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REVIEW ARTICLE

Acute Kidney Injury at the Neurocritical Care Unit

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Abstract

Neurocritical care has advanced substantially in recent decades, allowing doctors to treat patients with more complicated conditions who require a multidisciplinary approach to achieve better clinical outcomes. In neurocritical patients, nonneurological complications such as acute kidney injury (AKI) are independent predictors of worse clinical outcomes. Different research groups have reported an AKI incidence of 11.6% and an incidence of stage 3 AKI, according to the Kidney Disease: Improving Global Outcomes, that requires dialysis of 3% to 12% in neurocritical patients. These patients tend to be younger, have less comorbidity, and have a different risk profile, given the diagnostic and therapeutic procedures they undergo. Trauma-induced AKI, sepsis, sympathetic overstimulation, tubular epitheliopathy, hyperchloremia, use of nephrotoxic drugs, and renal hypoperfusion are some of the causes of AKI in neurocritical patients. AKI is the result of a sum of events, although the mechanisms underlying many of them remain uncertain; however, two important causes that merit mention are direct alteration of the physiological brain–kidney connection and exposure to injury as a result of the specific medical management and well-established therapies that neurocritical patients are subjected to. This review will focus on AKI in neurocritical care patients. Specifically, it will discuss its epidemiology, causes, associated mechanisms, and relationship to the brain–kidney axis. Additionally, the use and risks of extracorporeal therapies in this group of patients will be reviewed.

Keywords: Acute kidney injury, Critical care, Renal replacement therapy, Traumatic brain injury, Subarachnoid hemorrhage, Cerebral hemorrhage, Stroke, Dialysis

Introduction

Neurocritical care has advanced substantially in recent decades. New neuromonitoring techniques, therapies, and endovascular procedures have emerged [1] to meet the needs of patients with more complicated conditions who require a multidisciplinary approach to achieve better clinical outcomes.

Acute kidney injury (AKI) is a systemic disease that is one of the most frequent and severe complications in patients who are critically ill because of its high morbidity and mortality and economic impact [2, 3]. The increased mortality associated with it is even higher when it is present along with dysfunction of another organ; in this case, mortality can be as high as 60–80% [4]. This is a frequent scenario; there are reports of additional organ dysfunction apart from central nervous system (CNS) lesions in up to 81% of patients [5].

This review will focus on AKI in neurocritical care patients. Specifically, it will discuss its epidemiology, causes, associated mechanisms, and relationship to the brain–kidney axis. Additionally, the use and risks of extracorporeal therapies in this group of patients will be reviewed.

Epidemiology and Outcomes of AKI in Neurocritical Pathologies

Nonneurological complications in neurocritical patients are known to be independent predictors of worse clinical outcomes [6]. There are few reports on the incidence, prognosis, and risk factors of AKI in

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neurocritical patients or on individual pathologies, such as acute ischemic stroke (AIS) [7], traumatic brain injury (TBI) [8], intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH) [9]. Neurocritical patients tend to be younger, have less comorbidity, and have a different risk profile, given the diagnostic and therapeutic procedures they undergo.

Different research groups have reported an AKI incidence of 11.6% in neurocritical patients in general, with rates that vary according to the specific pathology: an incidence of 9.2% has been reported in patients with TBI [10], 14.5% to 20.9% in patients with AIS, 19% in patients with ICH, and 12% to 23.1% in patients with SAH [9–15] (Table 1). AKI can result in an up to fivefold increase in mortality in direct relation to its severity, lead to poorer functional recovery, and increase the possibility of moderate-to-severe disability at hospital discharge [9, 12, 16, 17]. An incidence of 3% to 12% of stage 3 AKI, according to the Kidney Diseases: Improving Global Outcomes [18], has been reported to require dialysis; this is linked to higher mortality rates (50% to 70%) and severe disability because of a lower possibility of intrahospital rehabilitation in this subgroup of patients [12, 19].

