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REVIEW

Nephrotic Syndrome Complications – New and Old. Part 1

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ABSTRACT

Nephrotic syndrome is a rare condition with an incidence of 2-7 cases/100.000 children per *year and three new cases/100.000 adults* per *year. It occurs as a result of severe alteration of the glomerular filtration barrier of various causes, allowing proteins, mostly albumin, to be lost in the urine. Nephrotic syndrome complications are driven by the magnitude of either proteinuria or hypoalbuminemia, or both. Their frequency and severity vary with proteinuria and serum albumin level. Besides albumin, many other proteins are lost in urine. Therefore, nephrotic patients could have low levels of binding proteins for ions, vitamins, hormones, lipoproteins, coagulation factors. The liver tries to counterbalance these losses and will increase the unselective synthesis of all types of proteins. All of these changes will have different clinical consequences. The present paper aims to discuss the pathophysiological mechanism and new therapeutic recommendations for nephrotic syndrome edema and thromboembolic complications.*

Keywords: nephrotic syndrome, nephrotic edema, diuretics, thromboembolic complications, anticoagulant therapy.

INTRODUCTION

The nephrotic syndrome (NS) is the result of a severe alteration in the glomerular filtration barrier of different causes, allowing large quantities of proteins to be lost in urine. It is defined by proteinuria over 3.5 g *per* day in adults or 40 mg/m^2 *per* hour in children, in association with a low serum albumin (< 3.5 g/dL). Both criteria are mandatory for diagnosis (1). However, sometimes, hypoalbuminemia does not occur simultaneously with proteinuria, hence serum albumin and proteinuria should be considered in dynamic to establish the diagnosis.

Proteinuria over 3.5 g *per* day without hypoalbuminemia is defined as nephrotic-range proteinuria and it is rather the result of glomerular hyperfiltration related to obesity, reduction in nephron mass, or other glomerular lesions. The two conditions are not synonymous, having different etiologies, treatment and prognosis.

The other manifestations seen in nephrotic patients – e.g., edema, hyperlipidemia, infections, acute kidney injury – are frequent but inconstant. Therefore, they are not essential for

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diagnosis. However, the most common clinical presentation of nephrotic patients is edema, which should be differentiated from generalized edema of two other conditions frequently seen in common practice, heart failure and liver cirrhosis. Two clinical clues facilitate the differentiation. As patients with heart failure or cirrhosis are uncomfortable lying flat, they do not develop facial edema, and their urine is not foamy (1).

Thus, the diagnosis of NS is based on laboratory data. Nephrotic syndrome should be suspected when a dipstick test gives an intense positive reaction for protein. Accordingly, urine should be tested with a dipstick in every edematous patient. The 24-hour urine collection is the gold-standard method to quantify proteinuria. However, the collection of a 24-hour urine sample being time-consuming and inconvenient, it is frequently inaccurate. Protein-creatinine ratio in spot urine is easier to obtain, but has a greater variability, so it should be rather used for monitoring or screening than for NS diagnosis (1, 2).

As mentioned, a low serum albumin is also required for diagnosis, and should be measured in patients with heavy proteinuria.

Patients diagnosed with NS should be referred to a nephrologist, as only in few cases – non-hematuric diabetic patients, pediatric patients – a kidney biopsy is not recommended for diagnostic and specific therapy of the underlying condition.

The cause of NS is a severe alteration of the glomerular filtration barrier, allowing large quantities of protein, mostly albumin, to freely pass in urine. Various glomerular lesions are associated with NS. Their type varies with age, sex and ethnicity. Given the high prevalence of diabetes mellitus, diabetic nephropathy is the commonest, followed by minimal change disease in children, focal and segmental glomerulosclerosis in adults with African ancestry and membranous glomerulopathy in Caucasian adults. In young females, systemic lupus erythematosus should be suspected and in patients over 65 years, solid cancers, lymphomas or clonal B cell proliferations are seen with increasing frequency. As many of these conditions could benefit from the use of a specific therapy, a histopathologic diagnosis is necessary.

Currently, genetic abnormalities of some components of the glomerular filtration barrier are identified. Consequently, genetic testing is regarded as a new tool for diagnosis but it is costly and available in a limited number of centers.

Although NS is a rare condition, with an incidence of 2-7 cases/100.000 children *per* year and three new cases/100.000 adults *per* year, in many cases it needs specific therapy; also, its complications are frequent and should be acknowledged and properly treated.

Nephrotic syndrome complications are driven by the magnitude of either proteinuria, hypoalbuminemia or both, and their frequency and severity increase when proteinuria is higher than 8 g/day serum or when albumin decreases under 2 g/dL. Although proteinuria is the initiating event, the relationship between serum albumin level and proteinuria is inconstant, as part of patients do not develop hypoalbuminemia despite massive proteinuria. Thus, the precise mechanism of hypoalbuminemia is still debated. Hepatic synthesis seems not surpassed by albuminuria, in absence of inflammation. As inflammation is frequent in NS, this could be an explanation. Other possible explanations are the high catabolic rate of filtered albumin, reabsorbed by the proximal tubules, gastrointestinal losses or capillary hyperpermeability but none of these has been proved so far (3, 4).

Besides albumin, many proteins are lost in urine because of the altered filtration barrier. Therefore, nephrotic patients could have low levels of many binding proteins for ions (iron, copper, zinc), vitamins (vitamin D), hormones (steroid or thyroid hormones). Also, lipoproteins, coagulation factors or different drugs (like coumarin anticoagulant or diuretics) are lost in urine with different clinical consequences. The liver is stimulated to counterbalance the losses and the unselective synthesis of all types of proteins will increase, also with clinical consequences (5).

Therefore, the manifestations of NS are thought to be generated by a combination of increased urinary losses and higher hepatic synthesis (5).

Nephrotic edema

Edema is the commonest clinical expression of NS. Its onset varies from gradual (for example, in focal and segmental glomerulosclerosis or membranous nephropathy) to sudden, often "overnight", like in minimal change disease. The clinical expression ranges from simple weight gain to

soft, fluffy white declive edemas, or rarely development of serous effusions, even anasarca. However, one third of patients with NS do not have edema.

Mechanisms of nephrotic edema formation

The mechanism of edema formation in NS is still incompletely understood. Edema formation involves a combination of hypoalbuminemia, renal salt retention and increased permeability for water of the peripheral capillaries. Over time, two theories have been proposed: secondary renal sodium retention (the "*underfill*" hypothesis) and primary renal sodium retention (the "overfill" hypothesis) (Figure 1).

Underfill hypothesis

The underfill hypothesis considers that the main pathogenetic factor is a hypoalbuminemia-induced decrease in plasma oncotic pressure. As the serum albumin level falls with a consequent drop in intravascular oncotic pressure, the intravascular–interstitial albumin gradient of concentration decreases, which allows the extravasation of intravascular water to the interstitium. Hypovolemia decreases blood pressure and induces orthostatic hypotension.

The low intravascular volume activates the systems of volume control (renin-angiotensin-aldosterone, non-osmotic vasopressin enhanced secretion, decrease in natriuretic peptides), which stimulates sodium and water retention. Thus, edema is formed due to the coupled action of the leak of water in the interstitium and the secondary renal water and sodium retention. Finally, blood volume is restored, blood pressure normalizes and coexists with edema.

However, albumin concentration was also proved to decrease in the interstitium, which mitigates the oncotic gradient and limits the intravascular–interstitial water shift. Moreover, clinically, only a third of analbuminemic patients have edema and signs of a low intravascular volume are frequently missing in nephrotic patients. Therefore, the underfill hypothesis seems to work only in certain nephrotic edema.

