

REVIEW ARTICLE

# Kidney Dysfunction After Traumatic Brain Injury: Pathophysiology and General Management



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## Abstract

Traumatic brain injury (TBI) remains a major cause of mortality and morbidity, and almost half of these patients are admitted to the intensive care unit. Of those, 10% develop acute kidney injury (AKI) and 2% even need kidney replacement therapy (KRT). Although clinical trials in patients with TBI who have AKI are lacking, some general principles in this population may apply. The present review is an overview on the epidemiology and pathophysiology of AKI in patients with TBI admitted to the intensive care unit who are at risk for or who have developed AKI. A cornerstone in severe TBI management is preventing secondary brain damage, in which reducing the intracranial pressure (ICP) and optimizing the cerebral perfusion pressure (CPP) remain important therapeutic targets. To treat episodes of elevated ICP, osmolar agents such as mannitol and hypertonic saline are frequently administered. Although we are currently awaiting the results of a prospective randomized controlled trial that compares both agents, it is important to realize that both agents have been associated with an increased risk of developing AKI which is probably higher for mannitol compared with hypertonic saline. For the brain, as well as for the kidney, targeting an adequate perfusion pressure is important. Hemodynamic management based on the combined use of intravascular fluids and vasopressors is ideally guided by hemodynamic monitoring. Hypotonic albumin or crystalloid resuscitation solutions may increase the risk of brain edema, and saline-based solutions are frequently used but have a risk of hyperchloremia, which might jeopardize kidney function. In patients at risk, frequent assessment of serum chloride might be advised. Maintenance of an adequate CPP involves the optimization of circulating blood volume, often combined with vasopressor agents. Whether individualized CPP targets based on cerebrovascular autoregulation monitoring are beneficial need to be further investigated. Interestingly, such individualized perfusion targets are also under investigation in patients as a strategy to mitigate the risk for AKI in patients with chronic hypertension. In the small proportion of patients with TBI who need KRT, continuous techniques are advised based on pathophysiology and expert opinion. The need for KRT is associated with a higher risk of intracranial hypertension, especially if osmolar clearance occurs fast, which can even occur in continuous techniques. Precise ICP and CPP monitoring is mandatory, especially at the initiation of KRT.

**Keywords:** Traumatic brain injury, Acute kidney injury, Intracranial hypertension

## Introduction

Traumatic brain injury (TBI) is a major cause of hospital admissions and deaths, with more than 50,000 yearly deaths in Europe. Several observational studies have reported variable incidences of acute kidney injury (AKI) in patients with TBI depending on the used definition and the severity and the timing during intensive care

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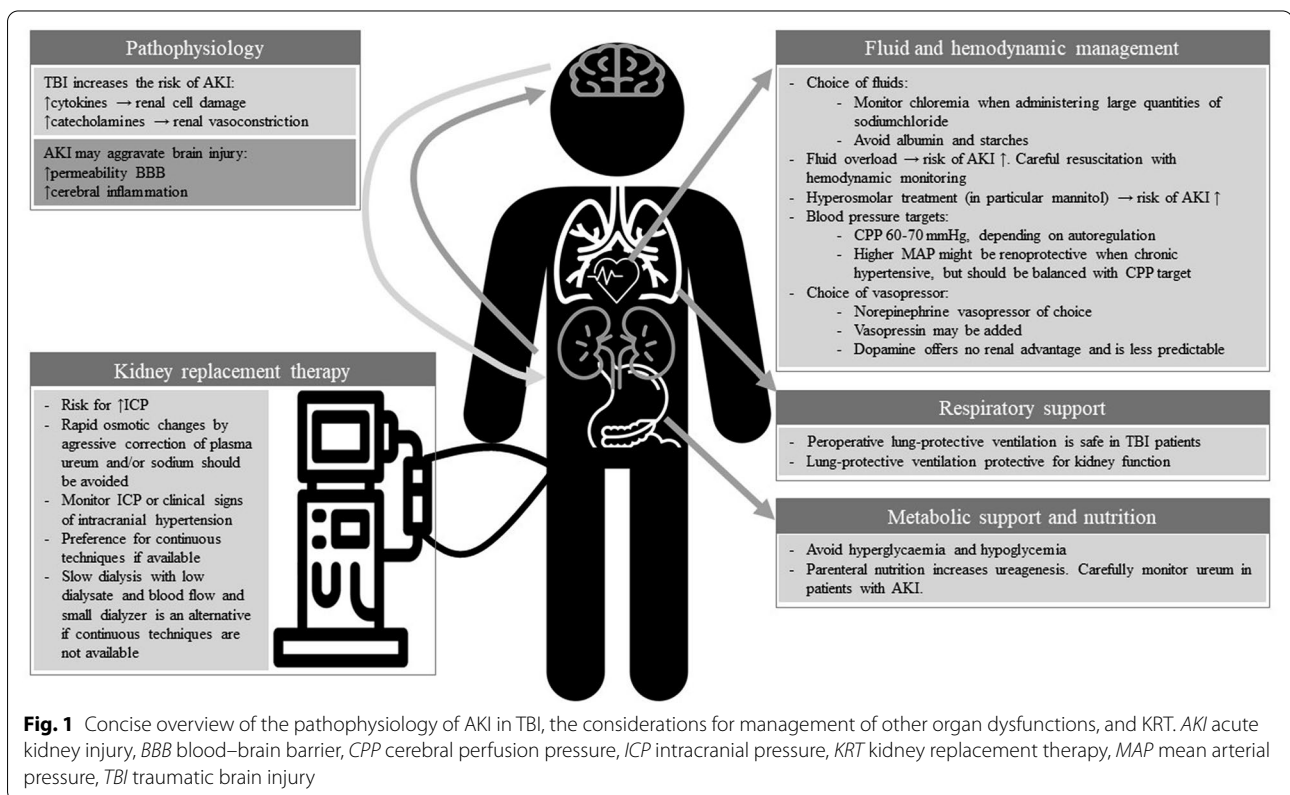
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unit (ICU) stay. In the Collaborative European Neurotrauma Effectiveness Research TBI (CENTER-TBI) study, almost half of all patients with TBI were admitted to the ICU, and more than 40% had a systemic disease [1]. Of the patients admitted to the ICU, 25% were older than 65 years and 55% had extracranial lesions. Consequently, many patients with TBI are at risk of developing AKI. A preplanned subanalysis of CENTER-TBI in patients with an ICU stay of more than 72 h showed that 12% developed AKI based on the serum creatinine criteria of Kidney Disease Improving Global Outcome (KDIGO) during the first week of ICU stay [2]. AKI occurred early during ICU admission, with a median onset at day 2, and was associated with longer ICU length of stay and higher disability 6 months after trauma. In the post hoc analysis of the erythropoietin in TBI (EPO-TBI), 15.9% of the patients with TBI developed AKI during the first 3 weeks of ICU stay based on serum creatinine KDIGO criteria [3]. An Australian study showed comparable incidences of AKI in 9.2% of the patients with TBI admitted to the ICU based on the Risk-Injury-Failure-Loss-End criteria and an association between AKI and mortality [4]. An American cohort of 37,851 patients with TBI showed an incidence of 2.1% of severe AKI, which was associated with a higher hospital mortality, more morbidity, and an

