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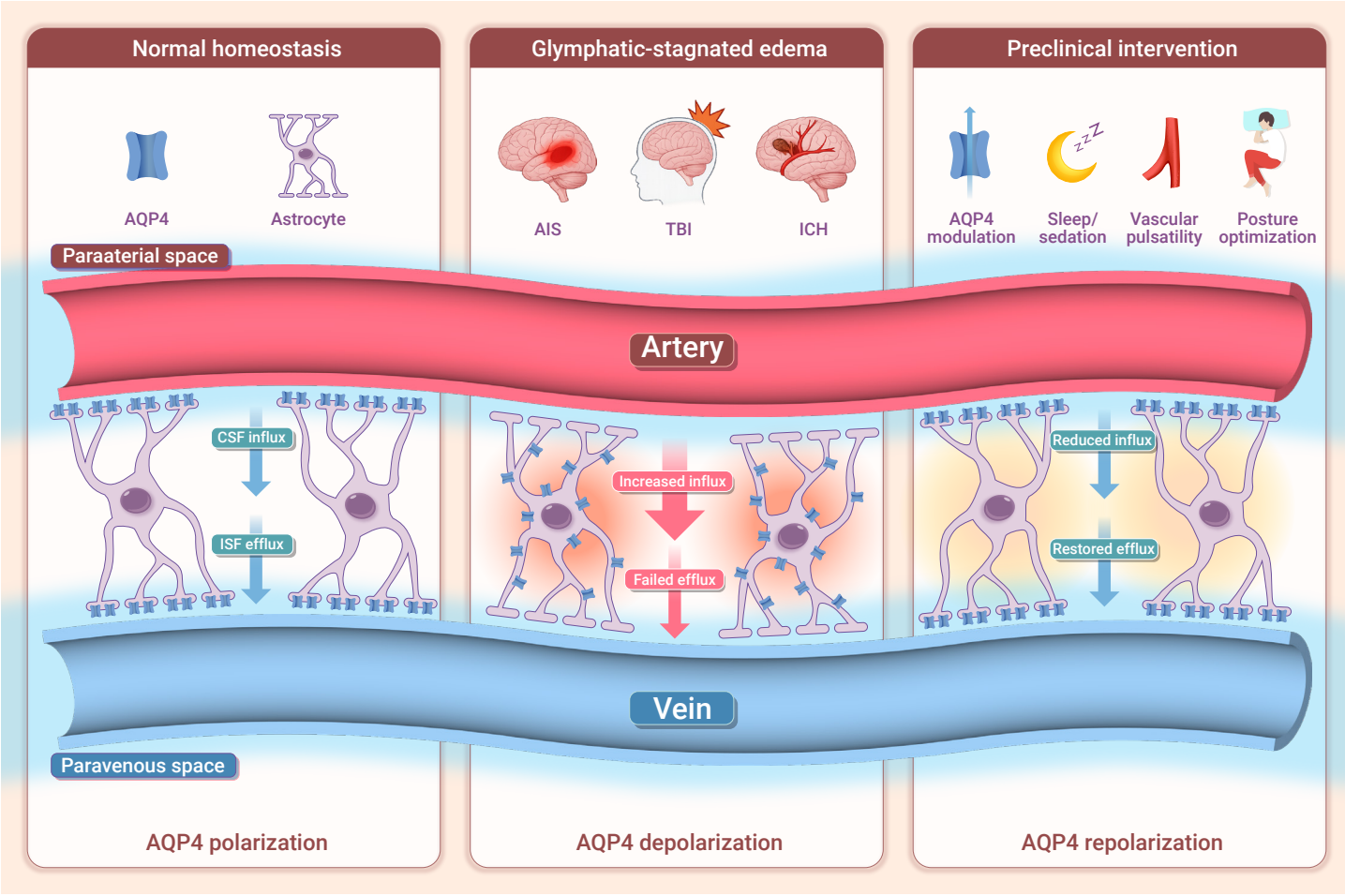
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Cerebral edema after stroke, bleeding, or trauma can worsen injury and threaten life.
- The glymphatic system is a brain-wide fluid transport network that may influence edema over time.
- Studies suggest that early fluid entry can drive swelling, while poor clearance can make it last.
- Aquaporin-4 may promote fluid entry or removal, depending on injury type and timing.
- More human studies are needed before treatments can be recommended.

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Glymphatic dysfunction and cerebral edema: A transport-based framework, evidence, and therapeutic implications

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Cerebral edema is a major cause of secondary injury after acute brain insults. Classical categories describe the compartment of water accumulation and the integrity of relevant barriers, but they less directly capture fluid sources, transport routes, and clearance over time. The glymphatic system supports cerebrospinal fluid (CSF)-interstitial fluid (ISF) exchange and may influence brain water movement. Here, we critically evaluate evidence linking glymphatic dysfunction to edema after ischemic, hemorrhagic, and traumatic brain injury (TBI). Building on the term introduced by Eide and Ringstad, we use glymphatic-stagnated edema as a provisional transport-based framework to organize evidence across injury types, temporal phases, and transport dysfunctions. We distinguish aquaporin-4 (AQP4) abundance from perivascular polarization and establish a hierarchical evidence framework ranging from direct tracer imaging to clinical imaging studies. We also identify injury-specific transport patterns: hyperacute CSF entry in ischemia, intervention-responsive efflux failure in TBI, and context-dependent AQP4 effects. Given that the evidence is predominantly preclinical, human validation requires multicenter studies pairing serial transport measures with independent edema quantification. We outline testable predictions and a translational roadmap for evaluating glymphatic-directed interventions in neurocritical care.

