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Review

Cerebral Oedema After Ischaemic Stroke: Pathogenesis, Natural History, and Potential Medical Treatments From Bench to Bedside

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Abstract

The development of cerebral oedema after ischaemic stroke is a common and potentially devastating complication associated with increased mortality and disability. Despite this, there currently exists no definitive medical treatment for cerebral oedema, and the efficacy of commonly used agents is unclear. In recent decades there has been a significant amount of research attempting to describe the pathogenesis of cerebral oedema in ischaemic stroke which has begun to lead to the development of new potential treatments. In this review we will aim to, firstly, provide a comprehensive overview of the pathogenesis and natural history of cerebral oedema in ischaemic stroke, including cellular mechanisms, breakdown of the blood-brain barrier, the role of the immune system, and potential effects of reperfusion. We will then summarise the evidence base for currently used treatments for cerebral oedema in ischaemic stroke such as hyperosmolar agents, as well as emerging treatments which are still under investigation. Where available, this review will highlight outcomes of clinical trials for these proposed treatments.

Keywords: brain edema; ischemic stroke; blood-brain barrier; osmotic therapy; matrix metalloproteinase 9; neuroprotective agents

1. Introduction

Ischaemic stroke accounts for approximately 65% of all strokes worldwide, with 7.8 million new incidences each year [1]. Although significant advances have been made with regard to treatment of acute ischaemic stroke such as thrombolysis and mechanical thrombectomy, certain challenges remain. Namely, the development of cerebral oedema is an inevitable consequence of ischaemic stroke and significant cause of mortality and disability. Despite this, treatment options for cerebral oedema in ischaemic stroke are extremely limited. Decompressive hemicraniectomy remains the only intervention with a demonstrated effect on survival in patients with cerebral oedema, but is not routinely available, often excludes older patients with multiple comorbidities, and carries risk of significant potential complications [2]. There are a number of proposed medical treatments for cerebral oedema in ischaemic stroke, and some treatments (e.g., hyperosmolar agents) are used in current practice. However, none of these treatments has yet been shown both to reduce cerebral oedema and improve outcome after ischaemic stroke in phase III trials. As a result, critical appraisal of currently available medical therapies and the development of new treatments for cerebral oedema in ischaemic stroke is of high importance.

This review therefore has four aims. (1) To briefly describe the clinical course of cerebral oedema after ischaemic stroke and the factors that predict its severity. (2) To set out the mechanisms by which it develops, including those aspects that remain contested. (3) To appraise the evidence for each medical agent that has been proposed or trialled, graded by the strength of that evidence. (4) To identify the obstacles that have prevented translation and the steps required to overcome them.

References for this narrative review were identified through searches of PubMed/MEDLINE, Embase and the Cochrane Library for articles published up to July 2025, with the search updated in August 2026 prior to final submission. The search terms used were ‘ischaemic stroke’, ‘cerebral oedema’, ‘malignant oedema’ and ‘medical management’, alone and in combination. Ongoing and unpublished trials were identified by a separate search of ClinicalTrials.gov. Further articles were identified from the reference lists of retrieved papers and from the authors’ own files. Only articles published in English were reviewed. The final reference list was generated on the basis of relevance to the scope of this review.

2. Natural History of Cerebral Oedema in Ischaemic Stroke

Cerebral oedema is an inevitable consequence of ischaemic stroke, however only a minority of patients develop brain swelling of clinical significance. Malignant cerebral oedema capable of causing a symptomatic rise in intracranial pressure is thought to arise in approximately 1 in 10 ischaemic stroke patients, typically within the first 72 hours of stroke onset [3]. Radiological evidence of oedema

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can be evident from hours to days, typically reaching its maximum between 48 and 96 hours post-stroke, although both rapid clinical deterioration within the first 48 hours and delayed deterioration beyond the first week have been described [4,5]. The clinical presentation consists of a severe hemispheric deficit with progressive reduction in level of consciousness, accompanied with signs of raised intracranial pressure such as headache, vomiting, and pupillary asymmetry as transtentorial herniation occurs [6]. Importantly, this can occur prior to a measurable rise in global intracranial pressure. Predictors of malignant oedema include a large infarct volume, early hypodensity involving more than one third of the middle cerebral artery territory, early midline shift, severe neurological impairment, and subsequent pneumonia. Meanwhile, brain atrophy and successful recanalisation are associated with a lower risk of malignant oedema [3,7]. Prognosis without swift intervention is poor, with mortality of approximately 80% with standard intensive-care management alone, and whilst surgical decompression substantially reduces this mortality, one third of surviving patients remain severely disabled and fully dependent on care [2]. Whilst malignant swelling is life-threatening, sub-malignant oedema that may be clinically silent can also have prognostic implications, with oedema volumes as small as 11 mL independently predicting worse functional outcome at 90 days, irrespective of final infarct size [8].

3. Pathogenesis of Cerebral Oedema in Ischaemic Stroke

The stages of cerebral oedema in ischaemic stroke were first described in the 1960's [9]. Cytotoxic oedema is thought to begin early after ictus and occurs due to redistribution of water from the extracellular space into the intracellular space, resulting in cellular swelling. This is followed by a vasogenic phase which is characterised by blood-brain barrier (BBB) disruption and subsequent water influx from the intravascular space, resulting in whole brain swelling. In the last few decades there has been a significant improvement in our understanding of this pathophysiology, which we will describe in further detail.

3.1 Cytotoxic & Ionic Phases

The first 24 hours following an ischaemic stroke is predominated by the cytotoxic phase of cerebral oedema, characterised by the swelling of neurons and glia as water shifts from the extracellular to the intracellular space due to intracellular Na^+ accumulation [10]. This is the direct consequence of oxygen deprivation and metabolic failure, beginning initially with dysfunction of the Na^+/K^+ ATPase, followed by increased activity of the Na^+/H^+ exchanger as hypoxia causes cell acidification [11]. The resulting rise in intracellular Na^+ causes excessive cell depolarisation and subsequent release of neurotransmitters that excite neighbouring cells and further drive intracellular Na^+ in a spreading process known as excitotoxicity [12,13]. Further cell injury occurs when the intracellular Na^+ accumulates sufficiently to pathologically reverse the Na^+/Ca^{2+} exchanger, causing Ca^{2+} influx that further injures the cell [14]. Ultimately, these mechanisms establish a significant osmotic gradient that promotes massive intracellular water influx, causing the cell to swell. In the context of an oxygen-depleted environment, such as acute ischaemic stroke, this process is exacerbated by intracellular accumulation of lactate which also acts to draw water into the cell [15]. It is suggested that cytotoxic oedema does not cause whole brain swelling as there is no increase in total brain water content, only a redistribution of pre-existing brain water from the extracellular to the intracellular space. However, cytotoxic oedema is the initial driver for the later osmotic forces that lead to intravascular fluid entering the area of brain infarction and causing brain swelling.

The process of ionic oedema in ischaemic stroke was first described in 2007 and attempted to explain how intravascular water can move into the brain parenchyma prior to the onset of BBB dysfunction seen in the later vasogenic phase of cerebral oedema [16]. Cytotoxic oedema results in a compressed extracellular space that is relatively depleted of Na^+ and water, thereby establishing an electrical and osmotic gradient that promotes Na^+ and water movement from the intravascular space and into the brain across the BBB. The exact mechanisms are unclear given that the BBB is intact at this stage and endothelial cells lack the voltage-gated Na^+ channels used by neurons and glia [17]. It is suggested that ionic oedema occurs primarily through secondary active transport according to the gradients established by the cytotoxic phase. One candidate for this process is the sulfonylurea receptor 1-regulated $NC^{Ca\text{-}ATP}$ (SUR1-$NC^{Ca\text{-}ATP}$ or SUR1-TRPM4), a non-selective cation channel that is upregulated in ischaemic neurons, astrocytes and hypoxic brain endothelium after injury [18,19,20,21]. However, when adenosine triphosphate (ATP) is depleted, the SUR1-TRPM4 channel becomes persistently open and allows for excess Na^+ influx, making it an inadvertent facilitator of cerebral oedema in sustained ischaemia [22]. Furthermore, its existence in both endothelial and brain parenchymal cells may at least partly explain how Na^+ can travel across an otherwise intact BBB and contribute to ionic oedema. Secondary active transport of Na^+ across the BBB may also be promoted by the $Na^+/K^+/2Cl^-$ (NKCC1) co-transporter, which has also been shown to be upregulated during ischaemia, similar to the SUR1-TRPM4 channel [23,24]. The NKCC1 is also expressed on the luminal surface of endothelial cells and on neurons, although its expression in mature astrocytes *in vivo* is disputed [25]. Despite the existence of these channels however, the specific mechanism by which water follows this Na^+ gradient across the BBB is less clear. The BBB is semi-impermeable to water, restricting passive movement to transmembrane aquaporin (AQP) channels. AQP4 is highly expressed on the astrocyte foot processes that make up the parenchymal sur-

face of the BBB and allow for water entry into the brain, but endothelial cells do not express AQP4 nor other ubiquitous CNS aquaporins such as AQP1 [26]. As a result, water can enter the brain following Na^+ influx into the intracellular space via AQP4, although the route by which water first crosses the endothelium, and the significance of aquaporin localisation to astrocyte endfeet, remain unclear. It should be noted that the classification of ionic oedema also remains debated [24,25]. Some authors argue that ionic oedema is not a separately observable phenomenon from cytotoxic oedema, and that SUR1-TRPM4's time for meaningful upregulation would actually place the channel's opening in the medium term rather than the earliest phase [25]. Such arguments also place greater emphasis on the movement of cerebrospinal fluid (CSF) as an early contributor to oedema in stroke.

