Current Pediatrics Reports (2022) 10:182–194
https://doi.org/10.1007/s40124-022-00270-3

RENAL (D NOONE, SECTION EDITOR)

Management of edema in pediatric nephrotic syndrome – Underfill or overfill?

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Accepted: 4 August 2022 / Published online: 25 August 2022

Abstract

Purpose of review To explore the mechanisms underlying edema formation in nephrotic syndrome. We highlight new methods of volume assessment and a stepwise approach to the management of edema.

Recent findings New tools are available for intravascular volume assessment. New medications and modalities have been developed for the management of edema.

Summary Edema is a major feature of nephrotic syndrome in children. It can be secondary to multiple mechanisms. Regardless of the causing mechanism, targeted management of edema should be guided by an adequate assessment of the intravascular volume. Urine studies e.g. urine sodium and potassium, as well as echocardiogram, can prove to be valuable tools. Besides diuretics, new agents and modalities are being developed for edema management including Aquaretics and isolated ultrafiltration.

Keywords Edema · Nephrotic syndrome · Fluid overload · Sodium retention

Introduction

Edema is a presenting feature of nephrotic syndrome (NS) in children and is first noticed in the periorbital area. Kidney Disease Improving Global Outcomes (KDIGO) guidelines define NS as having edema, urine protein/creatinine ratio ≥2 mg/mg, and hypoalbuminemia ≤ 2.5 g/dl. Edema manifests in the form of weight gain and is worse in the lower limbs. It can be local or generalized and may progress to pleural and pericardial effusions, ascites, scrotal or labial edema, anasarca, and bowel wall edema. Edema can significantly affect the quality of life of children by causing pain, fatigue, anxiety, and discomfort which adds a psychological burden [1, 2].

The main treatment for NS is steroids. Known complications of NS include increased risk of thrombosis, infections, and possibly acute kidney injury in case of severe volume depletion. However, addressing edema and the complications associated with it is paramount especially when severe and causing significant discomfort. Severe persistent edema is accentuated in children who fail to respond to steroids.

Understanding the mechanisms involved in the development and worsening of edema in children with NS is essential in making management decisions. Therefore, we designed this review to: (I) describe the currently known mechanisms of edema formation in NS, (II) define the factors involved in sodium retention in NS, and (III) identify the management options for children with edema and NS

Mechanisms of edema formation in nephrotic syndrome

Proposed mechanisms

There are two proposed hypotheses to explain edema formation in patients with NS. The "underfill hypothesis" has been the prevailing one for decades. It suggests that a decrease in capillary oncotic pressure (secondary to hypoalbuminemia due to albuminuria) leads to leakage of fluids to the interstitium. The resultant hypovolemia reduces the effective renal blood flow and, therefore, activates the

This article is part of the Topical Collection on *Renal*

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renin-angiotensin-aldosterone system and arginine vasopressin. The result is salt and water retention. It is believed that this is the main mechanism in patients who have massive proteinuria, marked hypoalbuminemia, minimal or no renal inflammation, and normal kidney function as is the case in children with minimal change NS [3].

On the other hand, the "overfill hypothesis" proposes that the main drive for edema formation is salt and water retention occurring secondary to a reduced filtered load of sodium. Though this is understandable in the setting of reduced GFR or renal inflammation, it has also been demonstrated to occur as a primary mechanism in patients with NS due to increased activation of epithelial sodium channels (ENAC) in the collecting ducts, which results in sodium retention. This occurs despite initial hypoalbuminemia. The intravascular volume is preserved or expanded in this hypothesis [4].

Body fluid compartments and fluid transport

Total body water (TBW) is distributed into intracellular and extracellular compartments. The latter forms around one-third of TBW and is divided into interstitial fluid and intravascular plasma. The role of the interplay between hydrostatic and oncotic pressures of the capillary and interstitium in determining the movement of fluids between the different compartments in the body was described by Starling in 1896 after an experiment that he performed on dogs [5].

The following equation has served as the basis of our understanding of fluid transport for several decades:

$$Jv = Kf\ ([Pc - Pi] - \sigma[\pi c - \pi i])$$

Where Jv is the net fluid transport, Kf is the hydraulic permeability coefficient, Pc the capillary hydrostatic pressure, Pi the interstitial hydrostatic pressure, σ the reflection coefficient to proteins, πc the capillary oncotic pressure, and πi the interstitial oncotic pressure.

