(3):465. https://doi.org/10.1016/J.ANCLIN.2016.04.002.
[36] Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. Arch Surg. 2001;136(10):1118–23. https://doi.org/10.1001/ARCHSURG.136.10.1118.
[37] Berry C, Ley EJ, Bukur M, et al. Redefining hypotension in traumatic brain injury. Injury. 2012;43(11):1833–7. https://doi.org/10.1016/J.INJURY.2011.08.014.
[38] Cohen MJ, Brohi K, Ganter MT, Manley GT, Mackersie RC, Pittet JF. Early coagulopathy after traumatic brain injury: the role of hypoperfusion and the protein C pathway. J Trauma. 2007;63(6):1254–62. https://doi.org/10.1097/TA.0B013E318156EE4C.
[39] van der Jagt M. Fluid management of the neurological patient: a concise review. Crit Care. 2016;20(1). https://doi.org/10.1186/S13054-016-1309-2.
[40] Tohme S, Delhumeau C, Zuercher M, Haller G, Walder B. Prehospital risk factors of mortality and impaired consciousness after severe traumatic brain injury: an epidemiological study. Scand J Trauma Resusc Emerg Med. 2014;22(1):1–9. https://doi.org/10.1186/1757-7241-22-1/TABLES/4.
[41] Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA. 2004;291(11):1350–7. https://doi.org/10.1001/JAMA.291.11.1350.
[42] Vassar MJ, Perry CA, Gannaway WL, Holcroft JW. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. Arch Surg. 1991;126(9):1065–72. https://doi.org/10.1001/ARCHSURG.1991.01410330019002.
[43] Vassary M, Perry C, Holcroft J. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran - a controlled trial. The Journal of Trauma: Injury, Infection, and Critical Care. 1992;33(1):165. Accessed December 5, 2023. https://journals.lww.com/jtrauma/Citation/1992/07000/PREHOSPITAL_RESUSCITATION_OF_HYPOTENSIVE_TRAUMA.96.aspx.
[44] Rowell SE, Fair KA, Barbosa RR, et al. The impact of pre-Hospital Administration of Lactated Ringer's solution versus Normal saline in patients with traumatic brain injury. J Neurotrauma. 2016;33(11):1054–9. https://doi.org/10.1089/NEU.2014.3478.
[45] Bergmans SF, Schober P, Schwarte LA, Loer SA, Bossers SM. Prehospital fluid administration in patients with severe traumatic brain injury: a systematic review and meta-analysis. Injury. 2020;51(11):2356–67. https://doi.org/10.1016/J.INJURY.2020.08.030.
[46] Dhillon NK, Huang R, Mason R, et al. Vasopressors in traumatic brain injury: quantifying their effect on mortality. Am J Surg. 2020;220(6):1498–502. https://doi.org/10.1016/J.AMJSURG.2020.09.016.
[47] Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355–65. https://doi.org/10.1056/NEJMOA1214609.
[48] Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375(11):1033–43. https://doi.org/10.1056/NEJMOA1603460/SUPPL_FILE/NEJMOA1603460_DISCLOSURES.PDF.
[49] Krishnamoorthy V, Chaikittisilpa N, Kiatchai T, Vavilala M. Hypertension after severe traumatic brain injury: friend or foe? J Neurosurg Anesthesiol. 2017;29(4):382–7. https://doi.org/10.1097/ANA.0000000000000370.
[50] Zafar SN, Millham FH, Chang Y, et al. Presenting blood pressure in traumatic brain injury: a bimodal distribution of death. Journal of Trauma - Injury, Infection and Critical Care. 2011;71(5):1179–84. https://doi.org/10.1097/TA.0B013E3182140D38.
[51] Barmparas G, Liou DZ, Lamb AW, et al. Prehospital hypertension is predictive of traumatic brain injury and is associated with higher mortality. J Trauma Acute Care Surg. 2014;77(4):592–8. https://doi.org/10.1097/TA.0000000000000382.
[52] Sellmann T, Miersch D, Kienbaum P, Flohé S, Schneppendahl J, Lefering R. The impact of arterial hypertension on polytrauma and traumatic brain injury. Dtsch Arztebl Int. 2012;109(49):849–56. https://doi.org/10.3238/ARZTEBL.2012.0849.
[53] Ley EJ, Singer MB, Clond MA, et al. Elevated admission systolic blood pressure after blunt trauma predicts delayed pneumonia and mortality. J Trauma. 2011;71(6):1689–93. https://doi.org/10.1097/TA.0B013E31823CC5DF.
[54] Butcher I, Maas AIR, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24(2):294–302. https://doi.org/10.1089/NEU.2006.0032.
