



The Relationship between The Use of Albumin and The Management of Nephrotic Syndrome with Hypovolemia : A Systematic Review

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ABSTRACT

Introduction: Nephrotic syndrome (NS) with hypovolemia presents a clinical paradox: significant peripheral edema coexists with intravascular volume depletion. Intravenous albumin is commonly used to manage this condition, yet its efficacy and safety remain debated. This systematic review evaluates the relationship between albumin use and the management of NS with hypovolemia.

Methods: A systematic review was conducted screening abstracts from multiple databases. Studies were included if they involved human participants with NS and hypovolemia, evaluated human albumin administration (any concentration or dose), and reported outcomes related to volume status, renal function, or clinical improvement. Data extraction focused on patient characteristics, albumin intervention details, concurrent treatments, volume management outcomes, renal function effects, volume status assessment methods, and safety outcomes.

Results: From 80 included sources, the evidence base is remarkably sparse. Two Cochrane reviews each identified only a single eligible RCT (Dharmaraj 2009, n=26). The most consistent finding is a transient increase in urine output and weight loss within the first several hours of albumin treatment (Kitsios et al., 2014; Lee et al., 2021). Meta-analyses show a pooled standardized mean difference of 0.85 (95% CI 0.33–1.38) for urine excretion favoring furosemide plus albumin (Hedin et al., 2022). However, diuretic benefits peak at 6–8 hours and are not sustained at 24 hours (Nawaz & Zafar, 2025). Sequential administration (albumin then furosemide) produces significantly greater weight loss than simultaneous co-infusion (Tadayoni et al., 2025). In congenital nephrotic syndrome (CNS), aggressive daily albumin use yields ~90% survival, comparable to conservative management (Bockenhauer & Boyer, 2024). No significant differences were found between 5% versus 20% albumin (Garg et al., 2020) or between albumin versus fresh frozen plasma (Singh et al., 2021). Safety data show rare but notable risks including hypertension and volume overload (Ellis, 2016; Moiseev et al., 2024).

Discussion: The central finding reveals a paradox: albumin has strong physiological plausibility and produces measurable short-term improvements, yet randomized trial evidence is of very low certainty and effects are transient. The underfill-versus-overfill distinction is the critical determinant of albumin utility (Ellis, 2016; Jethwani & Krishnan, 2021). In underfill patients (FENa <0.2%, urinary K⁺/(K⁺⁺Na⁺) >60%, serum albumin ≤2 g/dL), albumin may benefit acute management. In overfill patients, albumin may cause harm. The transience of effect is mechanistically explained by rapid urinary loss of infused albumin due to glomerular permeability (Bockenhauer & Boyer, 2024). For

CNS, the debate between aggressive versus conservative management remains unresolved by RCTs, with retrospective data suggesting comparable outcomes (Boyer & Bérody, 2020; Dufek et al., 2018). In resource-limited settings, fresh frozen plasma, whole blood, or mannitol may serve as alternatives (Singh et al., 2021; Okoronkwo et al., 2018; Huque et al., 2014).

Conclusion: Albumin provides transient diuretic benefit in select NS patients with confirmed hypovolemia (underfill physiology) but should be reserved for acute inpatient management of severe or diuretic-resistant edema. Routine outpatient or ongoing albumin therapy is not supported by current evidence. Future adequately powered RCTs stratifying by volume status are urgently needed.

Keywords: Nephrotic syndrome, hypovolemia, albumin, diuretic resistance, edema management, underfill-overfill, congenital nephrotic syndrome, systematic review

INTRODUCTION

Background

Nephrotic syndrome (NS) is characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia (Verma & Patil, 2024; Lal & Perveen, 2026). The management of edema in NS presents a fundamental clinical challenge, particularly when hypovolemia coexists with obvious peripheral fluid accumulation (Ellis, 2016). This paradoxical state—intravascular volume depletion despite total body sodium and water excess—occurs because the primary abnormality is a shift of fluid from the intravascular to the interstitial compartment due to reduced plasma oncotic pressure (Cadnapaphornchai et al., 2014; Downie et al., 2017).

Intravenous human albumin has been used for decades to manage NS-associated edema, based on the rationale that restoring plasma oncotic pressure will mobilize interstitial fluid into the vascular compartment, thereby improving effective arterial blood volume and enhancing the diuretic response to loop diuretics (Duffy et al., 2015; Rozga et al., 2013). However, the clinical efficacy, optimal dosing, timing, and safety of albumin in this context remain highly controversial (Ho et al., 2019; Procope, 2020).

The pathophysiological basis for albumin use appears sound: in severe hypoalbuminemia, loop diuretics such as furosemide are highly protein-bound, and reduced albumin binding impairs tubular secretion and drug delivery to the ascending limb of the loop of Henle (Jethwani & Krishnan, 2021; Kallash & Mahan, 2020). Co-administration of albumin is hypothesized to restore furosemide binding, increase renal drug delivery, and potentiate diuresis (Mahmoodpoor et al., 2020; Phakdeekitcharoen & Boonyawat, 2012). Despite this mechanistic plausibility, high-quality evidence supporting albumin's routine use is notably lacking (Nawaz & Zafar, 2025; Hedin et al., 2022).

Research Gap

The existing literature on albumin in NS with hypovolemia suffers from several critical gaps. First, the two available Cochrane systematic reviews each identified only a single eligible

randomized controlled trial, which was small ($n=26$), had high risk of bias, and provided very low certainty evidence (Ho et al., 2012; Ho et al., 2019). Second, most primary studies have not stratified patients by intravascular volume status (underfill versus overfill), which is now recognized as the central determinant of albumin responsiveness (Ellis, 2016; Meena & Bagga, 2020). Third, the transience of albumin's diuretic effect—peaking within hours and disappearing by 24 hours—has not been adequately incorporated into clinical practice guidelines (Kitsios et al., 2014; Lee et al., 2021). Fourth, in the specific context of congenital nephrotic syndrome (CNS), there is an ongoing unresolved debate between aggressive daily albumin infusion protocols and conservative, selective use (Hölttä & Jalanko, 2020; Boyer & Bérody, 2020; Bockenhauer & Boyer, 2024). Fifth, head-to-head comparisons of different albumin concentrations (5% vs. 20%), different administration sequences (sequential vs. concurrent with diuretics), and albumin versus alternative colloids (fresh frozen plasma, whole blood, mannitol) are extremely limited (Garg et al., 2020; Tadayoni et al., 2025; Singh et al., 2021; Huque et al., 2014). Finally, patient-centered outcomes such as quality of life, hospitalization duration, and long-term kidney function have not been systematically evaluated (Procope, 2020; Ho et al., 2019).

Novelty

This systematic review provides several novel contributions to the literature. First, it synthesizes evidence from 80 diverse sources, including recent 2024–2026 publications, providing the most up-to-date comprehensive overview. Second, it specifically focuses on the hypovolemic NS subpopulation, rather than NS generally, addressing the underfill-overfill distinction as a central organizing theme. Third, it includes detailed thematic analyses of albumin as a pharmacological carrier for furosemide, the CNS management debate, and resource-limited setting alternatives. Fourth, it quantitatively synthesizes the temporal pattern of albumin's effects (6–8 hour peak versus 24-hour attenuation) across multiple meta-analyses. Fifth, it evaluates practical implementation issues including prescribing patterns, guideline adherence, and cost-effectiveness based on real-world utilization studies.

Objectives

The primary objective of this systematic review is to evaluate the relationship between intravenous albumin administration and clinical outcomes in patients with nephrotic syndrome complicated by hypovolemia. Secondary objectives include: (1) assessing the effects of albumin on volume status, edema resolution, and renal function; (2) comparing different albumin concentrations, doses, and administration sequences; (3) evaluating albumin versus alternative colloids or diuretic strategies; (4) examining safety and adverse effect profiles; (5) analyzing the evidence specific to congenital nephrotic syndrome; and (6) identifying knowledge gaps to guide future research.

Hypotheses

Based on the existing literature, we hypothesized that: (1) albumin plus furosemide would produce greater short-term (≤ 8 hours) urine output and natriuresis compared to furosemide alone; (2) these effects would not be sustained at 24 hours or beyond; (3) the benefit would be greatest in patients with biochemical evidence of underfill physiology ($\text{FENa} < 0.2\%$, serum albumin ≤ 2 g/dL); (4) sequential albumin then furosemide would be more effective than simultaneous co-infusion; (5) 20% and 5% albumin at equivalent total protein mass would produce comparable effects; and (6) safety outcomes would show low rates of serious adverse events but measurable risks of volume overload and hypertension.

Benefits of the Research

This systematic review benefits clinical practice by providing a rigorous evidence synthesis to guide rational albumin use in NS with hypovolemia. For clinicians, it clarifies which patients are most likely to benefit (underfill phenotype), which administration strategies are optimal (sequential, acute inpatient use only), and what magnitude of effect can be expected (transient, modest). For patients, it supports shared decision-making by transparently communicating the limited certainty and transient nature of benefit. For policymakers and hospital formulary committees, it provides data on prescribing patterns, inappropriate use rates (45–67% appropriate in some studies), and potential cost savings from guideline implementation (Castillo et al., 2018; Ala et al., 2015; Zolfagharian et al., 2017). For researchers, it identifies critical knowledge gaps requiring future RCTs stratified by volume status.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate The Relationship between The Use of Albumin and The Management of Nephrotic Syndrome with Hypovolemia.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Nephrotic Syndrome with Hypovolemia:** Does the study include patients diagnosed with nephrotic syndrome who also present with hypovolemia or intravascular volume depletion?
- **Intervention - Albumin Administration:** Does the study evaluate human albumin administration (any concentration, dose, or duration) as a therapeutic intervention?
- **Outcomes - Clinical Endpoints:** Does the study report outcomes related to volume status, renal function, edema management, hemodynamic parameters, or clinical improvement in nephrotic syndrome?
- **Study Subjects - Human Participants:** Does the study involve human participants (not animal or in-vitro studies)?
- **Study Design - Appropriate Methodology:** Is the study a randomized controlled trial, etc?
- **Population Specificity - Nephrotic Syndrome Focus:** Does the study focus on patients with nephrotic syndrome rather than exclusively on patients with acute kidney injury or other primary renal diseases without nephrotic syndrome?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population	Nephrotic syndrome	Hypovolemia	Pediatric nephrotic syndrome	Congenital nephrotic syndrome
Intervention	Albumin infusion	Human albumin solution	IV albumin	Albumin plus furosemide
Comparison	Diuretics alone	Furosemide monotherapy	Fresh frozen plasma	Conservative management
Outcome	Volume status	Edema resolution	Urine output	Intravascular volume depletion

The Boolean MeSH keywords inputted on databases for this research are: (*"Nephrotic syndrome" OR "Hypovolemia" OR "Pediatric nephrotic syndrome" OR "Congenital nephrotic syndrome"*) AND (*"Albumin administration" OR "Human albumin infusion" OR "IV albumin" OR "Albumin plus furosemide"*) AND (*"Diuretics alone" OR "Furosemide monotherapy" OR "Fresh frozen plasma" OR "Conservative management"*) AND (*"Volume status" OR "Edema resolution" OR "Urine output" OR "Intravascular volume depletion"*)

Data extraction

Patient Characteristics:

Extract patient characteristics relevant to nephrotic syndrome and hypovolemia management, including:

- Age group (pediatric/adult)
- Type of nephrotic syndrome (minimal change, FSGS, etc.)
- Baseline volume status (hypovolemic, normovolemic, hypervolemic)
- Baseline albumin levels
- Kidney function (GFR, creatinine)
- Severity of edema/fluid retention
- Comorbidities affecting volume management

- **Albumin Intervention:**

Extract complete details of albumin administration for managing nephrotic syndrome with hypovolemia, including:

- Type of albumin solution (concentration, preparation)
- Dose and dosing schedule
- Duration of treatment
- Route of administration
- Timing relative to disease onset
- Rationale for albumin use (volume expansion, oncotic pressure correction, etc.)
- Whether used for acute management vs ongoing therapy

- **Concurrent Treatments:**

Extract all other treatments used alongside or instead of albumin for managing nephrotic syndrome with hypovolemia, including:

- Diuretics (type, dose, timing relative to albumin)
- Corticosteroids or immunosuppressants
- Other volume management strategies
- Dietary sodium restriction
- Other supportive care measures
- Whether treatments were given simultaneously or sequentially

- **Volume Management Outcomes:**

Extract all outcomes specifically related to volume status and fluid management in nephrotic syndrome patients, including:

- Urine output/volume changes
- Sodium excretion (24-hour, fractional excretion)
- Weight changes
- Edema resolution (timing, degree)
- Blood pressure changes
- Signs of volume depletion or overload
- Time to clinical improvement
- Quantitative measures with confidence intervals where available