For decades, the prevailing theory to explain molecular transport exchange across the capillary wall was the "pore theory" [6]. In 1980, Curry and Michel proposed the "fiber matrix theory" as an alternative to the "pore theory" as they highlighted the role that the matrix of glycoprotein chains has in determining capillary permeability [7, 8]. Further studies laid the basis for the revised Starling equation which differs from the original one in that the oncotic pressures involved are those of the endothelial surface layer (πesl) and the area beneath it which is the sub-glycocalyx (πb) rather than those of the capillary and the interstitium [9–11].

$$Jv = Kf\left([Pc - Pi] - \sigma[\pi es| - \pi b]\right) \text{ [12]}$$

The reflection coefficient (σ) of a substance reflects its permeability through the capillary membrane. A σ of 1 means that the substance would not pass, while a σ of 0 means that it is completely permeable [13]. Studies have shown that the σ of albumin decreases in response to inflammation or injury [14, 15] and is mediated by inflammatory mediators e.g. histamine and bradykinin [16]. Kf is the product of the capillary surface area and the hydraulic conductance. Kf has been shown to increase in cases of hyperglycemia or high intravascular pressure [17, 18]. Both Kf and σ reflect vascular permeability. The current understanding of the role of the glycocalyx in fluid transport explains the changes in vascular permeability occurring as a result of glycocalyx injury after ischemia-reperfusion [19], TNF-alpha release as is the case in sepsis [20], hypervolemia secondary to ANP release [21] and hyperglycemia [22]. More importantly, is the impact that this has on our understanding of the fluid distribution in different tissues in different disease states and on the varied response to fluid therapy. Fluid distribution depends on the type of capillaries present in a tissue (continuous, fenestrated, or sinusoidal) [12].

Applications of these principles in nephrotic syndrome

Changes in the aforementioned factors that comprise the Starling equation explain the edema state occurring in patients with NS.

Changes in the capillary oncotic pressure (πc)

The basis of the "underfill hypothesis" is that a decrement in capillary oncotic pressure (πc) relative to the interstitial oncotic pressure (πi) results in an exodus of fluids from the intravascular compartment to the interstitium. However, studies performed in the 1980s using the wick technique to measure the interstitial fluid oncotic pressure have shown a parallel decrease in this pressure compared to the capillary pressure in NS patients [23, 24]. It is possible that fluid released in the interstitial space reduces the concentration of the proteins and then increases their clearance via lymphatics [25–27]. This is a protective mechanism occurring in slowly developing hypoalbuminemia and serves to preserve the intravascular compartment and reduce edema formation. No studies were done after the release of the revised Starling equation.

Changes in hydrostatic pressure gradient between the capillary and interstitium

Researchers have tried to estimate the blood volume in NS patients as this may help support one of the two hypotheses for edema formation. Geers et al. attempted to measure blood volume (BV) and extracellular fluid volume (ECFV)

using 131I-albumin and 82Br, respectively, in 20 adult NS patients before, during, and after treatment of edema with diuretics. Blood volume remained intact despite the decrease in ECFV as the edema resolved. Plasma renin activity (PRA) increased as ECVF decreased, however, PRA at baseline was higher in NS patients compared to controls [28]. A similar study in adults showed no difference in BV in NS patients compared to controls [29]. These studies argue against the underfill hypothesis as the BV was maintained though the patients had hypoalbuminemia. Using a similar technique, a third study in 43 children with NS who were divided into 4 groups: remission, incipient nephrotic (normal serum albumin), symptomatic active nephrotic, and active nephrotic without hypovolemic symptoms. Patients with active NS had only slightly lower BV compared to patients in remission. Blood volume was similar in both groups and the study concluded that the development of these symptoms reflects the rate of edema formation rather than the actual BV. The mean levels of plasma norepinephrine, renin, and aldosterone were higher in the symptomatic nephrotic group compared to the asymptomatic one [30, 31]. Similarly, at an experimental level, rapid severe hypoproteinemia -induced by plasmapheresis with isotonic fluids in dogs- resulted in a decrease in BV and a rise in plasma renin and aldosterone [32]. The blood volume is decreased either in case of rapidly developing edema or possibly if there are acute fluid losses e.g. aggressive diuretic use, diarrhea, or vomiting.