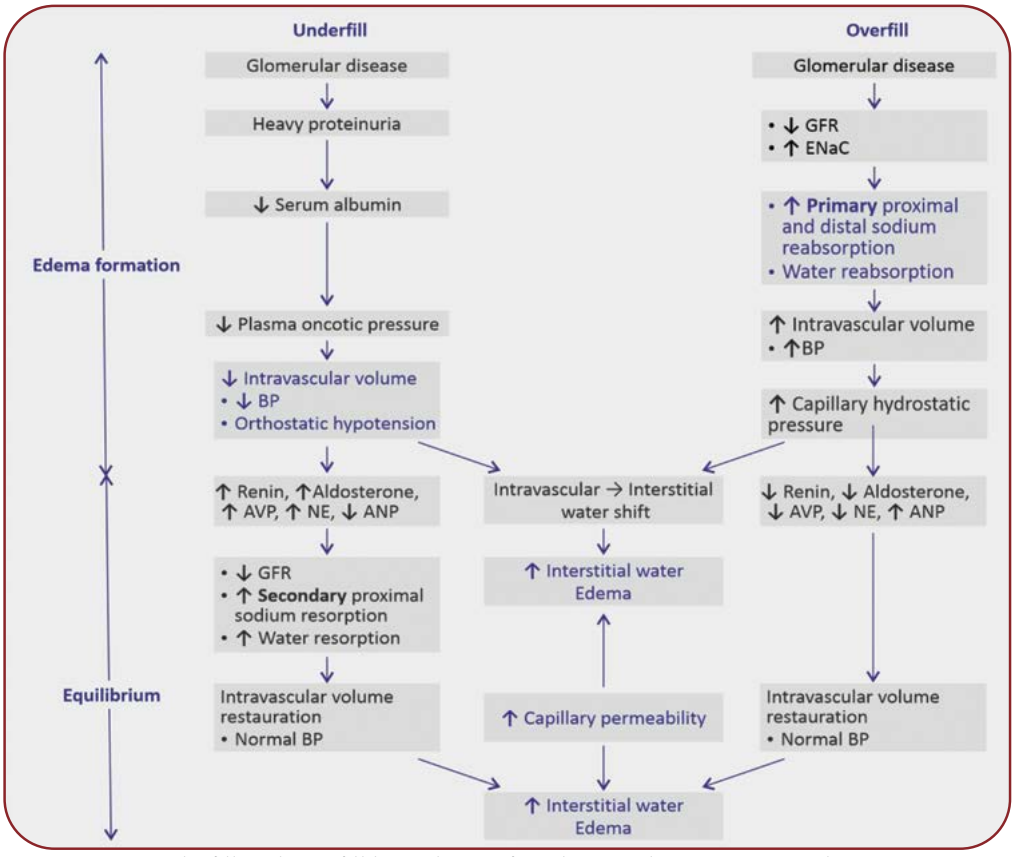

FIGURE 1. Underfill and overfill hypothesis of nephrotic edema. ANP=atrial natriuretic peptide; AVP=arginine vasopressin; BP=blood pressure; ENaC=epithelial natrium channel; NE=norepinephrine

Overfill hypothesis

The overfill hypothesis is based on experimental evidence. In a rat model of unilateral nephrotic kidney, only the nephrotic kidney avidly retained sodium, suggesting that, in NS, sodium retention is primary, not secondary renal. Thereafter, the hyperactivity of amiloride sensitive epithelial sodium channel (ENaC), located in the distal convoluted tubule, was identified as responsible of the increased sodium reabsorption.

Filtered along with other proteins, serin-proteases can open ENaC by cleaving its extracellular loops subunits α and ϒ, thus increasing sodium reabsorption. For instance, under the action of urokinase, filtered plasminogen is converted to plasmin, which opens ENaC by cleaving its extracellular loops. Activation of ENaC by filtered proteases was proved even in patients with non-nephrotic proteinuria (6, 7).

In contrast to other proteases, PCSK9, a member of the proprotein convertase family, which modulates LDL receptor expression, also regulates ENaC expression by increasing its degradation in proteasome, thus limiting sodium reabsorption. However, in animal models, PCSK9 showed a neutral effect on blood pressure. The precise role of PCSK9 remains to be studied, as kidney is a major source of plasma PCSK9 in nephrotic syndrome (8-12).

Renal reabsorption of sodium and water, resulting from uncontrolled ENaC activation, increases blood volume and transcapillary hydraulic pressure, shifting water from capillaries to the interstitium. Thus, primary renal increased reabsorption of sodium seems to be the first step in extracellular volume expansion in some patients, and in conjunction with hypoalbuminemia, to participate in formation of nephrotic edema. This is therapeutically important, because ENaC is selectively inhibited by amiloride. Moreover, emerging clinical data suggest that amiloride can be a more targeted therapy in the overfill nephrotic edema (12, 13). Thereafter, at equilibrium, water shift in the interstitium and suppression of volume control systems – renin-angiotensin-aldosterone, AVP and natriuretic peptides – restores blood volume and normalizes blood pressure.

The variability of clinical presentation of nephrotic edema seems related to these two pathogenic mechanisms. Low blood pressure, severe hypoalbuminemia (<1 g/dL) and low glomerular filtration rate, more frequently seen in minimal change disease, are associated with the underfill mechanism, while primary sodium retention is associated with high blood pressure, less severe hypoalbuminemia (2.5-2 g/dL) and almost normal GFR. These clinical clues are useful to personalize therapy of nephrotic edema (Table 1). To note, the pathogenetic mechanism of edema can change over time in the same patient.

Capillary hyperpermeability

Capillary permeability for proteins and the hydraulic permeability for water is increased two-fold in NS and changes in capillary basement membrane thickness and composition were reported (15, 16). However, the mechanism of these changes is still not known. A permeability factor, probable a byproduct of the originary immunopathogenic mechanism of underlying glomerulopathy, was proposed but never proved. Accordingly, the magnitude of hyperpermeability may vary depending on the underlying glomerulopathy and can be influenced by immunosuppression. Recently, a putative target for the hyperpermeability factor – cytokine receptor-like factor 1 – was suggested (17).

A study investigating the mechanism of ascites formation in rats with puromycin induced NS found an increase in peritoneum water filtration coefficient on paracellular and transcellular pathways and a decrease in the reflection coefficient of proteins. These changes were related to an oxidative stress-associated overexpression of NF-B and aquaporins, and were prevented by reactive oxygen species scavenging and inhibition of NF-B (18). It is not known whether similar abnormalities exist in other territories but this observation underlines the complexity of nephrotic edema formation.

TABLE 1. Factors which help to differentiate overfill from underfill nephrotic edema [adapted from (14)]

Factors	Overfill	Underfill
GFR (% of normal)	>50%	<75%
Serum albumin	>2 g/dL	<2 g/dL
Hypertension	+	-
Postural hypotension	-	+
Inferior vena cava diameter	>2.5 cm	<1.5 cm
Inferior vena cava collapsibility index >50%	<20%	>50%
Minimal change disease	-	-+

Nevertheless, capillary hyperpermeability could contribute to edema formation in both underfill and overfill hypothesis (Figure 1).

Therapy of nephrotic edema

Nephrotic edema should be looked like a consequence of the glomerular lesion. Accordingly, its final therapy should be addressed to underlying glomerulopathy. However, to increase patients' comfort or prevent organ dysfunction by severe serous effusions, pathophysiologically-oriented edema-treatments are needed. Thus, therapy of edema should be considered as a symptomatic therapy.

As edema formation implies sodium (and water) retention, the only purpose of the nephrotic edema therapy is to obtain a negative sodium balance by dietary sodium restriction and diuretic therapy.

Dietary salt restriction

Salt restriction is the first line of nephrotic edema therapy, which can improve minor edema without diuretics.