The consideration of CSF raises another important issue. It is now known that the brain can also participate in fluid exchange via the glymphatic system, in which CSF mixes with interstitial fluid and circulates through the brain parenchyma via perivascular routes mediated by the AQP4-expressing astrocytic endfeet of the BBB [27]. Animal models of ischaemic stroke have demonstrated that CSF enters the infarct site via the perivascular route within minutes of arterial occlusion, thought to be triggered by spreading excitotoxic depolarisation and subsequent vasoconstriction that enlarges the perivascular space and promotes CSF influx [28]. Although human data is lacking regarding the role of the glymphatic system in both physiological and pathological contexts, earlier models of cerebral oedema in ischaemic stroke should be revised to consider the possibility that CSF entry may be an important early source of oedema prior to the vasogenic phase previously described. Theoretically, disruption of the glymphatic system may also impair cerebral oedema resolution. The perivascular space not only provides an entry point for CSF but also an exit route, but this can become disrupted when the AQP4-astrocytic endfeet of the BBB undergo breakdown as previously described in the vasogenic phase of oedema accumulation. Again, human evidence is limited and the relative contribution of glymphatic in-flow and out-flow to the onset and resolution of cerebral oedema is still unknown, but worth consideration by future research.

3.2 Vasogenic Phase

Under normal conditions the BBB is entirely or selectively impermeable to most substances within the plasma. This is achieved on the intravascular surface via endothelial tight junctions, and on the intraparenchymal side by astrocyte foot processes and pericytes wrapped around the basement membrane [29]. The BBB begins to break down within 3–12 hours of ischaemia onset, evidenced by the entry of plasma macromolecules (e.g., albumin) to which it is usually entirely impermeable, and is grossly compromised by 24 hours [25,30]. This marks the beginning of the vasogenic phase of cerebral oedema and is thought to be the most significant stage for water entry and subsequent brain swelling. Key mechanisms contributing to this process include endothelial and pericyte dysfunction, proteolysis, and inflammation, the pathophysiology of which we will review in more detail.

3.2.1 Endothelial, Pericyte, & Astrocyte Dysfunction

It is important to highlight that the earliest sign of BBB disruption may not be its physical breakdown, but rather a shift in both the function and structure of endothelial cells in response to ischemia. In pre-clinical studies of ischaemic stroke, dysfunctional endothelial transcytosis (passage of materials from the luminal surface of the cell to the parenchymal side) has been shown to occur prior to actual loss of the endothelial tight junctions [31]. This process requires expression of specific proteins known as caveolins, however mice lacking the caveolin-1 gene develop greater hemispheric swelling than wild-type animals after ischaemia, alongside reduced perivascular AQP4 expression [32]. Therefore, whilst caveolins have been previously implicated in oedema development due to their potential role in dysfunctional transcytosis, reducing caveolin activity appears to exacerbate oedema due to impairment of AQP4 localisation and disruption of neurovascular remodelling following ischaemia. Research has also highlighted that the actin cytoskeleton of the endothelial cells undergoes increased polymerisation as a consequence of ischaemia which destabilises the endothelial tight junctions of the BBB, promoting leakage and cerebral oedema [33]. Suppression of RhoA/Rho-kinase/Myosin light chain pathway activity and overexpression of heat shock protein 27 (HSP27) appears to have a protective effect on this process by stabilising the cytoskeleton, and is associated with improved outcomes in mice models [34,35]. However these studies have not yet been translated to clinical settings, and so it is unclear to what extent these processes may contribute to development of cerebral oedema following ischaemic stroke in humans.

Meanwhile, pericytes are closely related to endothelial cells and are a major component of the BBB, but their role in the pathogenesis of cerebral oedema in ischaemic stroke is unclear. Pre-clinical studies have suggested that pericytes, under ischaemic conditions, contribute towards BBB degradation via excess capillary restriction [36], release of proteases [37], and promotion of infiltration by pro-inflammatory leucocytes [38]. However, studies have shown that when pericyte-deficient mice undergo ischaemic brain injury, they have worse cerebral oedema than controls [39]. This suggests that whilst pericytes may be in some way deleterious to the BBB after ischaemic stroke, their actions could also be protective.

Finally, astrocytes are the principal cells to swell during the cytotoxic phase, and their endfeet, bearing AQP-4, form the parenchymal surface of the BBB and the route by

which water enters and leaves the tissue either via vascular or perivascular routes. They also play additional roles, such as limiting excitotoxic injury through uptake of extracellular glutamate and forming a glial scar which restricts the spread of injury whilst impeding later repair [10].

3.2.2 Proteolysis

Inevitably, the protein matrices which make up the endothelial tight junctions and basement membrane of the glia limitans suffer proteolytic damage following ischaemic stroke. Free radicals generated by ischaemic tissue cause particular insult to the endothelial tight junctions that ordinarily prevent the paracellular movement of Na^+ and water into the brain [39]. There are a variety of mediators upregulated in response to this endothelial damage (and ischaemic conditions generally), which we will discuss.

Thrombin may be best known as a constituent of the clotting cascade, but it also has pro-inflammatory action via protease-activated receptors (PARs) which have numerous downstream effects [40]. Thrombin is likely upregulated as a protective mechanism to minimise bleeding and haemorrhagic transformation of an infarct but contributes to cerebral oedema by activating microglia and infiltrating neutrophils via PARs, which then in turn release a number of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) that promote BBB permeability and breakdown [41]. One particular property of these cytokines is their capacity to upregulate activity of matrix metalloproteinases (MMPs). Under physiological conditions MMPs maintain, renew, and repair the basement membrane of the BBB, but when upregulated in pathological conditions MMPs contribute to its degradation [42]. In the context of stroke, MMP-9 specifically has been shown to have increased concentrations in human stroke patients, with greater concentrations being associated with more severe cerebral oedema, although evidence for an association with functional outcome is mixed [43,44]. Both MMP-3 and MMP-9 are released by microglia in response to pro-inflammatory cytokines, whilst oxygen deprivation and subsequent depletion of ATP activate hypoxia-inducible factor-1α (HIF-1α) which eventually results in activation of the constitutively expressed MMP-2 [45]. The levels of these MMPs following stroke also appear to correlate with timings (12–72 hours) of BBB breakdown and onset of vasogenic oedema [46]. MMPs can also be activated by vascular endothelial growth factor (VEGF) which is known to be released by endothelial and glial cells in hypoxic conditions [47]. VEGF is instrumental for angiogenesis and neuroprotection, but following ischaemia can increase BBB permeability primarily through MMP activation [48]. Ischaemic stroke also inevitably results in DNA damage and release from necrotic cells, causing activation of poly(ADP-ribose) polymerase (PARP) enzymes which subsequently activate a range of pro-apoptotic and pro-inflammatory pathways that further contribute to breakdown of the BBB [49]. Of the pro-inflammatory cytokines, TNF-α is particularly implicated where *in vitro* it drives MMP activity, oxidative stress, and apoptosis in cells of the barrier [50]. Its effects are attenuated by suppression of protein kinase C-α [51].