Mechanisms for sodium retention in NS (Fig. 1)

Renin-angiotensin-aldosterone system (RAAS) activation

The RAAS activation regulates blood pressure and ECFV. The Underfill hypothesis suggests that the activation of the renin-angiotensin-aldosterone system is secondary to hypovolemia. The previously described study done by Vande Walle et al showed elevated levels of renin-aldosterone and norepinephrine in patients with active nephrotic syndrome with hypoalbuminemia compared to patients with incipient NS or in remission. However, the levels were only significantly higher in those with symptoms of hypovolemia [30]. An early study done in 12 NS patients of ages ranging between 12-60 years with idiopathic NS showed that the PRA and aldosterone were elevated in the NS patients, while BV -as measured by chromium tagged RBCs- was only mildly elevated compared to controls [33]. A more recent study compared the results of aldosterone levels at debut and remission in 20 patients with childhood nephrotic syndrome. The group that had significantly higher aldosterone levels at debut did not show symptoms of hypovolemia, but the estimated GFR was significantly lower possibly due to hypovolemia [34]. Another study confirmed the finding of elevated aldosterone, renin, and norepinephrine in children with non-MCD but only those presenting with symptoms of hypovolemia [35]. It can be concluded that the levels of these hormones -PRA and aldosterone- are elevated in cases of "symptomatic' hypovolemia but not in stable patients with hypoalbuminemia.

Renal sympathetic stimulation

Sympathetic stimulation causes salt retention both directly and through stimulation of renin release (See Fig.1). The above-mentioned studies demonstrate evidence of sympathetic stimulation in some patients with active NS especially when symptoms of hypovolemia are present [30, 35].

Atrial natriuretic peptide (ANP)

ANP is released in response to volume overload manifested in the form of atrial stretch. It then acts as a counter-regulatory hormone that promotes natriuresis. The prevailing understanding is that in NS there is a blunted response to the effect of ANP even when it is elevated. In a study that was done on 31 adult patients with NS and primary GN, the ANP levels were elevated at baseline compared to controls [36]. It has been suggested that the blunted response is due to enhanced cGMP-phosho-di-esterase activity [37]. In a study of childhood NS, ANP levels were the highest in the active NS patients followed by those in remission and then controls. Urinary sodium levels were significantly lower in those with active NS. Certain polymorphisms for the genes controlling ANP: ANP gene (A2843G), the natriuretic peptide clearance receptor (NPRC) gene polymorphism C (-55) A, and ScaI polymorphism of ANP gene were studied in both active NS patients and those in remission but there were no significant differences in their frequencies [38].

The role of Corin

Corin is a transmembrane protease that cleaves pro ANP and pro Brain natriuretic peptide (pro-BNP) to the active forms. A decrease in corin expression has been shown in puromycin aminonucleoside (PAN)-induced nephrosis rat models [39]. A reduction in corin would lead to salt and water retention. Data in humans suggest that corin defects may be linked to hypertension and heart failure [90, 93].

Arginine vasopressin (AVP)

Earlier studies have shown that AVP levels were higher in NS patients compared to controls both at baseline state [40] and after water loading [41]. AVP levels in NS patients remained high after water loading but decreased after