Sodium intake should be reduced under 90 mmol/day (the equivalent of 2 g of salt) but adherence to a low-salt diet is problematic and incompliance to diet is a common cause of resistance to diuretic therapy. Thereby, dietary counselling should be offered to help institute a low-sodium diet (19).

Diuretics

Diuretic therapy is added to negativize sodium balance. Loop diuretics (such as furosemide) are the first line of therapy and are indicated in moderate to severe edema.

Furosemide

Free furosemide in urine blocks the Na/K/2Cl (bumetanide-sensitive) channel, located at the apical (endolumenal) pole of nephrocytes in the thick ascending loop of Henle, and inhibits sodium and water resorption (Figure 2). As furosemide is transported in blood highly bound to albumin, it is not filtered by the glomerulus and can reach its site of action only after being secreted in the glomerular filtrate by the proximal tubule cells. In nephrotic patients, serum albumin is low, and less bound furosemide is available to proximal tubule cells for transport in free form to urine. At the same time, albuminuria is

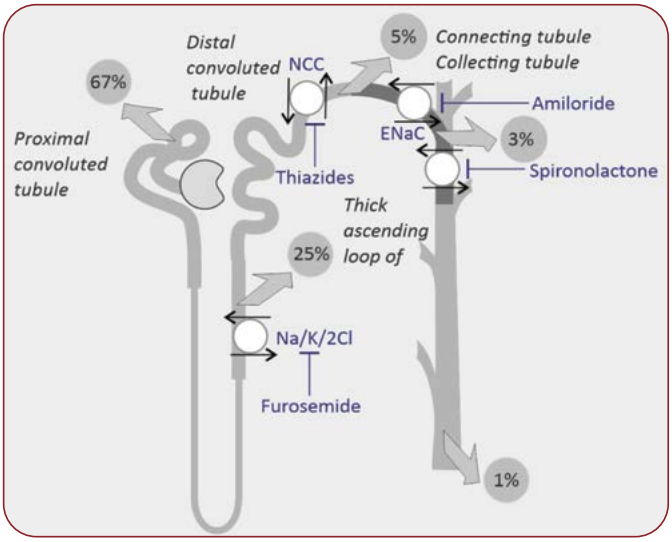

FIGURE 2. Sodium reabsorption along the nephron (percent) and diuretic site of action. ENaC: amiloride-sensitive epithelial sodium channel; Na/K/2Cl: bumetanide-sensitive sodium-potassium-chloride channel; NCC: thiazide-sensitive Na/Cl cotransporter

high and bounds free furosemide in glomerular filtrate, reducing with 50-60% its concentration at the site of action and limiting the diuretic effect. That is why higher initial furosemide doses (80-120 mg) are needed in nephrotic patients.

On the other hand, after administration of an albumin infusion, most of infused albumin will be lost in urine along with furosemide, diminishing its diuretic action. Accordingly, simultaneous furosemide and albumin infusions should be avoided (20).

Absorption of furosemide from the digestive tract is erratic, so its bioavailability on oral route is under 50%, further reduced by intestinal edema. For this reason, parenteral administration is preferred in severe nephrotic patients. Major part of furosemide is excreted unchanged in urine (Table 2).

Duration of diuretic action of furosemide is about seven hours. Correspondingly, the daily dose should be fractioned in two or three portions. Moreover, the risk of ototoxicity is higher in bolus administration of large doses. Thus, administration in perfusion is recommended when high doses are prescribed.

The natriuretic effect of furosemide is proportional with the excess of extracellular volume. In chronic administration, the natriuretic effect diminishes as the extracellular volume contracts, and sodium excretion equals sodium intake

TABLE 2. Clinical pharmacology of diuretics usually used in nephrotic edema

	Bioavailability	Protein binding	Excretion	Diuretic effect		
				Onset	Duration	Doses
Furosemide	≈50%	>90%	U 50-60%* B 6-9% F 7-9%	0.3 h (IV) 1.45 h (PO)	6-8 h	40-480 mg/day b.i.d.
Amiloride	50%	Minimal	U 50% F 40%	2 h	24 h	5-20 mg/day b.i.d.
Hydrochlorothiazide	65-75%	40-80%	U >90%*	2-4 h	6-12 h	25-100 (200) mg/day b.i.d.
Indapamide	>90%	76-79%	U 60-70% F 16-20%	2-4 h	24 h	2.5-5 mg/day b.i.d.
Spironolactone	>90%	>90%	U 50%† F 15%	2-3 days	2-3 days	200 mg b.i.d.
Eplerenone	?	50%	U 67%* F 32%	6-8 h	24 h	100 mg b.i.d.

*Unchanged; †active metabolites (canrenone)

B=biliary excretion; F=fecal excretion; U=urinary excretion

(''braking'' phenomenon). This is due to remodeling – hypertrophy and hyperplasia – of nephrocytes in the distal nephron in response to excessive sodium load, angiotensin II and aldosterone stimulation and to changes in potassium balance (21). The "braking" of furosemide natriuretic effect could be a problem when the extracellular volume persists in spite of escalation in furosemide doses, a frequent situation in NS. Association of diuretics inhibiting sodium absorption in the distal nephron, *i.e.*, thiazides, can promote natriuresis, thus overcoming the "braking" phenomenon.

Since furosemide firstly reduces the intravascular water and hypoalbuminemia impedes rapid water transfer from the interstitium to blood vessels, abrupt decongestion may cause hypovolemia and produce even acute renal injury in some cases. Also, NS-associated thrombotic risk could be augmented by diuretic-induced hypovolemia, and anticoagulant treatment should be considered. Moreover, not only salt and water are excreted while on furosemide therapy, but also potassium, calcium and magnesium. Thus, edema should be reversed slowly aiming a less than 2 kg/day reduction in weight, and therapy in alternate days is recommended. To avoid diuretic-associated adverse events, clinical (blood pressure, weight, diuresis) and laboratory (serum creatinine, urea and electrolytes) parameters should be monitored (19, 22, 23).

Thiazides (hydrochlorothiazide) and **thiazide-like** (metolazone, chlorothiazide, indapamide) diuretics decrease sodium reabsorption in the distal convoluted tubule by inhibiting the thiazide-sensitive Na/Cl cotransporter (NCC) (Figure 2). Like furosemide, they act at the endolumenal pole of nephrocytes and must be secreted by active transport in urine by proximal tubule cells. They are well absorbed orally, widely distributed and subjected to a variable degree of hepatic metabolism. The diuretic effect starts 2-4 hours after administration. In opposition to hydrochlorothiazide, thiazide-like diuretics, of which only indapamide is available in Romania, have a longer diuretic effect (24 hours in slow-release formulations) (Table 2) (19).

Hypokalemia, hyponatremia, hypomagnesemia, hyperuricemia and, eventually, hypercalcemia or hypochloremic alkalosis were associated with thiazide therapy. Notably, thiazides and thiazide-like diuretics adversely affect blood lipids and increase the risk of diabetes mellitus. All these adverse effects are dose dependent (24). Because of the sulphone amide moiety, thiazides and furosemide could produce various allergic reactions, and some may be severe (vasculitis, Stevens-Jones syndrome).

Thiazides are largely used in the treatment of hypertension but are not recommended as first line therapy in NS because they increase the natriuresis with less than 5%. However, thiazides are useful in case of resistance to loop diuretic, because they promote natriuresis distally from furosemide site of action, thus opposing to braking phenomenon. Although their diuretic action declines with eGFR and are not effective when eGFR is lower than 30 mL/min when used in monotherapy, in association with furosemide, thiazides in larger doses (hydrochlorothiazide 50-100 mg/day fractioned in two doses or indapamide 2-5 mg/day) still increase diuresis even at eGFR <30 mL/min.