Risk Factors of AKI in Neurocritical Care Unit Patients

Acute kidney injury risk prediction is fundamental for planning diagnostic and therapeutic procedures in neurocritical patients. Multiple specific renal severity scores have been published (Liaño, Bullock, and Chertow, among others) [20], but only one nomogram for neurocritical patients has been reported [21]. An et al.'s [21] nomogram specified ten risk factors for predicting the occurrence of AKI, with an area under the curve of 0.87. The risk factors included are Glasgow Coma Scale classification; hypertension; coronary disease; pneumonia and heart failure in the first 7 days of hospitalization; and use of furosemide, torsemide, dopamine, and norepinephrine [21]. Covic et al. [11] reported the independent risk factors of AKI of older age, reduced glomerular filtration rate (GFR), and type of AIS. One of the most often reported risk factors for the onset of AKI in neurocritical and nonneurocritical patients is the presence of chronic kidney disease [12].

These severity scores have the limitation of limited external validation, which suggests a poor capacity to discern at-risk patients.

Physiopathology of AKI in Neurocritical Care Unit Patients

The Brain–Kidney Connection

The brain and kidneys share a complex crosstalk to maintain homeostasis. The term crosstalk refers to organ interaction via biological communication through central and peripheral pathways (Fig. 1) [22]. Given this relationship, AKI can generate anatomical, functional, and biochemical changes in the brain, such as changes in the concentration of neurotransmitters and cytokines, acid–base homeostasis, and drug metabolism; this can cause direct and indirect injuries [23]. Concomitantly, efferent impulses from the CNS can increase renal sympathetic activity causing renin secretion, increasing tubular sodium absorption, and decreasing renal blood flow [24].

Table 1 Studies showing incidence of AKI in neurological diseases

Study	Year published	Patients (*n*)	Diseases	Incidence	Diagnosis criteria
Tsagalis [7]	2009	1,350	Stroke	14.29%	AKIN
Corral [8]	2012	224	TBI	8%	RIFLE
Zacharia [9]	2009	787	SAH	23.1%	RIFLE
Moore [10]	2010	207	TBI	9.2%	RIFLE
Covic [11]	2008	1,090	Stroke	14.5%	RIFLE
Büttner [12]	2020	681	All[a]	11.6%	AKIN
Zorrilla-Vaca [13],b	2017	5,147,754/615,623	Stroke/ICH	12.9%/19%	AKIN
Tujjar [14]	2017	202	SAH	12%	AKIN
Wang [15]	2018	647	Stroke	20.9%	KDIGO
LI [16]	2011	136	TBI	23%	AKIN
Sadan [54]	2017	1,267	SAH	16.7%	KDIGO
Eagles [87]	2019	413	SAH	38%	KDIGO

AKI acute kidney injury, *AKIN* acute kidney injury network, *CNS* central nervous system, *ICH* intracerebral hemorrhage, *KDIGO* Kidney Disease: Improving Global Outcomes, *RIFLE* Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, *SAH* subarachnoid hemorrhage, *TBI* traumatic brain injury

[a] Neurologic autoimmune disorder, intracranial hemorrhage, infection of the CNS, ischemic stroke, tumor, others