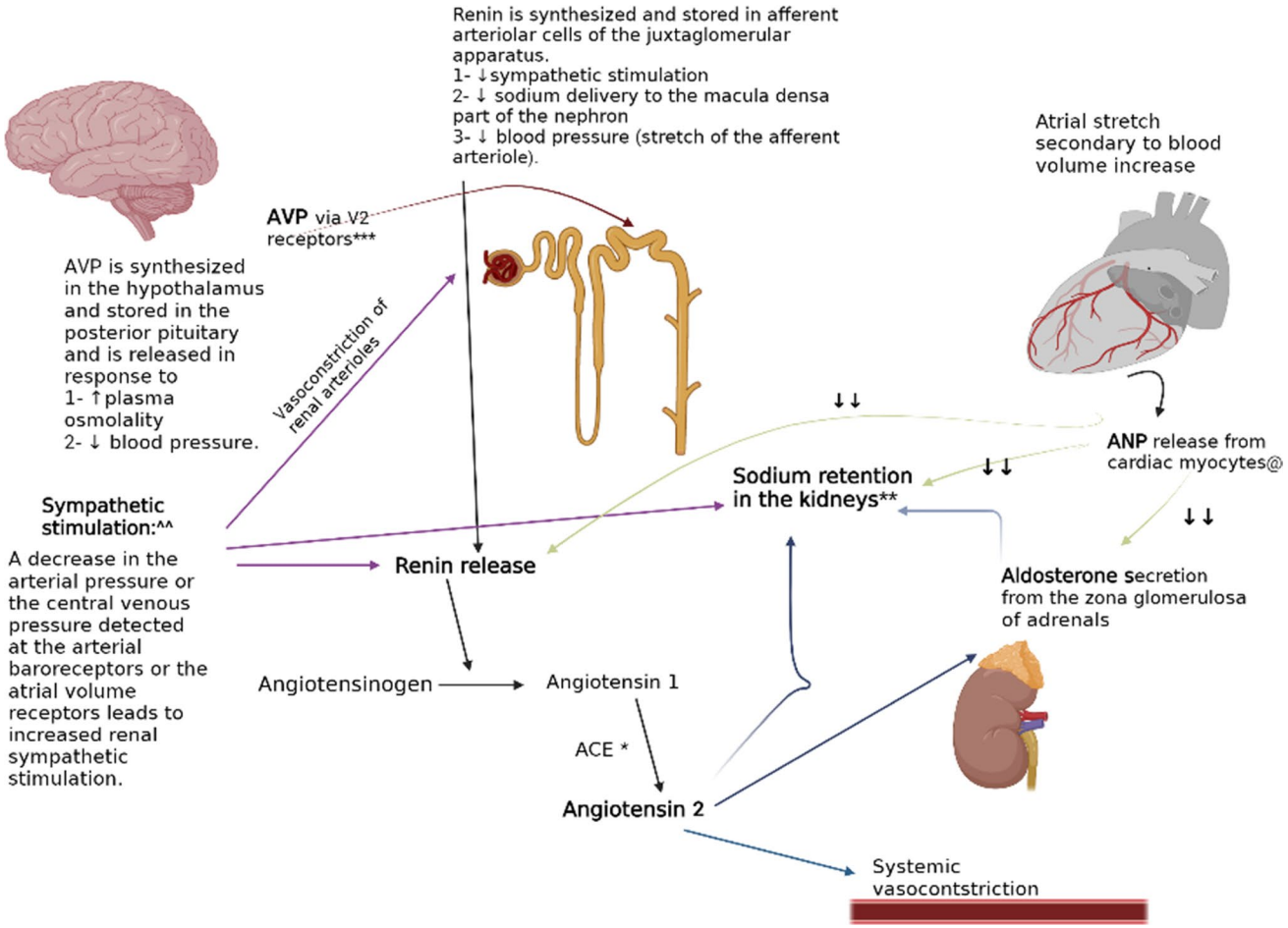

Fig. 1 Mechanisms of sodium retention and natriuresis. *ACE* Angiotensin converting enzyme. ** Sodium retention mechanism: Angiotensin 2 acts on the proximal tubules and the thiazide-sensitive NaCl channels in the distal tubules [92]. Aldosterone acts on the mineralocorticoid receptors within the principal cells of the distal tubules and collecting ducts. Sodium reabsorption is then stimulated secondary to upregulation of the basolateral Na/K pump as well as the ENaC channels in the collecting ducts. Aldosterone also increases sodium absorption from the gut. Sympathetic stimulation acts on the proximal tubules and thick ascending limb of Henle [36]. *** AVP action on the kidney is mediated by the V2 receptors located in the basolateral membrane of the principal cells in the late distal tubule and collecting duct [36]. Activation of V2 receptors leads to insertion of aquaporin2 (AQP2) channel into the apical membrane and consequently water reabsorption. ^^ Sympathetic stimulation causes vasoconstriction of afferent and to a lesser extent efferent arteriole. @ ANP suppresses Aldosterone release, sodium retention in the kidneys and renin release

albumin 20% infusion [42]. A more recent study confirmed the AVP activation in adults with NS as the levels of copeptin, which is the glycosylated peptide of the C-terminal area of the AVP precursor, were found to be elevated. Copeptin is more stable than AVP and is considered a marker of AVP release [43].

Aquaporin

The action of AVP is mediated by the V2 receptors whose activation leads to the insertion of Aquaporin 2 (AQP2) into the apical membrane of principal cells resulting in increased water reabsorption. In addition to AQP2, other aquaporins are found in the kidney (AQP1, AQP3, AQP4). AQP1 is responsible for permanent high water permeability and is present in apical and basolateral membranes of proximal tubules and the descending limb of the loop of Henle [33]. Studies done in rats have shown decreased expression of AQP2, 3, and 4 in the collecting ducts in response to Adriamycin injections [44]. Urinary AQP2 was found to be elevated along with copeptin in adults with NS [43]. However, further studies are needed to ascertain whether the increase in AQP2 is a direct result of high AVP or "an escape mechanism" to counteract the elevated levels and avoid excessive water reabsorption.