Mineralocorticoid receptor antagonists (MRAs) – non-selective (spironolactone), selective (eplerenone) – are potassium-sparing diuretics which competitively inhibit mineralocorticoids receptors in the distal convoluted tubule, promoting sodium and water excretion and potassium reabsorption (Figure 2). Unlike furosemide and thiazides, MRAs reach the distal tubule nephrocytes through blood, not through urine, and therefore do not need to be secreted in urine. They are well absorbed (absorption is enhanced when taken with food), extensively metabolized in the liver and excreted as metabolites, some active (canrenone) in case of spironolactone, in urine. For this reason, MRAs are not recommended when eGFR is lower than 30 mL/min. The diuretic action of spironolactone starts few days after administration, while that of eplerenone only 6-8 hours, and it lasts 2-3 days and 24 hours, respectively (Table 2).

Aldosterone has not only mineralocorticoid but also proinflammatory and profibrotic actions. Mineralocorticoid receptor antagonists antagonize all these actions not only in the kidney but also in the heart, blood vessels and brain. Thus, they are indicated in treatment of hypertension, heart failure, myocardial infarction and edema of liver cirrhosis. In NS, MRAs were less tested, with good results in diabetic kidney disease (reduction of proteinuria by 31%) but with contradictory results in small studies in NS of other causes (25, 26). Accordingly, MRAs could be useful in association with furosemide in resistant NS. However, their dose should be higher (spironolactone 200 mg/day) than indicated for hypertension or heart failure. Moreover, MRAs could reduce proteinuria and prevent kidney interstitial fibrosis.

The main MRAs adverse effect is hyperkalemia, which is more frequent in patients with decreased renal function. Because some of their metabolites are similar to progesterone, spironolactone, but not eplerenone, has progestogenic and antiandrogenic effects.

To avoid these adverse effects, new non-steroid selective MRAs were developed. Finerenone had more potent anti-inflammatory and antifibrotic effects than steroidal MRAs. In a controlled study in patients with diabetic kidney disease, many with albuminuria >300 mg/day, finerenone not only reduced albuminuria by 30% but also improved both kidney composite endpoint (a more than 40% reduction in eGFR or death of renal causes) and cardiovascular composite end-point (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) by 18% and 14%, respectively. However, hyperkalemia was two-fold higher than in the placebo group (15.5 *vs.* 7.7%) (27). To date, there are no study investigating finerenone in NS. Another non-steroid selective MRA, AZT9977, has also showed natriuretic effects, and could be useful in future in nephrotic edema (28).

Aldosterone effects mediated by its receptors were recently described as "genomic", in contrast to the "non-genomic", no receptor-mediated, effects, *i.e.*, fibrosis and inflammation. Mineralocorticoid receptor antagonists block aldosterone receptors but increase the adrenal secretion of aldosterone, potentially enhancing the "non-genomic" effects. To overcome the exacerbation of the "non-genomic effects", inhibitors of aldosterone synthetase were developed and are now tested in preclinical studies (29).

Potassium binders, patiromer and sodium zirconium cyclosilicate, tested for prevention of RAASi-induced hyperkalemia, could be also a solution for MRAS-related hyperkalemia (30, 31).

Amiloride is a potassium-sparing diuretic which increases natriuresis by selectively blocking ENaC in the distal connecting tubule (Figure 2). After oral administration, it has a bioavailability of 50% (reduced to 30% when taken with food), it is distributed in a large volume, not being protein-bound, and is excreted unchanged, 50% in urine and 40% in feces. The natriuretic effect starts two hours after admini-

stration, it is maximal after 6-10 hours and persists for 24 hours (Table 2) (32).

Because in normal conditions only 5% of filtered sodium is available for reabsorption in the distal nephron, amiloride has a lower natriuretic effect than loop diuretics, and it is recommended in hypertension in association with other diuretics, usually thiazides. However, as ENaC is upregulated by aldosterone, blocking ENaC is also useful in the case of primary or secondary hyperaldosteronism. In patients with nephrotic edema, amiloride could be useful in two situations: firstly, in overfill patients, where ENaC activation seems to be the primary mechanism of increased distal sodium reabsorption and amiloride inhibits urokinase, and urokinase generates plasmin from filtered plasminogen, which opens ENaC, but there are few clinical data (12, 13); and secondly, in association with loop diuretics, to overcome the aldosterone-induced hipokalemia and diuretic resistance (*vedi infra*). However, the amiloride–furosemide association was not properly investigated (14).

The distal tubule reabsorption of cations – K+, H+, Ca2+ and Mg2+ – depends on the lumen-negative transepithelial voltage created by ENaC-mediated resorption of sodium. Accordingly, hiperkalemia is the main adverse effect of amiloride; it is more frequent in the case of low kidney function and when associated with MRAS, renin-angiotensin system inhibitors (RASIs) or non-steroidal anti-inflammatory drugs (NSADs). Hyperkalemic acidosis is also possible (32). Acute kidney injury is also a possibility, as described by Hinrich *et al*, who have reported that the rapid amiloride-induced depletion of extracellular water resulted in dangerous hyperkalemia and acute kidney injury, imposing reduction of amiloride doses (12).

Vaptans are "aquaretics" used to treat dilutional hyponatremia associated with diuretic use in heart failure and liver cirrhosis. Vaptans act by selectively antagonizing vasopressin V2 receptors in the collecting tubules, resulting in reduced expression of aquaporin-2 and increased excretions of free water. Tolvaptan (15, increased to 30 mg/day) was given to three patients with diuretic-resistant nephrotic edema (two membranous nephropathy, one minimal change disease) in conjunction with furosemide. Two patients responded with an increase in diuresis and, surprisingly, sodium urinary levels also increased but sodium plasma levels were stable. In the not-responding patient, aquaporin-2 expression in the collecting group and its urinary excretion were lower, in contrast to responders. However, as diuresis increased after corticotherapy, the authors suggested that aquaporine-2 expression was restored by immunosuppressive treatment (33). On the other hand, they speculated that tolvaptan also inhibited the AVP-induced overexpression of ENaC, which explained the higher sodium excretion and had stabilized plasma sodium level (34).

Although preliminary, the reports suggest a role of vaptans in the therapy of resistant NS.

Synthetic analogs of human natriuretic atrial hormone (ANP) increase natriuresis and were tested in edema of heart failure and in acute kidney injury. Carperitide in association with furosemide reduced more weight and increased less serum creatinine when compared to furosemide alone in a controlled study in diabetic patients with nephrotic edema. However, ANP inhibits RAS, lowers blood pressure and induces renal vasodilation. Accordingly, in hypovolemic nephrotic patients, it could precipitate acute kidney injury (35).

Management of nephrotic edema

As there are no guidelines for therapy of nephrotic edema, the management is guided by the severity of edema, volemic status and therapeutic response. In every situation, therapy of the underlying glomerulopathy should be considered because it is the only way to attenuate proteinuria. Moreover, in some situations, e.g., minimal change disease, immunosuppressive therapy could reduce proteinuria and solve edema in a short time (97-14 days), mitigating the need of diuretics.

Minor edema (small pedal edema and puffy eyes, weight gain around 5 kg) could benefit from salt restriction and, eventually, thiazides 24-50 mg when eGFR 50 mL/min) or orally furosemide (40-80 mg/day, in 2-3 portions, when eGFR <50 mL/min) (36).