INTRODUCTION

Cerebral edema contributes substantially to early deterioration, raised intracranial pressure, and poor neurological outcome after acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and traumatic brain injury (TBI).[1–2] Edema can worsen perfusion, amplify tissue injury, and increase the need for neurocritical care. Osmotherapy, ventilatory management, and decompressive surgery can mitigate life-threatening swelling, but these interventions are primarily reactive.[3–4] Mechanism-directed treatment remains limited because the sources, routes, and clearance of excess brain water change across injury types and over time.[6–7] A transport-based perspective may help address this gap by specifying the sources, routes, and temporal dynamics of excess brain water.

Classical frameworks describe cytotoxic, ionic, vasogenic, and interstitial edema according to the location of excess water, the distribution of osmolytes, and blood-brain barrier integrity.[2,5,10] These categories remain essential for linking swelling to cellular energy failure, transvascular ion and fluid entry, endothelial disruption, or ventricular pressure. However, compartment-based labels do not by themselves specify how fluid enters, redistributes within, and leaves the injured brain. A transport perspective instead identifies the routes and dynamics that dominate net water accumulation or clearance during each phase of injury.

Iliff and colleagues described a paravascular pathway for CSF influx and interstitial solute clearance, which was later termed the glymphatic system.[8] Subsequent studies linked perivascular transport and aquaporin-4 (AQP4) organization to brain water movement, although the magnitude and mechanisms of glymphatic flow remain debated.[9–10,21–22] Acute injury can alter vascular dynamics, perivascular geometry, intracranial pressure, astrocyte structure, and AQP4 localization.[7,11–12] These changes may affect edema, though observed associations do not by themselves establish that glymphatic failure is the primary cause of swelling.

Eide and Ringstad introduced glymphatic-stagnated edema in the context of TBI.[13] The present review extends this framework across ischemic, hemorrhagic, and traumatic brain injury by distinguishing AQP4 abundance from polarization and isoform organization and by organizing influx, clearance failure, and recovery along a temporal axis. We evaluate the strength of supporting evidence hierarchically—from direct tracer imaging through interventional studies to clinical associations—and identify tractable barriers to clinical translation.

CLASSICAL CEREBRAL EDEMA AND THE UNRESOLVED TRANSPORT DIMENSION

Cytotoxic edema denotes intracellular swelling caused by energy failure and impaired ion homeostasis, particularly in neurons and astrocytes.[2,10,14,16] Ionic edema describes net entry of ions and water from outside the parenchyma across an initially intact or partially altered blood-brain barrier (BBB). The two processes are mechanistically connected but are not synonymous: intracellular redistribution alone does not increase total tissue water unless additional solute and water enter the brain.

Vasogenic edema results from increased BBB permeability and the extracellular accumulation of plasma-derived fluid and proteins.[2,15] Interstitial edema is also extracellular, but conventionally refers to transependymal CSF movement into periventricular tissue during hydrocephalus or raised intraventricular pressure.[17] These categories can overlap within the same lesion and can change as injury evolves.

The classical framework is strongest when identifying where water accumulates and which cellular or barrier process is altered. It is less explicit about three linked transport variables: where that water comes from, by what routes it moves, and how it is ultimately cleared. In the hyperacute phase, CSF and transvascular routes may contribute alongside osmotic redistribution, but their relative importance differs by model.[18–19] During later phases, edema can persist or resolve despite continuing BBB abnormalities, raising the possibility that clearance capacity also shapes tissue water burden.[7]

A transport-based framework therefore complements rather than replaces classical edema biology. It asks whether net swelling reflects increased influx, reduced efflux, or both, and whether these processes change across hyperacute, acute, and resolution phases. This distinction is necessary because the same reduction in tracer movement can reflect reduced entry, impaired clearance, altered distribution, or a combination of these effects.

OPERATIONAL DEFINITION OF GLYMPHATIC-STAGNATED EDEMA

Building on the formulation by Eide and Ringstad, we use glymphatic-stagnated edema to describe a potential transport state in which abnormal perivascular CSF influx, inadequate interstitial–perivascular clearance, or both, contribute to net tissue water accumulation or delayed edema resolution.[13] The term denotes a potential mechanistic dimension, not a mutually exclusive edema subtype.

Three evidentiary features are relevant to this working definition. First, net tissue swelling or delayed resolution must be demonstrated independently of a glymphatic surrogate. Second, altered CSF–ISF transport should be measured directly or supported by convergent evidence and should be tracked in the relevant phase of edema. Third, the proposed transport abnormality can add explanatory value beyond cytotoxic, ionic, vasogenic, or inter-