Primary sodium retention

Ichikawa et al demonstrated in PAN-induced NS rats persistent sodium retention despite normal GFR suggesting that

the mechanism for sodium retention was related to renal handling of sodium rather than to reduced GFR [45]. Kim et al showed increased abundance and apical targeting of the γ-subunit of ENaC in the same rat model, however, the aldosterone level was elevated in this experiment [46]. Other studies in the same rat model showed increased activity and expression of Na/K ATPase in the cortical collecting ducts [47] and that it is independent of aldosterone [48]. ENaC channels undergo activation by serine proteases mainly plasmin [49]. In rats, cleavage of the γ-subunit of ENaC is increased in pathological states with proteinuria. Plasminogen filtered due to proteinuria is activated by urokinase released from the tubular epithelium [50, 51]. In patients with type 1 diabetes, a high level of urinary plasminogen was found to be a risk factor for hypertension supposedly because of salt retention and volume expansion [52]. This suggests that sodium retention may be linked to albuminuria itself rather than hypovolemia. Increased urinary plasminogen-plasmin was found to be a risk factor for edema in adult patients with NS [53]. In another study, ACEi did not promote natriuresis despite the reduced level of aldosterone [54].

Approach to a child with edema and nephrotic syndrome (Table 1)

The possible mechanisms of edema that we have discussed so far show that the underfill and overfill hypotheses can be seen as "dynamic states" rather than a sole mechanism for each patient. A patient can have "underfill", in other words, low intravascular volume initially if edema develops too fast or if subjected to volume losses (e.g. diarrhea). Blood volume can be stable despite hypoalbuminemia and the presence of edema. Patients can shift into an "overfill" i.e., volume expansion state if renal impairment is superimposed. Thus, when approaching a child with NS, it is important to view this as a quest to accurately estimate intravascular volume. The appropriate management relies on accurate determination of the intravascular volume.

Several tools can be used to assess intravascular volume. The first is the clinical assessment. Whenever there are signs of hypovolemia (volume contraction), it is advisable to use other complementary tools to assess the volume status of children (as outlined in Table 1).

Non-invasive techniques for volume assessment

- Point of care echocardiography has been increasingly used to assess volume status both in the emergency room and ICU settings. Estimation of changes in cardiac output and stroke volume occurring 1 to 2 minutes after passive leg raising (PLR) is used to check for fluid responsiveness [55]. Several studies have applied this tool to childhood NS. An early study showed no difference in inferior vena cava (IVC) collapsibility index and left atrial diameter (LAD) in children with NS and different grades of edema despite the presence of elevated levels of aldosterone and renin initially [56]. LAD was found to be significantly lower in hypovolemic children with active INS in a more recent study [57]. In a third study, IVC diameter and LAD along with plasma renin and aldosterone were used to assess volume status in 19 patients with NS before treatment and while in remission. The results of the hormones and the echo parameters were not statistically significant [57]. More studies are needed in patients with NS to determine if echocardiography can be used in this population for intravascular volume assessment.

Bioelectrical impedance

Water in the extra and intracellular compartments contains ions. The conductance or resistance to different frequencies will depend on the composition of the various tissues. Single-frequency bioelectrical impedance analysis and Bioimpedance spectroscopy (BIS) have been used to estimate total body water and intracellular body water using mathematical models [58]. They were validated against the standard radioisotope dilution methods [59]. BIS showed increased ECW in active NS compared to those in remission [60]. It should be noted that the provided data do not discern the different compartments of extracellular water.

Management of edema in nephrotic syndrome

Edema management in many cases is a temporizing measure to relieve symptoms. Steroids and other immunomodulators -which are utilized to induce remission and reduce proteinuria- are the most effective ways to control edema.

1- General measures when managing edema in children with NS

- Maintaining activity and exercise as able will decrease the risk of thrombosis and help mobilize fluids.
- Family education

Initial and ongoing family education on NS is critical. Regular monitoring of weight, blood pressure, and urine output at home is recommended. The managing physician should be notified if symptoms of palpitation or orthostatic dizziness develop. Children are at risk of infections, so fevers and fluid losses e.g., diarrhea or vomiting should also be reported.

Table 1 Clinical and investigational tools to differentiate states of intravascular volume depletion and expansion