3.2.3 Inflammatory Cell Infiltration

Both endothelial cells and the brain's native cells (particularly microglia) are potent releasers of cytokines when injured by ischaemia, and this promotes entry of immune cells into the brain's tissue via the leaky BBB. As with most injuries, neutrophils appear to be the early entrants to the ischaemic brain parenchyma [52], though it is difficult to determine whether neutrophils cause BBB disruption or whether BBB disruption simply allows more neutrophils to enter an area of infarct. However, studies have shown that activated neutrophils are known not only to release further pro-inflammatory cytokines but also to activate the aforementioned MMP-9 which is responsible for BBB proteolysis [53]. A recent review of pre-clinical studies found that neutrophilia was associated with worse brain injury in ischaemic stroke, but also that the presence of some sub-types (i.e., 'N2' neutrophils) in the peri-infarct region may have protective properties [54]. These appear to be preferentially activated by inhibition of toll-like receptor 4 (TLR4) [55] and activation of peroxisome proliferator-activated receptor-y (PPAR-y) [56]. Microglia, the resident immune cells of the brain, have also been found to exist on a similar biphasic spectrum of relative pro- or anti-inflammatory activity in the context of stroke, again influenced by TLR signalling [57]. Their roles in ischaemic stroke are extensive, including cytokine release, both degradation and protection of the BBB, removal of cellular debris, and release of both angiogenic and neurotrophic factors required for maintenance and remodelling of the infarct site [58]. Proposed treatments that may act on the TLR system to allow influence over microglia and neutrophil phenotype are yet to be identified. Regulatory T-cells are the other major immune cell discussed with regard to ischaemia and cerebral oedema. Some studies have found deleterious effects of CD4+ T-cells in mice models [59], whereas others have found protective effects on the BBB via inhibition of the aforementioned MMP-9-releasing neutrophils [60]. Authors later discovered that this protective effect may occur via programmed death ligand-1 activation, which requires direct cell contact [61]. CD8+ T-cells have also shown neuroprotective properties, though the exact mechanism by which they are associated with reduced infarct size in animal models is not clear [62].

3.2.4 Patient Factors & Venous Flow

There are clinical factors associated with cerebral oedema that are intrinsic to the patient or their environment, although these are not related to BBB dysfunction specifically but are likely implicated in vasogenic oedema. Examples include hyperglycaemia [63], increased fluid in-

take following stroke [64], and even exposure to air pollution [65]. Anatomical factors may also contribute to the development of cerebral oedema. As expected, having good collateral arterial supply protects against infarct progression [66], but cerebral oedema itself may be related to poor venous outflow. One study found that stroke patients with relatively smaller ipsilateral dural sinuses were significantly more likely to experience cerebral oedema sufficient to cause midline shifting [67]. Similarly, a much larger study found that poor filling of the ipsilateral superficial middle cerebral vein is associated with poorer outcomes following reperfusion therapy primarily due to the development of cerebral oedema [68]. Conversely, normal venous outflow following ischaemic stroke is associated with improved clinical outcomes and reduced incidence of cerebral oedema [69]. It is postulated that poor venous flow results in increased venous pressure, which in turn creates higher capillary pressures at the site of ischemia, which results in driving plasma into the brain parenchyma. Others have suggested that restrictions in venous flow may affect reabsorption of CSF, which influences overall brain solute and water reabsorption which could contribute to oedema development.

3.3 Reperfusion Phase - Iatrogenic Oedema?

With the advent of reperfusion therapies such as intravenous thrombolysis and mechanical thrombectomy, the potential for 'iatrogenic' cerebral oedema deserves discussion. In order to prevent further cell death, blood flow must be restored in a timely fashion following ischaemic stroke. However, logic suggests that in order for vasogenic oedema to persist there should be a continuous driving source of water (i.e., blood) [16]. Whilst there does exist some human evidence that reperfusion can exacerbate cerebral oedema [70,71] the majority of evidence for this rationale is from experimental studies [72,73]. One study used gadolinium-enhanced MRI to examine for hyperintense acute injury marker (HARM) as a predictor of haemorrhagic transformation and measure of BBB disruption. The results demonstrated that intravenous thrombolysis was more associated with the presence of 'HARM' than endovascular treatments [74]. This may be explained by the thrombolytics' effect on the coagulation cascade, which as previously discussed is an important mediator in the activation of MMPs. Despite this, clinical data demonstrate that successful reperfusion through intravenous thrombolysis or mechanical thrombectomy is associated with reduced severity of cerebral oedema [75,76,77].

Another important concept in reperfusion and the development of cerebral oedema is the 'mismatch volume' which refers to the relative difference on imaging between the size of the infarct core (unsalvageable brain) and the surrounding hypoperfused area (salvageable tissue). One study utilising data from 415 trial patients suggested that the benefits of reperfusion on cerebral oedema are only found in patients with a large mismatch volume (i.e., significant salvageable tissue), whereas those with small mismatch volumes appear not to experience the same benefit [77]. This suggests that the benefits of reperfusion on cerebral oedema may come from stabilising hypoperfused areas that otherwise would have continued to contribute to vasogenic oedema. Importantly, this same study also demonstrated that unsalvageable tissue experienced the same extent of cerebral oedema regardless of whether or not reperfusion was established. This is contrary to the same research group's earlier findings that very large infarct cores (>130 mL) can experience worsened cerebral oedema following reperfusion, but agrees with their finding that patients with any other infarct size did not appear to experience additional oedema from reperfusion [71]. Since this time, two larger studies looking at data from mechanical thrombectomy trials have not only corroborated the finding that reperfusion is associated with reduced cerebral oedema, but that this reduction in cerebral oedema may be the largest contributor to the patient's functional improvement following reperfusion [78,79].

3.4 Summary of Mechanisms

To summarise, there are a multitude of pathways and processes that contribute to the formation of cerebral oedema in ischaemic stroke and they are best visualised as an interconnected network rather than a series of steps (Fig. 1). Whilst there is a sequential relationship seen in the development of the cytotoxic phase that produces the gradients required for the ionic phase which in turn predisposes to the BBB failure of the vasogenic phase, other elements do not follow this pattern. For example, hypoxia and metabolic failure both drive the cytotoxic phase due to ATPase failure and cellular acidification, but independently also promote the SUR1-TRPM4 upregulation of the ionic phase and the proteolysis of the vasogenic phase. This means that simply targeting the early phase of oedema will not necessarily prevent the late phase from occurring if the underlying ischaemia is not reversed. Similarly, there is significant redundancy in the system with Na^+ being able to drive water influx through a number of different channels and a variety of cell-mediated mechanisms converging on BBB breakdown, meaning blockade of one target alone would be likely insufficient. There also exist multiple biphasic relationships within this network. As discussed, inflammatory cells of various types (i.e., neutrophils, microglia, and T-cells) express both pro- and anti-inflammatory phenotypes in different contexts and at different time points in the ischaemic event. Likewise, specific molecular mechanisms such as MMPs and VEGF both promote BBB permeability acutely during ischaemia but are vital for neurovascular remodelling and angiogenesis during recovery. AQP4 meanwhile is both the proposed entry route for a significant amount of oedema as well as a potential mechanism for its clearance later on.