[55] Tran QK, Frederick H, Tran C, et al. Blood pressure variability and outcome in traumatic brain injury: a propensity score matching study. West J Emerg Med. 2022;23(5):769–80. https://doi.org/10.5811/WESTJEM.2022.6.55549.
[56] Malesker MA, Hilleman DE. Intravenous labetalol compared with intravenous nicardipine in the management of hypertension in critically ill patients. J Crit Care. 2012;27(5):528.e7–528.e14. https://doi.org/10.1016/J.JCRC.2011.12.005.
[57] Liu-DeRyke X, Janisse J, Coplin WM, Parker D, Norris G, Rhoney DH. A comparison of nicardipine and labetalol for acute hypertension management following stroke. Neurocrit Care. 2008;9(2):167–76. https://doi.org/10.1007/S12028-008-9057-Z.
[58] Poyant JO, Kuper PJ, Mara KC, et al. Nicardipine reduces blood pressure variability after spontaneous intracerebral hemorrhage. Neurocrit Care. 2019;30(1):118–25. https://doi.org/10.1007/S12028-018-0582-0.
[59] Rosenfeldt Z, Conklen K, Jones B, Ferrill D, Deshpande M, Siddiqui FM. Comparison of Nicardipine with Clevidipine in the Management of Hypertension in acute cerebrovascular diseases. J Stroke Cerebrovasc Dis. 2018;27(8):2067–73. https://doi.org/10.1016/J.JSTROKECEREBROVASDIS.2018.03.001.
[60] Cottrell JE, Patel K, Turndorf H, Ransohoff J. Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. J Neurosurg. 1978;48(3):329–31. https://doi.org/10.3171/JNS.1978.48.3.0329.
[61] Ghani GA, Sung YF, Weinstein MS, Tindall GT, Fleischer AS. Effects of intravenous nitroglycerin on the intracranial pressure and volume pressure response. J Neurosurg. 1983;58(4):562–5. https://doi.org/10.3171/JNS.1983.58.4.0562.
[62] Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Neuropharmacology. 2019;145(Pt B):230–46. https://doi.org/10.1016/J.NEUROPHARM.2018.08.004.
[63] Al-Mufti F, Mayer SA. Neurocritical care of acute subdural hemorrhage. Neurosurg Clin N Am. 2017;28(2):267–78. https://doi.org/10.1016/J.NEC.2016.11.009.
[64] Stevens RD, Shoykhet M, Cadena R. Emergency neurological life support: intracranial hypertension and herniation. Neurocrit Care. 2015;23 Suppl 2(Suppl. 2):76–82. https://doi.org/10.1007/S12028-015-0168-Z.
[65] Faiver L, Hensler D, Rush SC, Kashlan O, Williamson CA, Rajajee V. Safety and efficacy of 23.4% sodium chloride administered via peripheral venous access for the treatment of cerebral herniation and intracranial pressure elevation. Neurocrit Care. 2021;35(3):845–52. https://doi.org/10.1007/S12028-021-01248-7.
[66] Cook AM, Morgan Jones G, Hawryluk GWJ, et al. Guidelines for the acute treatment of cerebral edema in Neurocritical care patients. Neurocrit Care. 2020;32(3):647–66. https://doi.org/10.1007/S12028-020-00959-7.
[67] Venkatasubramanian C, Lopez GA, O'Phelan KH, et al. Emergency neurological life support: fourth edition, updates in the approach to early Management of a Neurological Emergency. Neurocrit Care. 2020;32(2):636–40. https://doi.org/10.1007/S12028-019-00810-8.
[68] Busey K, Ferreira J, Aldridge P, Crandall M, Johnson D. Comparison of weight-based dosing versus fixed dosing of 23.4% hypertonic saline for intracranial pressure reduction in patients with severe traumatic brain injury. J Emerg Trauma Shock. 2020;13(4):252–6. https://doi.org/10.4103/JETS.JETS_66_19.
[69] Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, third edition: update of the brain trauma foundation guidelines, Executive Summary. Neurosurgery. 2019;84(6):1169–78. https://doi.org/10.1093/NEUROS/NYZ051.
[70] Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017;80(1):6–15. https://doi.org/10.1227/NEU.0000000000001432.
[71] Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J. Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients - a randomized clinical trial [ISRCTN62699180]. Crit Care. 2005;9(5):R530. https://doi.org/10.1186/CC3767.
[72] Chalard K, Quintard H. Brain oedema post TBI: In search of the Holy grail. Anaesth Crit Care Pain Med. 2021;40(4). https://doi.org/10.1016/J.ACCPM.2021.100929.
[73] Winkler EA, Minter D, Yue JK, Manley GT. Cerebral edema in traumatic brain injury: pathophysiology and prospective therapeutic targets. Neurosurg Clin N Am. 2016;27(4):473–88. https://doi.org/10.1016/J.NEC.2016.05.008.