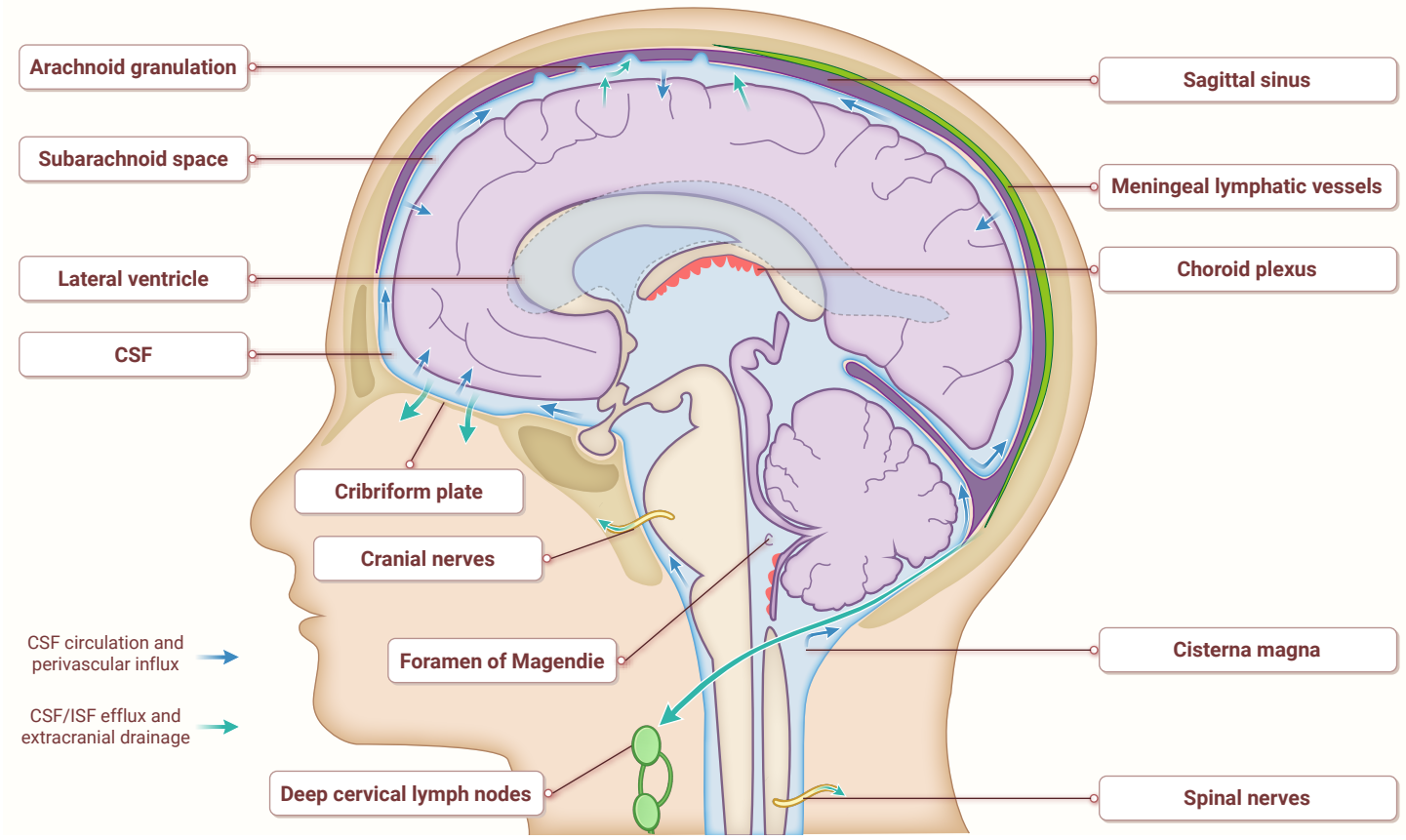

Figure 1. Overview of glymphatic influx and efflux pathways in brain water homeostasis

stitial mechanisms rather than merely accompany them.

BBB disruption and glymphatic dysfunction can therefore coexist and jointly contribute to the pathophysiology of post-injury cerebral edema. Their relative contributions must be evaluated by injury type, temporal phase, transport direction, and measurement method.

BRAIN WATER HOMEOSTASIS AND GLYMPHATIC TRANSPORT

CSF circulates through the ventricular and subarachnoid compartments and exchanges with fluid along several perivascular, white matter, and lymphatic routes.[20–21] In contrast to traditional descriptions of CSF circulation, the glymphatic model emphasizes periarterial CSF entry, exchange with ISF near astrocytic endfeet, and subsequent clearance through multiple efflux pathways (Figure 1).[8,10] This model is well supported for tracer and solute transport in rodents, although its quantitative contribution to human brain water homeostasis remains under active investigation.

Cerebrospinal fluid (CSF) communicates with the brain along perivascular, white matter, cranial, and lymphatic routes. Blue arrows denote proposed influx routes from subarachnoid CSF, and green arrows denote major extracranial or venous-associated efflux routes, including arachnoid granulations, meningeal lymphatic vessels, the cribriform plate, and deep cervical lymph nodes.

Perivascular transport is influenced by arterial and low-frequency vascular dynamics, respiration, sleep–wake state, anesthesia, and body position.[23–28,34] Sleep and some anesthetic states are associated with altered extracellular geometry and increased tracer clearance in rodents.[23–25] Together, these studies indicate that perivascular tracer transport is modulated by physiological state.[23–28] Acute brain injury can simultaneously change vascular compliance, intracranial pressure, respiration, and astrocyte architecture, highlighting the need for multimodal measurements that combine tracer kinetics with independent edema quantification.[29]

Experimental studies associate acute brain injury with altered CSF tracer influx, delayed interstitial clearance, perivascular remodeling, and changes in tissue water.[7,12,18,31–32] Because tracer kinetics do not directly quantify net tissue water, their relationship to edema must be interpreted alongside vascular pressure, ionic gradients, BBB function, and astrocyte organization. Even within this constraint, several lines of evidence support a phase- and injury-dependent contribution of glymphatic dysfunction to edema kinetics. Hyperacute perivascular CSF entry has been directly visualized in ischemia and anoxia.[18–19] Clearance failure has been causally linked to edema through interventional studies in TBI and is also temporally associated with edema progression in ischemia and subarachnoid hemorrhage.[7,32,65] The available data therefore support a model in which glymphatic dysfunction modifies edema kinetics in a manner that depends on injury type, temporal phase, and the dominant direction of pathological water movement.