[b] Meta-analysis

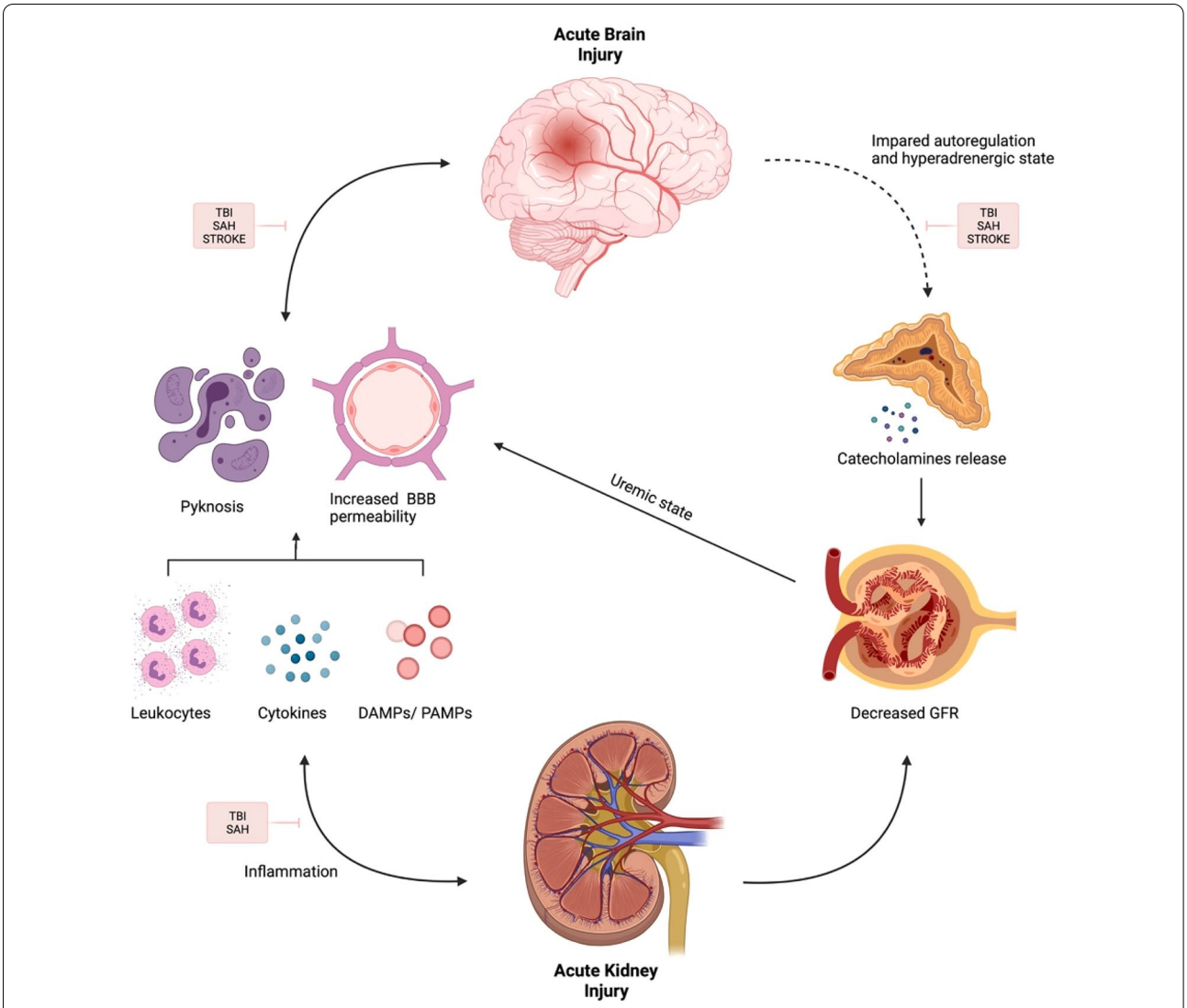

Fig. 1 Kidney–brain axis interaction. Role of acute kidney injury and acute brain injury in inflammation, sympathetic nervous system, uremic state, and diseases related to these mechanisms. DAMPs, damage-associated molecular patterns, GFR, glomerular filtration rate, PAMPs, pathogen-associated molecular patterns, SAH, subarachnoid hemorrhage, TBI, traumatic brain injury