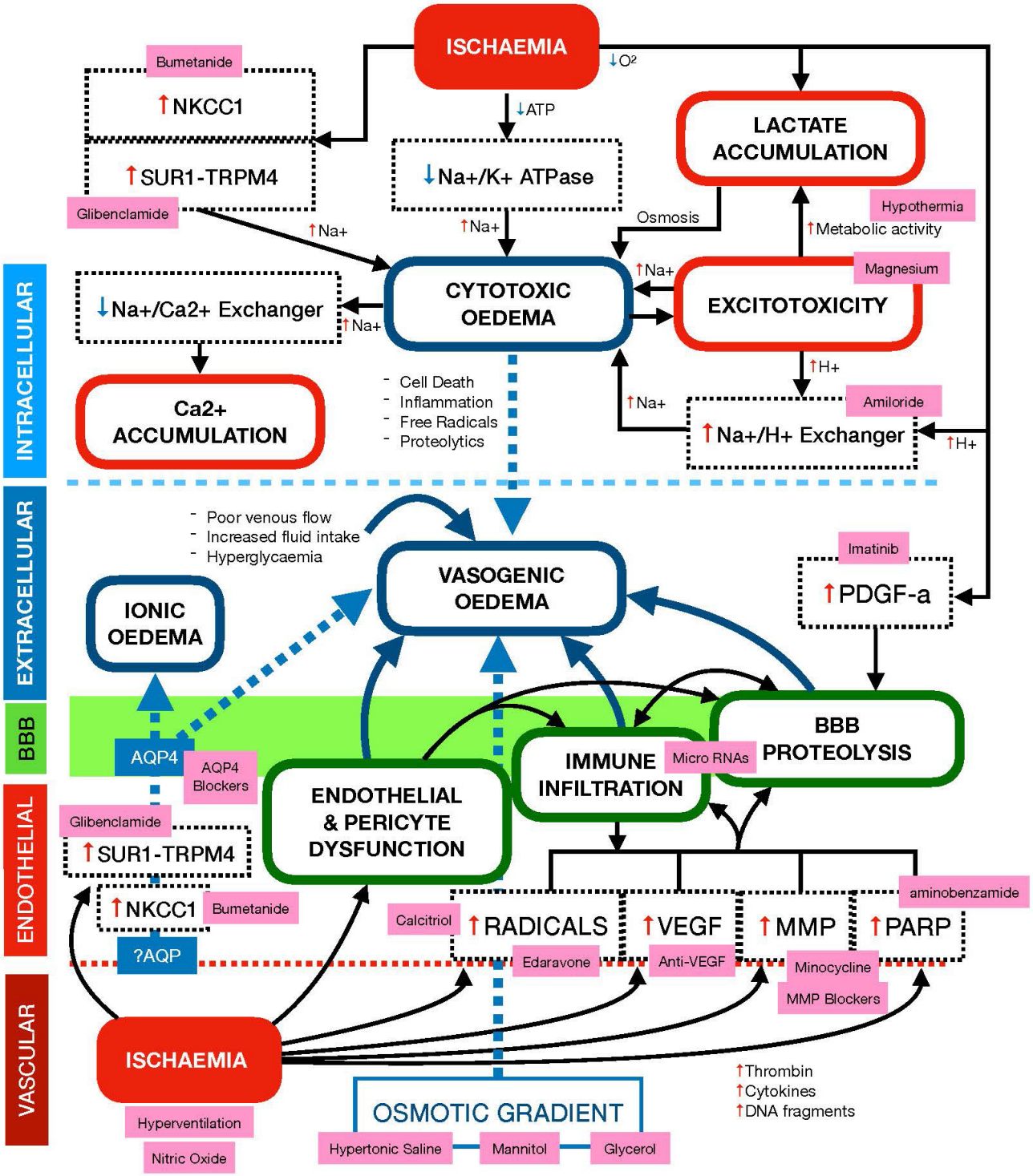


Fig. 1. Summary of the pathophysiology of cerebral oedema in ischaemic stroke and the sites of action of potential treatments (pink boxes). Black arrows indicate the direction of a biochemical pathway and blue dashed arrows the direction of cerebral oedema. Red upward arrows denote increased activity or presence and blue downward arrows decreased activity or presence. Labels on the left indicate the compartment involved (intracellular, extracellular, blood-brain barrier, endothelial, and vascular). Figure created by author SA using Apple Pages (Apple Inc, Cupertino, CA, USA, V14.4). NKCC1, $Na^+/K^+/2Cl^-$; BBB, blood-brain barrier; MMP, matrix metalloproteinase; PARP, poly(ADP-ribose) polymerase; VEGF, vascular endothelial growth factor; PDGF, platelet-derived-growth factor; AQP, aquaporin; ATP, adenosine triphosphate.

Together, these relationships suggest that cerebral oedema should be seen as a balance between multi-factorial fluid entry and clearance rather than a strict linear cascade. This has practical consequences when considering

both therapeutic targets and timing given that interruption of any one process can readily be overcome by another, and that one treatment which interrupts oedema formation may subsequently impede its resolution at a later time point. This will be discussed in greater detail in the next section where we will look at both existing and emerging treatments.

4. Current and Prospective Medical Interventions for Cerebral Oedema

Thus far an overview of the key mechanisms that contribute to the development of cerebral oedema in ischaemic stroke has been provided (Fig. 1). By understanding these mechanisms it is now possible to examine where potential treatments might act to protect against the development of cerebral oedema or provide benefit after oedema formation. The number of existing and proposed management options is vast, but each one deserves individual evaluation. Where possible, we have focussed on human randomised controlled trials specifically, which are summarised below (Table 1, Ref. [80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103]). Where no randomised controlled trials have been performed, we discuss observational and prospective studies. In some cases, no human data is available at all and thus discussion is limited to pre-clinical animal or *in vitro* studies.

Before discussing individual agents in depth, it is worth noting the current recommendations of key guidelines. The American Heart Association/American Stroke Association highlights osmotic agents as a potential short-term medical treatment for cerebral oedema in ischaemic stroke, whilst recognising that the potential benefits and harms of such treatment remain unclear [104], a position that is also shared by the Neurocritical Care Society [105]. The European Stroke Organisation recommends against routine use of osmotic agents [106]. No medical therapy is recommended specifically, and surgical decompression is regarded as the only intervention that has any demonstrated benefit on mortality and disability. This is the evidence gap which the agents below are seeking to address.

4.1 Non-Pharmacological Interventions

4.1.1 Hypothermia

Hypothermia reduces the brain's metabolic activity, which in the context of hypoxia from cardiac arrest has been shown to have protective effects [107]. However, the potential benefit in ischaemic stroke and cerebral oedema is less clear. It has been suggested that hypothermia may be neuroprotective in ischaemic stroke through a variety of mechanisms, such as promotion of cell survival pathways and maintaining BBB integrity [108,109]. It is conceivable that there may be an additional benefit on cerebral oedema, but evidence from human trials is lacking. There have been two clinical trials looking specifically into whole-body hypothermia in ischaemic stroke [80,81]. Both trials showed no difference in functional outcomes and one found worse outcomes for cooled patients due to complications such as pneumonia [81]. Similarly, studies looking into therapeutic cooling for stroke patients who have undergone decompressive hemicraniectomy have either shown no benefit or no differences [110,111]. A recent meta-analysis concluded that whilst hypothermia may have a positive effect, it did not improve mortality and was associated with higher rates of complications compared to conventional stroke treatments [112]. It has been suggested that the lack of hypothermia's efficacy and its increased risks may be that it often requires mechanical ventilation or other forms of airway management, which in stroke patients, who typically breathe spontaneously, may negate any possible benefits [113]. There is also the fact that whole-body cooling may result in negative effects on other body systems, particularly in stroke patients with significant comorbidities. Unfortunately, whilst selective brain cooling has been shown to have a positive outcome in experimental animal models [114], clinical evidence is limited to small feasibility studies, which have not demonstrated benefit on outcome or on volume of cerebral oedema [115,116]. As such, the role of hypothermia in cerebral oedema after ischaemic stroke is questionable. This is also reflected in a meta-analysis performed by the European Stroke Organisation which found no evidence that hypothermia reduces death or poor outcome in space-occupying hemispheric infarction, with the quality of that evidence rated as very low [106].

4.1.2 Hyperventilation

Hyperventilation is thought to exert protective effects on the hypoxic brain by preventing hypercapnia. Carbon dioxide (CO_2) is a known vasodilator, and therefore can increase intracranial pressure, which could be deleterious in the presence of cerebral oedema. However, it is now understood that hyperventilation is only a short-term measure in reducing intracranial pressure as the relative vasoconstriction eventually results in cerebral hypoxia and subsequent vasodilation [117]. In the context of ischaemic stroke, there have been few studies investigating the role of therapeutic hyperventilation, all conducted in the 1970s [118,119]. No benefit was found and the intervention has not been formally tested in this population since, possibly because the notion of inducing vasoconstriction in patients with brain hypoxia is controversial. Research suggests that hyperventilation can be used as a bridging therapy before definitive management of malignant cerebral oedema by decompressive hemicraniectomy, but the rationale for this appears to be in regard to relieving intracranial pressure via temporary vasoconstriction rather than by actually reducing cerebral oedema [120]. Furthermore, there is emerging pre-clinical evidence that administration of CO_2 to induce hypercapnia may actually be beneficial in the context of ischaemic stroke [121]. Current guidance from the European Stroke Organ-

Table 1. Summary of clinical trials and evidence levels for interventions for cerebral oedema in ischaemic stroke.