increased hospital length of stay [5]. Because AKI is a frequently encountered complication in patients with TBI in the ICU, we give an overview of the prevention and treatment strategies for patients with TBI who have or are at risk for AKI (Fig. 1; Table 1).

### Pathophysiology

The pathophysiology of AKI in TBI is not fully elucidated, but circulating molecules that are released on tissue damage probably play an important role. TBI leads to an inflammatory response, with the release of cytokines in the cerebrospinal fluid and serum. Interleukin-6 (IL-6) has been studied extensively in several diseases, and increased IL-6 levels have been associated with AKI in patients who underwent cardiac surgery and septic patients [6, 7]. In patients with TBI and in animal models of TBI, IL-6 increases within 1 h after injury, and a high IL-6 level is associated with poor outcome [8]. Serum IL-6 concentrations are lower than concentrations in the cerebrospinal fluid, as an intact blood–brain barrier (BBB) has a low permeability for IL-6. Nevertheless, it has been shown that IL-6 serum levels in patients with TBI are positively correlated with neutrophil gelatinase–associated lipocalin, a biomarker of renal cell damage [9]. Immediately after TBI, IL-6 levels (and also IL-8



**Fig. 1** Concise overview of the pathophysiology of AKI in TBI, the considerations for management of other organ dysfunctions, and KRT. AKI acute kidney injury, BBB blood–brain barrier, CPP cerebral perfusion pressure, ICP intracranial pressure, KRT kidney replacement therapy, MAP mean arterial pressure, TBI traumatic brain injury

**Table 1 Overview of the epidemiology and the practical considerations for management of patients with TBI at risk for or with AKI**

Epidemiology		Evidence for practice		Suggestions for clinical practice	
Hemodynamic and ICP management MAP and CPP target		<p>Current guidelines recommend CPP between 60 and 70 mm Hg</p> <p>Unclear if individualized CPP targets based on autoregulation assessment could improve outcomes</p> <p>Higher MAP (85 mm Hg) may be beneficial on kidney outcome in septic patients with chronic hypertension [21]</p> <p>In patients older than 65 years, lower MAP targets (60–65 mm Hg) may reduce mortality in those without preexisting hypertension [22]</p>		<p>Target a higher MAP in patients with chronic hypertension</p> <p>Carefully assess ICP and other neuromonitoring signals, if available, to assess whether higher MAP targets do not result in increases in ICP in case of deficient cerebrovascular autoregulation [23]</p>	
Resuscitation fluids		<p>Hypertonic chloride as fluid bolus results in an increased MAP in patients with trauma [29] and a decreased ICP in patients with TBI [30]</p> <p>Albumin 5% results in a higher mortality in patients with TBI [33]</p> <p>Starches were associated with a higher mortality and AKI incidence, especially in patients with TBI [40]</p> <p>In a recent trial, patients with TBI treated with bolus saline had a lower mortality and no increased AKI risk compared with patients treated with balanced crystalloids [44]</p>		<p>Albumine 5% and starches should be avoided in patients with TBI</p> <p>In the subgroup of patients with TBI, resuscitation with saline is a better alternative than balanced crystalloids</p> <p>Hypertonic saline as resuscitation fluid may decrease ICP in patients with TBI</p>	
Patients with TBI who develop AKI receive more colloids during the first three ICU days compared with patients with TBI who did not have AKI					
Fluid dose		<p>In patients with TBI, assessment of the volume state with transthoracic echocardiography results in a reduced mortality and less fluid administration [25]</p> <p>Fluid overload is associated with a higher mortality and a lower probability of renal recovery [43]</p>		<p>Restrict fluids and monitor fluid balance and volume status with cardiac ultrasound</p>	
Vasopressors		<p>Sympathomimetics with beta activity increase cerebral metabolism [55, 56]</p> <p>Increased ICP has been found in patients with TBI treated with dopamine [52]</p> <p>Vasopressin increases water resorption, but a retrospective analysis showed no difference in serum sodium levels and lower doses of hyperosmolar therapy were needed in patients who received vasopressin [57]</p> <p>A small study showed a higher incidence of AKI in patients with TBI treated with vasopressin compared with treatment with catecholamines [63]</p>		<p>Dopamine should not be used in patients with TBI</p> <p>Further research is needed to evaluate the role of catecholamines and vasopressin in patients with TBI at risk for AKI</p>	