When **edema is moderate** (massive lower limb edema, weight gain around 10 kg) or **severe edema** (massive edema, pleural effusion, therapy ascites, weight gain >15 kg), salt restriction should also be instituted. Loop diuretics are the first line of therapy (furosemide PO/IV starting from 160 mg/day and increasing up to 480 mg/day in

Minor edema (Small pedal edema and puffy eyes, weight gain around 5 kg)	• Salt restriction (3 g/day) + eGFR >50 mL/min • Hydrochlorothiazide PO 25-50 mg b.i.d. *OR* • Indapamide PO 2.5-5 mg o.d. eGFR <50 mL/min • Furosemide PO 40-80 mg b.i.d.
Moderate edema (Massive lower limb edema, weight gain around 10 kg)	• Salt restriction (3 g/day) + • Furosemide PO 120-240 mg b.i.d.
Severe edema (Massive edema, pleural effusion, therapy ascites, weight gain >15 kg)	• Salt restriction (3 g/day) + • Furosemide IV 120→480 mg b.i.d. + • Amiloride PO 5 mg b.i.d. *OR* • Indapamide 2.5 mg o.d. *OR* • Hydrochlorothiazide 50-100 mg b.i.d. *OR* • Spironolactone 200 mg b.i.d. *OR* • Eplerenone 100 mg o.d.

TABLE 3. Therapy of nephrotic edema

case of unsatisfactory response). In severe nephrotic edema, association with thiazides, MRAs, amiloride or indapamide may hasten edema depletion. To note, amiloride seems to be a better second line solution in overfill patients due to ENaC role in sodium retention. The utility of albumin in underfill patients is controversial. It could be a solution in severe hypoalbuminemic patients, unresponsive to loop diuretics (*vedi infra*) (Table 3) (36).

Unresponsive edema is defined as a failure to achieve the therapeutically desired reduction in edema even when a maximal dose of diuretic is employed (37). In most cases, this is due to non-adherence to medical advice, but pharmacokinetic and pharmacodynamic effects could also be implied (Table 4).

To overcome diuretic resistance, it is cautious to follow a gradual approach. First of all, the possibility of not following a low-sodium diet and the use of drugs interfering with diuretics (most commonly, non-steroidal anti-inflammatory agents) should be ruled out.

Then, furosemide should be switched to intravenous administration, and its frequency and dosage should be reviewed and adjusted. In case there is n no response after correction, furosemide should be administered in infusion (20 mg/min).

Association of diuretics of different classes is the next step. The largest experience is with thiazides administration, which potentiates the diuretic action of furosemide by preventing sodium reabsorption in the distal convoluted tubule (Figure 2). In combination with furosemide, thiazides increase diuresis even when eGFR is low. However, doses should be increased to 50-100 mg for hydrochlorothiazide, 2.5-5 mg for indapamide, in two portions, 12 hours apart. As the diuretic effect of thiazides peaks al 2-4 hours after oral administration, furosemide should be given four hours after thiazides.

Amiloride (5 mg/day in two doses) seems a better option, especially in overfill patients, as sodium reabsorption mediated by ENaC was

TABLE 4. Refractory nephrotic edema – causes and solutions

Causes	Solutions
Nonadherence to recommended sodium restriction	• Dietetic counseling
Drugs interfering with furosemide actions: • Nonsteroidal anti-inflammatory agents (interfere with prostaglandin-dependent Na and Cl resorption) • Thiazolidinediones (rosiglitazone) increase proximal sodium reabsorption and upregulate ENaC	• Stop offending medication
Furosemide restricted access to its site of action: • Decreased oral absorption (intestinal mucosal edema, reduced intestinal motility) • Inadequate dose or frequency • Decreased tubular secretion: o Hypoalbuminemia-induced restricted access to proximal tubule for secretion in urine o Heavy albuminuria reduces free furosemide urine concentration o Hypovolemia-induced low glomerular filtration rate	• Correct doses/frequency • Switch from oral to parenteral administration • Albumin infusions
Enhanced distal tubular sodium reabsorption: • ENaC overactivation by filtered proteases • Hyperaldosteronism induced by low circulating volume and negative sodium balance • Adaptative tubular cells hypertrophy secondary to hypokalemia in chronic diuretic treatment	• Add thiazides • Add aldosterone antagonist (amiloride, spironolactone, eplerenone)
Proteinuria-related tubule cells lesions (including AKI)	

AKI=acute kidney injury; ENaC=epithelial sodium channel; RAASi=renin angiotensin aldosterone inhibitor

demonstrated in nephrotic syndrome. Although amiloride could become even a first line diuretic in overfill NS, the clinical experience with amiloride in NS is very limited.

Mineralocorticoid receptor antagonists – spironolactone, eplerenone – in anti-proteinuric doses (200 mg and 100 mg, respectively) also seem to be beneficial, as in other conditions with reduced proteinuria, but their utility in association with loop diuretics in nephrotic proteinuria was not properly tested. Finerenone, a non-steroidal MRA, could be a solution, if tested, as it reduced proteinuria by 30% in diabetic patients (37).

As previously mentioned, vaptans were also prescribed in diuretic-resistant proteinuria with encouraging results, but the clinical experience is very limited.

Albumin infusions (hyper-oncotic >20 g% or hypo-oncotic <5%) were thought to ameliorate diuretic resistance by ameliorating furosemide pharmacokinetics and restoring circulating volume.

Improving the abnormalities of furosemide pharmacokinetics in diuretic-resistant nephrotic edema were based on animal experiments.

On one hand, as furosemide is highly bound to albumin, in severe hypoalbuminemic nephrotic patients, less furosemide is bound to albumin, resulting in an expansion of its volume of distribution, *i.e.*, more furosemide is distributed to other tissues than the kidney. Only free furosemide in urine inhibits Na/K/2Cl transporter. Because free furosemide reaches urine after being secreted by the proximal tubule cells, which can be accessed only when albumin-bound, hypoalbuminemia could reduce the availability of free furosemide at its site of action. In other words, hypoalbuminemia could blunt the furosemide diuretic action. Thus, albumin

infusion could restore the diuretic action of furosemide in hypoalbuminemic nephrotic patients.

On the other hand, in animal experiments, an albumin infusion increases albuminuria, and the increased urinary albumin binds free furosemide, diminishing its diuretic effect by limiting its access to distal tubular cells. However, human studies proved that furosemide binding to albumin in urine has only minor effects on its diuretic action, and hypoalbuminemia does not seem to influence furosemide access to tubular cells for secretion. Thus, albumin supplementation seems to minimally influence furosemide in hypoalbuminemic nephrotic edema (38).

There are few controlled clinical studies properly investigating the efficacy of albumin–furosemide combination compared to furosemide alone. Albumin (5% or 20%) and furosemide were administrated either concomitantly or in succession. Not in all studies and in a recent metanalysis combined albumin–furosemide therapy was superior to furosemide in increasing natriuresis or diuresis and if the favorable effect existed, it was transient and short-lived (eight hours). However, not all studies reported whether patients were non-responders to furosemide alone (20, 39).

As albumin solutions increase plasma oncotic pressure, it could also improve the response to furosemide by restoring the circulating volume without external supplementation with other solutions. However, because of massive albuminuria, the effect of albumin infusion in restoring the blood volume is short-lived (24-48 hours), and some experimental and clinical data suggest that increased albuminuria following albumin infusion can be even toxic for the tubule cells (40).

Moreover, the increase in circulating volume could generate pulmonary edema in patients with renal or heart failure (22, 23).

Thus, the benefic effects of adding albumin to furosemide in resistant nephrotic edema is minimal. Accordingly, albumin infusion (hyper-oncotic, 20%, low salt) seems indicated in non-responding to furosemide underfill nephrotic edema and in case of diuretic-induced symptomatic hypovolemia, only in patients with good kidney and heart function (36).

In extremely severe refractory, life-threatening edema, **ultrafiltration** may be tried. Also, as an extreme measure for patients with NS and severe treatment-resistant proteinuria, bilateral renal artery embolization may be recommended to avoid hypoproteinemia-associated debilitating risks (22, 41).