AQP4 AS A CONTEXT-DEPENDENT WATER-PERMEABILITY PATHWAY

AQP4 is the predominant astrocytic water channel in the adult brain and is enriched at perivascular endfeet and other brain-fluid interfaces (Figure 2).[35–36] This distribution places AQP4 at sites of CSF-ISF and blood-brain water exchange. AQP4 increases membrane water permeability but does not itself impose a direction on water movement, because net flux follows the prevailing osmotic, ionic, and hydrostatic gradients. Consequently, the same channel facilitates water entry when osmotic and ionic gradients drive net influx and facilitates water removal when those gradients reverse, making the timing and direction of AQP4 modulation therapeutically critical. Total abundance, perivascular polarization, anchoring, and isoform organization must therefore be considered separately.

In the perivascular space (PVS), aquaporin-4 (AQP4) is highly enriched and polarized at astrocyte endfeet surrounding cerebral blood vessels, a spatial organization thought to support directed water movement between cerebrospinal fluid (CSF) and the brain parenchyma. In the periventricular zone, AQP4 is localized predominantly at the basolateral membrane of ependymal cells and at the astrocyte endfeet underlying the ependymal layer. The left panel shows the anatomical relationship of these structures within the cerebral vascular and ventricular system. The upper right panel presents representative immunofluorescence image showing AQP4 localization at the

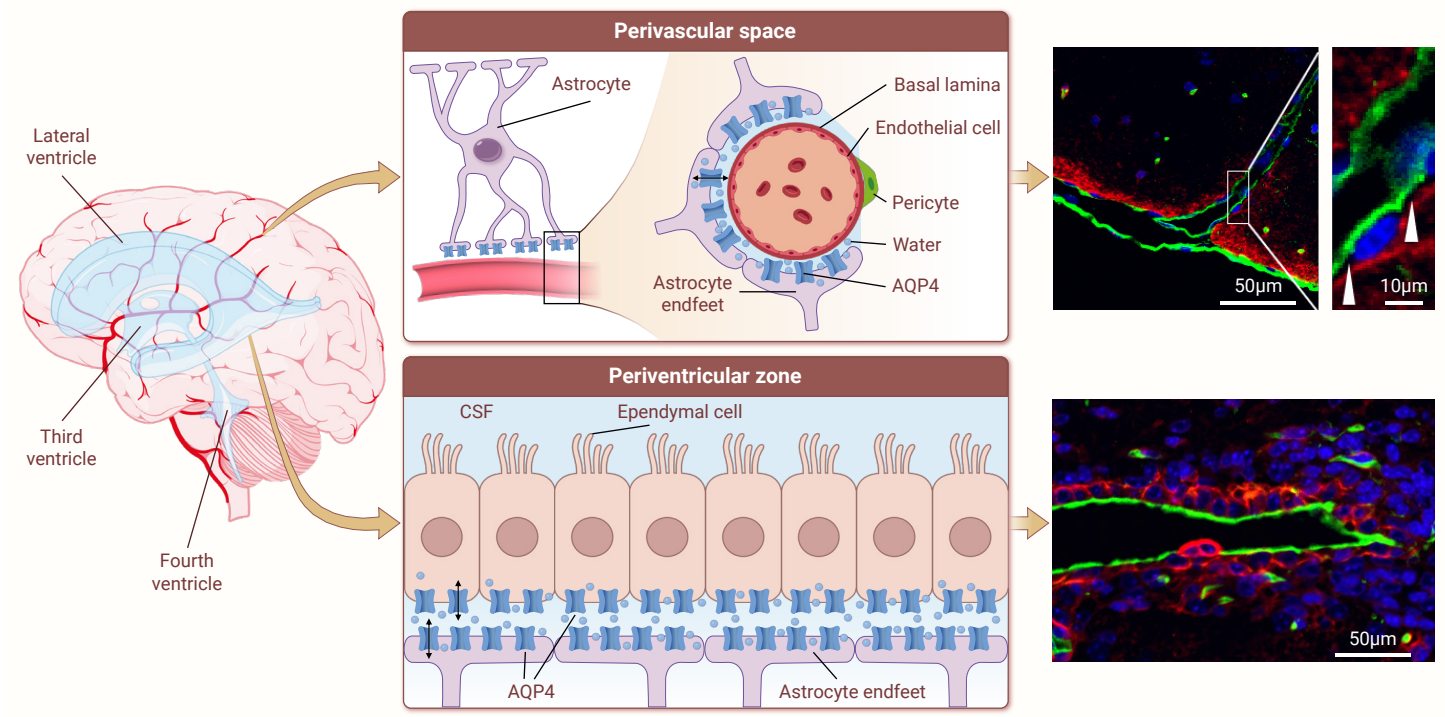

Figure 2. AQP4 localization at brain-fluid interfaces relevant to perivascular and periventricular transport

perivascular interface (AQP4, red; lectin, green; DAPI, blue), whereas the lower right panel shows representative immunofluorescence images of AQP4 in the periventricular region (AQP4, red; lectin, green; DAPI, blue). The immunofluorescence images were provided by Jianying Zhang. Created with BioGDP.com.[80]