**Table 1 (continued)**

Epidemiology	Evidence for practice	Suggestions for clinical practice
ICP monitoring	Higher risk for intracranial hypertension in patients with AKI [2] ICP monitoring more frequently [2]	No specific data in patients with AKI
Hyperosmolar therapy	More need for hyperosmolar therapy in patients with TBI who have AKI [2] Multivariable analyses suggest a higher risk to develop AKI when mannitol is administered versus hypertonic chloride [2, 3] Hyperchloremia might be associated with AKI	Hypertonic saline is safer option than mannitol in patients at risk for AKI Monitor chloremia and in case of hyperchloremia, mannitol might be an alternative Avoid the use of mannitol in volume-depleted patients
Mechanical ventilation	Patients with TBI who have AKI have an increased risk of respiratory failure and have an increased duration of mechanical ventilation [2] The multicenter observational study on practice of ventilation in brain injured patients is running to evaluate the practices of mechanical ventilation in patients with TBI (VENTIBRAIN)	Although evidence in this specific population is lacking, lung-protective ventilation has been associated with better renal outcome in patients without TBI as well as better respiratory outcome in patients with TBI
Metabolic control and nutrition Glycemia control	Hyperglycemia is associated with worse outcome [73]	Severe hyperglycemia in patients with TBI at risk for AKI should be treated, while avoiding hypoglycemia; experienced centers might choose a tighter glucose control
Nutritional support	Observational data show an association between early feeding and outcome [80, 81] Feeding can lead to an increased ureagenesis [82, 83]	Evaluate the renal function and ureum levels before initiating feeding
Kidney replacement therapy	1.8% of patients with TBI admitted to the ICU need KRT [2] Pathophysiologically, continuous techniques may be safer than intermittent techniques in patients with TBI with elevated ICP Even in continuous KRT, brain herniation can occur [89]	Be aware of disequilibrium syndrome, especially in patients with a high ureum and/or hypernatremia If continuous techniques are not available, intermittent KRT can be used if dialysate flow and blood flow are reduced in order not to cause a rapid decline in osmoles Regional citrate anticoagulation is associated with increased filter survival in continuous KRT

AKI acute kidney injury, CPP cerebral perfusion pressure, CSF cerebrospinal fluid, ICP intracranial pressure, ICU intensive care unit, KRT kidney replacement therapy, MAP mean arterial pressure, RCT randomized controlled trial, SOS Sugar or Salt, TBI traumatic brain injury, VENTIBRAIN Multicenter observational study on practice of ventilation in brain injured patients

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and IL-10 levels) were strongly associated with renal and other organ dysfunction and with multiple organ dysfunction syndrome [10]. In addition, incubation of tubular cells with serum of patients with TBI induced an increased neutrophil adhesion and apoptosis compared with incubation with the serum of healthy volunteers [9]. Although these findings show that circulating mediators affect renal tubular cells, it remains unclear whether TBI-associated AKI is directly induced by IL-6 or by other inflammatory mediators and pathophysiological processes. Another pathway that may induce renal dysfunction in TBI is the catecholamine release that affects the renal perfusion by vasoconstriction of the afferent renal vasculature and an increased sodium reabsorption [11]. It has been shown that circulating levels of epinephrine and norepinephrine are associated with brain injury severity [12]. In addition, treatment strategies for secondary injury after TBI, for instance fluid resuscitation, vasoactive drugs, or hyperosmolar agents, may also affect the kidney function. The consequences of these strategies are discussed in more detail in the following sections of this article. Finally, TBI is frequently accompanied by major trauma, which has also been associated with AKI. The pathophysiology of AKI in patients with trauma is very diverse, including hypovolemic shock, rhabdomyolysis, direct kidney trauma, massive transfusion, nephrotoxic agents, and abdominal compartment syndrome [13].

Additionally, the organ crosstalk between brain and kidney is bidirectional: AKI might also affect the brain and, as such, jeopardize outcome in patients with TBI. In a mouse model of ischemic AKI, an increase in brain macrophages, pyknotic neurons, activation of glial cells, and BBB permeability was seen compared with sham mice [14]. Additionally, many other effects on the cerebral concentration of catecholamines and interleukins have been found in different animal models of AKI [15]. Consequently, it is of major importance that physicians treating patients with severe TBI use strategies to prevent further kidney injury, thus increasing the likelihood of good neurological outcome.