Thromboembolic complications

Thromboembolic events (TEs) are among the most serious complications of NS, as they are associated with a 6-12% mortality in the 30 days following the event (42). Although TEs could affect any blood vessel, venous thrombotic events (VTEs) are more frequent than arterial thromboses. Deep vein (30%) and renal vein (14%) thromboses are the most frequent, and they are complicated with pulmonary embolism in about 30% of cases (22, 43).

The VTEs rate of incidence in nephrotic patients (4/100 patient-years) is high and close to that reported in those with deep vein thrombosis from the general population (7/100 patient-years). The main predictive factors of VTEs are both a lower serum albumin (<2-2.5 g/dL) and a higher proteinuria (>8-10 g/day) but the cut-offs vary according to reports. Other factors, including age [higher frequency in adults than children (20-30% *vs.* 3-20%)], sex (higher frequency among women) and cause of NS [higher frequency in membranous nephropathy (38% incidence)], were also associated with VTE risk in NS (44-46). The risk of arterial thromboses is amplified by traditional risk factors for atherosclerosis (43).

However, the incidence of VTEs is not firmly established as pulmonary embolism and renal vein thromboses can be minimally symptomatic, needing extensive imaging evaluation (lung scans, angiography, Doppler color ultrasound), which is not routinely performed in reported studies. The increase in fibrin d-dimers level can guide the evaluation (47).

Pathogenesis of thromboembolic complications in nephrotic syndrome

The nephrotic syndrome-associated hypercoagulable, thrombophilic, state is thought to be produced by an imbalance between antithrombotic and procoagulant factors, resulting from the combination of urinary losses and increased hepatic synthesis, generated by lesions of the glomerular filtration barrier. Altered platelets activation and defective fibrinolysis may also contribute. There are some indices that the thrombophilic state is initiated within the diseased kidney. However, the pathogenesis of NS altered coagulation is not fully understood (Figure 3).

Plasma levels of procoagulant proteins with high molecular weight – factors V, VIII, fibrinogen and α2-macroglobulin – are markedly elevated due to increased hepatic synthesis, probably inflammation-mediated (47). High fibrinogen plasma levels enhance fibrin formation, platelet hyperaggregability, and increases blood viscosity. Of particular interest, high plasma fibrinogen and von Willebrand factor were shown to be risk factors of venous thrombosis even in the general population.

Endogen anticoagulants plasma levels also shift toward a prothrombotic state. Patients with NS have low antithrombin III (ATIII) levels, because of urinary loss (48). Protein C is a serine protease which regulates coagulation by proteolytically inactivating activated coagulation factors V and VIII. It is activated by thrombin and has protein S as cofactor. Proteins C and protein S are vitamin K-dependent proteins that are synthesized in the liver. As both proteins have molecular weights in the domain of albumin, they can be lost in urine. Moreover, the remaining protein S is avidly bound by C4b-binding protein, a component of the complement system (49). However, low free protein S levels were not consistently observed (50), and protein C levels were reported as preserved or even increased. These observations suggest that the nephrotic syndrome-associated risk of thrombosis may not be related to the deficiency of proteins C and S, which are more likely to have a protective role (51-54).

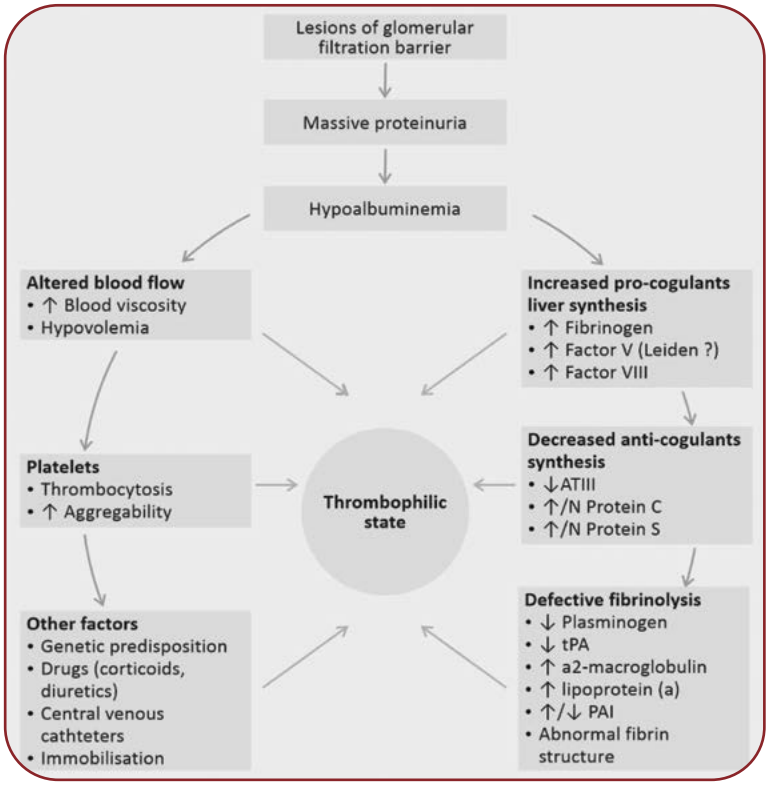

FIGURE 3. The mechanism of thromboembolism in NS is due to the combination of many factors, with podocyte injury playing a central role

The fibrinolytic system is also altered. Plasminogen and its activator, tissue-type plasminogen activator (tPA) decrease correlated to the severity of proteinuria (52, 55). Meanwhile, plasma levels of α2-macroglobulin and lipoprotein (a) are important inhibitors of fibrinolysis, which increase due to augmented liver synthesis (52, 56). Also, the nephrotic state alters the structure of fibrin monomers, affecting clots fibrinolytic and viscoelastic properties, which make them resistant to thrombolysis (57). All these changes suggest a diminished fibrinolytic activity supporting the NS-associated hypercoagulable status.

Mild increases in platelet count and platelet hyper-reactivity were reported in NS. Increase platelet aggregability, alteration in several platelet surface markers (P-selectin) and active substances released from α-granules (β-thromboglobulin) and phosphatidylserine exposure on membrane have been documented. Platelet hyper-reactivity is multifactorial and is associated with hypoalbuminemia, changes in lipids plasma levels and hyperfibrinogenemia (58).

Also, the low circulating volume decreases the blood flow, while hyperlipemia increases blood viscosity, favoring thrombosis.

All these abnormalities combine with individual genetic predispositions (mutations in genes of factor V Leiden, plasminogen activator inhibitor), which were reported to increase the VTE risk in about 30% of nephrotic patients with VTE, environmental and acquired risk factors such as inflammation, drugs (corticosteroids and diuretics), central venous catheters, and prolonged bed rest (47, 59).

Prophylactic anticoagulant therapy

Thromboembolic events are a preventable cause of morbidity and mortality in patients with NS but the decision to initiate prophylactic anticoagulant therapy should carefully balance the anticoagulation-associated risk of bleeding against the risk of thrombosis (Figure 4). However, there is a paucity of controlled studies evaluating these

aspects. As a result, the recommendations are consensual, based on studies addressing membranous nephropathy, which was more intensively investigated (60).

The anticoagulation-associated risk of bleeding was not properly evaluated in nephrotic patients, as there are no controlled studies. Accordingly, scales of risk used in the general population, including HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly, available at https://www.mdcalc.com/has-bled-score-major-bleeding-risk, are recommended. The risk is low for a HAS-BLED score 0-1, medium or 2 and high for 3+. Generally, anticoagulation is contraindicated when the risk of bleeding is high (43).