The clearest evidence for a pro-entry role comes from rodent ischemia. During the hyperacute phase, *Aqp4* deletion reduced perivascular CSF tracer entry and tissue swelling, while genetic deletion or acute pharmacological inhibition attenuated edema in several ischemia models.[18,37,43–45] These findings are consistent with AQP4 providing a low-resistance water pathway when ischemia creates steep ionic and osmotic gradients. These data support AQP4 as a permissive pathway for hyperacute water entry, rather than increased AQP4 abundance as the cause of edema. Once the net gradient shifts toward fluid clearance, continued AQP4 blockade could impede water removal and would therefore require a clearly defined early treatment window. Constitutive deletion can alter development and baseline fluid pathways, whereas acute inhibitors interrogate a limited time window. AER-271 suppressed both glymphatic influx and efflux in mice, illustrating that inhibition can restrict transport in either direction, so therapeutic AQP4 blockade in ischemia is plausible only during the hyperacute window when net gradients favor pathological entry.[67] After this window, polarization-preserving strategies may be safer than broad inhibition.

This phase dependence becomes particularly clear across injury settings. *Aqp4* deletion aggravated brain water accumulation after experimental subarachnoid hemorrhage and reduced protection in murine cerebral malaria.[38,46–48] After TBI, AQP4 changes are region- and time-dependent, while rodent evidence for edema reduction is strongest for restoration of suppressed glymphatic efflux rather than blockade of excessive influx.[32,42,50] These apparently contradictory results are therefore not interchangeable tests of one mechanism: they differ in injury biology, barrier status, inflammatory burden, phase, genetic versus pharmacological manipulation, and the measured endpoint. AQP4 should be interpreted as a context-dependent modifier of water exchange, not as a uniformly pro-edema or anti-edema factor.

Beyond total abundance, the spatial organization of AQP4 at astrocytic endfeet provides a second level of regulation. Perivascular AQP4 enrichment is maintained partly by the dystrophin-associated protein complex (DAPC), including α-syntrophin, dystrophin-71, and β-dystroglycan.[36,56–57] Ischemic injury can transiently redistribute AQP4 away from astrocyte endfeet even when total protein remains unchanged or increased.[40–41,52,55] Experimental disruption or restoration of DAPC components alters AQP4 localization, tracer transport, and tissue water in ischemic and hemorrhagic models.[58–59] These findings make polarization a plausible modifier of transport efficiency, but the frequent co-occurrence of astrocyte injury, BBB change, and vascular dysfunction means that polarization loss should not be treated as a standalone causal marker. AQP4-M1 and AQP4-M23 also differ in their tendency to form orthogonal arrays of particles (OAPs). The shorter M23 isoform strongly promotes OAP assembly, whereas the longer M1 isoform limits the size of these arrays and is more mobile within the membrane.[35,62] Recent mouse ischemia data suggest that an altered M1/M23 balance can destabilize perivascular clustering and impair tracer transport.[53]

Taken together, the principal AQP4 observations are summarized by injury context and phase in Table 1. This synthesis supports a qualified conclusion: AQP4-mediated permeability and perivascular organization can modify edema kinetics in experimental brain injury models, but neither total AQP4 abundance nor loss of polarization is sufficient to identify glymphatic-stagnated edema.

GLYMPHATIC TRANSPORT ACROSS EDEMA INITIATION, PERSISTENCE, AND RESOLUTION

The contribution of glymphatic transport is best evaluated as a time-varying balance between fluid entry, intraparenchymal redistribution, and clearance. No single direction of change applies to all acute brain injuries. The evidence is also hierarchical: direct tracer imaging with independent water measurements can establish temporal coupling, intervention studies can strengthen causal inference, and clinical imaging proxies can identify associations.

In rodent focal ischemia, spreading depolarizations trigger abrupt arterial constriction and expansion of surrounding perivascular spaces, drawing CSF tracers into tissue within minutes.[18] Anoxic cardiac arrest models likewise identify CSF as one source of early edema water.[19] These studies demonstrate that injury-specific CSF entry routes exist in ischemia and anoxia, but the transport abnormality differs by injury type: TBI data more strongly support suppressed efflux than excessive influx.[32] Human ICH studies, in contrast, have reported only associations with diffusion tensor imaging analysis along the perivascular space (DTI-ALPS)—a magnetic resonance imag-

Table 1. Injury- and phase-specific preclinical evidence linking AQP4, perivascular transport, and edema-related outcomes after acute brain injury.