	Intravascular volume contraction (hypovolemia)	Intravascular volume expansion (hypervolemia)	Mechanism	Comments
Clinical features	Pallor, orthostatic hypotension, tachycardia, abdominal pain, cold peripheries	Findings of pulmonary edema, hypertension	A decrease in arterial pressure or central venous pressure leads to sympathetic stimulation.	Symptoms of hypovolemia did not correlate with measured BV and aldosterone levels in one study. Symptoms may be related to the acuity of development of hypoalbuminemia [27]
	Oliguria	Variable		Though the urine output should be maintained if the intravascular compartment is replete, the presence of associated renal inflammation or injury may affect it.
Laboratory				
Serum sodium	Increasing Na levels compared to previous values	Decreasing Na levels compared to previous values		Hyponatremia can also be pseudohyponatremia (due to hyperlipidemia) or 2ry to diuretic use. Measuring the serum osmolality and comparing the result to the calculated serum osmolality can help differentiate true from pseudo hyponatremia.
Hematocrit	Elevated Hct compared to recent values	Lower Hct compared to previous values		
Serum albumin	< 2 g/dl [3]	>2 g/dl [3]		
Norepinephrine, renin, aldosterone and ADH	High [3, 37, 63••]	Low [3, 37, 63••]	RAAS activation as a result SNS* stimulation and reduced stretch of afferent arteriole.	ACEi, ARBs**, β-blockers, diuretics and aldosterone antagonists can affect the levels of renin and aldosterone.
Urinalysis	No hematuria or pyuria	May show hematuria or cellular casts denoting GN***		As mentioned previously, intravascular volume may be increased in adults with NS or those with renal impairment and GN.
Urinary sodium	Low FeNa < 0.2 [63••]	Normal FeNa >0.2-0.5 [63••]	Activation of RAAS occurs in hypovolemia.	This can be confounded by diuretic use.
UK/UNa+UK	>0.46[73]	< 0.46[73]	Urinary potassium correlates with aldosterone level. Aldosterone is elevated in hypovolemia [32]	Affected by diuretic use.

**SNS* Sympathetic nervous system

***ARBs* Angiotensin receptor blockers

****GN* Glomerulonephritis

– Adjunctive therapies

In some conditions with persistent proteinuria despite immunosuppressive treatment or with persistent low-grade proteinuria, ACEi or ARBs are used to reduce proteinuria and so preserve the renal function in the long term. Regular safety monitoring after starting these drugs is recommended (urine output, creatinine, K). Though not directed specifically at edema management, they can help minimize edema by reducing proteinuria [57].

– Avoiding nephrotoxic medications including NSAIDs as these medications not only predispose patients to the development of AKI (especially during intravascular depletion) but can also worsen fluid overload.

2- Diet

The first dietary modification recommended is salt restriction. The recommended salt intake for age is: 1–2 mEq/day for infants up to 6 months, 370 mg/day 6–12 months, 1 gm /day for children 1–3 years of age, 1.2 gm/day for 4–8 years and 1.5 gm/day for 9–18 years [62]. Children with NS are advised to eat 130–140% of the recommended daily protein intake for their age to make up for the urinary losses. Protein intake of 3-4gm/kg/day had been recommended in the past, however, it was noted to accelerate glomerular injury [63••]. The intake of foods rich in saturated fats and trans-fats should be reduced as they have been associated with inflammation. Carbohydrates should be in the form of starch or dextrin maltose but not sucrose as it increases lipid abnormalities [64]. Water restriction may only be needed in case of severe confirmed hyponatremia (< 125 meq/L) [64]. For those with persistent proteinuria, in addition to the initial dietary assessment, ongoing assessment should be done monthly in infants then every 3 months [65••]. For infants with congenital nephrosis, a high intake of calories (130 Kcal/kg/day) and proteins (4 g/kg/day) is recommended [65••]. In the presence of mild edema (< 7% weight gain), salt restriction might be enough [66••].

3- Medications

Medications targeted at edema or fluid management are only indicated in certain situations (see Table 1):

1- Symptoms of significant hypovolemia (Intravascular volume depletion) e.g. tachycardia, hypotension, oliguria (which may denote developing AKI) especially if occurring after fluid losses or excessive use of diuretics.
2- Symptoms of significant hypervolemia e.g. respiratory distress with physical findings of pulmonary edema, heart failure, and hypertension.
3- Distressing edema: ascites impairing daily activities, severe scrotal or labial edema, edema interfering with mobility or sleep.

Diuretics (Table 2)

Diuretics are indicated in the presence of symptoms or evidence of hypervolemia. They can also be used for symptomatic management of edema if there is significant (>7%) weight gain. Before deciding to use a diuretic, providers should exclude intravascular depletion using the methods described above. The use of diuretics alone in patients with increased intravascular volume is safe, effective, can prevent readmissions and improve the quality of life [67]. Oral Furosemide may initially be used at a dose of 1–4 mg/kg/day along with salt restriction. Spironolactone 2–3 mg/kg/day or amiloride 0.2–0.5 mg/kg/day may be added if there is poor response to furosemide. If refractory edema is present, one alternative is adding another diuretic e.g., metolazone 0.2–0.4 mg/kg/day or hydrochlorothiazide 1–2 mg/kg/day or IV Furosemide 1–2 mg/kg/Q12 hours may be used. The other alternative, or if there is a poor response, is to administer IV albumin 20% (or 25%) 0.5–1 g/kg with IV furosemide 1–2 mg/kg/dose at the end of the infusion [66••].