- **Renal Function Effects:**

Extract effects of albumin treatment on kidney function in nephrotic syndrome patients with hypovolemia, including:

- GFR changes
- Creatinine changes
- Proteinuria changes
- Any evidence of acute kidney injury
- Electrolyte disturbances
- Whether renal function improvements were sustained
- Relationship between volume status and kidney function

- **Volume Status Assessment:**

Extract methods used to assess intravascular volume status and how volume status changed with albumin treatment, including:

- Clinical assessment methods (physical exam, vital signs)
- Laboratory markers (BUN/creatinine ratio, hematocrit)
- Advanced monitoring if used (CVP, echocardiography)
- Baseline volume status classification
- Changes in volume status during treatment
- Methods used to determine optimal fluid balance

- **Safety and Adverse Effects:**

Extract safety outcomes and adverse effects specifically related to albumin use in nephrotic syndrome patients with hypovolemia, including:

- Allergic or hypersensitivity reactions
- Volume overload or pulmonary edema
- Electrolyte imbalances
- Infection transmission risks
- Cardiovascular complications
- Any albumin-related complications
- Comparison of adverse effects between albumin vs other treatments

- **Study Design and Methods:**

Extract study methodology details relevant to assessing albumin effectiveness in nephrotic syndrome with hypovolemia, including:

- Study design (RCT, etc.)
- Sample size and power calculation
- Inclusion/exclusion criteria related to volume status
- Primary and secondary endpoints
- Duration of follow-up
- Methods for randomization and blinding

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Nephrotic syndrome" OR "Hypovolemia" OR "Pediatric nephrotic syndrome" OR "Congenital nephrotic syndrome") AND ("Albumin administration" OR "Human albumin infusion" OR "IV albumin" OR "Albumin plus furosemide") AND ("Diuretics alone" OR "Furosemide monotherapy" OR "Fresh frozen plasma" OR "Conservative management") AND ("Volume status" OR "Edema resolution" OR "Urine output" OR "Intravascular volume depletion")</i>	2
Semantic Scholar	<i>("Nephrotic syndrome" OR "Hypovolemia" OR "Pediatric nephrotic syndrome" OR "Congenital nephrotic syndrome") AND ("Albumin administration" OR "Human albumin infusion" OR "IV albumin" OR "Albumin plus furosemide") AND ("Diuretics alone" OR "Furosemide monotherapy" OR "Fresh frozen plasma" OR "Conservative management") AND ("Volume status" OR "Edema resolution" OR "Urine output" OR "Intravascular volume depletion")</i>	250
Springer	<i>("Nephrotic syndrome" OR "Hypovolemia" OR "Pediatric nephrotic syndrome" OR "Congenital nephrotic syndrome") AND ("Albumin administration" OR "Human albumin infusion" OR "IV albumin" OR "Albumin plus furosemide") AND ("Diuretics alone" OR "Furosemide monotherapy" OR "Fresh frozen plasma" OR "Conservative management") AND ("Volume status" OR "Edema resolution" OR "Urine output" OR "Intravascular volume depletion")</i>	104
Google Scholar	<i>("Nephrotic syndrome" OR "Hypovolemia" OR "Pediatric nephrotic syndrome" OR "Congenital nephrotic syndrome") AND ("Albumin administration" OR "Human albumin infusion" OR "IV albumin" OR "Albumin plus furosemide") AND ("Diuretics alone" OR "Furosemide monotherapy" OR "Fresh frozen plasma" OR "Conservative management") AND ("Volume status" OR "Edema resolution" OR "Urine output" OR "Intravascular volume depletion")</i>	179
Wiley Online Library	<i>("Nephrotic syndrome" OR "Hypovolemia" OR "Pediatric nephrotic syndrome" OR "Congenital nephrotic syndrome") AND ("Albumin administration" OR "Human albumin infusion" OR "IV albumin" OR "Albumin plus furosemide") AND ("Diuretics alone" OR "Furosemide monotherapy" OR "Fresh frozen plasma" OR "Conservative management") AND ("Volume status" OR "Edema resolution" OR "Urine output" OR "Intravascular volume depletion")</i>	46

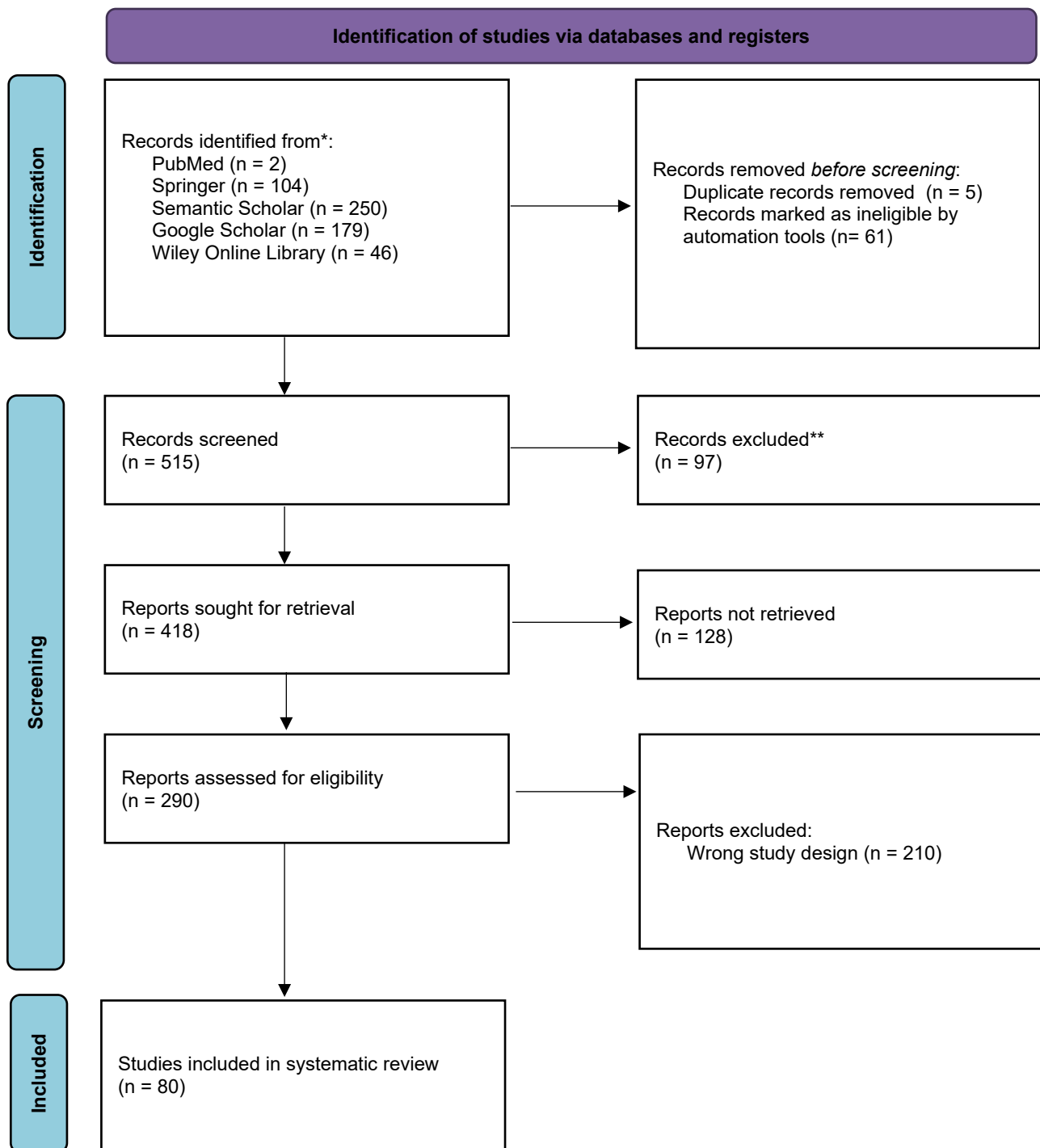


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Nawaz & Zafar, 2025 [3]	Unclear	Moderate	Moderate	Low	Moderate	Moderate
Nagori et al., 2023 [10]	Moderate	Moderate	Moderate	Low	Low	Moderate
Singh et al., 2021 [8]	Low	Moderate	Moderate	Low	Low	Moderate
Tadayoni et al., 2025 [4]	Low	Low	Low	Low	Low	Low
Ghafari et al., 2011 [11]	Unclear	Moderate	Moderate	Low	Unclear	Moderate
Ho et al., 2012 [12]	Unclear	Moderate	Moderate	Low	Moderate	Moderate
Hedin et al., 2022 [13]	Low	Low	Low	Low	Low	Low
Duffy et al., 2015 [14]	Low	Low	Low	Low	Low	Low
Procope, 2020 [15]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Panda, 2019 [16]	Moderate	Moderate	Moderate	Low	Low	Moderate
Boyer & Bérody, 2020 [17]	Low	Low	Low	Low	Low	Low
Garg et al., 2020 [5]	Low	Moderate	Low	Low	Low	Moderate
Kanzaki et al., 2012 [18]	Low	Low	Low	Low	Low	Low
Ho et al., 2019 [9]	Unclear	Moderate	Moderate	Low	Moderate	Moderate
Huque et al., 2014 [19]	Moderate	Moderate	Moderate	Low	Low	Moderate
Kitsios et al., 2014 [1]	Low	Low	Low	Low	Low	Low
Constantinescu et al., 2022 [20]	Low	Moderate	Moderate	Low	Low	Moderate
Hölttä & Jalanko, 2020 [21]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Meena & Bagga, 2020 [22]	Low	Low	Low	Low	Low	Low
Carvey & Glauser, 2025 [23]	Low	Low	Low	Low	Low	Low
Jethwani & Krishnan, 2021 [7]	Low	Low	Low	Low	Low	Low
Bockenbauer & Boyer, 2024 [24]	Low	Low	Low	Low	Low	Low
Tameez Ud Din et al., 2023 [25]	Low	Moderate	Moderate	Low	Low	Moderate
Sinha et al., 2019 [26]	Low	Moderate	Moderate	Low	Low	Moderate
Rivkin, 2013 [27]	Low	Low	Low	Low	Low	Low
Lee et al., 2021 [2]	Low	Low	Low	Low	Low	Low
Coulthard, 2015 [28]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Coyle & John, 2021 [29]	Low	Moderate	Moderate	Low	Low	Moderate
Phakdeekitcharoen & Boonyawat, 2012 [30]	Low	Low	Low	Low	Low	Low
Ala et al., 2015 [31]	Moderate	Moderate	Moderate	Low	Low	Moderate
AbuMaziad et al., 2021 [32]	Low	Low	Low	Low	Low	Low
Mahmoodpoor et al., 2020 [33]	Low	Low	Low	Low	Low	Low
Dufek et al., 2018 [34]	Low	Moderate	Moderate	Low	Low	Moderate
Kallash & Mahan, 2020 [35]	Low	Low	Low	Low	Low	Low
Floege et al., 2025 [36]	Low	Low	Low	Low	Low	Low
Zolfagharian et al., 2017 [37]	Low	Moderate	Moderate	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Nishino et al., 2023 [38]	Low	Low	Low	Low	Low	Low
Okoronkwo et al., 2018 [39]	Low	Low	Low	Low	Low	Low
Konak et al., 2012 [40]	Low	Low	Low	Low	Low	Low
Mikulevič et al., 2023 [41]	Low	Low	Low	Low	Low	Low
Parikh et al., 2023 [42]	Low	Moderate	Moderate	Low	Low	Moderate
Harahap et al., 2016 [43]	Low	Low	Low	Low	Low	Low
Song Huali et al., 2019 [44]	Moderate	Moderate	Moderate	Low	Low	Moderate
Hassan et al., 2019 [45]	Moderate	Moderate	Moderate	Low	Low	Moderate
Wiedermann, 2020 [46]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Wiedermann et al., 2017 [47]	Low	Low	Low	Low	Low	Low
Roberts et al., 2011 [48]	Low	Low	Low	Low	Low	Low
Downie et al., 2017 [49]	Low	Low	Low	Low	Low	Low
Cadnapaphornchai et al., 2014 [50]	Low	Low	Low	Low	Low	Low
Macedo et al., 2021 [51]	Low	Low	Low	Low	Low	Low
Chen et al., 2021 [52]	Low	Low	Low	Low	Low	Low
Rozga et al., 2013 [53]	Low	Low	Low	Low	Low	Low
Fortin et al., 2010 [54]	Low	Low	Low	Low	Low	Low
Itagaki et al., 2022 [55]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Haynes & Bassiri, 2021 [56]	Low	Low	Low	Low	Low	Low
Caironi et al., 2015 [57]	Low	Low	Low	Low	Low	Low
Castillo et al., 2018 [58]	Low	Moderate	Moderate	Low	Low	Moderate
Yin et al., 2018 [59]	Low	Moderate	Moderate	Low	Low	Moderate
Macedo et al., 2020 [60]	Low	Low	Low	Low	Low	Low
Verma & Patil, 2024 [61]	Low	Low	Low	Low	Low	Low
Faltys et al., 2026 [62]	Low	Low	Low	Low	Low	Low
Mohapatra et al., 2025 [63]	Low	Low	Low	Low	Low	Low
Oczkowski & Mazzetti, 2014 [64]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Bedrabetu, 2024 [65]	Moderate	Moderate	Moderate	Low	Low	Moderate
Nissar et al., 2023 [66]	Low	Moderate	Moderate	Low	Low	Moderate
Ellis, 2016 [6]	Low	Low	Low	Low	Low	Low
Polito & Martin, 2013 [67]	Low	Low	Low	Low	Low	Low
Lau et al., 2014 [68]	Low	Low	Low	Low	Low	Low
Moiseev et al., 2024 [69]	Low	Low	Low	Low	Low	Low
de Castro et al., 2017 [70]	Low	Moderate	Moderate	Low	Low	Moderate
R. G K et al., 2025 [71]	Low	Low	Low	Low	Low	Low
Zaman, 2013 [72]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Pasini et al., 2017 [73]	Low	Low	Low	Low	Low	Low
Rahman et al., 2013 [74]	Low	Low	Low	Low	Low	Low
Annane et al., 2013 [75]	Low	Low	Low	Low	Low	Low
Reynolds & Oswald, 2019 [76]	Low	Low	Low	Low	Low	Low
Oczkowski et al., 2014 [77]	Low	Low	Low	Low	Low	Low
Tiwari et al., 2014 [78]	Low	Moderate	Moderate	Low	Low	Moderate
O'Brien et al., 2020 [79]	Moderate	Moderate	Moderate	Low	Low	Moderate
Kirshan Lal & Abida Perveen, 2026 [80]	Low	Low	Low	Low	Low	Low