Classification	Treatment & Trials	Main Findings	Evidence Level
Non-pharmacological	Hypothermia - 2 RCTs, whole-body cooling via endovascular devices	- COOL-AID trial (n = 40) found cooling is feasible in stroke patients but was not associated with any clinical benefit [80]. - ICTuS-2 trial (n = 58) found cooling is feasible in stroke patients but was not associated with any clinical benefit and had increased risk of complications, particularly pneumonia [81].	- B: small RCTs only
	Hyperventilation	- No RCTs, data from observational or prospective studies only.	- C: no RCTs
Osmotic Therapies	Hypertonic Saline	- No RCTs, data from observational or prospective studies only.	- C: no RCTs
	Mannitol - 1 RCT	- Single RCT from 1978 (n = 166). Found no benefit from mannitol on survival. Did not follow up patients beyond day 10 [82]. - No data in relation to cerebral oedema.	- B: 1 small RCT
	Glycerol - 11 RCTs, all included haemorrhagic strokes. - Also includes RCTs using glycerol with other agents (e.g., hypertonic saline)	- Cochrane review (n = 975) concluded that glycerol may have very small improvement in survival in short-term but provides no benefit on long term survival. Only 2 RCTs measured disability and found no benefit on functional outcome [83]. - No data in relation to cerebral oedema.	- B: mixed ischaemic-haemorrhagic RCTs
Ion Channel Blockers	Glibenclamide - 3 RCTs, 2 using IV glibenclamide, 1 using PO glibenclamide - SE-GRACE was conducted exclusively in China.	- GAMES-RP trial (n = 86) showed no improvement in functional outcome or mortality [84]. Secondary analysis showed improvement in surrogate oedema markers, reduced risk of oedema-related death, but not sufficient to improve outcomes overall [85]. - CHARM (n = 431) and SE-GRACE (n = 272) trials showed no improvements in functional outcome or mortality [86,87]. CHARM was terminated early due to slow recruitment during the COVID-19 pandemic and was underpowered to make definitive conclusions.	- B: 1 phase 2 RCT, 1 phase 3 RCT terminated early and underpowered, 1 single-region RCT
	Bumetanide	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical
	Amiloride	- Nil evidence from human studies in ischaemic stroke outside the context of prevention.	- D: pre-clinical
MMP Blockers	Minocycline - 6 RCTs, 1 included haemorrhagic strokes	- EMPHASIS trial (n = 1724) reported improved functional outcome on modified Rankin scale at 90 days with oral minocycline started within 72 hours of stroke (52.6% vs 47.4%) [89]. - Meta-analysis of 5 RCTs (n = 242) reported minocycline associated with improved Rankin scores at 3 month follow-up for ischaemic stroke subgroup [88]. - No significant effect on neuroimaging data in the meta-analysis, suggesting cerebral oedema not affected. Cerebral oedema was not assessed in EMPHASIS.	- B: 1 powered single-region RCT
	Novel MMP9 Blockers	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical

Table 1. Continued.

Classification	Treatment & Trials	Main Findings	Evidence Level
Aquaporin Blockers	Novel AQP4 Blockers	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical
	Trifluoperazine	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical
Neuroprotectors	Magnesium - 7 RCTs, 4 registered intra-arterial trials: one completed 2020 without published results, one withdrawn, one terminated for poor enrolment, one ongoing	- Largest trials, IMAGES (n = 2589) and FAST-MAG (n = 1700), found no benefit of IV magnesium in stroke [90,91]. However these trials also included haemorrhagic patients. - Meta-analysis of 7 RCTs concluded there may be modest benefits on Rankin scale but only in ischaemic stroke patients and should be interpreted with caution due to low patient numbers [92]. - 4 registered intra-arterial trials: one completed 2020 without published results [93], one withdrawn [94], one terminated for poor enrolment [103], one ongoing [95]. - No data in relation to cerebral oedema.	- B: 2 powered RCTs in mixed ischaemic-haemorrhagic samples
	Imatinib - 1 RCT - 1 RCT in progress	- Phase II trial (n = 60) found improvements on Rankin scale with high dose (800 mg OD) group associated with reduced cerebral oedema [96]. - Phase III trial awaited [97].	- B: phase 2 only
	Nitric Oxide - 4 RCTs, all included haemorrhagic strokes - 1 RCT in progress	- ENOS (n = 4011) found no improvement overall, but subgroup analysis showed improvement in functional outcome and mortality in group given GTN <6 hrs from stroke [98]. - RIGHT-2 (n = 1149) reports no benefit with pre-hospital administration [99]. - MR-ASAP (n = 380) terminated early due to safety concerns re: haemorrhagic stroke. No benefit found for ischaemic patients [100]. - No data in relation to cerebral oedema.	- B: 2 powered RCTs in mixed ischaemic-haemorrhagic samples
	Edaravone - 7 RCTs - Almost exclusively studied in Asian populations.	- TASTE-SL (n = 914) reported modest but significant improvements in Rankin score at 90 days [102]. - Other RCTs are much smaller and report no benefit when results are pooled [101]. - No data in relation to cerebral oedema.	- B: 1 powered single-region RCT
	VEGF/Anti-VEGF	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical
	Calcitriol	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical
	3-aminobenzamide/PARP Inhibitors	- Nil evidence from human studies in ischaemic stroke. - Phase II trial for JPI-289 awaited.	- D: pre-clinical
Micro-RNAs	e.g., miRNA-1906, miRNA-132	- Nil evidence from human studies in ischaemic stroke.	- D: pre-clinical

This table highlights randomised controlled trials (RCTs) performed exclusively in ischaemic stroke, or in mixed ischaemic and haemorrhagic stroke populations. Evidence levels: (A) One or more adequately powered randomised controlled trials in ischaemic stroke. (B) Randomised evidence limited by small size, single region, phase 2 design or mixed ischaemic and haemorrhagic populations. (C) No randomised trials, observational or prospective data only. (D) Pre-clinical evidence only, no human data in ischaemic stroke. These levels refer to evidence for clinical outcome and no agent has demonstrated benefit specifically upon cerebral oedema in patients. ENOS, Efficacy of Nitric Oxide in Stroke; GAMES-RP, Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction.

isation advises against routine hyperventilation, reserving use strictly as a short-term rescue measure in patients with clinical signs of herniation who are awaiting surgical management [106].

4.2 Osmotic Therapies

The use of hyperosmolar substances is common in the treatment of cerebral oedema after ischaemic stroke. The rationale for their use is based on the principle that, as previously discussed, cerebral oedema is caused by a dysfunctional osmotic gradient and so treatments to reverse this gradient could lead to resorption of cerebral oedema into the blood. There are a variety of hyperosmolar substances used in osmotic therapy, but their overall and relative effectiveness is widely debated. Guidelines take a cautious position on all osmotic therapies, advising against routine use to reduce death or poor outcome whilst accepting a single or a few doses as a rescue measure where there are signs of raised intracranial pressure in those awaiting surgical decompression, with the choice between mannitol, hypertonic saline, and glycerol left to local practice [104,106].

4.2.1 Hypertonic Saline

Hypertonic saline is available in multiple concentrations (up to 24%). It is used frequently in neuro-intensive care settings for management of raised intracranial pressure secondary to various causes [120]. There is evidence that doses of hypertonic saline are equally as effective as osmolarity-matched doses of mannitol in reducing intracranial pressure temporarily [122]. However, treatment requires strict monitoring of serum sodium and placement of a central venous line [123]. However, despite its ubiquitous use there is a lack of high-quality data regarding the effects of hypertonic saline in acute ischaemic stroke. Experts from the 2020 Neurocritical Care Society's panel on cerebral oedema concluded that whilst there was evidence that hypertonic saline could reduce intracranial pressure (presumably through its effect on cerebral oedema), there was insufficient evidence to make recommendations on specific protocols, or on the effects on clinical outcome [105]. A systematic review of 5 studies analysed the use of continuous hypertonic saline in ischaemic stroke and concluded that the potential treatment effect on intracranial pressure did not translate into mortality benefit or improvement in neurological outcome compared to standard medical management [124]. A follow-up study from the same group assessed continuous hypertonic saline and radiological changes specifically, and found that treatment with hypertonic saline was associated with worsened cerebral oedema and no improved outcomes in stroke patients [125]. This is a particularly important finding as most research on hypertonic saline in this area did not utilise radiological evidence to determine treatment effects. Recently, a retrospective study of 175 stroke patients who received hypertonic saline concluded that hypertonic saline was associated with worse outcomes compared to controls [126]. Experts suggest the observed results may be due to a 'rebound' oedema given that the effects of treatment on intracranial pressure were temporary. Overall, there is little evidence to support the routine use of hypertonic saline to treat cerebral oedema caused by ischaemic stroke.

4.2.2 Mannitol

Mannitol is a sugar alcohol that acts as a powerful diuretic when administered intravenously, thereby reducing total body water content and brain water content. Mannitol is cheap and easily available which has made it a popular choice in the management of raised intracranial pressure [120] but the effects of mannitol on cerebral oedema after ischaemic stroke are unclear. Studies have shown that mannitol can reduce intracranial pressure in stroke patients [127], but it may be healthy tissue rather than infarcted oedematous tissue that is the source of water loss [128]. Furthermore, little is known about the effect of mannitol on clinical outcomes after stroke. A 2007 Cochrane review analysed three randomised controlled trials including a total of 226 stroke patients that received treatment with mannitol, placebo, or open control, and found no benefit [129]. However, it should be noted that only one of these trials included patients with ischaemic stroke and the numbers were small. Moreover, the study was conducted in the 1970's when little was known about acute treatment or prevention, and to our knowledge this remains the only mannitol trial in ischaemic stroke specifically [82]. More recent prospective studies attempting to elucidate functional outcomes of stroke patients who receive mannitol have concluded that it does not improve mortality or neurologic outcome [130]. It has been suggested that the potential cause of the observed results in mannitol studies is inter-cerebral mannitol accumulation and rebound oedema, although this has not been analysed prospectively [131]. Overall, there is a distinct lack of research investigating the use of mannitol to treat cerebral oedema in ischaemic stroke patients, despite its ubiquitous use. There is one ongoing trial analysing dose-escalation of mannitol to reduce oedema in acute intracerebral haemorrhage [132], and the results may inform the design for similar trials in ischaemic stroke.