Inflammation

Experimental evidence from an animal model of AKI has modeled the brain–kidney axis in regard to inflammation. High levels of inflammatory cytokines in the brain and cellular inflammation in astrocytes and microglia, together with anatomic and functional injuries, increased blood–brain barrier (BBB) permeability and pyknosis in neuronal cells [25]. The mechanism that underlies the increase in BBB permeability is not well described. AKI increases proinflammatory cytokines and decreases their clearance, thus increasing the inflammatory response [26]. This suggests that this inflammatory state, as well as other states by entities such as sepsis or liver failure, is a cause of BBB alteration [27, 28] through facilitation of an influx of water and solutes. Only in AKI models—not in other models of systemic inflammation—has an increase been observed in the cerebral cortex and corpus callosum of keratinocyte-derived chemoattractants and granulocyte colony-stimulating factor, along with specific markers of brain inflammation and extravasation of Evans blue dye in the brain [25]. In animal models, a direct effect of TNF-α and an indirect effect of the upregulation of matrix metalloproteinase 9 has been demonstrated, which can alter endothelial tight junctions with water and protein extravasation, resulting in vasogenic edema [29, 30]. This is enhanced through aquaporins-4 expression

that is 2.5 times higher than normal, an increase induced by the kidney disease [31].

This inflammatory state is also triggered from the brain to the kidney. Evidence from brain-dead kidney donors has shown greater renal inflammation, with infiltration of T-lymphocytes and macrophages. After perfusing these kidneys, cytokine release was observed, which is a stimulating factor of granulocyte colonies, IL-6, IL-9, and MCP-1 [32].

Neurotransmitter alteration

Neurotransmitter transport is also affected when there is an alteration of BBB permeability. Animal studies have shown that AKI interferes with the Na + independent cationic amino acid transporter (CAT1/SLC7A1), which regulates the influence of L-arginine and thus taurine, alanine, glycine, and creatine. This generates accumulation and/or depletion of amino acids and neurotransmitters in CNS as well as others that are strictly regulated to maintain low concentrations in cerebral tissue, such as glutamate, glycine, and gamma-aminobutyric acid [33].

Metabolic acidosis generated by AKI plays a role in altering neurotransmitter homeostasis and the traffic of neurotransmitters between astrocytes and neurons. Cell acidification increases the oxidative deamination of glutamate through glutamate dehydrogenase, generating an excess of ammonia and, in consequence, altering the cycle of neurotransmitters [27, 34, 35].

Blood flow dysregulation

The brain and kidney have a vascular autoregulation mechanism which maintains blood flow constant despite variations in blood pressure; there is a hemodynamic parallelism between the vascular beds of both organs to ensure adequate perfusion [36, 37] and close management of sodium correction, fluid tonicity, and water balance [38].

This cerebrovascular and renal regulation is altered in neurocritical patients. It has been observed that sustained cerebral autoregulation in patients with neurocritical pathologies is associated with renal hyperfiltration and that loss of cerebral autoregulation may contribute to an alteration of renal autoregulation, generating a decline in creatinine clearance and increasing susceptibility of developing AKI [39].

Kidney hyperfiltration is a frequent finding in neurocritical care patients and this phenomenon has implications on drug pharmacokinetics [39–41]. Several authors have reported faster elimination of levetiracetam after neurologic injury, with the consequent risk of underdosing for treatment or prophylaxis [42, 43]. The mechanisms that promote increased renal clearance remain poorly understood. Some of those which have been proposed are aggressive fluid resuscitation and vasopressor support, systemic inflammation after trauma, cytokine storm, hypertonic solutions, increased atrial natriuretic peptide and brain–kidney crosstalk in an inflammatory state, and increased sympathetic nervous system activity as common pathways [27, 44–48].

Causes of AKI in neurocritical care unit patients

TBI-induced AKI

Acute kidney injury develops without severe episodes of systemic hypoperfusion and nephrotoxin exposure [49]. The mechanisms proposed in the literature were the following (Table 2):