Injury/model and phase	AQP4 feature or experimental intervention	Transport and independent edema/fluid endpoint	Evidence and principal limitation
Focal ischemia, hyperacute (mouse; minutes)	Constitutive *Aqp4* deletion	Transport: Reduced injury-driven periarterial CSF tracer influx[18] Edema: Reduced early tissue swelling[18]	Direct tracer-swelling coupling in one model; constitutive deletion does not define an acute treatment window
Focal ischemia, early acute (rodent; 24 hours)	Constitutive *Aqp4* deletion or TGN-020	Transport: Not measured Edema: Reduced edema or swelling at 24 hours[43,45]	Genetic deletion and acute inhibition are not equivalent; developmental compensation and drug specificity limit inference
Ischemia, acute to recovery (mouse; days 1-7)	Dynamic perivascular AQP4 organization;[7,52] manipulation of the M1/M23 isoform balance or Dp71[53,58]	Transport: Maximal impairment near day 2 and recovery by day 7[7] M1/M23 modulation and Dp71 overexpression improved transport, whereas Dp71 loss impaired it[53,58] Edema: Paralleled the transport trajectory and decreased after selected interventions[7,53,58]	Reference 52 provides localization data only; BBB, vascular, and astrocytic recovery co-occur
SAH, early (rodent; 6 hours to 7 days)	*Aqp4* deletion or reduced perivascular AQP4 polarization	Transport: Suppressed after SAH[65] *Aqp4* loss further impaired transport[47] Edema: *Aqp4* deletion increased brain water and early injury[47-48]	Model-specific rodent evidence; BBB disruption and injury severity remain alternative mediators
TBI, AQP4 studies (mouse; hours to weeks)	Region- and time-dependent AQP4 redistribution;[50] constitutive *Aqp4* deficiency[44]	Transport: Not measured in references 44 and 50 Edema: *Aqp4* deficiency reduced edema and improved longer-term outcomes;[44] redistribution was descriptive[50]	Constitutive deletion and descriptive localization do not establish an acute treatment window
TBI, drainage intervention (mouse; acute)	Pan-adrenergic blockade (not AQP4-targeted)	Transport: Partly restored glymphatic and cervical lymphatic drainage[32] Edema: Reduced post-traumatic edema[32]	Intervention-based evidence, but systemic/venous effects and pleiotropy preclude transport-specific attribution
ICH, subacute (mouse; days 1-7)	Mifepristone increased AQP4 expression/polarization; comparison with *Aqp4* deletion or TGN-020	Transport: Mifepristone increased tracer distribution/drainage; *Aqp4* loss or inhibition reduced them[54] Edema: At day 3, mifepristone increased brain water and MRI edema but accelerated hematoma clearance; *Aqp4* deletion or TGN-020 reduced edema but delayed clearance[54]	Edema and hematoma clearance diverged; mifepristone is pleiotropic and not an established selective AQP4 agonist, so its effects cannot be attributed specifically to AQP4 activation
IVH with secondary hydrocephalus (rat; days 1-21)	c-Src/β-dystroglycan-associated AQP4 depolarization	Transport: Not measured; dysfunction was inferred from glial-vascular disorganization[59] Fluid endpoint: Secondary hydrocephalus/ventricular enlargement; edema was not measured[59]	Mechanistic rat evidence; not primary ICH or perihematomal edema

Abbreviations: AQP4, aquaporin-4; CSF, cerebrospinal fluid; Dp71, dystrophin isoform 71; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury. *Aqp4*, rodent gene; AQP4, protein; M1/M23, major AQP4 isoforms.

ing (MRI)-derived surrogate of directional diffusivity—and have not directly visualized CSF movement.[63]

Clearance failure may become more relevant as edema persists. In transient middle cerebral artery occlusion models, interstitial tracer clearance paralleled edema progression.[6–7] Critically, BBB leakage persisted even as tracer transport recovered and edema subsided. This temporal coupling between glymphatic function and edema formation and resolution, independent of BBB integrity, suggests that clearance capacity may help determine whether edema progresses or resolves. After experimental TBI, adrenergic suppression of glymphatic efflux was linked causally to edema, and pan-adrenergic antagonism restored drainage and reduced swelling.[32] Subarachnoid hemorrhage models similarly show prolonged transport suppression with AQP4 disorganization.[65] Together, these data support clearance failure in selected rodent settings.

During the resolution phase, restoration of glymphatic transport may facilitate removal of excess interstitial fluid, although the extent and timing of recovery vary across injury settings.[39] Physiologically, sleep-associated expansion of the interstitial space enhances CSF-ISF exchange and solute clearance.[25] After transient middle cerebral artery occlusion, recovery of tracer transport and perivascular AQP4 organization accompanied edema regression, while pharmacological enhancement or suppression of transport respectively accelerated or delayed edema resolution.[7,52] In experimental intracerebral hemorrhage, enhanced AQP4 expression and polarization improved tracer transport, reduced brain water content, and promoted clearance of hematoma-derived products.[54] Recovery is not universal, however, as post-ischemic tracer retention can remain spatially heterogeneous and persist into later phases.[64] Collectively, these findings support an injury-dependent model in which restored perivascular and interstitial clearance facilitates edema resolution in some settings, whereas incomplete recovery may prolong fluid and waste retention.

Together, these observations suggest a dual-phase model: an initial period of increased influx, impaired efflux, or both, during edema formation, followed

by variable recovery whose timing and completeness may determine the rate of edema resolution. Across injury types, however, the best-supported model remains conditional rather than universal. Hyperacute CSF entry has direct experimental support in ischemic and anoxic models.[18–19] Impaired clearance has intervention-based support in experimental TBI.[32] It also has temporal associations in ischemia and subarachnoid hemorrhage.[7,65] Human studies remain predominantly associative.[63,66] Glymphatic-stagnated edema therefore describes a candidate transport axis that can coexist with cytotoxic, ionic, vasogenic, and interstitial edema. The framework is most useful when altered transport tracks independently measured swelling or delayed resolution and adds explanatory value beyond barrier failure or cellular osmotic injury. In practice, the strongest evidence for glymphatic involvement currently exists for hyperacute CSF entry in ischemia and for efflux failure in TBI—settings in which transport-directed interventions have reduced edema in at least one interventional study in each setting.[18,32]