4.2.3 Glycerol

Glycerol is another hyperosmolar agent but it is less commonly used in clinical practice. One small study utilising MRI however showed that glycerol administration does not change tissue volume in the infarcted area [133]. A Cochrane review analysing 11 randomised trials showed that glycerol may improve short-term mortality after stroke, but no effect was seen on longer-term clinical outcomes [83]. It is important to highlight that these studies did not use neuroimaging and so the effect of glycerol on cerebral oedema in ischaemic stroke is unknown. Presently there are no ongoing studies of glycerol for cerebral oedema in

ischaemic stroke. This may be due to the fact that it is less commonly used when compared to hypertonic saline or mannitol.

4.3 Ion Channel Blockers

4.3.1 Glibenclamide

As previously discussed, the sulfonylurea receptor 1-regulated $NC^{Ca\text{-}ATP}$ (SUR1-$NC^{Ca\text{-}ATP}$ or SUR1-TRPM4) has been implicated in the development of ionic oedema in the context of experimental ischaemic stroke studies. Sulfonylureas, particularly glibenclamide (also known as glyburide), are inhibitors of the SUR1-TRPM4, and in animal models of ischaemic stroke are associated with reduced oedema and infarct size [134]. Clinical data however is less encouraging. Thus far there have been three randomised controlled trials investigating the use of glibenclamide in ischaemic stroke patients. The "Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction" (GAMES-RP) trial included 86 patients randomly assigned to a patented version of glibenclamide or a placebo group and found that treatment was safe and not associated with hypoglycaemia [84]. However, there was no significant effect on primary composite outcome of mortality, disability, and need for hemicraniectomy. Secondary analysis of patients from this trial suggested that whilst there were improvements in surrogate oedema markers (e.g., reduced midline shifting, reduced MMP-9 activity) however this did not translate to improved clinical outcome [85,135]. The "Intravenous glibenclamide for cerebral oedema after large hemispheric stroke" (CHARM) trial included 431 patients who received either a patented version of glibenclamide or placebo for severe cerebral oedema. Results showed no improvement on mortality or functional outcomes [86]. It should be noted that this trial was stopped early due to complications from the COVID-19 pandemic and was underpowered to make definitive conclusions. A recent analysis combining the GAMES-RP and CHARM trials concluded that intravenous glibenclamide likely had little to no effect on functional outcomes following ischaemic stroke [136]. One study used oral glibenclamide in ischaemic stroke and also found that there was no improvement in mortality or functional outcome [137]. This study led to the "Safety and Efficacy of Glibenclamide Combined with rtPA in Acute Cerebral Ischemia with Occlusion/Stenosis of Anterior Circulation" (SE-GRACE) trial investigating the use of oral glibenclamide in combination with thrombolysis but also found no benefit with regard to mortality or disability [87]. It is worth noting that the European Stroke Organisation appraised glibenclamide when only GAMES-RP was available, and rated the evidence as low to very low. The subsequent publication of CHARM and SE-GRACE does not alter this decision [106], and a subsequent 2025 GRADE-evaluated meta-analysis on glibenclamide reached the same conclusion [138]. Overall, based on the current evidence the use of glibenclamide for cerebral oedema after ischaemic stroke cannot be recommended and future trials could investigate other sulfonylureas.

4.3.2 Bumetanide

The $Na^+/K^+/Cl^-$ (NKCC1) co-transporter is another channel implicated in the development of cytotoxic and ionic oedema [24]. There is promising evidence from pre-clinical animal studies that bumetanide may be capable of blocking this channel at the BBB, sufficient to reduce oedema in ischaemic stroke [139]. However, there have been no clinical trials in humans and so evidently more research is needed to elucidate the potential benefits of bumetanide.

4.3.3 Amiloride

The Na^+/H^+ exchanger is also known to play a role in the accumulation of cytotoxic oedema [11] and can be blocked by amiloride [140]. Pre-clinical *in vitro* and animal studies suggest it may have benefit in the ischaemic brain [51,141], however amiloride has only been studied in humans in regards to stroke prevention, and studies are awaited to assess its effects on cerebral oedema.

4.4 Matrix Metalloproteinase Inhibitors

As highlighted, the activation of MMPs is an important step in BBB breakdown and subsequent formation of cerebral oedema in ischaemic stroke [45]. Many commonly used drugs are known to have a degree of inhibitory activity on MMPs (particularly MMP-9) beyond their primary mechanism of activation, with two noteworthy examples being statins [142] and tetracyclines [143]. Clinical data show that statin pretreatment attenuates the rise in plasma MMP-9 that follows intravenous thrombolysis, but this biochemical effect is not accompanied by any improvement in functional outcome or reduction in haemorrhagic transformation, indicating that suppression of MMP-9 alone is not sufficient to alter clinical outcome [144]. Of the tetracyclines studied, minocycline has been the preferred candidate due to its superior anti-MMP9 activity relative to doxycycline [143]. A meta-analysis of 5 randomised controlled trials (4 ischaemic and 1 mixed haemorrhagic and ischaemic sample) concluded that minocycline may improve functional outcomes at 3 months after ischaemic stroke [88]. This has since been supported by the EMPHASIS trial, in which 1724 patients were randomised to oral minocycline or placebo within 72 hours of ischaemic stroke onset. A greater proportion of treated patients achieved an 'excellent' functional outcome on the modified Rankin scale at 90 days (52.6% versus 47.4%) with no safety concerns [89]. However, the treatment effect was modest, recruitment was confined to a single country, enrolled strokes were predominantly of moderate severity, and the benefit was attenuated when missing outcome data were handled under a worst-case assumption. Importantly, the aforemen-

tioned meta-analysis found no significant effect on neuroimaging outcomes, and cerebral oedema was not assessed specifically. This suggests that whilst minocycline may have some degree of neuroprotection via MMP-9 inhibition, there remains no evidence that this translates into a reduction in cerebral oedema, and future trials should incorporate radiological endpoints to address this. Further work is also required to establish the optimal dosage. Although novel MMP-9 inhibitors do exist and have been used in clinical trials, they have thus far not been used with regard to ischaemic stroke [145]. These compounds are likely to provide more specific and potentially more potent inhibition of MMP-9, but at present their pharmacokinetics and safety profile with regard to ischaemic stroke are not entirely understood and clinical stroke trials are still required [146]. For example, one pertinent question to answer is regarding the timing and duration of potential MMP-9 inhibitor treatment, as there is some pre-clinical evidence that prolonged use may actually interfere with neurological recovery by preventing neurovascular growth [147].

4.5 Aquaporin Blockers

As discussed, AQP4 is the major aquaporin channel implicated in the development of cerebral oedema. However, there are two major issues when it comes to blocking AQP4 in this context. The first is that AQP4 is ubiquitously expressed across the body's tissues and therefore developing a drug that can selectively block AQP4 in the brain is challenging. The second is that in the context of oedema in ischaemic stroke, AQP4 may have both a contributory and protective role [148]. It has been suggested that AQP4 allows water entry into neurons and astrocytes during the cytotoxic phase of oedema, but then allows excess fluid gathered during the vasogenic phase to be cleared from the brain parenchyma [149]. As a result, the timing of any potential AQP4 blocker needs to be carefully assessed. At present, there are no approved direct aquaporin blockers for clinical use, but novel compounds (e.g., AER-271, TGN-020) exist and have been shown to improve cerebral oedema in preclinical models [150,151]. Trifluoperazine, which is an antipsychotic has also been shown to partially block AQP4 and reduce cerebral oedema in animal models of stroke [152]. Clinical trials of these agents are awaited.