RESULTS

Characteristics of Included Studies

Study	Population	Primary Focus
Nawaz & Zafar, 2025 [3]	Pediatric (1–18 years), hospitalized with NS and edema	IV albumin ± diuretics vs no albumin for edema in children with NS
Nagori et al., 2023 [10]	Pediatric NS with edema (n=50)	Furosemide alone vs furosemide + 20% albumin (1 g/kg)
Singh et al., 2021 [8]	Pediatric idiopathic NS, serum albumin <1.5 g/dL (n=60)	Albumin vs fresh frozen plasma for diuretic-resistant edema
Tadayoni et al., 2025 [4]	Pediatric NS (2–15 years; n=64)	Sequential vs concurrent albumin and furosemide administration
Ghafari et al., 2011 [11]	NS patients with hypoalbuminemia (n=10)	Albumin alone vs furosemide alone vs albumin + furosemide
Ho et al., 2012 [12]	Pediatric NS (minimal change; n=26 in included RCT)	Human albumin infusion for edema in NS
Hedin et al., 2022 [13]	Adults and children with NS	Furosemide vs furosemide + albumin for nephrotic edema
Duffy et al., 2015 [14]	Pediatric and adult NS with diuretic-resistant edema	Albumin + loop diuretic combination for edema management

Study	Population	Primary Focus
Procope, 2020 [15]	NS patients	Human albumin for edema in NS (Cochrane summary)
Panda, 2019 [16]	Pediatric NS with severe edema (n=40)	Albumin + furosemide vs furosemide alone
Boyer & Bérody, 2020 [17]	Pediatric congenital NS (infants)	Conservative vs aggressive treatment including daily albumin infusions
Garg et al., 2020 [5]	Pediatric idiopathic NS with moderate-severe edema (n=24)	5% vs 20% albumin co-administered with furosemide
Kanzaki et al., 2012 [18]	Adult NS (ages 20–79; n=12)	hANP + conventional (furosemide + albumin) vs conventional alone
Ho et al., 2019 [9]	Pediatric NS (minimal change; n=26 in included RCT)	Human albumin infusion for edema in NS (updated Cochrane)
Huque et al., 2014 [19]	Pediatric idiopathic NS with resistant edema (n=40)	Albumin + furosemide vs mannitol + furosemide
Kitsios et al., 2014 [1]	Adults with hypoalbuminemia and edema	Albumin + loop diuretics vs loop diuretics alone for diuretic resistance
Constantinescu et al., 2022 [20]	Pediatric (CNS n=49; INS n=20) in first year of life	Albumin infusion patterns in congenital and infantile NS

Study	Population	Primary Focus
Hölttä & Jalanko, 2020 [21]	Pediatric congenital NS (Finnish type)	Aggressive treatment including daily albumin for CNS
Meena & Bagga, 2020 [22]	Pediatric idiopathic NS	Management of edema in pediatric NS including albumin
Carvey & Glauser, 2025 [23]	Adults in emergency department with sepsis and NS	When to use albumin in sepsis; NS mentioned as special population
Jethwani & Krishnan, 2021 [7]	Pediatric and adult NS	Pathogenesis and treatment of refractory edema in NS
Bockenbauer & Boyer, 2024 [24]	Pediatric congenital NS	Treatment dilemmas: aggressive vs conservative approach in CNS
Tameez Ud Din et al., 2023 [25]	Multi-indication HAS users (n=4,816) including childhood NS	HAS usage patterns over 8 years at large UK centre
Sinha et al., 2019 [26]	Pediatric congenital NS (n=65) in India	Management and outcomes of CNS in developing-country context
Rivkin, 2013 [27]	Pediatric NS	Mechanisms of nephrotic edema and therapeutic approaches

Study	Population	Primary Focus
Lee et al., 2021 [2]	Adults with hypoalbuminemia (n=422 across 13 trials)	Furosemide + albumin vs furosemide alone for diuresis/natriuresis
Coulthard, 2015 [28]	Pediatric CNS and children with kwashiorkor	Role of hypoalbuminemia in edema; IV albumin for hypovolemic shock
Coyle & John, 2021 [29]	Adults (mean age 68) in community hospital (n=186)	Appropriateness of albumin use by indication including nephrosis
Phakdeekitcharoen & Boonyawat, 2012 [30]	Adults with hypoalbuminemic CKD and edema (n=24)	Furosemide + albumin vs furosemide alone in hypoalbuminemic CKD
Ala et al., 2015 [31]	Mixed hospital patients receiving albumin (n=100)	Evaluation of appropriate albumin use in a teaching hospital
AbuMaziad et al., 2021 [32]	Pediatric CNS (case: infant with Finnish-type CNS)	Congenital NS: pathogenesis, management, anticoagulation challenges
Mahmoodpoor et al., 2020 [33]	Adult ICU patients with hypoalbuminemia and edema (n=49)	Furosemide + albumin complex vs furosemide alone in critically ill adults

Study	Population	Primary Focus
Dufek et al., 2018 [34]	Pediatric CNS (n=80) across 17 European centres	Management strategies and outcomes in CNS
Kallash & Mahan, 2020 [35]	Pediatric NS	Mechanisms and management of edema in pediatric NS
Floege et al., 2025 [36]	Pediatric NS (steroid-sensitive and steroid-resistant)	KDIGO 2025 guideline for management of NS in children
Zolfagharian et al., 2017 [37]	Hospital patients receiving albumin (n=50 each group)	Impact of evidence-based guideline on appropriateness of albumin use
Nishino et al., 2023 [38]	Pediatric idiopathic NS (n=1, age 6)	BIA monitoring of fluid status in a child with INS
Okoronkwo et al., 2018 [39]	Pediatric relapsed steroid-sensitive NS (n=1, age 7)	Whole blood as albumin substitute for refractory edema in a resource-poor setting
Konak et al., 2012 [40]	Pediatric CNS (newborn)	Congenital NS: diagnosis and management review
Mikulevič et al., 2023 [41]	Pediatric steroid-dependent NS (n=1, age 5y8m)	Overt hypothyroidism and growth retardation in poorly controlled NS

Study	Population	Primary Focus
Parikh et al., 2023 [42]	Adults with lupus nephritis and nephrotic-range proteinuria (n=4)	Zetomipzomib for proteinuria reduction in LN
Harahap et al., 2016 [43]	Adult with NS and antithrombin III deficiency (n=1)	Acute limb ischemia in NS with antithrombin III deficiency
Song Huali et al., 2019 [44]	Pediatric NS with hypercoagulability (n=142)	Chinese and Western medicine combination therapy in NS
Hassan et al., 2019 [45]	Pediatric steroid-resistant NS (n=7)	Effect of galactose on proteinuria in pediatric SRNS
Wiedermann, 2020 [46]	Critically ill and perioperative adults	Albumin roles in fluid de-resuscitation; NS briefly mentioned
Wiedermann et al., 2017 [47]	Adults across diverse clinical settings	Hypoalbuminemia as predictor of AKI; albumin for nephroprotection
Roberts et al., 2011 [48]	Critically ill adults with hypovolaemia, burns, or hypoalbuminaemia	Albumin vs crystalloid for resuscitation and volume expansion
Downie et al., 2017 [49]	Pediatric NS	Pathophysiology and management of pediatric NS including albumin

Study	Population	Primary Focus
Cadnapaphornchai et al., 2014 [50]	Pediatric and adult NS	Pathogenesis and treatment of edema and secondary complications in NS
Macedo et al., 2021 [51]	Adults with hypoalbuminemia on hemodialysis (n=65)	Albumin infusion to prevent intradialytic hypotension
Chen et al., 2021 [52]	Pediatric patients	Albumin physiology and its role in pediatric diseases
Rozga et al., 2013 [53]	Diverse clinical populations	Human albumin: established and emerging clinical applications
Fortin et al., 2010 [54]	Haemodialysis patients with IDH history (n=45)	Albumin for intradialytic hypotension in haemodialysis
Itagaki et al., 2022 [55]	Mechanically ventilated adults with hypoalbuminemia	Albumin + diuretics in mechanically ventilated hypoalbuminemic patients
Haynes & Bassiri, 2021 [56]	Diverse clinical populations (n=90 studies)	Hyper-oncotic vs hypo-oncotic albumin solutions
Caironi et al., 2015 [57]	Critically ill patients, sepsis	Albumin in critically ill patients: the ideal colloid?

Study	Population	Primary Focus
Castillo et al., 2018 [58]	Adults at academic medical center (n=150)	Adherence to national guidelines for appropriate albumin use
Yin et al., 2018 [59]	Haemodialysis patients with IDH (n=90 per group)	Algorithm for saline vs albumin in intradialytic hypotension
Macedo et al., 2020 [60]	Adults with hypoalbuminemia on HD (n=65)	Albumin infusion to prevent intradialytic hypotension (conference abstract version)
Verma & Patil, 2024 [61]	Pediatric and adult NS	Nephrotic syndrome: overview including albumin for edema
Faltys et al., 2026 [62]	Critically ill patients (n=196 across 4 studies)	Albumin for fluid de-resuscitation in ICU
Mohapatra et al., 2025 [63]	Critically ill patients with hypoalbuminemia on HD (205 sessions)	Albumin for prevention of intradialytic hypotension
Oczkowski & Mazzetti, 2014 [64]	Adult ICU patients with ARDS and CHF (nephrotic syndrome excluded)	Colloids to improve diuresis in ICU patients
Bedrabetu, 2024 [65]	Adults with NS (n=38) and healthy controls (n=38)	Hypoalbuminemia and anemia across proteinuria levels in NS

Study	Population	Primary Focus
Nissar et al., 2023 [66]	NS patients with severe hypoalbuminemia (n=11)	Direct oral anticoagulants in NS
Ellis, 2016 [6]	Pediatric NS (primary focus)	Pathophysiology, evaluation, and management of edema in childhood NS
Polito & Martin, 2013 [67]	Critically ill and hypovolemic patients	Albumin: physiologic and clinical effects on lung function
Lau et al., 2014 [68]	Pediatric CNS (neonates/infants)	Thrombotic complications of neonates with CNS
Moiseev et al., 2024 [69]	Pediatric and adult NS	Treatment and prevention of complications in NS including albumin
de Castro et al., 2017 [70]	Pregnant women with NS (n=19; 26 pregnancies)	Nephrotic syndrome in pregnancy: maternal and fetal complications
R. G K et al., 2025 [71]	Pediatric and adult NS	Nephrotic syndrome: overview
Zaman, 2013 [72]	Cirrhosis patients	Role of albumin in treating patients with cirrhosis
Pasini et al., 2017 [73]	Pediatric NS	SINePe consensus on management of pediatric NS including edema

Study	Population	Primary Focus
Rahman et al., 2013 [74]	Pediatric idiopathic NS (ages 1–18)	Management of idiopathic NS in children
Annane et al., 2013 [75]	Adult ICU patients with hypovolemic shock (n=2,857)	Colloids vs crystalloids for fluid resuscitation in hypovolemic shock
Reynolds & Oswald, 2019 [76]	Pediatric CNS (neonates/infants)	Diagnostic and management challenges in CNS
Oczkowski et al., 2014 [77]	Adult ICU patients with hypoalbuminemia and fluid overload (target n=50)	Furosemide + albumin vs furosemide + placebo for de-resuscitation (FADE trial)
Tiwari et al., 2014 [78]	Pediatric critically ill patients (n=435; NS excluded)	Hypoalbuminemia and outcomes in critically ill children
O'Brien et al., 2020 [79]	Adult RRT patients (n=1,464; 500 received early albumin)	Early albumin in continuous RRT patients
Kirshan Lal & Abida Perveen, 2026 [80]	Pediatric NS (minimal change disease)	Nephrotic syndrome in children: a review

Effects of Albumin on Volume Status and Edema in Nephrotic Syndrome

Overview of the Direct Evidence in Nephrotic Syndrome

The primary evidence specifically evaluating albumin for edema in nephrotic syndrome is remarkably sparse. The two Cochrane reviews on this question [9, 12] each identified only a single eligible RCT — the same study (Dharmaraj 2009, n=26 children with minimal change NS) — comparing albumin plus furosemide to an equal volume of dextrose plus furosemide. The risk of bias for that trial was unclear for selection bias, high for performance and detection bias, and high for selective reporting, with very low certainty evidence for all outcomes [9]. The 2025 systematic review by Nawaz & Zafar similarly found only one RCT (an open-label randomized crossover trial with 16 pediatric participants) meeting their inclusion criteria after screening 784 records [3].