An order-of-magnitude comparison argues against attributing all ischemic swelling to retained glymphatic inflow. Extravascular solute clearances used to estimate rodent parenchymal fluid turnover are approximately 1 μL min^{-1} g^{-1}, whereas ischemic tissue swelling can reach approximately 3.5 μL min^{-1} g^{-1}.[93–94] These quantities are not identical and arise from different preparations, but the mismatch makes glymphatic outflow failure alone quantitatively insufficient for maximal ischemic edema. Net entry of solute and water across brain barriers remains necessary. Moreover, if injury reduces both glymphatic influx and efflux, fluid retention requires the relative fall in efflux to exceed the fall in influx; this balance has rarely been measured directly.

Concurrent normalization of ionic gradients, vascular function, astrocyte volume, and BBB properties during recovery prevents attribution of restored tracer transport to any single pathway. Therefore, a causal resolution mechanism would require phase-specific manipulation that accelerates water loss without changing initial injury severity, together with independent measurements of tissue water and net fluid flux. Moreover, tracer influx and clearance quantify movement of a probe, not net water accumulation. Apparent diffusion coefficient changes describe water mobility within an imaging voxel and cannot be read directly as total edema volume.[10] DTI-ALPS is influenced by white matter geometry, diffusion anisotropy, lesion location, and vascular or structural change; it is therefore an indirect index rather than a global measurement of glymphatic function.[51] Age-related impairment of perivascular clearance must also be considered when transport-sensitive measurements are compared across cohorts.[49] AQP4 inhibition further illustrates the interpretive problem because AER-271 reduced both influx and efflux.[67] Accordingly, a credible human test of this framework will require independent edema quantification, repeated transport-sensitive measurements, BBB assessment, and prespecified timing rather than inference from a single surrogate.[21–22,33]

PRECLINICAL THERAPEUTIC IMPLICATIONS AND CLINICAL TRANSLATION

Osmotherapy, neurocritical physiological management, and decompressive surgery remain the clinically established approaches for life-threatening cerebral edema, selected according to injury type and patient status.[3,16,68–69] A glymphatic perspective does not replace these established interventions but offers a complementary framework for understanding why certain treatments work in some injury types and fail in others.

Among mechanism-specific strategies, AQP4 inhibition has received the most preclinical attention. TGN-020 reduced early swelling in rodent ischemia, but systemic inhibition can also compromise clearance in hemorrhagic models.[45,70] AER-271 suppressed both tracer influx and efflux and was not tested as a universal antiedema therapy.[67] A recent angiopep-2-functionalized lipid nanoparticle delivered TGN-020 preferentially to injured tissue in experimental hemorrhagic and ischemic stroke, reducing edema while better preserving global tracer clearance.[70] Although lesion-targeted delivery could limit the transport consequences of systemic AQP4 inhibition, this approach has been evaluated only in preclinical models. Clinical translation requires reproducible target-engagement assays, brain and systemic pharmacokinetics, off-target profiling, dose–response data, and treatment windows matched to the direction of pathological water movement.

A second preclinical strategy is to preserve or restore perivascular organization rather than block all AQP4-mediated water movement. Transient receptor potential vanilloid 4 (TRPV4) inhibition, β-hydroxybutyrate, and combined salvianolic acid B plus ginsenoside Rg1 have been associated with improved AQP4 polarization, tracer transport, and edema endpoints in rodent ischemia.[60,71–72] In neonatal hypoxic-ischemic brain injury, melatonin also preserved the interaction between AQP4 and α-syntrophin and supported glymphatic function, although the developmental context limits extrapolation to adult stroke.[61] Adrenergic antagonism after experimental TBI provides stronger causal support because it restored suppressed efflux and reduced swelling.[32] Findings involving nimodipine, fingolimod, simvastatin, or astrocyte-derived exosomes are hypothesis-generating and should not be interpreted as evidence that these interventions are interchangeable.[40,73–75] Across these strategies, independent replication, comparison with standard edema care, and separation of transport effects from anti-inflammatory, vascular, or hemodynamic effects are still required before any can be considered a glymphatic-directed therapy.

Beyond pharmacological targeting of AQP4, physiological variables, including sleep-wake state, anesthesia, respiration, vascular tone, and posture, can also change tracer distribution in rodents.[23–28,76,78] Dexmedetomidine increased the distribution of intrathecally administered tracers and drugs in mice and rats, but this endpoint does not establish edema resolution.[77] Sedatives can also change blood pressure, carbon dioxide, cerebral blood volume, and intracranial physiology. Accordingly, anesthetic choice, sleep promotion, hypothermia, and lateral positioning represent modifiable physiological variables that may influence glymphatic transport, but their translation into edema treatments requires injury-specific trials with standard safety endpoints.[79]

Translating these preclinical observations to clinical practice faces several barriers. To date, the broader glymphatic literature has focused mainly on neurodegenerative disease models and on imaging-based or other forms of clinical validation.[30] Several interventional studies are beginning to test glymphatic-directed strategies in neurodegenerative conditions. These include pharmacological modulation of sleep-associated clearance using dexmedetomidine with or without midodrine (NCT07432997), transcranial magnetic stimulation in prodromal Alzheimer's disease (NCT07192913), trigeminal nerve stimulation to modulate cerebral blood flow and CSF transport (NCT07044596), and sleep enhancement or noninvasive vagus nerve stimulation in cerebral amyloid angiopathy (NL-OMON56712).[83–86] Although these studies were not designed to evaluate edema after acute brain injury, they may inform future trials by providing information on feasibility and safety and by helping to establish the target-engagement measures and imaging or fluid biomarkers required to test pharmacological, sleep-related, and neuromodulatory enhancement of glymphatic transport.