## **Management of Patients with TBI at Risk for AKI**

### **Management of Intracranial Pressure and Cerebral Perfusion Pressure**

#### ***Pathophysiological Background and Cerebral Perfusion Pressure Target***

Secondary brain injury is the additional brain damage induced by hypoxia, hypotension, and/or intracranial hypertension and occurs within hours and days after the primary injury. A cornerstone in TBI management is to prevent this secondary damage by applying a multimodal approach in which intracranial pathological

derangements and systemic complications are addressed [16]. Indeed, TBI may lead to cranial haematomas, contusions, hydrocephalus, and/or diffuse brain swelling, which all lead to an increased intracranial pressure (ICP). It is recommended to monitor and treat elevated ICP in severe TBI [17]. Epidemiological studies have shown that patients with AKI have a lower Glasgow Coma Scale at presentation and, consequently, they more frequently received ICP monitoring compared with patients with TBI who do not have AKI [2].

Perfusion of injured brain tissue depends on the cerebral perfusion pressure (CPP) which is defined as mean arterial pressure (MAP) minus ICP. Current guidelines recommend CPP targets between 60 and 70 mm Hg [17]. Cerebrovascular autoregulation (CAR) is often impaired in TBI, and the degree of impairment may vary between patients and over the course of time within the same patient. The pressure reactivity index (PRx) is the moving correlation coefficient between spontaneous fluctuations of MAP and ICP and has been proposed as a way to assess CAR to optimize CPP [18]. A single-center, retrospective, observational study found a positive association between the difference between CPP and PRx-based optimal CPP and better neurological outcome [18]. However, a randomized controlled trial (RCT) that compared PRx-based CPP management showed no difference in outcome, and the CPP target was achieved in less than half of the patients in the group randomly assigned to PRx-based management [19]. Likewise, autoregulation in the kidney is also disturbed in patients with AKI, and studies have shown that the autoregulatory range depends on the chronic blood pressure [20]. As such, increasing the MAP in septic patients with chronic hypertension may prevent severe AKI requiring kidney replacement therapy (KRT) [21]. However, in patients aged more than 65 years, mortality tended to be lower when permitting hypotension (MAP target between 60 and 65 mm Hg) as compared with usual care at the clinician's discretion (with a mean MAP of 72 mm Hg) after correction for baseline risk factors [22]. In the CENTER-TBI, more than 25% of all patients were older than 65 years [1]. Further research is necessary to define the optimal MAP in patients with TBI who have AKI, as individualization appears to be a promising strategy for both conditions. As older patients with preexisting hypertension are admitted, defining universal MAP targets might be challenging. As suggested in the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) guidelines, when manipulating the MAP, it is advisory to carefully evaluate the effects on ICP and other neuromonitoring parameters to avoid brain hypoperfusion or hyperperfusion [23].

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### **Resuscitation and Maintenance Fluids**

A recent multicentric survey showed that most physicians involved in the care of patients with TBI use a combination of crystalloids and vasopressors to achieve the CPP target [24]. Here, we will focus on the type and dose of fluids to optimize hemodynamic state in patients with TBI at risk for AKI.

**Fluid Type** Resuscitation fluids are administered immediately after trauma with the aim to restore the circulating volume, especially in TBI associated with extracranial lesions [25]. Observational studies in patients with TBI have shown a clear association between hypotension and mortality [26, 27]. An observational trial showed an association between low circulating volume (assessed with cardiac ultrasound) and mortality [28]. Consequently, hypertonic saline 7.5% may simultaneously be used to treat circulating volume depletion and intracranial hypertension. In patients with trauma, prehospital resuscitation using hypertonic saline is more efficient to increase the MAP compared with Ringer's Lactate [29]. In an RCT of patients with TBI ( $n=229$ ), prehospital bolus administration of hypertonic saline tended to result in a lower ICP compared with bolus of isotonic balanced solutions [30], although there was no difference in 6-month neurological outcome. No data on the incidence of AKI were reported in this study, but serum chloride and serum sodium were significantly higher in patients who received hypertonic saline compared with the control group [30]. Hyperchloremia has a known association with AKI, which is attributed to a higher load of chloride in the tubular fluid leading to vasoconstriction of the afferent arteriole, which, in turn, reduces glomerular blood flow [31]. A subsequent larger RCT ( $n=1331$ ) compared prehospital resuscitation with hypertonic saline/dextran, hypertonic saline, and normal saline and found no differences in the clinical outcome, such as Glasgow outcome scale at 6 months and acute mortality [32]. Unfortunately, no details on the renal function or chloremia were reported, but hypernatremia was more prevalent and average sodium levels were higher in the hypertonic saline group [32].