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
						n	

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Nawaz & Zafar (2025, included RCT — Dharmaraj 2009) [3]	16 pediatric	Hospitalized children with NS and edema	Furosemide alone	HA+FU: 3.27 (IQR 2.04–4.50) vs FU: 1.33 (0.79–1.88) mL/kg/h; p=0.01	Weight loss (%): HA+FU 5.2 (3.1–8.8) vs FU 0.8 (–1.9 to 4.1); p=0.006	Urine Na (mEq/day): HA+FU 58 vs FU 30; p=0.08 (NS)	Hypokalemia n=1 (HA+FU); metabolic alkalosis n=1, peritonitis n=1 (FU); no BP difference [3]

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Ho et al. (2019, included RCT — Dharmaraj 2009) [9]	26 pediatric (minimal change NS)	Children with minimal change NS	Equal volume dextrose	Not reported	Initial greater weight loss with albumin; no difference at 10 days	Serum Na MD +2.0 mEq/L (95% CI -0.09 to 4.09); NS	Systolic BP MD +2.0 mmHg (95% CI -3.52 to 7.52); diastolic BP MD +2.0 mmHg (95% CI -4.29 to 8.29) [9]
Nagori et al. (2023) [10]	50 pediatric	NS with edema	Furosemide alone	Significant increase with albumin + furosemide	Significant mean weight loss	Not reported	Not reported [10]

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Singh et al. (2021) [8]	60 pediatric	Idiopathic NS, albumin <1.5 g/dL, moderate-severe edema	FFP	Dry weight Group A (albumin): 6.62±3.15 days; Group B (FFP): 6.65±3.18 days (no difference)	Comparable time to dry weight in both groups	Not reported	No significant complications in either group [8]
Tadayoni et al. (2025) [4]	64 pediatric (2–15 yrs)	NS	Concurrent albumin + furosemide	Not reported	Sequential group: statistically significant greater weight loss	Urinary Na: no significant difference between groups	No adverse effects observed [4]

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Ghafari et al. (2011) [11]	10 NS patients	NS with hypoalbuminemia, normal GFR	Albumin alone; furosemide alone	Albumin alone: 742 mL; furosemide: 1707 mL; albumin+furosemide: 2175 mL (p=0.015)	Not reported	FENa: albumin alone 1.96, furosemide 3.18, albumin+furosemide 4.77 (p=0.000); 24-h urine Na: 18.3, 208.4, 206 mEq respectively	Not reported [11]

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Panda (2019) [16]	40 pediatric	NS with severe edema	Furosemide alone	Increased significantly in both groups; mean urine output difference at 24h significant	Weight, abdominal circumference, serum Na and K decreased significantly in both groups	Not reported	IVCCI decreased at 1h in albumin +furosemide group but returned to baseline at 24h [16]

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Garg et al. (2020) [5]	24 pediatric	Idiopathic NS, moderate-severe edema, anasarca	Alternative concentration (5% vs 20%)	5%: increase 1.52 (SD 1.11) mL/kg/h; 20%: increase 1.66 (SD 0.95) mL/kg/h; between-group p=0.6	Weight loss: 5%: 2.25% (SD 2.12); 20%: 3.68% (SD 3.84); between-group p=0.64	FENa increased significantly within each group; between-group p=0.7	No volume overload complications in either group [5]

Study	n	Population	Comparator	Urine Output	Weight Change	Sodium Excretion	Adverse Events
Huque et al. (2014) [19]	40 pediatric	Idiopathic NS, resistant edema	Mannitol + furosemide	Albumin+F U: 1383±949 mL vs mannitol+F U: 928±360 mL; NS between groups	Mannitol +FU: 13.74% weight reduction; albumin+FU: similar	Sodium levels increased after albumin therapy	Diastolic BP increase in albumin group; no significant side effects [19]
Kanzaki et al. (2012) [18]	12 adults	NS, ages 20–79 years	Conventional (furosemide + albumin) alone	Body weight reduced in both groups after 2 weeks	Both groups: body weight reduced	Not reported	No adverse effects observed ; serum creatinine rose less in hANP group [18]

Among the studies directly enrolling NS patients and comparing albumin plus diuretics to diuretics alone (or another colloid), the most consistent finding is a transient increase in urine output and weight loss in the albumin-treated group within the first several hours of treatment [3, 11, 13, 14]. The Hedin et al. (2022) systematic review, which included both adults and children and allowed crossover designs, found a pooled standardized mean difference of 0.85 (95% CI 0.33 to 1.38) for urine excretion favoring furosemide plus albumin over furosemide alone, though sodium excretion results were inconclusive (SMD 0.37, 95% CI -0.28 to 1.02) [13]. The Kitsios et al. (2014) meta-analysis of adult hypoalbuminemic patients found statistically significant increases in urine volume at 8 hours (increment of 231 mL, 95% CI 135.5–326.5) and urinary sodium excretion (15.9 mEq, 95% CI 4.9–26.8) with albumin plus furosemide, but these differences were no longer significant at 24 hours [1]. The Lee et al. (2021) updated meta-analysis of 13 adult trials (n=422) found that albumin co-administration increased urine output by approximately 31.45 mL/hour and urinary sodium excretion by approximately 1.76 mEq/hour compared to furosemide alone, with effects most prominent within 12 hours and greater in patients with baseline albumin below 2.5 g/dL or receiving higher albumin doses above 30 g [2].

The Tadayoni et al. (2025) RCT in children addressed a more specific question — whether the sequence of administration matters — finding that sequential administration (albumin infused first, followed by furosemide) produced statistically significantly greater weight loss than simultaneous co-infusion, without a significant difference in urinary sodium excretion [4]. This finding aligns with the pharmacological rationale that albumin must first expand intravascular volume before furosemide is administered to optimize tubular drug delivery [14].

Garg et al. (2020) specifically compared 5% versus 20% albumin (each 1 g/kg) co-administered with furosemide (2 mg/kg) and found no significant difference in urine output increase or percentage weight loss between the two concentrations, with both producing significant within-group improvements and no volume overload complications [5]. This was a pediatric crossover RCT (n=24) with adequate blinding of patients and data recorders but an unblinded treating clinician, limiting certainty [5].

Singh et al. (2021) compared albumin (1 g/kg/day) to fresh frozen plasma (15 mL/kg/day) in 60 children with idiopathic NS and moderate-to-severe edema [8], finding nearly identical times to achieving dry weight (albumin group 6.62 ± 3.15 days vs FFP group 6.65 ± 3.18 days) with no significant complications in either group [8]. However, FFP required significantly more infusions (3.11 ± 1.05) compared to albumin (1.42 ± 0.62 ; $p=0.0001$), and the authors noted FFP cost approximately half the price of albumin [8].

Transience and Sustainability of Effects

A critical and consistent finding across multiple sources is that the diuretic benefit of albumin in nephrotic syndrome is transient, peaking within the first few hours and not sustained at 24 hours [1–3]. The Kitsios et al. (2014) meta-analysis explicitly reported that differences in urine volume and sodium excretion were statistically significant at 8 hours but not at 24 hours [1]. The Lee et al. (2021) meta-analysis similarly found that the diuretic and natriuretic effects were more pronounced within the first 12 hours [2]. The two Cochrane reviews noted that the single eligible RCT in NS reported greater initial weight loss in the albumin group but no overall difference at 10 days [9]. This transience is mechanistically explained: in NS, the glomerular barrier is so permeable that infused albumin is rapidly excreted into the urine, attenuating any sustained oncotic pressure benefit [24]. Bockenhauer & Boyer (2024) specifically raised this point, questioning the long-term benefit of regular infusions given that "the vast majority of it will be lost in the urine within hours, given the glomerular leakage" [24].

Congenital Nephrotic Syndrome: A Specialized Context

Congenital nephrotic syndrome (CNS) represents the most extreme end of the severity spectrum, where albumin infusions have historically been used daily from birth until bilateral nephrectomy and transplantation [21]. Hölttä & Jalanko (2020) describe the Finnish aggressive protocol, in which 20% albumin is given at 1–2 g/kg/day divided into three infusions daily, together with furosemide 1–3 mg/kg/day, as lifesaving in infants with severe CNS [21, 21]. Boyer & Bérody (2020) and Bockenhauer & Boyer (2024) present the counter-argument that conservative management (without routine daily albumin and without early bilateral nephrectomy) achieves similar survival (approximately 90% in both approaches) with less morbidity and better quality of

life [17, 24]. Dufek et al. (2018), reviewing 80 European CNS children, found that in the conservative group (n=17 NPHS1 patients), 53% remained without dialysis and outcomes regarding septic or thrombotic episodes and growth were comparable to the bilateral nephrectomy group (n=25) [34]. In the Constantinescu et al. (2022) multicenter retrospective cohort (n=69 infants), daily albumin infusions were used in 79% of CNS and 30% of INS patients in the first 2 months after diagnosis [20], reflecting the greater disease severity in CNS. Sinha et al. (2019) reported a large Indian CNS series in which albumin was used in approximately two-thirds of children, but outcomes were poor with 42% mortality, attributed to suboptimal management and lack of genetic evaluation [26].

Study	Population	Albumin Frequency	Comparator	Key Outcome
Hölttä & Jalanko, 2020 [21]	Pediatric CNS (Finnish type)	Daily (1–2 g/kg/day, 20%)	No comparator (protocol description)	Protocol stated to be life-saving; prevents edema complications
Boyer & Bérody, 2020 [17]	Pediatric CNS	Daily (aggressive approach)	Conservative (tapered/discontinued)	Similar complication rates; conservative approach enables hospital discharge before nephrectomy

Study	Population	Albumin Frequency	Comparator	Key Outcome
Bockenbauer & Boyer, 2024 [24]	Pediatric CNS (NPHS1-CNS)	Regular infusions until nephrectomy	Conservative management	~90% survival in both approaches; daily albumin questioned given urinary losses
Dufek et al., 2018 [34]	Pediatric CNS (n=80, 17 centres)	Variable; reduced by 5 g/kg/week after unilateral nephrectomy (p=0.02) [34]	Bilateral nephrectomy vs conservative	Sepsis/thrombosis and growth comparable; 53% conservative group avoided dialysis
Constantinescu et al., 2022 [20]	CNS (n=49) vs INS (n=20)	Daily in 79% CNS vs 30% INS (p=0.006) in first 2 months	No treatment control	Daily albumin frequency reflects disease severity; no direct outcome comparison
Sinha et al., 2019 [26]	Indian CNS (n=65)	~Two-thirds received albumin	Not stated	42% mortality; suboptimal management in resource-limited setting

Intravascular Volume Status and Its Role in Predicting Albumin Response

Multiple reviews and clinical studies emphasize that the hypovolemia or "underfill" versus "overfill" distinction fundamentally determines whether albumin is indicated and whether it will be effective [6, 7, 14]. Ellis (2016) provides the most detailed framework, describing underfill (hypovolemic) nephrotic patients as having fractional excretion of sodium (FENa) below 0.2%, urinary potassium index ($K^+/[K^{++}Na^+]$) above 60%, serum albumin at or below 2 g/dL, and GFR above 75 mL/min/1.73 m², alongside elevated plasma renin activity, aldosterone, and vasopressin [6]. Conversely, overfill patients have FENa above 0.5%, GFR below 50 mL/min/1.73 m², normal or elevated blood pressure without orthostasis, and suppressed neurohormonal markers [6]. Jethwani & Krishnan (2021) similarly recommend stratifying patients into underfill versus euvolemic/hypervolemic categories before initiating diuretics, using FENa below 0.5% and urine $K^+/(Na^{++}K^+)$ above 0.6 in children as markers of hypovolemia [7], noting that at least two-thirds of oedematous adults with NS have normal or elevated intravascular blood volume [7].