Table 2 Relevant mechanisms in AKI

AKI in TBI	AKI in SAH	AKI in AIS and ICH
Sepsis-associated AKI	Sepsis-associated AKI	Sepsis-associated AKI
Trauma-related AKI Hemorrhagic shock Rhabdomyolysis Oxidative stress DAMPs/ PAMPs	Induced hydroelectrolytic disorders Hypernatremia Hyperchloremia	Renal hypoperfusion
Sympathetic hyperstimulation Hyperactivity of SNS Activation of HPA axis	Contrast induced AKI	Contrast associated AKI
Tubular epitheliopathy	Osmotic nephrosis	Osmotic nephrosis
Osmotic nephrosis	Drug-induced AIN: Levetiracetam [88–90] Phenytoin [90]	Drug-induced AIN: Levetiracetam [88–90] Phenytoin [90]
Drug-induced AIN: Levetiracetam [88–90] Phenytoin [90]	–	–

AIN acute interstitial nephritis, *AIS* acute ischemic stroke, *AKI* acute kidney injury, *DAMPs* damage-associated molecular patterns, *HPA* hypothalamic–pituitary–adrenal axis, *ICH* intracerebral hemorrhage, *PAMPs* pathogen-associated molecular patterns, *SAH* subarachnoid hemorrhage, *SNS* sympathetic nervous system, *TBI* traumatic brain injury

1. Activation of the brain–kidney axis:
    a. Sympathetic renal stimulation by sympathetic efferents, which induce the release of noradrenaline and adrenaline by the adrenal gland. Catecholamines stimulate beta 1 adrenergic receptors, increasing renin secretion by the juxtaglomerular cells, which increases Na^+ and water reabsorption in addition to producing a vasopressor effect. Catecholamines also stimulate alpha 1 adrenergic receptors in the kidney vasculature, decreasing renal blood flow, GFR, and urine output [50].
    b. Activation of the hypothalamic–pituitary–adrenal axis as a direct trauma-induced result that increases endogenous catecholamines [50].

2. Functional alterations and apoptosis of renal tubular epithelial cells secondary to a systemic inflammatory reaction in severe brain injury:
    a. Increased proteinuria and plasma neutrophil gelatinase-associated lipocalin (NGAL) have been shown in one in vitro study. These markers of tubular damage correlated with inflammatory mediators, suggesting that acute brain damage generates tubular injury. The cellular mechanism proposed is based on the inflammatory mediators such as IL-6, MCP-1, and MIP1 beta contained in the plasma of patients with TBI, which are involved in neutrophil adhesion to tubular epithelial cells. This injures the epithelium through the disassembly of tight junctions and the degradation of elastases and matrix metalloproteinases [49].
3. Autonomic nervous system dysregulation:
    a. An imbalance in the parasympathetic and sympathetic pathway in patients with severe TBI results in hyperactivity of the sympathetic nervous system, causing a hyperadrenergic state or paroxysmal sympathetic hyperactivity, as this clinical condition is known. Any anatomical injury to areas that control the autonomic nervous system can result in autonomic dysregulation (hypothalamus, nucleus of the solitary tract, areas A1 to A5 of the medulla, and subfornical organ) and the increased sympathetic tone results in renal vasoconstriction and decreased renal perfusion [51].

AKI in Subarachnoid Hemorrhage

In contrast to TBI-induced AKI, SAH is not an early complication. Most episodes occur > 1 week after intensive care unit admission [14] because of intensive care unit-specific interventions and medical management strategies, such as use of hyperosmolar therapy and potential exposure to nephrotoxic agents such as intravenous contrast media [52] (Table 2). The mechanisms are the following:

1. Hypernatremia and hyperchloremia due to use of hypertonic saline therapy:
    a. Hypertonic saline therapy is often used to control intracranial hypertension and hyponatremia. Hypernatremia and hyperchloremia produce intravascular dehydration and vasoconstriction either directly or through tubuloglomerular feedback mechanisms [52]. A randomized trial comparing a low-chloride (NaCl/Na-acetate) versus high-chloride hypertonic solution (NaCl) for patients who required hyperosmolar therapy for SAH revealed that the rate of AKI was higher in the NaCl group (53.3% vs. 11.8%, $p = 0.01$) and suggested that patients with a chloride level of 109 mmol/L or above are those at highest risk for AKI [53, 54].
2. Contrast-induced AKI:
    a. The patient population with SAH has an increased risk of contrast-induced nephropathy through multiple exposures to IV contrast media secondary to the diagnosis and treatment of intracranial aneurysm, such as computed tomography angiography and coil embolization [55].