Over the past decades, resuscitation fluids in critically ill patients have been extensively studied, but few studies have investigated the effect of fluids in patients with TBI. A post hoc subgroup analysis of 460 patients with TBI included in the randomized controlled Saline versus Albumin Fluid Evaluation trial, comparing albumin 4% with saline, showed a higher mortality in patients who received albumin [33]. Further investigation in 321 patients in whom ICP was monitored showed that ICP and ICP slope were significantly higher during the first week in patients who received albumin compared with those who received saline [34]. In addition, patients

who were treated with albumin received more sedatives, analgesics, and vasopressors and had a higher temperature. Although only speculative, the interrupted BBB in patients with TBI may leak the administered albumin, leading to an increase of cerebral edema [34]. Nevertheless, a recent multicenter survey on the use of supportive treatment in patients with TBI revealed that 23% of the correspondents still use albumin [24]. The effect of albumin on kidney function is unclear. The Saline versus Albumin Fluid Evaluation trial showed no difference in the need for KRT when albumin 4% or saline was used [35]. In the Albumin Italian Outcome Sepsis trial, supplementation of albumin with 20% concentration until serum albumin is higher than 30 g/dl did not affect the rate of KRT in patients with sepsis and septic shock [36]. However, the clinical effect of albumin may become clearer in large-volume resuscitation. For this reason, a retrospective, propensity-matched cohort analysis has evaluated the effect of adding albumin 5% in large volume resuscitation ( $>60$  ml/kg in 24 h) on outcome and showed that albumin 5% is associated with a higher risk to develop severe AKI in the following 72 h but a lower mortality and decreased major adverse kidney event at 30 days compared with saline after multivariable correction [37]. Further research is necessary to understand the role of albumin in resuscitation of patients at risk or with AKI, but up until then, albumin should be avoided especially in patients with severe TBI at risk for AKI, as the potential benefits do not outweigh the disadvantages.

Several RCTs have shown an increased mortality and risk to develop AKI in critically ill patients who received starches compared with patients treated with saline [38, 39]. One RCT evaluated the mortality in the subgroup of patients with TBI, but the number of patients with TBI was low and no conclusions could be made [39]. In a retrospective analysis of 2225 patients with trauma, resuscitation with 6% hetastarch was associated with a higher mortality and a higher AKI risk, and this effect was most pronounced in patients with major TBI [40]. Consequently, the European Society of Intensive Care Medicine task force recommends against the use of colloids in patients with head injury [41]. Data from CENTER-TBI support this recommendation, as patients with AKI received colloids more frequently than patients without AKI during the first 3 days of ICU stay (34.5% vs. 17.5%, respectively,  $p<0.001$ ) [2], which could not be explained by other confounders.

Because starches have been abandoned for patients in the ICU, the focus shifted to the effect of different types of crystalloids on outcome. Several RCTs have compared buffered crystalloids and saline in the ICU and emergency department. The 0.9% Saline versus Plasma-Lyte 148 for ICU fluid therapy trial was a cluster-randomized,

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double-crossover trial with 2278 patients that found no difference in the incidence of AKI when saline was compared with balanced crystalloids [42]. The outcome in patients with TBI was reported separately but the number ( $n=47$ ) was too small to draw a conclusion. The Isotonic Solution and Major Adverse Renal Events Trial was a larger, cluster-randomized trial that compared saline and balanced crystalloids in 15,802 critically ill patients. The primary end point was major adverse kidney event within 30 days, a composite of death, KRT, or persistent renal dysfunction. There was no significant difference in major adverse kidney event within 30 days in the subgroup of 1363 patients with TBI [43]. Later, a Brazilian RCT found a significantly lower 90-day mortality in patients with TBI resuscitated with saline compared with those who received balanced crystalloids, whereas the rates of AKI stage 2 during the first week were not different [44]. Recently, the Plasma-Lyte 148 versus Saline trial compared saline with Plasma-Lyte in more than 5000 patients and found no difference in mortality or renal outcome, although a clear rise in serum chloride was found in the saline group [45]. The study was stopped early due to the coronavirus disease 2019 pandemic, and patients with TBI were excluded [45]. Nevertheless, it is reassuring that even in the presence of hyperchloremia, no difference in the rate of AKI was found in this large population, although subclinical forms of AKI might still be a concern [46]. In conclusion, it seems safe to use saline as resuscitation fluid in patients with TBI, as it may reduce mortality in this subgroup compared with balanced crystalloids, and large RCTs found no overt increase in the rate of AKI and major adverse kidney events (MAKE). Because hyperchloremia may affect the renal function especially in patients at risk for AKI, monitoring chloride levels might be advisable.

**Fluid Dose** Careful evaluation of volume status in patients with TBI is important, as it has been shown that hypovolemia is associated with higher mortality [24], but also that patients with TBI admitted to an ICU in a country with high AKI incidences had a higher fluid balance at 3 days after admission [2]. Large, prospective, observational trials show that fluid accumulation occurs frequently in patients with AKI, starts before AKI onset, and rises further after AKI occurs [42]. Moreover, fluid accumulation in critically ill patients has been independently associated with ICU mortality and in patients with AKI with a lower chance of renal recovery [43]. Recently, the Restrictive Fluid Management Versus Usual Care in Acute Kidney Injury pilot trial has shown that a restrictive fluid management in combination with diuretics in patients with early AKI is associated with a lower risk for worsening renal function [44]. Whether this strategy may also

be valuable in patients with TBI is currently unknown. Fluid resuscitation guided by transthoracic ultrasound on admission in the emergency department has been shown to reduce the amounts of fluids administered, which was associated with a reduced mortality compared with conventional care in a subgroup of 72 patients with TBI [25]. Several new strategies to evaluate the intravascular volume status are currently available and may help to guide fluid dose [47]. However, several methods use low-volume ventilation or the effect of recruitment and end-expiratory and inspiratory occlusions, of which the safety has not been assessed in patients with TBI.