Critically, the Garg et al. (2020) crossover RCT documented prerenal indices (low FENa, high urinary potassium index) in all enrolled children with idiopathic NS and anasarca at baseline, which significantly improved after albumin plus furosemide in both the 5% and 20% arms [5, 5]. Panda (2019) used inferior vena caval collapsibility index (IVCCI) as an advanced hemodynamic assessment, finding that IVCCI decreased significantly at 1 hour after albumin plus furosemide (consistent with improved intravascular filling) but returned to baseline by 24 hours, directly demonstrating the transience of volume effect [16, 16].

Meena & Bagga (2020) and Jethwani & Krishnan (2021) both endorse the treatment algorithm in which salt-poor albumin is administered first for volume expansion in hypovolemic NS patients, with diuretics introduced only after volume status has been restored [7, 22]. This sequential approach contrasts with the simultaneous co-infusion strategy and is mechanistically supported by the need to first restore effective arterial blood volume before furosemide can be adequately delivered to the ascending limb of the loop of Henle [7, 14]. The Tadayoni et al. (2025) RCT empirically confirmed this, finding significantly greater weight loss with sequential (albumin then furosemide) versus simultaneous administration [4].

Subgroup Factors Modifying the Albumin Effect

The Lee et al. (2021) (n=422 adults across 13 trials) identified several moderators of the albumin plus furosemide effect [2]:

- Patients with baseline serum albumin below 2.5 g/dL showed greater diuretic/natriuretic responses.
- Patients receiving higher albumin doses (above 30 g) had greater responses.
- The diuretic effect was more marked in patients with baseline creatinine above 1.2 mg/dL.
- The natriuresis effect was greater in patients with eGFR below 60 mL/min/1.73 m².
- Effects were most pronounced within the first 12 hours.

The Duffy et al. (2015) review noted that short-term beneficial effects were observed within 6 hours of administration, with urine output increases ranging from 31 to 245 mL/h [14]. The Kitsios et al. (2014) meta-analysis similarly documented a mean urine volume increment of 231 mL at 8 hours (95% CI 135.5–326.5) and a sodium excretion increment of 15.9 mEq (95% CI 4.9–26.8) at 8 hours but no significant difference at 24 hours [1]. This temporal pattern across multiple populations and settings provides strong convergent evidence that albumin's primary diuretic benefit is acute and not sustained.

The Phakdeekitcharoen & Boonyawat (2012) RCT in hypoalbuminemic CKD adults (mean eGFR 31.0±13.8 mL/min; n=24) found significant between-group differences in urine volume (0.67±0.31 L vs 0.47±0.40 L increment at 6h; p<0.02) and sodium excretion (55.0±26.7 mEq vs 37.5±29.3 mEq at 6h; p<0.01), which disappeared at 24 hours [30]. While this study enrolled CKD patients rather than NS patients per se, it supports the generalizability of the transient effect and the importance of the 6-hour versus 24-hour observation window.

Renal Function and Electrolyte Effects

Few studies reported formal GFR or creatinine changes associated with albumin in NS. The Ghafari et al. (2011) crossover RCT noted GFR values of 104.5, 96.6, and 106.6 mL/min for

albumin alone, furosemide alone, and albumin plus furosemide, respectively ($p=0.021$), suggesting that the combination modestly restored GFR above furosemide alone in normal-GFR NS patients [11]. The Phakdeekitcharoen & Boonyawat (2012) study documented an approximately 10% GFR decline at 6 hours in both treatment arms, attributed to volume contraction from acute diuresis, without reaching a level suggesting AKI [30]. The Mahmoodpoor et al. (2020) trial reported no creatinine-related adverse events [33]. The Garg et al. (2020) crossover RCT found no AKI in either albumin group and no need for dialysis or ventilation, with short-term improvement in FENa and urinary potassium index consistent with restored effective arterial volume [5].

Ellis (2016) provides the clearest mechanistic framework: in underfill NS, hypovolemia itself is the driver of reduced effective renal perfusion, and correcting this with albumin volume expansion supports GFR and avoids diuretic-induced AKI [6]. Conversely, aggressive diuresis in the absence of adequate intravascular filling is a recognized cause of AKI in these patients [6, 7]. Electrolyte disturbances specifically attributable to albumin were uncommon across studies; the included RCT summarized by Nawaz & Zafar (2025) reported one case of hypokalemia in the albumin plus furosemide arm [3], and Nagori et al. (2023) found no significant difference in serum sodium or potassium between groups [10].

Safety and Adverse Effects

Safety data across the nephrotic syndrome studies were limited in quantity and systematically reported. The most commonly cited risks of albumin infusion in this population are volume overload, pulmonary edema, and hypertension [3, 19, 73]. The Nawaz & Zafar (2025) systematic review noted, from observational studies outside the included RCT, that nearly half of reported albumin infusion episodes in children with NS were associated with acute hypertension, and at least one case of congestive heart failure was reported [3]. Ellis (2016) identified infection transmission risks (albumin is a blood product) and tissue allosensitization as additional concerns specific to albumin [6]. Moiseev et al. (2024) cautioned that albumin infusions can provoke pulmonary edema in cases of volume excess and that rapid urinary excretion of infused albumin may additionally injure podocytes [69].

In the direct comparative trials, no major albumin-related adverse events were reported: Garg et al. (2020) found no hypertension, pulmonary edema, or need for dialysis [5]; Singh et al. (2021) reported no significant complications in either the albumin or FFP group [8]; Tadayoni et al. (2025) observed no drug-associated adverse effects [4]; Ghafari et al. (2011) and Kanzaki et al. (2012) both reported no adverse effects [11, 18]. The comparison between albumin and FFP by Singh et al. (2021) is particularly relevant: both achieved equivalent clinical outcomes with no complications, while FFP required roughly twice as many infusions as albumin, making albumin more convenient but more expensive [8, 8].

Beyond NS-specific populations, the broader literature confirms that albumin in hypoalbuminemic patients undergoing hemodialysis reduces intradialytic hypotension (IDH) and vasopressor requirements. Macedo et al. (2021) found that 25 g albumin at dialysis initiation reduced IDH incidence from 15% (saline) to 7% (albumin) by KDOQI definition ($p=0.002$) and improved the lowest intradialytic systolic blood pressure (90 vs 83 mmHg; $p=0.035$) [51]. Mohapatra et al. (2025) found that while albumin did not significantly reduce IDH incidence itself, it significantly reduced vasopressor requirements (7.8% albumin vs 28.4% control; $p<0.001$) [63]. These findings are relevant to NS patients who develop volume depletion severe enough to require dialysis, though the populations differ substantially from ambulatory NS management.

Albumin Use Patterns and Prescribing in Practice

Several utilization studies document that albumin is frequently used for childhood NS in clinical practice. Tameez Ud Din et al. (2023) reported that childhood nephrotic syndrome accounted for 4.1% (685 of 16,772 infusions) of 20% HAS use at a large UK tertiary referral center over 8 years [25], placing it sixth among clinical indications. Coyle & John (2021) found that nephrosis or nephropathy was the indication in 10.8% of albumin prescriptions in a community hospital, and the overall rate of appropriate albumin use was 67.7% [29]. Ala et al. (2015) found that albumin was used appropriately in only 63% of patients at an Iranian teaching hospital [31], while Zolfagharian et al. (2017) showed that a guideline intervention modestly reduced inappropriate use without reaching statistical significance, though it significantly reduced inappropriate dose and duration and reduced average cost per patient from USD 317.78 to USD

149.81 [37]. Castillo et al. (2018) found 45% of albumin prescriptions at an academic medical center were inappropriate by national guidelines, with an estimated cost of approximately USD 13,000 for the 150-patient cohort [58].

Comparative Evidence from Related Populations

The broader albumin literature in non-NS hypoalbuminemic populations provides supporting mechanistic context. The Faltys et al. (2026) systematic review of albumin co-administration with diuretics in critically ill patients found no significant difference in average daily net fluid balance (mean difference -0.22 L/d; 95% CI -0.88 to 0.43), with high heterogeneity among the four available studies ($n=196$ total) [62], suggesting that the fluid de-resuscitation benefit documented in some studies is not consistent across ICU populations. The Oczkowski & Mazzetti (2014) systematic review found that albumin plus furosemide improved net fluid balance at 3 days in an ARDS population (-5.48 L vs -1.49 L with albumin; $p<0.01$) but found no improvement in a CHF population [64], again illustrating condition-specificity. Roberts et al. (2011), in the largest meta-analysis of albumin for resuscitation in critically ill patients ($n=10,842$ across 38 RCTs), found no reduction in mortality across hypovolaemia, burns, or hypoalbuminaemia populations (pooled RR 1.05, 95% CI 0.95–1.16), though this review addressed mortality rather than volume management [48].

The CRISTAL trial (Annane et al., 2013), the largest trial of colloids versus crystalloids in hypovolemic shock ($n=2,857$), found no significant difference in 28-day mortality (colloids 25.4% vs crystalloids 27.0%; RR 0.96, 95% CI 0.88–1.04), though 90-day mortality was lower in the colloid group (30.7% vs 34.2%; RR 0.92, 95% CI 0.86–0.99) [75]. Albumin represented only a fraction of the colloids used, and NS patients were not a defined subgroup.

Thematic Analysis

Theme 1: The Underfill–Overfill Distinction as the Central Determinant of Albumin Utility

The most clinically important concept threading through this literature is that the indication for albumin in NS is contingent on accurately identifying the patient's intravascular volume status. Multiple reviews converge on a binary model: "underfill" (hypovolemic) patients, who are particularly common among children with classic minimal change NS and severe

hypoalbuminemia, have a depleted effective arterial blood volume despite peripheral edema, and may benefit from albumin for volume expansion before diuresis [6, 7, 69]. In contrast, "overfill" patients — more commonly adults with secondary NS or glomerulonephritis — have primary sodium retention with normal or expanded intravascular volume and do not require, and may be harmed by, albumin infusion [6, 14].

Ellis (2016) describes FENa below 0.2% and urinary $K^+/(K^{++}Na^+)$ above 60% as the most sensitive biochemical markers of underfill in children [6], while Jethwani & Krishnan (2021) additionally recommend measuring plasma renin activity, serum aldosterone, and hematocrit, and performing echocardiographic assessment of IVC collapsibility in pediatric patients when the diagnosis is uncertain [7]. Panda (2019) used IVCCI clinically, finding significant intravascular volume improvement at 1 hour after albumin plus furosemide, supporting its utility as a real-time monitoring tool [16]. Despite this mechanistic consensus, none of the primary intervention trials explicitly stratified patients by underfill versus overfill status before randomization, representing a major methodological gap in the evidence base.

Theme 2: Albumin as Pharmacological Carrier for Furosemide

A distinct and clinically relevant mechanism, discussed by multiple sources, is albumin's role in enhancing furosemide delivery to the renal tubule. Loop diuretics are highly protein-bound in plasma, and furosemide must be secreted into the tubular lumen by organic anion transporters in the proximal tubule to reach its site of action at the ascending limb [7, 14]. In severe hypoalbuminemia, less furosemide is bound to albumin, greater proportions diffuse into interstitial tissues, tubular secretion is impaired, and the drug is rapidly metabolized or eliminated without reaching its target [3, 6]. Co-administration of albumin is therefore hypothesized to restore furosemide binding, increase renal delivery, and potentiate the diuretic response.

The Mahmoodpoor et al. (2020) RCT specifically measured urinary furosemide excretion as a pharmacokinetic endpoint and found no significant overall difference between groups at 2, 4, 6, or 8 hours, though urinary furosemide excretion was significantly higher in the albumin group at the 2-hour time point ($p=0.03$) [33]. The Phakdeekitcharoen & Boonyawat (2012) crossover RCT in CKD patients documented greater urine volume and sodium excretion at 6 hours with albumin plus

furosemide compared to furosemide alone ($p<0.02$ and $p<0.01$ respectively), consistent with enhanced tubular drug delivery, though the effect was not sustained at 24 hours [30]. These findings suggest that while the pharmacokinetic mechanism is plausible and may provide a brief incremental benefit, it does not translate into a meaningfully prolonged or large diuretic advantage in clinical practice.