For infants with congenital nephrosis, diuretics should be given with caution and stopped in case of anuria. In most cases, they can improve diuresis and allow the provision of adequate nutrition. Furosemide 2–5 mg/kg/day PO (max 10 mg/kg/day) is usually given in combination with a thiazide or a potassium-sparing diuretic (preferably amiloride) [65••].

Furosemide resistance is defined as an absence of diuresis 2-4 hours after an oral dose. This may be due to poor adherence to salt restriction, decreased bioavailability due to gut edema, severe hypoalbuminemia, hypovolemia, or salt reabsorption in the distal tubule. Furosemide is >90% albumin-bound, so in cases of severe hypoalbuminemia (< 2 g/dl) it diffuses into the tissues and fewer amounts are filtered through the glomerulus to reach their binding sites in the kidney tubules [68]. Furosemide is also bound to the albumin that is filtered which may decrease its activity, however, inhibition of this binding with sulfisoxazole did not show any benefit [69].

Adding a thiazide provides the benefit of "double block" given that their action is on the distal tubules.

Given the evidence that ENaC channels are activated during active NS, the use of amiloride may be beneficial. In mouse models, amiloride was found to decrease the sodium absorption from the collecting tubules regardless of the level of aldosterone [70]. Amiloride was noted to have an added benefit as an antiproteinuric. Adding Amiloride to ACEi and ARBs in a group of 14 children with SRNS reduced proteinuria [71]. However, another study in adults concluded

Table 2 Drug therapy in Nephrotic syndrome

	Mechanism of action	Dose	Special side effects	Comments
Furosemide	Inhibits the Na/K/2Cl channel in the ascending limb of the loop of Henle.	PO: 0.5-4 mg/kg. Max is 6 mg/kg/day IV: 1-2 mg/ kg/dose up to Q6 hours.	Hypokalemia, hypomagnesemia, hypocalcemia, hypercalciuria (may lead to kidney stones or nephrocalcinosis) and hypersensitivity reactions [79]	-More potent compared to thiazide diuretics but shorter duration of action which may lead to compensatory sodium reabsorption near the end of the dosing interval [82]
Bumetanide		Child: PO/IV/IM 1–2 mg/kg/dose q 12–24 h [75••]		-Oral bioavailability is 85% (higher than furosemide)
Chlorothiazide	Inhibits the Na-Cl cotransporter in the early distal tubule Inhibits the Na-Cl cotransporter in the distal tubule	IV: 1-Infants < 6 months: 1-2 mg/kg/dose every 6 to 12 hours [79] 2-> 6 months of age: 5-10 mg/kg/day in divided doses. Max is 20 mg/kg/day or 500 mg/dose [80]	Hypokalemia, hyponatremia, impaired glucose tolerance, mild elevation in LDL cholesterol and triglycerides, hyperuricemia [78]	-Not effective in GFR < 30 -Poor oral bioavailability: 11-20% [75••]
Hydrochlorothiazide (HCTZ)		PO: 1-3 mg/kg/day divided BID up to 50 mg/day		-Not effective in GFR < 30 -Oral bioavailability 60-75% [75••]
Metolazone	Thiazide-like effect but can inhibit proximal tubular sodium reabsorption	PO: 0.2-0.4 mg/kg/day up to 20 mg/day [75••]		-Active in GFR < 30 -Oral bioavailability is 85% -More potent than HCTZ [75••]
Spironolactone	Decreases tubular expression of ENaC and ROMK channels in the distal tubules and collecting ducts.	PO: 2-3 mg/kg divided every 12 or 6 hours. Max is 6mg/kg/day or 400 mg/day [81]	Antiandrogen effect (gynecomastia). Hyperkalemia and less frequently other electrolyte imbalances [79]	
Amiloride	An antagonist of ENaC in the distal convoluted tubules and collecting ducts	PO: 0.625 mg/kg/day divided every 12 hours. Max is 20 mg/day [82]	Hyperkalemia.	-Oral bioavailability is 50%.
Aquaretics (Vasopressin receptor antagonists)	V2R on the basolateral surface of the epithelial cells of the collecting ducts. Aquaresis starts 2-4 hours after oral Tolvaptan.			Tolvaptan has been used alone to manage edema and/or correct hyponatremia in NS patients in case reports [83, 84]. It can be used with furosemide [85]. Tolvaptan is approved for use in adults with autosomal dominant polycystic kidney disease [85]
Carperitide	Synthetic ANP therefore it has vasodilator and natriuretic effect.			It is approved for heart failure in Japan [86]. It has been used once in case series in adults with NS.
Other potential therapies:				
Sacubitril/valsartan	Sacubitril is a Neprilysin inhibitor, so it increases the levels of natriuretic peptides.			This combination has been approved for use in patients with heart failure with reduced ejection fraction. It reduced the diuretic requirement [87]. It has not been used in the setting of nephrotic syndrome.