4.6 Neuroprotectors

4.6.1 Magnesium

Magnesium is a well-known neuro-protectant (e.g., in the treatment of pre-eclampsia), but its efficacy in ischaemic stroke is still under investigation. Pre-clinical models suggest that magnesium can have beneficial effects on cerebral oedema in stroke by attenuating excitotoxicity via its inhibition of NMDA receptors, blockage of voltage-gated calcium channels [153], and its antioxidant and BBB-stabilising properties [154]. To date, two large clinical trials have investigated the use of intravenous magnesium in stroke, including 2589 and 1700 patients respectively [90,91]. Neither trial found any benefit in functional outcome or mortality associated with IV magnesium administration. A meta-analysis of 7 human studies testing the use of intravenous magnesium in acute ischaemic stroke concluded that there may be modest benefit on functional outcome, but that this must be interpreted with caution due to low numbers of patients [92]. 4 studies have investigated the use of intra-arterial magnesium in ischaemic stroke, two of them in combination with other agents. One was prematurely terminated due to poor enrolment [154], one has been withdrawn [94], one completed in 2020 but results remain unpublished [93], and one is ongoing [95]. It is suggested that an intra-arterial delivery of magnesium could be more effective than intravenous delivery as it provides a more direct route to the infarcted tissue and can easily be given at the same time as treatment such as mechanical thrombectomy [153,155].

4.6.2 Imatinib

Imatinib is a tyrosine kinase inhibitor most commonly used in the treatment of haematological cancers. Its capacity to inhibit the signaling of platelet-derived growth factor alpha (PDGF-alpha) on perivascular astrocytes has been associated with improved BBB integrity in animal models of ischaemic stroke [156]. A phase II trial found promising results with high-dose administration of imatinib (800 mg daily) from days 0 to 5 of an acute stroke in patients who also received thrombolysis [96]. The high-dose patients had improved neurological outcomes, comparable to those of mechanical thrombectomy, relative to the control and lower-dose groups (400 mg daily and 600 mg daily), as well as reduced volumes of cerebral oedema on neuroimaging. There were no differences in the rates of haemorrhagic conversion or other adverse events. These results are encouraging, however it must be noted that only 60 patients were recruited into this study and thus larger trials of imatinib in ischaemic stroke are still required to confirm its potential beneficial effects. A phase III trial is currently recruiting [97].

4.6.3 Nitric Oxide

Originally, nitric oxide (NO) was investigated for use in stroke due to its anti-hypertensive properties, and there is pre-clinical evidence that NO may reduce oedema via a number of pathways in the early stages of stroke [157]. The Efficacy of Nitric Oxide in Stroke (ENOS) trial recruited 4011 stroke patients with a systolic blood pressure of >140 mmHg and randomly assigned to receive a transdermal glyceryl trinitrate (GTN), an NO donor patch or no treatment [98]. The trial was neutral but patients who received GTN within 6 hours appeared to have improved functional outcomes and reduced mortality [158]. This finding was also observed in the "The rapid intervention with glyceryl trinitrate in hypertensive stroke" (RIGHT)

trial which assessed transdermal GTN in the pre-hospital setting, although the sample size in this trial was much smaller, only including 41 patients [159]. RIGHT showed improved outcomes for suspected stroke patients treated with GTN within 4.5 hours of stroke but, the results were not replicated in the larger phase 3 RIGHT-2 trial [99]. Another trial, performed in the Netherlands, also tested GTN in the pre-hospital setting, however, it was terminated early due to safety concerns [100]. The ENOS-2 trial is currently underway and testing GTN within 4.5 hours of ischaemic stroke with results awaited [160]. Importantly, none of the aforementioned trials reported the effect of GTN on cerebral oedema specifically.

It is noteworthy that impaired endothelial nitric oxide synthase (eNOS) activity contributes to cerebral endothelial dysfunction and ensuing BBB breakdown. During or after ischaemic injury, attempts to compensate by modulating eNOS are often ineffective because NO levels fall while reactive oxygen species rise and neutralise NO. Nonetheless, several therapies can boost eNOS activity by enhancing components of the Akt/eNOS/NO pathway. These include NO donors, statins, ACE inhibitors, calcium channel blockers, phosphodiesterase-3 inhibitors, aspirin, dipyridamole and ellagic acid. Many of these agents have anti-platelet effects, increase eNOS expression, or prevent eNOS uncoupling and tetrahydrobiopterin oxidation. As more eNOS-modulating compounds are identified, further research is needed to clarify how they prevent or reverse endothelial dysfunction, BBB integrity, and cerebral oedema [161].

Several reasons account for the difficulty in translating this therapeutic target. Firstly, NO is not a single pharmacological entity. Endothelial nitric oxide synthase-derived NO is vasoprotective, whereas NO generated by ischaemia contributes to oxidative injury, so a systemic donor cannot selectively reproduce beneficial effects and could simultaneously drive harmful effects. Furthermore, NO-induced blood pressure reduction in the hyperacute phase risks compromising perfusion of the ischaemic penumbra, and it was on these safety grounds that pre-hospital administration was halted in the trial conducted in the Netherlands [100]. Finally, as noted above, no trial has measured cerebral oedema, so any anti-oedema effect remains inferred from pre-clinical work rather than demonstrated.

4.6.4 Edaravone

Edaravone is an antioxidant capable of scavenging peroxyl radicals, and has been approved for use in ischaemic stroke in Japan [162]. Pre-clinical evidence suggests it may have protective effects on oedema development [163] and a recent systematic review and meta-analysis including 19 studies investigating the use of edaravone in ischaemic stroke concluded that treatment appears to have a beneficial effect on both functional outcomes and mortality [101]. However, the majority of these studies were observational and there was a risk of bias. When restricted to only the 5 randomised controlled trials, the review found that edaravone was not associated with any significant effect on outcomes. This may be because these trials were primarily looking into safety rather than efficacy, and included a very small number of patients. Furthermore, all studies except one [164], were conducted in Asia (Japan, most commonly), and so caution should be taken when applying results to other populations. Since this review, there have been at least three further studies testing the effects of edaravone. This includes one trial in China which recruited 914 stroke patients to receive placebo or sublingual edaravone and found that 64.4% of edaravone patients had a modified Rankin scale of 1 or less at 90 days compared to 54.7% in the placebo group [102]. A recent phase II trial of 200 patients who had achieved recanalisation found that treatment with edaravone made no difference to the Rankin scores at 90 days [165]. There is no data on mortality, and the rates of adverse effects were similar between the treatment groups, however it should also be noted that this trial enrolled substantially more patients with low National Institutes of Health Stroke Scale (NIHSS) scores. A large observational study of 4401 Chinese stroke patients reported improvements in functional outcome with edaravone but there was no difference in mortality [166].

4.6.5 Vascular Endothelial Growth Factor (VEGF) & Anti-VEGF

The role of VEGF in ischaemic stroke is not entirely clear. Pre-clinical evidence seems to predominantly suggest that use of anti-VEGF drugs is neuroprotective and reduces the development of cerebral oedema in mouse models of stroke [47]. One study however found that giving VEGF early post-ischaemia worsened oedema but treatment at 48 hours was associated with improved functional outcomes [167]. Another study has similarly shown improved functional outcomes and reduced infarct volumes with intraventricular administration of VEGF starting at a later time window [168]. This suggests that VEGF may not be helpful in the initial period due to increased capillary permeability and MMP activity but may exert protective effects in the sub-acute phase of ischaemia. This may be due to its directly protective effects on neurons, but whether it affects cerebral oedema is unclear [47].

4.6.6 Calcitriol

Calcitriol is the active form of vitamin D and has been shown in multiple animal and *in-vitro* studies to have protective effects on ischaemic neurons, likely through reduced calcium influx and antioxidant and anti-apoptotic actions [169]. Animal models of ischaemic stroke have also demonstrated that calcitriol administration can reduce cerebral oedema, suggesting it may act to attenuate BBB breakdown, likely via anti-oxidant action and up regulation of neurotrophic factors [170]. Despite this, calcitriol has not been tested clinically, likely due to specific translational difficulties. Calcitriol has a narrow therapeutic index, and

the doses required to reproduce the neuroprotective effects seen in rodents also risk hypercalcaemia in human patients [171]. Furthermore, any trial must stratify by baseline vitamin D status and might show benefit only in those who are depleted. Finally, the pre-clinical evidence rests largely on pre-treatment or immediate post-ischaemic administration, whilst studies giving calcitriol after stroke onset have not reproduced the benefit, representing a considerable translational gap [171].

4.6.7 3-Aminobenzamide & PARP Inhibitors

Ischaemic activation of PARP is one of the many mechanisms thought to contribute to BBB breakdown and subsequent development of oedema [49]. 3-aminobenzamide is a first-generation inhibitor of PARP and there is pre-clinical evidence that it can reduce infarct size and neutrophil infiltration following transient focal cerebral ischaemia [172]. One study measuring its impact on cerebral oedema specifically has been retracted however [173]. The evidence for an effect on oedema comes from later, more potent agents in the same class. In rat models of both transient and permanent middle cerebral artery occlusion, the PARP-1 inhibitor JPI-289 (amelparib) administered two hours after occlusion reduced infarct volume and brain swelling on MRI at both 24 hours and seven days, with improvements in neurological function sustained to 28 days [174]. A phase 2 trial of JPI-289 in acute ischaemic stroke is registered, although no results have been published [175].