AKI in AIS and Intracerebral Hemorrhage

The mechanisms were the following:

1. Intensive reduction of systolic blood pressure in ICH:
    a. As recommended by current guidelines, an acute reduction of systolic blood pressure to 140 mm Hg can improve functional outcomes in patients with ICH [56], but it is strongly associated with AKI [57].
2. Contrast-associated AKI in endovascular thrombectomy in AIS:
    a. Additional exposure to contrast media in addition to what is received during diagnostic imaging techniques along with use of intraarterial contrast increase the risk of contrast-associated AKI more than intravenous contrast media. It occurs in 1 out of 30 patients [58].
3. Infusion rate of mannitol used to decrease intracranial pressure in patients with ICH:

a. Mannitol accumulation in the extracellular space causes an increase in local renal osmolality and osmotic nephrosis, renal vasoconstriction, and deterioration of the GFR [59].

Renal Replacement Therapy in Neurocritical Care

Despite the undisputed benefit of renal replacement therapy (RRT) in encephalopathy due to retention of nitrogen products and toxic drugs, metabolic acidosis, and sodium and water balance, these therapies may pose a risk to neurocritical patients. They may cause dialysis-associated neurovascular injury and affect the treatment prescribed by the rest of the neurocritical unit team, regardless of the type of therapy used.

Intermittent and continuous therapies have been found to be equally effective regarding mortality and/or dialysis dependence, but reports have shown significant differences in neurocritical patients [60]. The mechanism and speed at which blood purification occurs is the major difference between the two types of therapies: the goal of removal uremic solutes through diffusion is achieved in a short period of time in the case of intermittent therapies [61].

This scenario affects the brain–kidney connection because of an effective therapy. The neurological consequences include de novo cerebral edema or an increase of existing edema, herniation, neurological impairment, or death; thus, neurocritical patients merit special consideration when planning RRT [62]. Our therapeutic goals must be to prevent secondary damage by maintaining proper cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) together with intracranial pressure (ICP) control, which may be significantly affected by these therapies, with their consequent prognostic implications [63]. Continuous RRT (CRRT) has proven to be associated with better mean blood pressure, cardiac output, and oxygen delivery outcomes compared with intermittent hemodialysis (IHD). It offers a better hemodynamic profile and, therefore, better CPP and CBF control, which leads it to be associated with better neurological outcomes [63, 64].

Significant changes in the density of white and gray matter have been observed after an IHD session in all patients with increased water content in the brain, but these changes were not observed after CRRT [65]. In addition, IHD has also been shown to lead to decreased circulating blood volume and decreased CBF, as has been demonstrated by transcranial Doppler imaging. Furthermore, the absolute brain tissue oxygen tension level was lower during IHD [66, 67] and hypotension was more frequently reported as a complication of IHD compared to CRRT [68]. Possible mechanisms that could explain this are increased oxygen consumption secondary to ICP surges (associated with brain hypermetabolism and increased oxygen consumption) and limited brain oxygen diffusion due to increased brain water content [69].