#### **Hyperosmolar Therapy**

When ICP is increased in spite of sedation and analgesia, ventilatory support, and temperature management, guidelines advise the administration of hyperosmolar therapy to increase serum osmolarity and redirect interstitial fluid to the intravascular space, resulting in reduced cerebral edema and ICP [17, 23]. In addition, serum hypertonicity also increases the circulating volume and cardiac output. Both mannitol and hypertonic saline are used for this purpose. The CENTER-TBI trial has shown that patients with TBI who also have AKI received osmotic therapy more frequently, but it is not clear whether this is a causal relation or an increased risk of intracranial hypertension due to the AKI itself or whether it is solely an association due to the fact that more severe TBI causes more renal injury [2]. They also found a higher hazard to develop AKI when mannitol was used compared with hypertonic saline [2]. Comparable results were found in Australian and New Zealand patients with TBI, where higher AKI incidence was present in patients receiving hypertonic saline or mannitol, but only mannitol was associated with time to AKI in cox proportional hazard analysis [3]. On the basis of these results, hypertonic saline may be a safer option to treat intracranial hypertension compared with mannitol, especially in patients at risk for AKI. However, as hypertonic saline increases the risk of hyperchloremia, it may also come with a cost of renal function. In the CENTER-TBI trial, hypernatremia was associated with AKI with a hazard ratio of 1.972 after correction for other risk factors [2]. Unfortunately, no details are available on the degree of hyperchloremia. Recently, a retrospective analysis in 123 patients with TBI found that the duration of hyperchloremia, but not the maximum chloride concentration, is independently associated with AKI after correction for multiple variables [13]. However, this study only included patients with a continuous infusion of hypertonic saline (>2%), so no data are available in patients in whom saline was administered as acute treatment for intracranial

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hypertension [13]. Current knowledge is based on retrospective data, so prospective RCTs are urgently needed to answer the question of whether mannitol or hypertonic saline is preferred for treating intracranial hypertension in patients at risk for AKI [14]. The Sugar or Salt multicenter RCT that compares mannitol and hypertonic saline in severe TBI is currently recruiting [48]. Electrolyte disturbances and AKI are the major safety end points, and the results of this study will give more insight into this topic.

A hypertonic solution with a lower chloride concentration by supplementation with acetate has been evaluated in hyperchloremic patients with cerebral edema caused by subarachnoid hemorrhage [49]. This pilot study showed a trend toward a lower increase in chloride in the sodiumacetate compared with the sodiumchloride group and a lower rate of AKI KDIGO stage 1 and 2. Although promising, the study has a lot of limitations because it was stopped early, and AKI occurred at a median hospital stay of 3 days while randomization was done on an average of 3.1 days and 2.8 days in the sodiumchloride and sodiumacetate-groups, respectively. As far as we know, other trials in patients with subarachnoid hemorrhage are lacking and no studies have been performed in patients with TBI. Hypertonic sodiumlactate is another solution that can be used to reduce ICP and offers the theoretical benefit of optimizing brain metabolism because lactate is a substrate of the central nervous system. A systematic review showed that sodiumlactate is as effective as mannitol to reduce ICP, but the effect had a longer duration and 30 min after administration, patients treated with sodiumlactate had a higher CPP compared with mannitol [50]. As far as we know, there are no studies that compare sodiumlactate with hypertonic saline, and data on the use of sodiumlactate in patients with AKI are not available.

### **Vasopressors**

Vasopressive agents are administered to increase MAP; however, their effect on the vessel tone may interfere with CAR [51]. Several vasopressors are available in clinical practice. In a retrospective analysis of 114 patients with severe TBI, phenylephrine and norepinephrine were most commonly used, and 22% received dopamine [52]. However, early studies in patients with TBI have shown that dopamine increased ICP compared with norepinephrine, despite the same MAP [53]. In addition, the effect of norepinephrine on the CPP is more predictable than the effect of dopamine [54], and dopamine has shown deleterious effects on the levels of the anterior-pituitary hormones [55]. Moreover, animal studies have shown that a higher permeability of the BBB may result in a higher cerebral metabolism when

beta-adrenergic agents are administered [56, 57]. This increased metabolism leads to an augmented cerebral blood flow (CBF) by metabolic coupling, but metabolism increases more than CBF, resulting in a perfusion mismatch [57]. Consequently, there is no evidence for the use of dopamine in patients with TBI.

A recent review evaluated the available data on phenylephrine in human TBI and animal models. Phenylephrine has shown to increase MAP and CPP in patients with TBI, but it also increases ICP in patients in whom autoregulation is not preserved. Animals studies have shown that phenylephrine increases CBF despite a constriction of the cerebral vessels [51]. However, the methods to evaluate CAR were not consistent and it is hard to draw strong conclusions from these data.