4.7 Micro-RNA

Micro-RNAs (miRNAs) are transcriptional regulators of proteins, and their expression significantly changes in response to acute stroke [176]. Multiple miRNAs have been implicated in processes such as neurogenesis, apoptosis, inflammation, and angiogenesis, but importantly some miRNAs including miRNA-1906 and miRNA-132 appear to specifically modulate BBB degradation and the development of oedema in ischaemic stroke [177,178,179]. Modulation of these miRNAs in pre-clinical studies has shown promise, but much more research is needed in the clinical setting. Moreover, since miRNAs also play important roles in key mechanisms associated with the pathogenesis of stroke, including energy failure, inflammation and cell death, it is possible that miRNAs may serve as reliable blood-based markers for risk prediction, diagnosis and prognosis of ischaemic stroke [180]. A systematic review of 17 studies including 1443 patients found that circulating miRNAs correlate with infarct volume in acute ischaemic stroke, with nine indicators positively and six negatively associated [181]. The evidence is limited however. The correlation was contradictory across studies for the brain-specific miRNA-9 and miRNA-124, no study controlled for confounding, and all were conducted exclusively in Chinese cohorts. It should also be emphasised that these associations concern infarct volume rather than oedema specifically, and no miRNA has yet been shown to predict or track oedema formation, midline shift or malignant progression in patients. The obstacles to therapeutic use of miRNAs are also considerable. The primary difficulty is that a single miRNA regulates large numbers of transcripts and may be protective in one cell type whilst harmful in another, making off-target effects highly likely and difficult to predict. There is at present no validated means of confirming target engagement in patients, and sequence and target differences between species limit what can be inferred from rodent studies. Furthermore, oligonucleotides cannot readily pass through an intact BBB, and therefore would require an additional vector for transport if being intended for early use in stroke before the BBB has been sufficiently degraded. For these reasons the nearer-term clinical application of miRNAs in stroke is likely to be diagnostic and prognostic rather than therapeutic.

5. Considerations for Future Research

Progress in the field of cerebral oedema in ischaemic stroke has been limited not only by the underlying biological complexities of the subject matter, but also by study design. The following sections set out the principal limitations of the current evidence base and barriers to translation, research priorities, and the problems of cerebral oedema measurement and biomarker validation.

5.1 Limitation

Experimental models typically use young, healthy rodents with occlusions of fixed duration, and the Stroke Therapy Academic Industry Roundtable criteria intended to close the gap to clinical practice have not prevented agents from failing in patients [182]. Beyond these methodological differences, the biology itself is highly complex. Treatment timing must match the phase of oedema being targeted, several targets have opposing actions early and late, Na^+ and water enter by parallel routes so that single-target blockade may be compensated, and any anti-oedema effects are readily diluted in trials that recruit unselected populations. Trials are also powered for functional outcome rather than oedema, and where oedema is measured the methods are heterogeneous which limits pooling across studies [183]. The obstacle is therefore as much one of study design and measurement as of pharmacology. Agents directed at cytotoxic and ionic oedema may be given as early as possible, including in the pre-hospital setting or alongside thrombectomy, whereas agents directed at barrier breakdown and inflammation could be administered in the subacute period. Sequential combination therapy follows from the same logic, where pairing an agent acting on early ion and water transport with one directed at later barrier failure and repair may produce synergistic benefit. Enrolment should also be enriched using validated prediction models and imaging criteria so that trials recruit patients at genuine risk of malignant oedema. Accelerating translation will also

require change in pre-clinical work. Greater use should be made of aged animals with relevant comorbidities, outcomes should correspond to what is measured in patients (for example midline shift on imaging rather than brain water content alone), and randomisation, blinded assessment and pre-specified analysis should be standard, with neutral results published.

5.2 Priorities for Future Trials

Several specific trials should be prioritised, with the most pressing gap concerning agents currently in use. An adequately powered randomised comparison of mannitol, hypertonic saline and standard care in ischaemic stroke, with radiological as well as functional endpoints, is overdue. Confirmation of the minocycline result in populations outside the trial in which it was obtained, and with cerebral oedema measured, would establish whether that benefit is reproducible and whether it is mediated by an effect on swelling. The reporting of the phase III imatinib trial and of the outstanding intra-arterial magnesium studies should be awaited before further agents of the same class are taken forward. Glibenclamide has repeatedly demonstrated no clinical benefit despite multiple adequately powered RCTs, and so value in continuing its investigation is questionable. Multicentre pre-clinical studies, conducted in the manner of clinical trials, would provide a more reliable estimate of effect before human studies, and early-phase clinical trials incorporating imaging endpoints and evidence of target engagement should precede definitive trials. Finally, as intravenous thrombolysis and mechanical thrombectomy are standard treatment, understanding how therapeutic reperfusion alters the development of oedema, and in whom, will be central to both clinical decision-making and the design of the next generation of trials.

5.3 Measurement & Biomarkers

Measurement of oedema deserves equal attention. Radiological measures such as net water uptake, midline shift and displacement of cerebrospinal fluid offer direct measurement of the process being treated, and their standardisation and validation as surrogate endpoints would allow an anti-oedema effect to be demonstrated in smaller trials. Consensus definitions of cerebral oedema and 'malignant oedema' particularly would also make individual studies comparable. Circulating markers such as MMP-9, miRNAs, and other inflammatory mediators may help stratify patients by risk at presentation and confirm that an administered drug has engaged its intended target, information that almost no trial in this field has collected. It should be emphasised that no biomarker has yet been validated as a surrogate for clinical outcome in cerebral oedema, and that their value at present lies in patient selection and mechanistic confirmation rather than as a replacement for clinical endpoints.

6. Conclusion

Cerebral oedema is a common and potentially devastating consequence of ischaemic stroke. Mild oedema may be clinically silent but is associated with worse functional outcome, whilst severe or 'malignant' oedema is a significant contributor to overall mortality. Considerable progress has been made in understanding its pathogenesis, however this has not yet translated into treatment. No medical therapy has demonstrated the capacity to both reduce cerebral oedema and confer clinical benefit in human phase III trials, and available treatments used in current practice lack contemporary and adequately powered evidence. Of those tested in humans, only minocycline, edaravone, and imatinib have shown potential clinical benefit as a primary trial outcome, but an effect on cerebral oedema itself has not been established. Several further candidates remain under investigation, but appropriately designed studies will be needed to adequately explore their clinical potential. Cerebral oedema evolves through overlapping phases with distinct mechanisms, so the timing of administration and the selection of patients at genuine risk of developing severe oedema are key factors. Most importantly, oedema itself must be measured. An anti-oedema effect cannot be demonstrated by trials powered only for functional outcome, and until the radiological measures of swelling are standardised and validated, an effective treatment and an ineffective one will be difficult to distinguish.

Key Points

• Cerebral oedema is an inevitable consequence of ischaemic stroke and, in its most severe form, carries a mortality of up to 80% without surgical intervention, yet no medical treatment has been shown to reduce cerebral oedema sufficiently to improve clinical outcome in human phase III trials.

• Cerebral oedema develops in overlapping phases, beginning with cytotoxic swelling driven by energy failure and disrupted ion transport, progressing to an ionic phase in which sodium and water cross an intact blood-brain barrier, with cerebrospinal fluid entering along perivascular routes, and culminating in vasogenic oedema once the barrier itself breaks down.

• Blood-brain barrier breakdown is driven by multiple mechanisms including endothelial and pericyte dysfunction, proteolysis (notably by matrix metalloproteinases), and inflammatory cell infiltration, all of which may be targets for future treatments.

• Clinical data have demonstrated that successful reperfusion is associated with reduced severity of cerebral oedema, which may be a major driver of functional recovery, particularly in patients with large mismatch volumes.

• Hypertonic saline, mannitol and glycerol are widely used to treat cerebral oedema despite being poorly supported by high-quality trials, and neither hypothermia nor hyperventilation has demonstrated clear benefit.

• Several mechanism-targeted agents remain under investigation, but their evaluation will require trials that match the timing of administration to the phase of oedema being targeted, consider sequential combination therapy, and utilise radiological markers of cerebral oedema.

Availability of Data and Materials

Not applicable.

Author Contributions

SA contributed to the preparation and analysis of the figures and tables and drafted the initial version of the manuscript. SA, UB, NS, PMB, and KK all contributed to the manuscript's overall structure and design. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

AI was not used at any point in the research or writing of the original draft of this narrative review. Following peer review, AI was used for citation tracking as well as grammatical proofreading prior to final submission. After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

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