[74] Moore EE, Moore HB, Kornblith LZ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers. 2021;7(1):1–23. https://doi.org/10.1038/s41572-021-00264-3.
[75] Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg. 2012;147(2):113–9. https://doi.org/10.1001/ARCHSURG.2011.287.
[76] Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013;17(10):1–80. https://doi.org/10.3310/HTA17100.
[77] Zhang J, He M, Song Y, Xu J. Prognostic role of D-dimer level upon admission in patients with traumatic brain injury. Medicine. 2018;97(31). https://doi.org/10.1097/MD.0000000000011774.
[78] Chen H, Chen M. The efficacy of tranexamic acid for brain injury: a meta-analysis of randomized controlled trials. Am J Emerg Med. 2020;38(2):364–70. https://doi.org/10.1016/J.AJEM.2019.158499.

[79] Rowell SE, Meier EN, McKnight B, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. JAMA. 2020;324(10):961–74. https://doi.org/10.1001/JAMA.2020.8958.
[80] Al Lawati K, Sharif S, Al Maqbali S, et al. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. Intensive Care Med. 2021;47(1):14–27. https://doi.org/10.1007/S00134-020-06279-W.
[81] Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on Management of Bleeding in patients on Oral anticoagulants: a report of the American College of Cardiology Solution set Oversight Committee. J Am Coll Cardiol. 2020;76(5):594–622. https://doi.org/10.1016/J.JACC.2020.04.053.
[82] Rossaint R, Afshari A, Bouillon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care. 2023;27(1). https://doi.org/10.1186/S13054-023-04327-7
[83] Frontera JA, Lewin Iii JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine, 24; 2024. https://doi.org/10.1007/s12028-015-0222-x.
[84] Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. J Thromb Haemost. 2006;4(9):1853–63. https://doi.org/10.1111/J.1538-7836.2006.01986.X.
[85] Hunt BJ, Levi M. Urgent reversal of vitamin K antagonists. BMJ. 2018:360. https://doi.org/10.1136/BMJ.J5424.
[86] Brekelmans MPA, van Ginkel K, Daams JG, Hutten BA, Middeldorp S, Coppens M. Benefits and harms of 4-factor prothrombin complex concentrate for reversal of vitamin K antagonist associated bleeding: a systematic review and meta-analysis. J Thromb Thrombolysis. 2017;44(1):118–29. https://doi.org/10.1007/S11239-017-1506-0.
[87] Fuh L, Goldstein JN, Hayes BD. Initiation of a fixed-dose four-factor prothrombin complex concentrate protocol. J Thromb Thrombolysis. 2020;50(1):217–20. https://doi.org/10.1007/S11239-019-01984-W.
[88] Gilbert BW, Morton L, Huffman JB, et al. Modified version of the American College of Cardiology's recommendation for low-dose prothrombin complex concentrate is effective for warfarin reversal. Am J Emerg Med. 2020;38(4):806–9. https://doi.org/10.1016/J.AJEM.2019.12.005.
[89] Khorsand N, Veeger NJGM, van Hest RM, Ypma PF, Heidt J, Meijer K. An observational, prospective, two-cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract vitamin K antagonists in 240 bleeding emergencies. Haematologica. 2012;97(10):1501–6. https://doi.org/10.3324/HAEMATOL.2012.063701.
[90] Schwebach AA, Waybright RA, Johnson TJ. Fixed-dose four-factor prothrombin complex concentrate for vitamin K antagonist reversal: does one dose fit all? Pharmacotherapy. 2019;39(5):599–608. https://doi.org/10.1002/PHAR.2261.
[91] Milling TJ, Middeldorp S, Xu L, et al. Final study report of Andexanet alfa for major bleeding with factor Xa inhibitors. Circulation. 2023;147(13):1026–38. https://doi.org/10.1161/CIRCULATIONAHA.121.057844.
[92] Panos NG, Cook AM, John S, Jones GM. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. Circulation. 2020;141(21):1681–9. https://doi.org/10.1161/CIRCULATIONAHA.120.045769.
[93] Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. Thromb Haemost. 2018;118(5):842–51. https://doi.org/10.1055/S-0038-1636541.
[94] Gómez-Outes A, Alcubilla P, Calvo-Rojas G, et al. Meta-analysis of reversal agents for severe bleeding associated with direct Oral anticoagulants. J Am Coll Cardiol. 2021;77(24):2987–3001. https://doi.org/10.1016/J.JACC.2021.04.061.
[95] Parsels KA, Seabury RW, Zyck S, et al. Andexanet alfa effectiveness and safety versus four-factor prothrombin complex concentrate (4F-PCC) in intracranial hemorrhage while on apixaban or rivaroxaban: a single-center, retrospective, matched cohort analysis. Am J Emerg Med. 2022;55:16–9. https://doi.org/10.1016/J.AJEM.2022.02.036.