Arginine vasopressin (AVP) is a potent vasopressor that has no inotropic effect and consequently no effect on the cerebral metabolism. However, AVP acts as an antidiuretic hormone increasing water resorption in the collecting tubules, which may lead to hyponatremia and increase cerebral edema [58]. Nevertheless, a retrospective, observational trial showed that patients with TBI who receive vasopressin have similar levels of natremia and require lower doses of mannitol and 3% NaCl than the patients who received catecholamines [58]. In addition, vasopressin has also shown to improve the cerebrovascular compliance assessed by the effect of CO<sub>2</sub> inhalation on ICP [59]. These data suggest that AVP is a safe option to increase MAP and CPP in patients with TBI. Early small studies have suggested that vasopressin may also have a beneficial effect on kidney function, especially in patients with vasopressin deficiency such as septic patients and patients after cardiac surgery. This effect was not found in an RCT ( $n=778$ ) comparing vasopressin with norepinephrine versus norepinephrine monotherapy in patients with septic shock [60]. However, in a post hoc analysis ( $n=108$ ), AKI progression occurred less frequently in the patients treated with vasopressin compared with norepinephrine [61]. A second RCT ( $n=421$ ) evaluated the impact of vasopressin versus norepinephrine monotherapy in septic shock and found no difference in the number of days with AKI stage 3 but a lower risk for the need of KRT in the vasopressin group [62]. Vasopressin deficiency is also frequently found in patients after cardiac surgery. In these patients, Hajjar et al. [63] found a significant reduction in AKI in vasopressin-treated patients compared with norepinephrine-treated patients. Much less is known on the role of vasopressin in the management of patients with TBI. An RCT with 96 patients showed a significantly higher incidence of AKI in patients with TBI treated with vasopressin compared with those treated with catecholamines [64].



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However, the number of patients who required vasopressors was small and the baseline characteristics of the patients were different. In conclusion, AVP is likely safe in patients with TBI and potentially beneficial for the kidney function, but additional studies are necessary to confirm this hypothesis.

The use of angiotensin II in vasodilatory shock has recently been approved by the U.S. Food and Drug Administration and the European Medicines Agency. Angiotensin II as an add-on to norepinephrine has shown to be effective and safe in a multicentric RCT [65]. As far as we know, no data are available on the use of angiotensin II in patients with TBI.

In conclusion, norepinephrine remains the first choice in patients with severe TBI, and the role of phenylephrine, vasopressin, and angiotensin II in patients with TBI needs to be further explored.

### **Respiratory Support**

Respiratory dysfunction is the most frequently found nonneurologic organ dysfunction in patients with TBI [10]. Hypercapnia causes cerebral vasodilation and shortens the MAP plateau of autoregulation [66], but hypocapnia might cause vasoconstriction and reduce CBF. As such, most patients with severe TBI are intubated and ventilated, and in the absence of intracranial hypertension, CO<sub>2</sub> targets between 35 and 45 mmHg are advised. Patients with TBI who develop AKI have an increased risk of respiratory failure and a longer need for mechanical ventilation (MV) [2, 67]. Despite the frequent need for invasive MV, the role of lung-protective MV has not been investigated in patients with TBI. Moreover, patients with increased ICP were even excluded in an RCT comparing low and high tidal volume ventilation due to the potential risk to increase CO<sub>2</sub> and ICP [68]. Data from observational studies in patients with TBI have shown that high tidal volume ventilation is associated with acute lung injury [69] and that increasing the positive end-expiratory pressure of 5 to 10 cm H<sub>2</sub>O does not affect ICP [70]. Recently, it has been shown that lung-protective ventilation during surgery in patients with TBI resulted in a lower number of postoperative pulmonary complications and a lower rise in brain injury biomarkers [71]. Several studies have found that lung-protective ventilation also affects other organs, including the kidneys, especially in patients with acute respiratory distress syndrome (ARDS) [68]. A post hoc analysis of an RCT comparing conventional and lung-protective ventilation in patients with ARDS showed a significant increase in renal dysfunction in conventional MV, whereas kidney function remained stable in patients with lung-protective ventilation [72]. On the basis of the available evidence, the Acute Disease Quality Initiative advises lung-protective

ventilation in all critically ill patients at risk for or with AKI [73]. A multicenter, observational trial on the practice of MV in patients with TBI is now running and will provide more insight in the practices and safety of lung-protective ventilation in patients with TBI [74]. In conclusion, lung-protective ventilation is likely protective for the kidney function and probably safe to apply in patients with TBI.

### **Glucose Control and Nutritional Support**

#### **Glucose Control**

As in other critically ill patients, the severity and duration of stress-induced hyperglycemia after TBI is associated with poor outcome [75]. Van den Berghe et al. [76] studied the effect of intensive insulin therapy aiming at a blood glucose levels between 80 and 110 mg/dl in a subgroup of 63 patients with brain injury and found a lower ICP and a better outcome at 12 months follow-up compared with patients with a higher glucose level. In this small cohort, the rate of hypoglycemia was not significantly different in the two groups. The same research group found a renoprotective effect of tight glycemic control [77]. However, two other RCTs could not confirm these findings. In a subgroup of patients with TBI in another multicentric RCT ( $n=188$ ), intensive insulin treatment targeting glucose levels between 80 and 108 mg/dl did not affect the 90-day neurological outcome compared with conventional glucose treatment (100–162 mg/dl), but more episodes of hypoglycemia were present in the intensive insulin group [78]. Similarly, the subgroup of patients with TBI in the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multinational RCT ( $n=315$ ) had a significantly higher rate of moderate and severe hypoglycemic events, but no difference was found in the neurologic outcome 2 years after trauma in patients who were treated with intensive compared with the conventional glycemia control [79]. Moreover, the beneficial effect on the renal function was also absent in this study [80]. However, several underlying methodological differences might explain the contradicting results [81]. Finally, a retrospective analysis in 44,964 patients with preexisting diabetes mellitus showed that moderate glycemic control targeting a mean blood glucose between 110 and 180 mg/dl was associated with a lower mortality than aiming a blood glucose level between 80 and 110 mg/dl [82]. As far as we know, no specific data on the effect of glycemic control in patients with TBI with preexisting diabetes mellitus are available. In conclusion, although tight glycemic control might improve the outcome of both AKI and TBI, this benefit disappears when frequent episodes of hypoglycemia occur and in patients with underlying diabetes mellitus. As such, this intervention