The VTEs risk is clearly related to the severity of NS reflected by serum albumin (sAlb) level, but it also depends on the underlying glomerulopathy. The VTE risk thresholds levels for albumin were best investigated in membranous nephropathy, where the risk seems the highest as compared to other nephrotic glomerulopathies, where the risk seems lower, implying a lower albumin threshold (61). Some additional factors could increase the VTEs risk and should be taken into account in the clinical decision to start anticoagulation (Table 4) (19, 62, 63). However, there is insufficient information to define a risk score, and the decision to indicate prophylactic anticoagulation needs clinical judgement based on these VTE risk factors.

Anticoagulant drugs. Warfarin is recommended by KDIGO 2021 for TEs prophylaxis, and low molecular weight heparins (LMMWH) as an alternative, in similar doses, to those recommended for deep vein thrombosis prophylaxis in the general population (19, 61). However, this recommendation is not based on evidence, as controlled studies against placebo or other comparator to evaluate the efficacy and safety in TEs prophylaxis in nephrotic syndrome were not conducted. In a recent retrospective study, Keddal *et al* compared the outcomes between group anticoagulated prophylactically with warfarin or LMWH and a control group without anticoagulation in 79 non-diabetic patients with NS. They concluded that prophylactic anticoagulation with either agent considerably reduced the number of clinically diagnosed TEs in nephrotic patients with serum albumin <2 g/dL without a statistically significant risk of bleeding.

The pharmacokinetics and pharmacodynamics of both drugs could be modified in NS. As warfarin is highly bound to albumin, its free level increases in NS and its elimination time is shortened, making its pharmacokinetic unpredictable (64). Low molecular weight heparins act by potentiation of antithrombin which could have low levels in NS; they are protein bound and

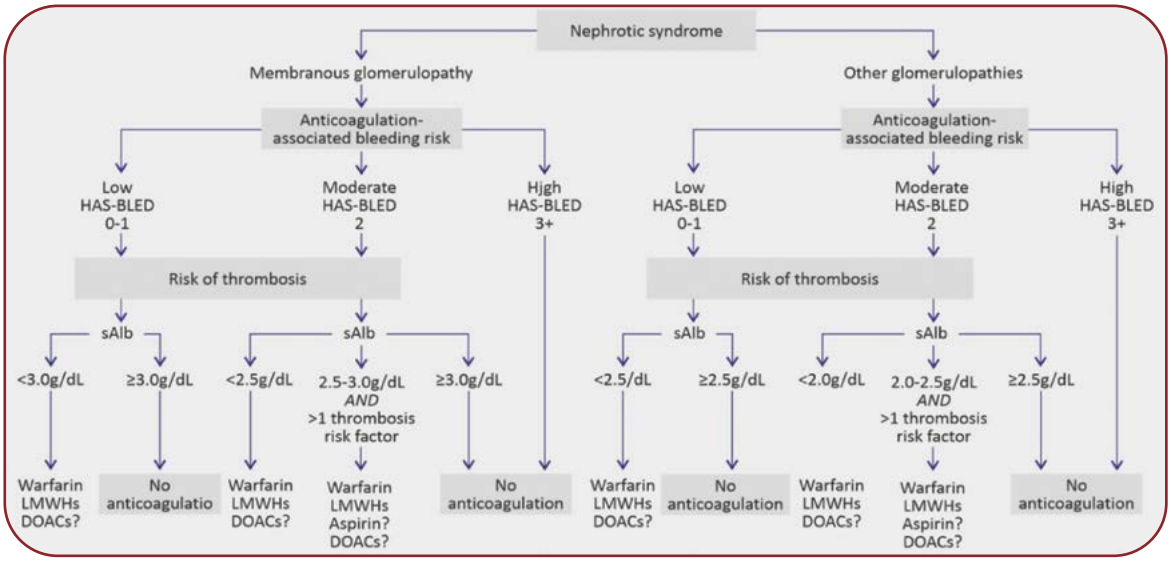

FIGURE 4. Algorithm for anticoagulant therapy in nephrotic syndrome – adapted after (62).
DOACs=direct-acting oral anticoagulants; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years) score; LMWHs=low molecular weight heparins; sAlb=serum albumin

TABLE 5. Factors associated with venous thromboembolic events in nephrotic syndrome (65)

• Serum albumin level (membranous nephropathy)
○ low risk - sAlb ≥3 g/dL
○ moderate risk - sAlb 3-2.5 g/dL
○ high risk – sAlb <2.5 g/dL
• Serum albumin level (other than membranous nephropathy)
○ low risk - sAlb ≥ 2.5 g/dL
○ moderate risk - sAlb 2.5-2.0 g/dL
○ high risk – sAlb <2.0 g/dL)
with one or more of the following:
• Proteinuria >10 g/day
• BMI >35 kg/m^2
• Documented genetic predisposition to thromboembolism
• NYHA class III/IV congestive heart failure
• Recent abdominal/orthopedic surgery
• Prolonged immobilization
Evidence level 2C
BMI-body mass index, NYHA-New York Heart Association

hypoalbuminemia could increase free drug fraction (and activity); also, they are primarily excreted in urine (43).

Thus, close monitoring of coagulation is necessary in users of the two above-mentioned drugs. In case of warfarin, the international normalized ratio (INR) should be maintained between 1.5-2.5, while in case of LMWHs, activated partial thromboplastin time (aPTT) or anti-factor XIa activity should be occasionally assessed (48, 65).

Aspirin (75 mg) was also used for TEs prophylaxis in NS, and when retrospectively compared to LMWH and no prophylaxis, it has better prevented VTEs (66). In another study, a personalized regimen of prevention according to serum albumin level – LMWH switched thereafter to warfarin (when albumin <2 g/dL) or aspirin (when serum albumin 2-3 g/dL) – was administered to 143 patients with NS of various primary glomerulopathies. No VTEs were observed in patients on established prophylaxis for one week and major gastrointestinal bleeding was observed only in one, and only two patients needed blood transfusion (67). Others proposed aspirin prophylaxis even when the risk of both VTEs and bleeding is high as well as in patients at medium risk for VTE (albumin ≥2.5 g/dL) and at high risk for cardiovascular events (high Framingham score) (68). Thus, aspirin can be a solution in nephrotic patients with moderate risk bleeding and VTE. Also, prophylactic aspirin has been proposed for patients with serum albumin levels ≥ 2.5 g/dL but elevated Framingham risk scores due to high rates of arterial cardiovascular events (69).

Direct-acting oral anticoagulants (DOACs) – factor Xa direct inhibitors (apixaban, rivaroxaban) or direct thrombin inhibitors (dabigatran) – would have some advantages in NS-associated TEs prophylaxis, because they can be administered orally and do not need monitoring. However, as they are protein bound, their pharmacokinetics could be altered in NS, resulting in sub- or supra-therapeutical levels, and their safety is uncertain when eRFG is lower than 30 mL/min, as they are mainly excreted in urine (43, 62). In a randomized study on dialysis patients with atrial fibrillation (69), the incidence of bleedings was similar in those treated with apixaban (5 mg bid) or warfarin, but the study was underpowered as it was prematurely stopped due to lack of funding, and many patients in the warfarin arm were not in anticoagulation target (70).

Additionally, the clinical experience with DOACs in NS is limited to a small pilot randomized trial and few case or series were prescribed not for prophylaxis but for therapy of thromboses. Although preliminary, these results are encouraging. Therefore, DOACs could be an option in nephrotic patients with side effects, inadequate therapeutic effects from warfarin or LMMW (19).

The duration of prophylactic treatment is unknown but it most likely extends to the remission of nephrotic syndrome or when albumin level is above 3 g/dL (19, 63).