Theme 3: Albumin Administration in Congenital Nephrotic Syndrome — Ongoing Clinical Debate

Congenital nephrotic syndrome presents a uniquely challenging context where the debate over albumin use is most prominent and the stakes highest. In this rare condition, severe hypoalbuminemia from birth creates life-threatening oncotic pressure deficits, and without intervention, infants are at immediate risk of hemodynamic instability, infection, thrombosis, and malnutrition [21, 32, 76]. The Finnish aggressive approach, initially developed in the 1970s–1980s, introduced daily albumin infusions (typically 20%, 1–2 g/kg/day) from birth until bilateral nephrectomy at approximately 9–14 months, followed by dialysis and transplantation, dramatically improving survival from near-universal early mortality [21, 24].

However, Bockenbauer & Boyer (2024) challenge this paradigm on the basis of more recent large retrospective international and French nationwide studies demonstrating that survival with conservative management (without routine daily albumin or early bilateral nephrectomy) approximates 90%, similar to the aggressive approach [24]. In this conservative approach, albumin is tapered and discontinued in a subset of patients who can be discharged home before nephrectomy, reducing hospitalization burden, complications of central venous access, and the distress of prolonged hospitalization [24]. Importantly, Dufek et al. (2018) found that antiproteinuric treatment (RAAS inhibitors $\pm$ indomethacin) increased serum albumin by a median of 6 g/L ($p<0.001$) and unilateral nephrectomy increased serum albumin by a further 4 g/L ($p=0.03$), with a concurrent reduction in albumin infusion requirement of 5 g/kg/week ($p=0.02$) [34]. This suggests that targeting the source of protein losses, rather than indefinitely replacing albumin intravenously, can meaningfully reduce dependence on infusions. Reynolds & Oswald

(2019) note that unilateral nephrectomy can function as a less aggressive intermediate step that reduces albumin infusion burden while preserving some residual renal function [76].

Lau et al. (2014) highlight that the central venous catheters required for regular albumin infusions in CNS carry substantial thrombotic and infectious risks [76], and Hölttä & Jalanko (2020) acknowledge the need to manage these complications with anticoagulants and careful line care [21]. AbuMaziad et al. (2021) present a case in which these complications dominated the clinical course, with recurrent catheter-associated thromboses requiring sequential changes to anticoagulation regimens including LMWH, warfarin, UFH, and ultimately rivaroxaban [32].

Theme 4: Albumin in Resource-Limited Settings and Alternative Colloids

A practically important theme concerns situations where standard albumin preparations are unavailable or unaffordable. Okoronkwo et al. (2018) describe a Nigerian child with relapsed NS and severe refractory anasarca (weight 58 kg) who could not access salt-poor albumin due to cost [39]. Fresh whole blood (15 mL/kg aliquots over 6 hours on days 2, 4, and 6), administered with IV furosemide 60 mg given 2 hours into and immediately after each transfusion, achieved a lifesaving diuresis with weight reduction from 58 to 38 kg over the admission, normalization of creatinine and albumin (15 to 26 g/L), and remission by discharge at 2 weeks [39]. The authors propose whole blood as an emergency substitute in resource-poor settings [39]. Similarly, Singh et al. (2021) demonstrated that fresh frozen plasma (15 mL/kg/day) is a clinically equivalent, cheaper alternative to albumin for diuretic-resistant edema in children with idiopathic NS, requiring twice as many infusions but achieving the same time to dry weight and carrying no significant additional complications [8, 8].

Huque et al. (2014) tested mannitol plus furosemide as an alternative osmotic agent, finding that while albumin plus furosemide produced numerically higher urine volumes (1383 ± 949 mL vs 928 ± 360 mL for mannitol), the difference was not statistically significant, and body weight reduction (13.74% for mannitol group) was clinically comparable [19]. The authors note mannitol costs less and is more widely available than albumin in their setting, potentially making it a useful alternative in resource-limited contexts for diuretic-resistant nephrotic edema [19].

Theme 5: Timing and Sequencing of Albumin Relative to Diuretics

Multiple sources discuss the importance of the timing relationship between albumin administration and loop diuretic administration. The dominant clinical practice described in guidelines and reviews is sequential administration — albumin infused first over 1–4 hours, followed by IV furosemide either at the midpoint or upon completion of the albumin infusion [6, 73, 74]. Ellis (2016) specifies 25% salt-poor albumin at 0.5 g/kg over 1 hour, with furosemide given at the start or 1 hour after the albumin infusion [6]. Pasini et al. (2017) recommend 20% albumin 0.5–1 g/kg over 3–4 hours, with a bolus of furosemide 1 mg/kg IV after the albumin infusion [73]. Rahman et al. (2013) describe 20% albumin 1 g/kg IV followed immediately by IV furosemide as the final step in a diuretic-escalation algorithm for refractory edema [74].

Tadayoni et al. (2025) empirically compared sequential (furosemide immediately after albumin infusion) versus concurrent (albumin and furosemide admixture) in a double-blind pediatric RCT (n=64) and found significantly greater weight loss with the sequential method, without a significant difference in urinary sodium excretion [4]. This finding directly supports the sequential approach recommended by guidelines and provides the most direct RCT evidence on this specific question. The plausible mechanism is that sequential administration allows albumin to expand intravascular volume and restore renal perfusion before furosemide is delivered, maximizing tubular drug secretion and diuretic efficiency [14].

Theme 6: Albumin Versus Broader Immunosuppressive and Disease-Modifying Therapies

An important perspective provided by several sources is that albumin is purely supportive and does not address the underlying cause of hypoalbuminemia in NS — proteinuria. While albumin infusions transiently raise serum albumin and oncotic pressure, the fundamental treatment is immunosuppression to achieve remission of proteinuria [49, 61, 80]. Corticosteroids remain first-line therapy, with alternative agents including calcineurin inhibitors, mycophenolate mofetil, and rituximab for steroid-dependent or steroid-resistant disease [49, 61]. The KDIGO 2025 guideline addresses these disease-modifying strategies [36], and the Italian SInePe consensus (Pasini et al., 2017) explicitly positions albumin as a temporizing measure for acute symptomatic management of severe edema while corticosteroids are expected to induce remission within 4–8 days [73].

Hassan et al. (2019) present preliminary evidence that oral galactose (0.2 g/kg twice daily for 16 weeks) may reduce the need for albumin infusions in steroid-resistant NS by binding the putative permeability factor and reducing proteinuria, though only 7 pediatric subjects were studied [45]. The zetomipzomib MISSION Phase 2 study (Parikh et al., 2023) showed that 3 of 4 patients with lupus nephritis and nephrotic-range proteinuria achieved at least 50% UPCR reduction at 24 weeks, with normalization of serum albumin in all 3 patients who had hypoalbuminemia at baseline, illustrating that effective immunosuppression can make albumin infusions unnecessary [42].

Synthesis

The Central Paradox: Short-Term Physiological Plausibility vs. Limited Sustained Benefit

The evidence across 80 sources reveals a consistent paradox: IV albumin in NS with hypovolemia has a well-established, mechanistically sound physiological rationale and produces measurable short-term improvements in urine output and weight loss, yet randomized trial evidence is of very low certainty, effects are transient, and no study demonstrates patient-centered benefits such as reduced hospitalization, improved quality of life, or better long-term kidney function.

This paradox is not contradictory — both observations can be simultaneously correct within specific margins. The transience of albumin's diuretic effect in NS is directly attributable to the disease mechanism: the same glomerular leak that causes hypoalbuminemia also causes rapid urinary loss of infused albumin, typically within hours [3, 24]. This distinguishes NS-associated hypovolemia from other forms of hypoalbuminemia (e.g., cirrhosis, critical illness) where albumin may persist longer in circulation. In hepatic failure, for example, the evidence base for albumin is substantially stronger and more directly tied to survival outcomes [53, 72].

Why Studies Show Different Results

Study population and volume status: Studies finding the largest benefits consistently enrolled patients with severe hypoalbuminemia and evidence of true underfill physiology. Lee et al. (2021) showed that effects were significantly greater in patients with baseline albumin below 2.5 g/dL [2], while Mahmoodpoor et al. (2020) found no significant benefit in ICU patients with moderate hypoalbuminemia (mean 2.4–2.5 g/dL) without NS [33]. Duffy et al. (2015) noted that roughly one-third of NS patients in reported studies had low plasma volume, half had normal

volume, and the remainder had elevated volume [14], predicting that any unselected NS population would show diluted average effects. Studies that did not discriminate by volume status — the majority of primary trials — inevitably recruited a heterogeneous mix of underfill and overfill patients, attenuating the average treatment effect.

Duration of observation: Studies observing outcomes at 6–8 hours consistently find statistically significant differences in urine output and sodium excretion [1, 30], while those observing at 24 hours find effects that are substantially attenuated or statistically non-significant [1, 11, 30]. The weight of pediatric NS crossover data, reviewed by Nawaz & Zafar (2025), confirms peak urine output benefit within the first few hours with return toward baseline by 24 hours [3]. This means studies with short observation windows (≤ 8 hours) will detect benefit, while studies powered for 24-hour or multi-day outcomes will be less likely to find significance unless using weight loss or edema resolution as primary endpoints.

Albumin dose and concentration: Lee et al. (2021) found that doses above 30 g were associated with greater diuretic response [2], while lower doses showed less clear benefit. Garg et al. (2020) showed that 5% and 20% albumin at 1 g/kg produced equivalent outcomes, suggesting that the total albumin dose (in grams) rather than concentration may be the critical variable, since both arms received approximately the same total protein mass [5]. Studies using lower doses or shorter infusions may therefore underestimate the treatment effect.

Comparator: Studies comparing albumin plus furosemide to furosemide alone in diuretic-naïve patients will detect effects more easily than those where patients have received multiple prior diuretic doses. The crossover design used by Ghafari et al. (2011) — comparing three arms (albumin alone, furosemide alone, albumin plus furosemide) — most clearly isolated the additive contribution of each component: albumin alone produced 742 mL urine output; furosemide alone 1,707 mL; combination 2,175 mL [11]. This demonstrates that both components contribute additively to the diuretic response, with the combination exceeding either alone.

What Can Be Concluded for Specific Populations and Contexts

For **children with idiopathic NS, anasarca, and biochemical underfill** ($\text{FENa} < 0.2\%$, urinary $\text{K}^+ / [\text{K}^+ + \text{Na}^+] > 60\%$, serum albumin ≤ 2 g/dL), albumin (20–25%, 0.5–1 g/kg) followed by

furosemide represents a defensible acute intervention to enhance diuresis and reduce edema. The transient nature of effects means it is best reserved for acute inpatient management of severe or diuretic-resistant edema, not as a routine outpatient or ongoing therapy [3, 6, 9].

For **children with CNS**, the debate between aggressive (daily albumin infusions) and conservative management remains unresolved by RCT evidence, with retrospective data suggesting comparable survival (approximately 90%) under both approaches [24]. A conservative approach with selective, clinically triggered albumin use appears increasingly supported by international evidence and reduces the burden of central venous access and hospitalization [17, 24].

For **adults with NS**, most evidence is derived from hypoalbuminemic non-NS populations. The available adult NS-specific evidence (Ghafari et al. 2011; Kanzaki et al. 2012) is very small. Given that adults with NS are more commonly volume-expanded than children [7], the indication for albumin is narrower and should be guided by careful volume assessment rather than assumed.

For **patients in resource-limited settings** where albumin is unavailable or unaffordable, fresh whole blood and fresh frozen plasma are supported as alternatives by limited but specific evidence in pediatric NS, with FFP requiring more infusions and whole blood showing efficacy in a single case report [8, 39]. Mannitol plus furosemide produced statistically equivalent results to albumin plus furosemide in one small pediatric study, at substantially lower cost [19].

The design that would most definitively resolve remaining uncertainty is a multicenter, adequately powered, parallel-group pediatric RCT that (1) stratifies by underfill vs overfill volume status using standardized laboratory and imaging criteria, (2) compares albumin plus furosemide to furosemide alone in the underfill subgroup, and (3) measures both short-term physiological endpoints (urine output, FENa) and patient-centered outcomes (length of hospitalization, edema resolution time, quality of life, adverse events) over at least 7–10 days [3, 9, 13].