One of the problems with IHD that is associated with the rapid removal of urea, sodium, and other osmoles from the vascular compartment is the compartmentalization of these osmoles at the intracranial level. As this area has a slower removal rate, an osmolar gradient is generated between the two compartments, which triggers the diffusion of water into the brain and a significant increase in ICP during treatment [70, 71]. This phenomenon of dialysis disequilibrium syndrome and cerebral vasogenic edema [72] can be explained through different mechanisms. First, the reverse urea effect occurs, which is slower removal of urea from cerebrospinal fluid than from the blood during IHD, causing the aforementioned gradient. This is subsequently supported by findings of urea transporters, which are downregulated in uremic states, causing a reduced adaptive response in the brain to rapid changes in plasma urea and accentuated by overregulation of aquaporin channels, increasing water entry into the brain regardless of the degree of urea reduction [31, 70, 73, 74]. The second mechanism underlying dialysis disequilibrium syndrome is the hypothesis of idiogenic osmoles, in which osmotically active molecules (not including urea, Na^+, K^+, or Cl^-) contribute to cerebral edema [75]. The third mechanism is the hypothesis of paradoxical CNS acidosis, in which the decreased brain pH produced by the correction of systemic acidosis through RRT with elevated bicarbonate concentrations in the dialysate generates an osmotic gradient through the release of intracellular protein-bound sodium and potassium. This mechanism is accentuated by a reduction in CPP caused by the therapy, causing cerebral hypoxia and cerebral acidosis with the production of local vasodilators, increasing vasogenic edema [76, 77].

Unlike CRRT, IHD treatments can worsen the clinical conditions of patients with cerebral edema because of a postdialytic influx of fluid into the brain (Fig. 2) [78]. Therefore, CRRT should be the first option in these patients (Table 3). Moreover, it has been suggested that citrate may provide neuroprotection by attenuating hypoxic brain injury through its effects on astrocytes and oxidative phosphorylation [79].

Nevertheless, if only IHD is available, the initial decline in osmolality should be moderated by slower dialysate and blood flows coupled with a smaller dialyzer surface, a high dialysate sodium content, and daily treatment to reduce changes in serum urea [80]. These factors must be taken into account independently of the type of

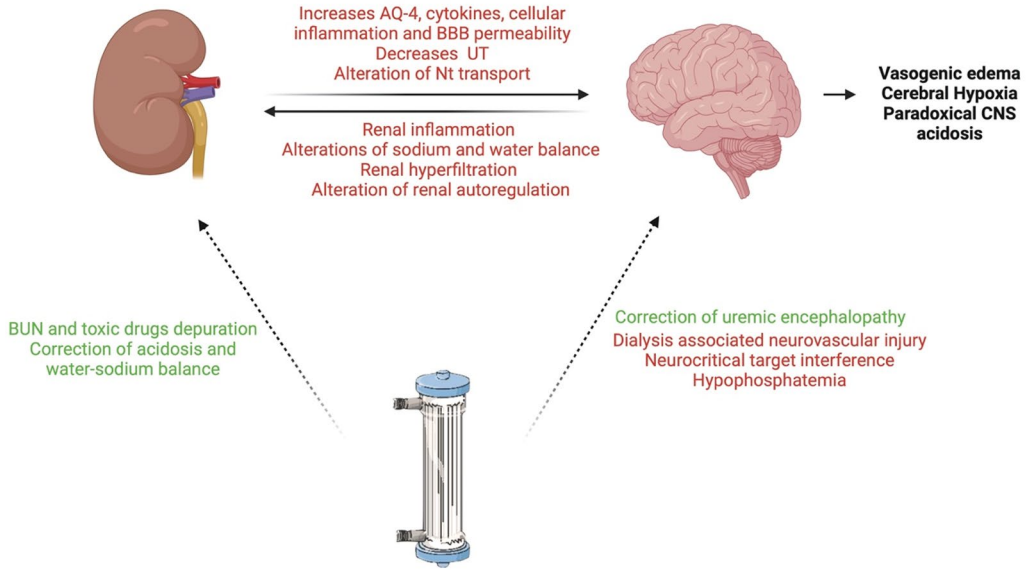

Fig. 2 Kidney–brain axis interaction and renal replacement therapy. AQ-4, aquaporin 4, BBB, blood–brain barrier, BUN, blood urea nitrogen, CNS, central nervous system, Nt, neurotransmitters, UT, urea transporter

Table 3 Central nervous system effects of CRRT versus IHD

IHD	CRRT
Decreased circulatory blood volume	Prefixed sodium
Decreased CBF	Hypophosphatemia induced hypoxia due to high affinity
Decreased PbtO2	Anticoagulation
Increased ICP	–
Cerebral vasodilation	–
Changes in density of white and gray matter	–
DDS/DANI	–

CBF cerebral blood flow, *CRRT* continuous renal replacement therapy, *DANI* dialysis-associated neurovascular injury, *DDS* dialysis disequilibrium syndrome, *ICP* intracranial pressure, *IHD* intermittent hemodialysis, *PbtO2* brain tissue oxygenation

technique used and the patient's plasma osmolality and sodium and blood urea nitrogen (BUN) levels should be routinely monitored.