Human imaging studies provide complementary, although still noninterventional, evidence. In ischemic stroke, a single-center study of 50 patients and 44 controls found lower DTI-ALPS values in the hemisphere ipsilateral to the infarction than those in the contralateral hemisphere and in controls.[66] In spontaneous intracerebral hemorrhage, the ipsilateral DTI-ALPS index was associated with relative edema volume and 90-day outcome in 55 patients.[63] These associations link directional diffusivity to injury severity but cannot establish whether altered diffusion causes edema, results from edema, or reflects lesion-related white matter damage. More direct evidence comes from serial intrathecal contrast-enhanced MRI: delayed gadobutrol enrichment was observed in 27 patients after subarachnoid hemorrhage compared with 22 controls.[81] However, a 2026 study of 56 participants with CSF disorders found only limited agreement between DTI-ALPS and intrathecal contrast-enhanced MRI, with no association at 48 h.[82] DTI-ALPS should therefore be regarded as a localized surrogate rather than a validated whole-brain measure of glymphatic function. Future studies should combine serial tracer imaging with independent edema volumetry, BBB assessment, and prespecified physiological covariates in multicenter cohorts before this framework can inform clinical decisions.

Clinical translation of glymphatic-directed edema therapy remains preliminary. The most direct ongoing study is a phase II sham-controlled trial of transcutaneous auricular vagus nerve stimulation in acute intracerebral hemorrhage (NCT06918964), which uses relative perihematomal edema as its primary endpoint and diffusion kurtosis imaging analysis along the

perivascular space (DKI-ALPS) as an exploratory glymphatic index.[87] Two registered phase III trials in large ischemic stroke and intracerebral hemorrhage (NCT06863571 and NCT06863558) are evaluating a combined α- and β-adrenergic antagonist regimen, with imaging-defined edema at 5–7 days as the primary endpoint.[88,89] However, neither of the two studies incorporates direct measurement of CSF or interstitial fluid transport. A phase II cilostazol study (NCT06504576) assesses hematoma resorption and meningeal lymphatic drainage, whereas studies in acute ischemic stroke and subarachnoid hemorrhage remain primarily imaging-based.[90] Phase I studies of AER-271 in healthy volunteers have been completed, but results from these studies and efficacy data in patients with cerebral edema have not been publicly reported (NCT03804476 and NCT05200728).[91,92] No completed interventional study has yet demonstrated that restoring glymphatic transport reduces cerebral edema in humans.

SCOPE AND LIMITATIONS

This review synthesizes evidence linking glymphatic transport to cerebral edema across ischemic, hemorrhagic, and traumatic brain injury. Several limitations should be stated. First, the term "glymphatic-stagnated edema" is used throughout as a provisional transport framework, not as a validated clinical subtype, a formal diagnosis, or an established therapeutic target. Second, direct evidence in humans remains limited to imaging associations and a small number of intrathecal tracer studies; no human trial has yet established the safety or efficacy of a glymphatic-directed intervention for cerebral edema. Third, most mechanistic data derive from rodent models whose brain size, CSF geometry, vascular compliance, and edema kinetics differ from those of humans. Fourth, current methods, including tracer imaging, DTI-ALPS, and apparent diffusion coefficient measurements, each capture different aspects of fluid movement, and none directly quantifies net water accumulation. These limitations do not invalidate the framework; rather, they define the conditions under which its predictions must be tested.

CONCLUSION

Cerebral edema after acute brain injury is best understood through complementary compartmental and transport perspectives. Across injury types, current evidence supports three transport-level principles: hyperacute CSF influx through perivascular routes contributes to early edema formation; impaired fluid clearance promotes edema persistence; and AQP4 acts as a phase- and context-dependent regulator of water exchange, with its net effect determined by prevailing osmotic, ionic, and hydrostatic gradients, as well as by perivascular polarization and isoform organization. This framework is useful for organizing evidence and generating testable predictions across injury types. It has not yet been validated as a clinical classification or therapeutic paradigm, and multicenter validation studies are needed before the framework can guide bedside decisions. Nevertheless, it generates testable predictions, including that early AQP4 inhibition may be more effective than delayed inhibition in ischemia, that restoration of fluid efflux may provide greater benefit than influx blockade in TBI, and that perivascular AQP4 polarization may serve as a treatment-response biomarker. Immediate priorities include multicenter studies combining serial intrathecal contrast imaging with independent edema volumetry, early-phase pharmacokinetic and safety studies of timed or lesion-targeted AQP4 modulation, and comparative physiological studies of how brain size, CSF geometry, and vascular compliance affect the translation of findings from rodent models. These studies will determine whether the transport-based framework can become clinically actionable or should be revised, thereby advancing the field beyond the classical compartmental taxonomy.

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AUTHOR CONTRIBUTIONS

Z.W. drafted the manuscript and prepared the figures. J.Z. revised the manuscript and contributed to figure preparation. W.C. and Q.D. designed the study and provided overall guidance. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.