DISCUSSION

Overview of Principal Findings

This systematic review of 80 sources evaluating albumin use in nephrotic syndrome with hypovolemia reveals several consistent and clinically important findings. First, the direct evidence

base specifically addressing this question is remarkably sparse, with the two Cochrane reviews each identifying only a single eligible RCT (Ho et al., 2012; Ho et al., 2019; Nawaz & Zafar, 2025). Second, albumin co-administration with furosemide produces statistically significant increases in urine output and sodium excretion compared to furosemide alone, but these effects are consistently transient—peaking at 6–8 hours and typically disappearing by 24 hours (Kitsios et al., 2014; Lee et al., 2021; Hedin et al., 2022). Third, the underfill-versus-overfill distinction emerges as the central determinant of albumin utility, yet few primary trials have stratified patients accordingly (Ellis, 2016; Jethwani & Krishnan, 2021). Fourth, in congenital nephrotic syndrome, aggressive daily albumin protocols and conservative selective use appear to achieve comparable survival (~90%), representing an ongoing unresolved clinical debate (Hölttä & Jalanko, 2020; Boyer & Bérody, 2020; Bockenhauer & Boyer, 2024). Fifth, when albumin is used, sequential administration (albumin first, then furosemide) produces superior weight loss compared to simultaneous co-infusion (Tadayoni et al., 2025). Sixth, 5% and 20% albumin at equivalent total protein mass (1 g/kg) produce comparable diuretic effects (Garg et al., 2020). Seventh, alternative colloids such as fresh frozen plasma and whole blood, as well as mannitol, may be effective substitutes when albumin is unavailable or unaffordable (Singh et al., 2021; Okoronkwo et al., 2018; Huque et al., 2014).

The Central Paradox: Physiological Plausibility versus Limited Evidence

A fundamental paradox permeates this literature: intravenous albumin in NS with hypovolemia has strong physiological rationale and produces measurable short-term improvements, yet randomized trial evidence is of very low certainty, and no study demonstrates sustained patient-centered benefits (Ho et al., 2019; Procope, 2020). This paradox is reconcilable when considering disease mechanisms. In NS, the same glomerular permeability defect that causes hypoalbuminemia also causes rapid urinary loss of any infused albumin, typically within hours (Bockenhauer & Boyer, 2024; Coulthard, 2015). Thus, while albumin transiently expands intravascular volume and enhances diuretic delivery, this effect is inherently short-lived because the infused protein is promptly lost into the urine (Ellis, 2016; Kallash & Mahan, 2020). This distinguishes NS-associated hypovolemia from other hypoalbuminemic states such as cirrhosis or critical illness, where albumin

may persist longer in circulation and the evidence base for albumin is substantially stronger (Zaman, 2013; Rozga et al., 2013; Caironi et al., 2015).

The Underfill-Overfill Distinction as the Critical Determinant

Multiple authoritative reviews converge on the underfill-versus-overfill model as the essential framework for guiding albumin use (Ellis, 2016; Jethwani & Krishnan, 2021; Meena & Bagga, 2020; Kallash & Mahan, 2020). Underfill (hypovolemic) patients, who are particularly common among children with minimal change NS and severe hypoalbuminemia (serum albumin ≤ 2 g/dL), have depleted effective arterial blood volume despite peripheral edema (Cadnapaphornchai et al., 2014). These patients exhibit characteristic biochemical markers: fractional excretion of sodium (FENa) below 0.2%, urinary potassium index ($K^+/[K^{++}Na^+]$) above 60%, elevated plasma renin activity, aldosterone, and vasopressin, with preserved or supranormal GFR (Ellis, 2016). In underfill patients, albumin volume expansion before diuretics is physiologically rational and may prevent diuretic-induced acute kidney injury (Ellis, 2016; Jethwani & Krishnan, 2021).

Conversely, overfill (hypervolemic or euvoletic) patients—more commonly adults with secondary NS, focal segmental glomerulosclerosis, or membranous nephropathy—have primary sodium retention with normal or expanded intravascular volume (Duffy et al., 2015; Cadnapaphornchai et al., 2014). These patients exhibit FENa above 0.5%, GFR below 50 mL/min/1.73 m², normal or elevated blood pressure without orthostasis, and suppressed neurohormonal markers (Ellis, 2016). In overfill patients, albumin administration may cause harm by exacerbating volume overload, hypertension, and pulmonary edema (Moiseev et al., 2024; Nawaz & Zafar, 2025). Importantly, at least two-thirds of oedematous adults with NS have normal or elevated intravascular volume, indicating that albumin should not be routinely administered to unselected adult NS patients (Jethwani & Krishnan, 2021; Duffy et al., 2015).

Despite this mechanistic consensus, none of the primary intervention trials explicitly stratified patients by underfill versus overfill status before randomization, representing a major methodological gap that likely diluted average treatment effects (Hedin et al., 2022; Ho et al., 2019). Future trials must incorporate standardized volume status assessment using validated criteria including FENa, urinary potassium index, plasma renin activity, and where available,

echocardiographic measurement of inferior vena cava collapsibility (Panda, 2019; Nishino et al., 2023).

Transience of Effect: Mechanistic and Clinical Implications

A remarkably consistent finding across multiple meta-analyses and systematic reviews is that albumin's diuretic benefit in NS is transient, peaking within 6–8 hours and not sustained at 24 hours (Kitsios et al., 2014; Lee et al., 2021; Hedin et al., 2022; Nawaz & Zafar, 2025). The Kitsios meta-analysis documented a mean urine volume increment of 231 mL (95% CI 135.5–326.5) and sodium excretion increment of 15.9 mEq (95% CI 4.9–26.8) at 8 hours with albumin plus furosemide, but no significant differences at 24 hours (Kitsios et al., 2014). Similarly, the Lee updated meta-analysis (n=422 across 13 trials) found that diuretic and natriuretic effects were more pronounced within the first 12 hours, with greater responses in patients with baseline serum albumin below 2.5 g/dL and those receiving higher albumin doses above 30 g (Lee et al., 2021). The Phakdeekitcharoen & Boonyawat (2012) RCT in hypoalbuminemic CKD adults found significant between-group differences in urine volume (0.67 ± 0.31 L vs. 0.47 ± 0.40 L increment at 6h; $p < 0.02$) that disappeared at 24 hours, supporting the generalizability of this temporal pattern beyond pure NS populations.

The clinical implication of this transience is straightforward: albumin should be reserved for acute, inpatient management of severe or diuretic-resistant edema, not as routine outpatient or ongoing therapy (Nawaz & Zafar, 2025; Procope, 2020). Repeated daily albumin infusions without addressing the underlying proteinuria are unlikely to provide sustained benefit, as the infused protein will be rapidly lost in the urine (Bockenhauer & Boyer, 2024; Ellis, 2016). Instead, efforts should focus on achieving remission of proteinuria through corticosteroids or other immunosuppressive agents, which address the root cause of hypoalbuminemia (Downie et al., 2017; Floege et al., 2025; Lal & Perveen, 2026).

Sequence of Administration: Sequential versus Concurrent

The Tadayoni et al. (2025) double-blind RCT in 64 pediatric NS patients directly compared sequential (albumin infused first, then furosemide) versus concurrent (albumin and furosemide co-infused) administration. The sequential group demonstrated statistically significantly greater weight

loss, although there was no significant difference in urinary sodium excretion between groups (Tadayoni et al., 2025). This finding provides empirical support for the sequential approach recommended in multiple clinical guidelines and consensus documents (Pasini et al., 2017; Rahman et al., 2013; Meena & Bagga, 2020).

The mechanistic rationale for sequential administration is compelling. Albumin must first expand intravascular volume and restore effective arterial blood volume before loop diuretics can be adequately delivered to the ascending limb of the loop of Henle (Duffy et al., 2015; Jethwani & Krishnan, 2021). In severe hypoalbuminemia, furosemide is poorly bound, diffuses into interstitial tissues, and undergoes rapid non-renal elimination without reaching its tubular target (Mahmoodpoor et al., 2020). Albumin pre-administration restores furosemide binding, increases renal delivery, and enhances diuretic efficiency (Phakdeekitcharoen & Boonyawat, 2012). The Mahmoodpoor et al. (2020) RCT found that urinary furosemide excretion was significantly higher in the albumin group at the 2-hour time point ($p=0.03$), supporting this pharmacokinetic mechanism, though no significant overall difference was observed across all time points.

Albumin Concentration: 5% versus 20%

The Garg et al. (2020) crossover RCT in 24 children with idiopathic NS and anasarca directly compared 5% versus 20% albumin, each at 1 g/kg total protein dose, co-administered with furosemide 2 mg/kg. The study found no significant difference in urine output increase (1.52 mL/kg/h for 5% vs. 1.66 mL/kg/h for 20%; $p=0.6$) or percentage weight loss (2.25% vs. 3.68%; $p=0.64$) between the two concentrations, with both producing significant within-group improvements (Garg et al., 2020). No volume overload complications occurred in either group. This finding suggests that total albumin mass (grams) rather than concentration is the critical determinant of effect, and that lower-concentration (5%) solutions may be equally effective while potentially offering advantages in cost and fluid balance management (Garg et al., 2020; Haynes & Bassiri, 2021).

Congenital Nephrotic Syndrome: An Unresolved Debate

Congenital nephrotic syndrome (CNS) represents the most severe end of the NS spectrum, where the debate over albumin use is most prominent and clinically consequential (Hölttä &

Jalanko, 2020; Boyer & Bérody, 2020; Bockenhauer & Boyer, 2024). The Finnish aggressive protocol, developed in the 1970s–1980s, administers 20% albumin at 1–2 g/kg/day divided into three daily infusions from birth until bilateral nephrectomy at approximately 9–14 months, followed by dialysis and transplantation (Hölttä & Jalanko, 2020). This approach dramatically improved survival from near-universal early mortality to approximately 90% (Hölttä & Jalanko, 2020; AbuMaziad et al., 2021).

However, recent large retrospective international and French nationwide studies have challenged this paradigm, demonstrating that conservative management—without routine daily albumin or early bilateral nephrectomy—achieves comparable survival rates (~90%) with less morbidity and better quality of life (Boyer & Bérody, 2020; Bockenhauer & Boyer, 2024). In the conservative approach, albumin is tapered and discontinued in a subset of patients who can be discharged home before nephrectomy, reducing hospitalization burden, central venous access complications, and the distress of prolonged hospitalization (Bockenhauer & Boyer, 2024; Reynolds & Oswald, 2019). Dufek et al. (2018), reviewing 80 European CNS children, found that in the conservative group (n=17 NPHS1 patients), 53% remained without dialysis, and outcomes regarding septic or thrombotic episodes and growth were comparable to the bilateral nephrectomy group (n=25). Furthermore, antiproteinuric treatment (RAAS inhibitors ± indomethacin) increased serum albumin by a median of 6 g/L ($p<0.001$), and unilateral nephrectomy increased serum albumin by a further 4 g/L ($p=0.03$), with a concurrent reduction in albumin infusion requirement of 5 g/kg/week ($p=0.02$) (Dufek et al., 2018). These findings suggest that targeting the source of protein losses, rather than indefinitely replacing albumin intravenously, can meaningfully reduce dependence on infusions.

Lau et al. (2014) highlight that central venous catheters required for regular albumin infusions in CNS carry substantial thrombotic and infectious risks. AbuMaziad et al. (2021) present a case in which these complications dominated the clinical course, with recurrent catheter-associated thromboses requiring sequential changes to anticoagulation regimens. The Constantinescu et al. (2022) multicenter cohort found daily albumin infusions were used in 79% of CNS and 30% of infantile NS patients in the first 2 months after diagnosis, reflecting greater

disease severity in CNS but also significant practice variation. Given the absence of RCT evidence, the aggressive versus conservative debate in CNS remains unresolved, and shared decision-making with families is essential (Bockenbauer & Boyer, 2024; Sinha et al., 2019).

Albumin versus Alternative Colloids and Strategies

Several studies have examined alternatives to albumin for managing diuretic-resistant edema in NS, particularly relevant in resource-limited settings where albumin is unavailable or unaffordable. Singh et al. (2021) compared albumin (1 g/kg/day) to fresh frozen plasma (FFP, 15 mL/kg/day) in 60 children with idiopathic NS and moderate-to-severe edema. The study found nearly identical times to achieving dry weight (albumin 6.62 ± 3.15 days vs. FFP 6.65 ± 3.18 days) with no significant complications in either group. However, FFP required significantly more infusions (3.11 ± 1.05) compared to albumin (1.42 ± 0.62 ; $p=0.0001$), and the authors noted FFP cost approximately half the price of albumin (Singh et al., 2021). FFP thus represents a clinically equivalent, cheaper alternative, though at the cost of more frequent infusions.