[96] Cohen AT, Lewis M, Connor A, et al. Thirty-day mortality with andexanet alfa compared with prothrombin complex concentrate therapy for life-threatening direct oral anticoagulant-related bleeding. J Am Coll Emerg Physicians Open. 2022;3(2). https://doi.org/10.1002/EMP2.12655.
[97] Connolly SJ, Sharma M, Cohen AT, et al. Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024;390(19):1745–55. https://doi.org/10.1056/NEJMOA2313040/SUPPL_FILE/NEJMOA2313040_DATA-SHARING.PDF.
[98] Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal — full cohort analysis. N Engl J Med. 2017;377(5):431–41. https://doi.org/10.1056/NEJMOA1707278/SUPPL_FILE/NEJMOA1707278_DISCLOSURES.PDF.
[99] Frontera JA, Gilmore EJ, Johnson EL, et al. Guidelines for seizure prophylaxis in adults hospitalized with moderate-severe traumatic brain injury: a clinical practice guideline for health care professionals from the Neurocritical care society. Neurocrit Care. 2024. https://doi.org/10.1007/S12028-023-01907-X. Published online.
[100] Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med. 1990;323(8):497–502. https://doi.org/10.1056/NEJM199008233230801.
[101] Young B, Rapp RP, Norton JA, Haack D, Tibbs PA, Bean JR. Failure of prophylactically administered phenytoin to prevent early posttraumatic seizures. J Neurosurg. 1983;58(2):231–5. https://doi.org/10.3171/JNS.1983.58.2.0231.
[102] Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006;61(3):246–55. https://doi.org/10.1111/J.1365-2125.2005.02529.X.
[103] Kruer RM, Harris LH, Goodwin H, et al. Changing trends in the use of seizure prophylaxis after traumatic brain injury: a shift from phenytoin to levetiracetam. J Crit Care. 2013;28(5):883.e9–883.e13. https://doi.org/10.1016/J.JCRC.2012.11.020.
[104] Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg. 1999;91(4):593–600. https://doi.org/10.3171/JNS.1999.91.4.0593.
[105] Glotzner FL, Haubitz I, Miltner F, Kapp G, Pflughaupt KW. Seizure prevention using carbamazepine following severe brain injuries. Neurochirurgia (Stuttg). 1983;26(3):66–79. https://doi.org/10.1055/S-2008-1053615.
[106] Manaka S. Cooperative prospective study on posttraumatic epilepsy: risk factors and the effect of prophylactic anticonvulsant. Jpn J Psychiatry Neurol. 1992;46(2):311–5. https://doi.org/10.1111/J.1440-1819.1992.TB00865.X.
[107] Temkin NR, Jarell AD, Anderson GD. Antiepileptogenic Agents How Close Are We?; 2024..
[108] Lowenstein D. Recent advances related to basic mechanisms of epileptogenesis. Epilepsy Res Suppl. 1996;11:45–60.
[109] Temkin NR. Preventing and treating posttraumatic seizures: the human experience. Epilepsia. 2009;50(Suppl. 2):10–3. https://doi.org/10.1111/J.1528-1167.2008.02005.X.
[110] Ratilal BO, Costa J, Pappamikail L, Sampaio C. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. Cochrane Database Syst Rev. 2015;2015(4). https://doi.org/10.1002/14651858.CD004884.PUB4.
[111] Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for Healthcare-associated Ventriculitis and meningitis. Clin Infect Dis. 2017;64(6):E34–65. https://doi.org/10.1093/CID/CIW861.
[112] Jimenez CM, Polo J, España JA. Risk factors for intracranial infection secondary to penetrating craniocerebral gunshot wounds in civilian practice. World Neurosurg. 2013;79(5–6):749–55. https://doi.org/10.1016/J.WNEU.2012.06.025.
[113] Harmon LA, Haase DJ, Kufera JA, et al. Infection after penetrating brain injury-an eastern Association for the Surgery of trauma multicenter study oral presentation at the 32nd annual meeting of the eastern Association for the Surgery of trauma, January 15-19, 2019, in Austin, Texas. J Trauma Acute Care Surg. 2019;87(1):61–7. https://doi.org/10.1097/TA.0000000000002327.
[114] Villalobos T, Arango C, Kubilis P, Rathore M. Antibiotic prophylaxis after basilar skull fractures: a meta-analysis. Clin Infect Dis. 1998;27(2):364–9. https://doi.org/10.1086/514666.
[115] Yellinek S, Cohen A, Merkin V, Shelef I, Benifla M. Clinical significance of skull base fracture in patients after traumatic brain injury. J Clin Neurosci. 2016;25:111–5. https://doi.org/10.1016/J.JOCN.2015.10.012.