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should probably be reserved for those centers capable of controlling blood glucose while avoiding hypoglycemia, and future research may provide more insight in the individualization of glycemic target [83]. Until then, avoiding the extremes of hyperglycemia by keeping blood glucose levels at 180 mg/dl is probably acceptable.

*Nutritional Support* The guidelines of the Brain Trauma Foundation advise to feed patients with basal caloric replacement at least by the fifth day post injury [17]. Studies focusing on feeding in patients with TBI show a strong association between early feeding and outcome, which may be caused by the retrospective and/or observational design [84, 85]. As far as we know, not much is known about the effect of nutrition on the kidney. In a large, multicenter study of critically ill patients, early feeding did not seem to affect the incidence of AKI, but an increased ureagenesis was found in patients who received parenteral nutrition irrespectively on the timing of feeding [86, 87]. Although no specific data on high protein supplements and ureagenesis are available, urea may increase even more when administering additional proteins in patients with AKI. From a physiological point of view, an increase ureagenesis likely affects ICP. Previously, urea has been successfully administered to increase serum osmolality and decrease ICP [88]. Although the initial effect of an increased urea may be a reduction of ICP, the high urea concentration in the brain tissue may augment the ICP in the later phase. As such, when considering the nutritional status of patients with TBI who have AKI, it might be a rational approach to consider the urea level and renal function, especially early during ICU stay.

#### **KRT in Patients with TBI**

In a secondary analysis of the CENTER-TBI study, 1.8% of all patients with TBI admitted to the ICU needed KRT [2]. Although a recent study has found no difference in outcome for when intermittent KRT is used compared with continuous techniques [89], there are several reasons to presume that this is not valid for patients with elevated ICP. The underlying mechanism is the compartmentalization, as osmoles stored in the central nervous system need time to diffuse to the intravascular space, resulting in a temporally increased intracranial osmotic pressure compared with the plasma during intermittent KRT. This phenomenon is also present in patients with chronic kidney disease, in which this so-called disequilibrium syndrome may result in complaints such as headache and nausea [90]. An observational trial has shown that ICP increases when KRT is initiated and that the maximum increase in ICP is associated with the baseline plasma urea concentration [91]. For this reason, many

experts advise the use of continuous KRT in patients with TBI to reduce the risk of disequilibrium and intracranial hypertension [92]. However, even with continuous techniques, brain herniation has been reported, especially in patients with hypernatremia [93]. In patients undergoing intermittent KRT, the dialysate sodium can be adapted, and higher sodium concentrations may be used in patients with TBI. In continuous KRT, sodium levels are fixed and low. In patients with a high risk of herniation, hemofiltration may be a safer alternative to hemodialysis or hemodiafiltration because small solutes are removed slower in hemofiltration. Because many patients with TBI who have AKI experience hypernatremia [2], serum sodium should be checked on a regular basis and hypertonic saline should be added if sodium levels are decreasing rapidly. Formulas to estimate the amount of added water when sodium is decreasing are available [94]. A more practical approach is to add sodium to the dialysate bags with the dose, depending on the serum sodium level, and combine this with adaptations in the KRT dose (e.g., by reducing the blood flow rate) [94]. If continuous KRT is not available, intermittent techniques can be an alternative, but the settings must aim at a slower decline in osmolality, which can be achieved by lowering the dialysate and blood flow, use a smaller dialyzer, increase the sodium concentration in the dialysate, and increase the length of dialysis sessions [92]. If the only indication for KRT is fluid overload refractory to diuretics, ultrafiltration can be performed without dialysis. This technique does not affect the serum osmolality, reducing the risk of cerebral edema.

Many patients with TBI have an increased risk of intracranial hemorrhage, so the anticoagulation strategy is most often regional citrate or KRT without anticoagulation. In addition to the longer filter survival when regional citrate is used [95], experimental data on cell cultures show that citrate may protect astrocytes in case of hypoxia [96]. Whether this effect also has an impact on clinical outcome is unknown.

#### **Future Directions**

Although recent reports give more insight in the epidemiology of AKI in patients with TBI, many questions remain on the optimal treatment. Future research needs to confirm whether the abovementioned strategies can improve patient outcome. To answer these questions, it is important to select a patient population at increased risk for AKI. Prognostic calculators to predict the risk of AKI [97], or specific prediction models for AKI in patients with TBI [98], may help to select patients with TBI fitted for an interventional trial to improve renal outcome. In the absence of specific evidence-based strategies for

patients with TBI at risk for AKI, the potential benefit of interventions needs to be balanced against the known risks while monitoring closely for side effects.

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GDV performed the literature review and drafted the manuscript. GM edited the manuscript. Both authors have approved the final version.

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None.

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