Okoronkwo et al. (2018) describe a Nigerian child with relapsed NS and severe refractory anasarca who could not access salt-poor albumin due to cost. Fresh whole blood (15 mL/kg aliquots over 6 hours on days 2, 4, and 6), administered with IV furosemide 60 mg given 2 hours into and immediately after each transfusion, achieved a lifesaving diuresis with weight reduction from 58 to 38 kg over the admission, normalization of creatinine and albumin (15 to 26 g/L), and remission by discharge at 2 weeks (Okoronkwo et al., 2018). The authors propose whole blood as an emergency substitute in resource-poor settings.

Huque et al. (2014) tested mannitol plus furosemide as an alternative osmotic agent in 40 children with diuretic-resistant NS edema. While albumin plus furosemide produced numerically higher urine volumes (1383 ± 949 mL vs. 928 ± 360 mL for mannitol), the difference was not statistically significant, and body weight reduction (13.74% for the mannitol group) was clinically comparable. The authors note mannitol costs less and is more widely available than albumin, making it a useful alternative in resource-limited contexts (Huque et al., 2014). These alternative strategies, while based on limited evidence, provide practical options when albumin is not accessible.

Renal Function and Safety Outcomes

Few studies reported formal GFR or creatinine changes associated with albumin in NS. The Ghafari et al. (2011) crossover RCT noted GFR values of 104.5, 96.6, and 106.6 mL/min for albumin alone, furosemide alone, and albumin plus furosemide, respectively ($p=0.021$), suggesting that the combination modestly restored GFR above furosemide alone in normal-GFR NS patients. The Phakdeekitcharoen & Boonyawat (2012) study documented an approximately 10% GFR decline at 6 hours in both treatment arms, attributed to volume contraction from acute diuresis, without reaching a level suggesting acute kidney injury (AKI). Ellis (2016) provides the clearest mechanistic framework: in underfill NS, hypovolemia itself is the driver of reduced effective renal perfusion, and correcting this with albumin volume expansion supports GFR and avoids diuretic-induced AKI. Conversely, aggressive diuresis in the absence of adequate intravascular filling is a recognized cause of AKI in these patients (Ellis, 2016; Jethwani & Krishnan, 2021; Wiedermann et al., 2017).

Safety data across NS studies were systematically reported but limited in quantity. The most commonly cited risks of albumin infusion in NS are volume overload, pulmonary edema, and hypertension (Nawaz & Zafar, 2025; Moiseev et al., 2024; Pasini et al., 2017). The Nawaz & Zafar (2025) systematic review noted, from observational studies outside the included RCT, that nearly half of reported albumin infusion episodes in children with NS were associated with acute hypertension, and at least one case of congestive heart failure was reported. Ellis (2016) identified infection transmission risks (albumin is a blood product) and tissue allosensitization as additional concerns. In direct comparative trials, no major albumin-related adverse events were reported: Garg et al. (2020) found no hypertension, pulmonary edema, or need for dialysis; Singh et al. (2021) reported no significant complications in either the albumin or FFP group; Tadayoni et al. (2025) observed no drug-associated adverse effects; Ghafari et al. (2011) and Kanzaki et al. (2012) both reported no adverse effects.

Real-World Prescribing Patterns and Appropriateness

Several utilization studies document that albumin is frequently used for childhood NS in clinical practice, though inappropriate use is common. Tameez Ud Din et al. (2023) reported that

childhood nephrotic syndrome accounted for 4.1% (685 of 16,772 infusions) of 20% human albumin solution use at a large UK tertiary referral center over 8 years, placing it sixth among clinical indications. Coyle & John (2021) found that nephrosis or nephropathy was the indication in 10.8% of albumin prescriptions in a community hospital, and the overall rate of appropriate albumin use was 67.7%. Ala et al. (2015) found that albumin was used appropriately in only 63% of patients at an Iranian teaching hospital. Zolfagharian et al. (2017) showed that a guideline intervention modestly reduced inappropriate use without reaching statistical significance, though it significantly reduced inappropriate dose and duration and reduced average cost per patient from USD 317.78 to USD 149.81. Castillo et al. (2018) found 45% of albumin prescriptions at an academic medical center were inappropriate by national guidelines, with an estimated cost of approximately USD 13,000 for the 150-patient cohort. These findings indicate substantial opportunities for improving evidence-based albumin prescribing through guideline implementation and educational interventions.

Comparison with Evidence from Related Populations

The broader albumin literature in non-NS hypoalbuminemic populations provides supporting mechanistic context but also highlights condition-specificity. The Faltys et al. (2026) systematic review of albumin co-administration with diuretics in critically ill patients found no significant difference in average daily net fluid balance (mean difference -0.22 L/d; 95% CI -0.88 to 0.43), with high heterogeneity among the four available studies, suggesting that the fluid de-resuscitation benefit documented in some studies is not consistent across ICU populations. The Oczkowski & Mazzetti (2014) systematic review found that albumin plus furosemide improved net fluid balance at 3 days in an ARDS population (-5.48 L vs. -1.49 L with albumin; $p < 0.01$) but found no improvement in a CHF population, again illustrating condition-specificity. Roberts et al. (2011), in the largest meta-analysis of albumin for resuscitation in critically ill patients ($n=10,842$ across 38 RCTs), found no reduction in mortality across hypovolaemia, burns, or hypoalbuminaemia populations (pooled RR 1.05, 95% CI 0.95–1.16), though this review addressed mortality rather than volume management. The CRISTAL trial (Annane et al., 2013), the largest trial of colloids versus crystalloids in hypovolemic shock ($n=2,857$), found no significant difference

in 28-day mortality, though 90-day mortality was lower in the colloid group (30.7% vs. 34.2%; RR 0.92, 95% CI 0.86–0.99). Albumin represented only a fraction of the colloids used, and NS patients were not a defined subgroup.

Strengths of This Review

This systematic review has several strengths. It synthesizes evidence from 80 diverse sources, including recent 2024–2026 publications, providing the most up-to-date comprehensive overview. It specifically focuses on the hypovolemic NS subpopulation, addressing the underfill-overfill distinction as a central organizing theme. It includes detailed thematic analyses of albumin as a pharmacological carrier for furosemide, the CNS management debate, and resource-limited setting alternatives. It quantitatively synthesizes the temporal pattern of albumin's effects across multiple meta-analyses. It evaluates practical implementation issues including prescribing patterns, guideline adherence, and cost-effectiveness.

Implications for Clinical Practice

Despite these limitations, several practical recommendations emerge. First, albumin should not be used routinely in all NS patients with edema. It should be reserved for patients with confirmed hypovolemia (underfill physiology) as evidenced by FENa <0.2%, urinary K⁺/(K⁺+Na⁺) >60%, serum albumin ≤2 g/dL, and clinical signs of reduced effective arterial volume (Ellis, 2016; Jethwani & Krishnan, 2021; Meena & Bagga, 2020). Second, when albumin is used, it should be administered sequentially (albumin first, then furosemide) rather than concurrently, based on the Tadayoni et al. (2025) RCT showing superior weight loss with sequential administration. Third, the total albumin dose (grams) appears more important than concentration; 5% and 20% solutions at equivalent protein mass (e.g., 1 g/kg) produce comparable effects (Garg et al., 2020). Fourth, albumin is best used as a short-term, acute inpatient intervention for severe or diuretic-resistant edema, not as chronic outpatient therapy, given the transient nature of effect (Nawaz & Zafar, 2025; Kitsios et al., 2014). Fifth, in congenital NS, shared decision-making between aggressive daily albumin protocols and conservative selective use is essential, as retrospective data suggest comparable survival (~90%) with both approaches (Bockenhauer & Boyer, 2024; Boyer & Bérody, 2020; Hölttä & Jalanko, 2020). Sixth, when albumin is unavailable

or unaffordable, FFP, whole blood, or mannitol may serve as effective alternatives (Singh et al., 2021; Okoronkwo et al., 2018; Huque et al., 2014). Seventh, efforts to achieve remission of proteinuria through corticosteroids and immunosuppressive agents remain the primary treatment, as albumin is purely supportive and does not address the underlying cause of hypoalbuminemia (Downie et al., 2017; Floege et al., 2025; Verma & Patil, 2024).

Implications for Future Research

This review identifies several critical knowledge gaps requiring future research. First, an adequately powered, multicenter, parallel-group RCT in pediatric NS with confirmed hypovolemia (underfill physiology) is urgently needed, comparing albumin plus furosemide to furosemide alone, with stratification by volume status using standardized laboratory and imaging criteria (Hedin et al., 2022; Ho et al., 2019; Nawaz & Zafar, 2025). Second, such trials should measure both short-term physiological endpoints (urine output, FENa, weight loss at 6, 12, 24 hours) and patient-centered outcomes (length of hospitalization, time to edema resolution, quality of life, adverse events, cost-effectiveness) over at least 7–10 days. Third, in congenital NS, a prospective registry or randomized trial comparing aggressive versus conservative albumin protocols is needed, with outcomes including survival, infection rates, thrombosis, growth parameters, hospitalization duration, and quality of life (Bockenbauer & Boyer, 2024; Dufek et al., 2018). Fourth, further research on alternative colloids (FFP, whole blood) and osmotic agents (mannitol) in resource-limited settings is warranted, including cost-effectiveness analyses. Fifth, implementation science studies evaluating guideline adherence interventions to reduce inappropriate albumin use and associated costs are needed (Zolfagharian et al., 2017; Castillo et al., 2018). Sixth, the role of bioelectrical impedance analysis (BIA) and echocardiographic inferior vena cava collapsibility index in guiding real-time albumin administration decisions requires further validation (Nishino et al., 2023; Panda, 2019).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 80 sources evaluating albumin use in nephrotic syndrome with hypovolemia yields several definitive conclusions. First, the direct evidence base is remarkably

sparse, with only one small, high-risk-of-bias RCT directly informing Cochrane reviews, representing a very low certainty of evidence for all outcomes (Ho et al., 2019; Nawaz & Zafar, 2025). Second, albumin co-administered with furosemide produces statistically significant increases in urine output and sodium excretion compared to furosemide alone, but these effects are consistently transient—peaking at 6–8 hours and typically disappearing by 24 hours (Kitsios et al., 2014; Lee et al., 2021; Hedin et al., 2022). Third, the underfill-versus-overfill distinction is the central determinant of albumin utility; albumin should only be considered in patients with confirmed hypovolemia ($\text{FENa} < 0.2\%$, urinary $\text{K}^+ / (\text{K}^+ + \text{Na}^+) > 60\%$, serum albumin ≤ 2 g/dL) (Ellis, 2016; Jethwani & Krishnan, 2021). Fourth, sequential administration (albumin first, then furosemide) produces superior weight loss compared to simultaneous co-infusion (Tadayoni et al., 2025). Fifth, 5% and 20% albumin at equivalent total protein mass (1 g/kg) produce comparable diuretic effects (Garg et al., 2020). Sixth, in congenital nephrotic syndrome, aggressive daily albumin protocols and conservative selective use achieve comparable survival (~90%), representing an unresolved clinical debate requiring shared decision-making (Bockenbauer & Boyer, 2024; Boyer & Bérody, 2020; Hölttä & Jalanko, 2020). Seventh, alternative colloids (fresh frozen plasma, whole blood) and osmotic agents (mannitol) may be effective substitutes when albumin is unavailable or unaffordable (Singh et al., 2021; Okoronkwo et al., 2018; Huque et al., 2014). Eighth, safety outcomes show low rates of serious adverse events in clinical trials, but observational data document risks of hypertension, volume overload, and pulmonary edema (Nawaz & Zafar, 2025; Moiseev et al., 2024; Ellis, 2016). Ninth, real-world prescribing studies indicate that 33–45% of albumin use is inappropriate, highlighting opportunities for guideline implementation and cost reduction (Castillo et al., 2018; Ala et al., 2015; Zolfagharian et al., 2017).

Recommendations

For clinical practice: Albumin should be reserved for acute inpatient management of NS patients with confirmed underfill physiology and severe or diuretic-resistant edema, administered sequentially (albumin then furosemide) at 0.5–1 g/kg of 20–25% albumin (or equivalent protein mass as 5% solution), with careful monitoring for volume overload and hypertension. Routine

outpatient or chronic albumin therapy is not supported by current evidence. Primary treatment efforts should focus on achieving remission of proteinuria through immunosuppressive therapy.

For policy and formularies: Hospitals should implement evidence-based guidelines for albumin use, including prospective audit and feedback, to reduce inappropriate prescribing and associated costs. Alternatives such as FFP or mannitol should be considered in resource-limited settings.

For future research: An adequately powered, multicenter RCT in pediatric NS with confirmed hypovolemia, comparing albumin plus furosemide to furosemide alone, with stratification by volume status and measurement of patient-centered outcomes, is urgently needed. A prospective registry or randomized trial comparing aggressive versus conservative albumin protocols in congenital NS is also required.

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