Table 2 (continued)

	Mechanism of action	Dose	Special side effects	Comments
Luteolin	Possibly by acting as a non-selective muscarinic antagonist.			Increased the diuretic effect of HCTZ and Amiloride when given in rats [88]
Urea transporter (UT) inhibitors	Inhibition of urea recycling in the vasa recta and its transport in the inner collecting duct. Urea acts as an osmotic agent promoting diuresis [90]			A triazolothieneopyrimidine UT-B inhibitor called UTB (inh)-14 injected intra-peritoneally in mice promoted diuresis [89]
CLC-K (Chloride channel) blockers, benzofuran derivatives MT-189 and RT-93	Similar to Bartter's syndrome.			These agents are probably specific to CIC-K1 as they induced a water diuresis with no effect on electrolytes in an experimental study [91]

that there was a reduction in proteinuria regardless of the class of diuretic added (Spironolactone vs HCTZ vs HCTZ + Amiloride) suggesting that the mechanism is probably related to a decrease in GFR [72].

The use of all diuretics- separately and more commonly in combination- carries the risks of causing hypovolemia, AKI, and electrolyte disturbances. (See Table 2)

Albumin

Patients with evidence of intravascular depletion and hypotension are managed with IV albumin 5% (10-15 ml/kg over 30-60 minutes). Another alternative if Albumin 5% is not available is to give IV saline. Albumin 20% or 25% 0.5-1 g/kg over 4 hours can be used after initial resuscitation [66••].

Patients with edema and weight gain >7% who are refractory to escalating therapy with diuretics are recommended to receive albumin 20% with furosemide as detailed above. A meta-analysis of 4 adult and pediatric studies comparing the use of albumin + furosemide vs furosemide alone revealed that more effective diuresis was achieved following the combination treatment. However, there was no change in natriuresis suggesting that albumin did not increase the efficacy of furosemide [73]. In another small adult study, there was a modest improvement in urine output when albumin was given alone [74]. This supports the revised Starling equation and the "no-absorption" rule where fluids escaping to the interstitium of tissues having continuous capillaries (muscles, lungs, connective tissues) are not pulled back to the intravascular compartment after the restoration of the oncotic pressure in that compartment. Diuretics are needed to achieve this mobilization [12].

In infants with congenital nephrosis, the practice varies between centers. While some centers only administer albumin when deemed clinically necessary, others use regular infusions (1-4 g/kg/day) to support growth, and psychomotor development and to maintain the intravascular volume [65••].

Adverse reactions to albumin infusions are usually mild and transient (e.g. fever, nausea). However, there is the risk of precipitating pulmonary edema, heart failure, or hypertension. This risk is higher if large doses are used, no diuretic is given or if there is renal impairment. Albumin should be given as a slow infusion over a few hours and under strict monitoring [72].

4- Isolated ultrafiltration

Patients with refractory edema may have fluid overload in the setting of kidney function impairment. In these cases, patients may require isolated ultrafiltration (UF) or dialysis [66••]. In infants and younger children with severe fluid overload with or without kidney function impairment, newer

therapies for ultrafiltration can be considered. Such therapies including aquapheresis via the AquadexTM can allow gentle fluid removal in patients with severe edema, even in smaller infants [76]. The use of these techniques requires the placement of a central IV access. The possible risks of infections and clotting may need to be put into consideration. The utilization, effectiveness, and safety of such therapies and ultrafiltration devices in children with NS need further attention.

5- Others

Head-out water immersion was tried in the past to promote diuresis and natriuresis in patients with refractory edema. It is no longer used in clinical practice. Aquaretics have been studied to promote water diuresis in NS. Diuretics as well as other medications and investigational therapies are listed in Table 2.

Conclusions

Edema is one of the main symptoms of NS and it may be the primary concern for children and their parents. Regardless of the mechanism underlying edema formation in children with NS, assessment of the intravascular volume is essential. New investigational tools have been developed to help the clinician in this task. Besides treatment with steroids and/or other immunosuppressives, management directed at the edema per se may be needed in certain cases. The currently available options for targeted- management of edema include diuretics and albumin. Novel ultrafiltration therapies to treat fluid overload in children with NS are understudied.

Declarations

Conflict of interest The authors report no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as: •• Of major importance

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