Natremia and CRRT

A controlled correction of natremia or maintaining a target natremia is essential when prescribing CRRT, given that despite the safety elements mentioned above regarding IHD, cases of significant reductions in osmolarity—up to 35 mOsm/kg within the first 24 h of starting CRRT—have been observed [81]. A problem with CRRT replacement solutions is that the sodium in them is prefixed, ranging from 136 to 140 mmol/L. Therefore, this must be managed through the dialysate/replenished fluid in order to achieve the desired goal. Practical algorithms, such as those reported by Dangoisse et al. [82]. or formulas according to the sodium kinetic model can be used. The must be modified for a single-pool, fixed-volume equation to quantify the changes of natremia during CRRT.

$$\mathrm{Na}_{(t)} = \mathrm{Na}_0 + \left(\mathrm{Na}_{\mathrm{dial/RF}}\right) - \mathrm{Na}_0\right) \times \left(1 - \mathrm{e}^{-Dt/V}\right) \quad (1)$$

where $\mathrm{Na}_{\mathrm{dial/RF}}$ is the sodium concentration in the solutions; Na_0 is the patient's initial sodium level; D is the effective sodium dialysance, which is almost the same as effective urea clearance; t is the time from the beginning of CRRT; and V is the total volume of body water, estimated via the Watson formula and with estimated edema volume added on [83].

Hypophosphatemia and RRT

Another key factor to consider during CRRT is the presence of hypophosphatemia, which has been reported in around 80% of patients who undergo these procedures [84]. Hypophosphatemia produces a decrease in 2,3-diphosphoglycerate in erythrocytes, increasing the affinity of hemoglobin for oxygen and causing a reduction in intracellular adenosine triphosphate [85]. This disorder caused by CRRT can alter the multimodal monitoring values in the case of brain tissue oxygen tension by causing hypoxia due to high affinity. Therefore, when it is present, supplementation with 1.2 to 2 mmol/L of

phosphorus in the replenishment/dialysis solutions is an option [86].

Regardless of the cause that leads to starting RRT, nephrologists must be extremely cautious with findings that suggest edema, dialysate composition, and changes in plasma osmolality. They must consider not only sodium and BUN but also the goals set by the neurocritical care team so as not to hinder them with interventions aimed at improving renal outcomes.

Conclusions

Acute kidney injury is a frequent complication in neurocritical patients that involves different pathologies, such as TBI, SAH, and stroke. Its presence in these patients is associated with worse clinical outcomes that directly affects morbidity, mortality, and functional dependence.

AKI in neurocritical patients is the result of a sum of events, although the mechanisms that underlie most of them remain uncertain. However, it is important to highlight the direct alteration of the physiological brain–kidney connection and exposure to injury as result of the specific medical management and well-established therapies these patients undergo.

Each neurocritical pathology has a specific risk for the development of AKI. Knowledge of these risks is necessary to minimize their incidence in our daily clinical practice. Furthermore, it is important to know the complications associated with RRT in this group of patients to prevent them while still maintaining our therapeutic objectives.

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Author Contributions

GRG, RBH designed the work, GRG, RBH collected and analyzed the data, GRG, RBH, and CR drafted the work or substantively revised it, and all authors read and approved the final manuscript.

Declarations

Conflict of interest

The authors report no conflicts of 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 article. The authors alone are responsible for the content and writing of this article.

Ethical Approval/Informed Consent

Not applicable.

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