Anticoagulation for thrombotic events

In case of thromboembolic (venous, arterial, pulmonary) events as well as in case of non-valvular atrial fibrillation, full anticoagulation is recommended for 6-12 months and/or for the duration of nephrotic syndrome (19, 61). ❑

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References

1. **Glassock RJ, Fervenza FC, Hebert L, Cameron JS.** Nephrotic syndrome redux. *Nephrology Dialysis Transplantation* 2015;30:1217. https://doi.org/10.1093/ndt/gfu077.
2. **Wilmer WA, Rovin BH, Hebert CJ, et al.** Management of glomerular proteinuria: a commentary. *J Am Soc Nephrol* 2003;14:3217-3232. doi: 10.1097/01.asn.0000100145.27188.33.
3. **Praga M, Borstein B, Andres A, et al.** Nephrotic proteinuria without hypoalbuminemia: clinical characteristics and response to angiotensin-converting enzyme inhibition. *Am J Kidney Dis* 1991;17:330-338. doi: 10.1016/s0272-6386(12)80483-5.
4. **Kaysen GA.** Albumin metabolism in the nephrotic syndrome: the effect of dietary protein intake. *Am J Kidney Dis* 1988;12:461-480. doi: 10.1016/s0272-6386(88)80097-0.
5. **Donckerwolke RA.** The nephrotic syndrome: Management, complications and pathophysiology. In: *Oxford Textbook of Clinical Nephrology*, Vol. 1, 3rd ed., Davison AM et al (eds), Oxford University Press, 2005, pp. 415-438.
6. **Svenningsen P, Bistrup C, Friis UG, et al.** Plasmin in nephrotic urine activates the epithelial sodium channel. *J Am Soc Nephrol* 2009;20:299-310. doi: 10.1681/ASN.2008040364.
7. **Bohnert BN, et al.** Aprotinin prevents proteolytic epithelial sodium channel (ENaC) activation and volume retention in nephrotic syndrome. *Kidney International* 2018;93:159-172. doi: 10.1016/j.kint.2017.07.023
8. **Sharotri V, Collier DM, Olson DR, et al.** Regulation of epithelial sodium channel trafficking by proprotein convertase subtilisin/kexin type 9 (PCSK9). *J Biol Chem* 2012;287:19266-9274. doi: 10.1074/jbc.M112.363382.
9. **Molina-Jijon E, Gambut S, Macé C, et al.** Secretion of the epithelial sodium channel chaperone PCSK9 from the cortical collecting duct links sodium retention with hypercholesterolemia in nephrotic syndrome. *Kidney Int* 2020;98:1449-1460. doi: 10.1016/j.kint.2020.06.045.
10. **Berger JM, Vaillant N, Le May C, et al.** PCSK9-deficiency does not alter blood pressure and sodium balance in mouse models of hypertension. *Atherosclerosis* 2015;239:252-259. doi: 10.1016/j.atherosclerosis.2015.01.012.
11. **Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR.** Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. *Adv Chronic Kidney Dis* 2015;22:179-184. doi: 10.1053/j.ackd.2014.11.006.
12. **Hinrichs GR, Jensen BL, Svenningsen P.** Mechanisms of sodium retention in nephrotic syndrome. *Curr Opin Nephrol* Hypertens 2020;29:207-212. doi: 10.1097/MNH.0000000000000578.
13. **Deschênes G, Guigonis V, Doucet A.** Mécanismes physiologiques et moléculaires de la constitution des oedèmes au cours du syndrome néphrotique [Molecular mechanism of edema formation in nephrotic syndrome]. *Arch Pediatr* 2004;11:1084-1094. doi: 10.1016/j.arcped.2004.03.029.
14. **Cadnapaphornchai MA, Tkachenko O, Shchekochikhin D, et al.** The nephrotic syndrome: pathogenesis and treatment of edema formation and secondary complications. *Pediatr Nephrol* 2014;29:1159-1167.
15. **Ellis D.** Pathophysiology, Evaluation, and Management of Edema in Childhood Nephrotic Syndrome. *Front Pediatr* 2016;3:111. doi: 10.3389/fped.2015.00111.
16. **Kottke MA, Walters TJ.** Where's the Leak in Vascular Barriers? A Review. *Shock* 2016;46(3 Suppl 1):20-36. doi: 10.1097/SHK.0000000000000666.
17. **Savin VJ, Sharma M, Zhou J, et al.** Multiple Targets for Novel Therapy of FSGS Associated with Circulating Permeability Factor. *Biomed Res Int* 2017;2017:6232616. doi:10.1155/2017/6232616
18. **Udwan K, Brideau G, Fila M, et al.** Oxidative Stress and Nuclear Factor κB (NF-κB) Increase Peritoneal Filtration and Contribute to Ascites Formation in Nephrotic Syndrome. *J Biol Chem* 2016;291:11105-1113. doi: 10.1074/jbc.M116.724690.
19. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, Kidney Disease Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100(Suppl 4):S1-S276. doi.org/10.1016/j.kint.2021.05.021.
20. **Duffy M, Jain S, Harrell N, et al.** Albumin and Furosemide Combination for Management of Edema in Nephrotic Syndrome: A Review of Clinical Studies. *Cells* 2015;4:622-630. Retrieved from https://doi.org/10.3390/cells4040622
21. **Ellison DH.** Clinical Pharmacology in Diuretic Use. *Clin J Am Soc Nephrol* 2019;14:1248-1257. doi: 10.2215/CJN.09630818.
22. **Orth SR, Ritz E.** The Nephrotic Syndrome. *New England Journal of Medicine* 1998;338:1202-1211. doi:10.1056/nejm199804233381707.
23. **Sterns RH, Emmett M, et al.** General principles of the treatment of edema in adults. Retrieved from UpToDate (Nov 2020).
24. **Langford AT, et al.** Underutilization of Treatment for Black Adults With Apparent Treatment-Resistant Hypertension. *Hypertension* 2020;76:1600–1607. doi.org/10.1161/HYPERTENSIONAHA.120.14836.
25. **Currie G, Taylor AHM, Fujita T, et al.** Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol* 2016;17:127. doi: 10.1186/s12882-016-0337-0.
26. **Cravedi P, et al.** Spironolactone Plus Full-Dose ACE Inhibition in Patients with Idiopathic Membranous Nephropathy and Nephrotic Syndrome: Does It Really Work? *Pharmaceuticals* (Basel) 2010;3:1-9. doi: 10.3390/ph3010001.
27. **Bakris GL.** Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med* 2020;383:2219-2229. doi: 10.1056/NEJMoa2025845.
28. **Erlandsson F, Albayaty M, Chialda L, et al.** Clinical safety, tolerability, pharmacokinetics and effects on urinary electrolyte excretion of AZD9977, a novel, selective mineralocorticoid receptor modulator. *Br J Clin Pharmacol* 2018;84:1486-1493. doi: 10.1111/bcp.13562.
29. **Frimodt-Møller M, et al.** Mitigating risk of aldosterone in diabetic kidney disease. *Curr Opin Nephrol Hypertens* 2020;29:145-151. doi: 10.1097/MNH.0000000000000557.
30. **Weir MR, Bakris GL, Bushinsky DA, et al.** Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;372:211-221. doi: 10.1056/NEJMoa1410853.
31. **Meaney CJ, Beccari MV, Yang Y, Zhao J.** Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate: A New Armamentarium for the Treatment of Hyperkalemia. *Pharmacotherapy* 2017;37:401-411. doi: 10.1002/phar.1906.
32. **Sun Q, Sever P.** Amiloride: A review. *J Renin Angiotensin Aldosterone Syst* 2020;21:1470320320975893. doi: 10.1177/1470320320975893.
33. **Tanaka A, et al.** Different Effects of Tolvaptan in Patients with Idiopathic Membranous Nephropathy with Nephrotic Syndrome. *Intern Med* 2017;56:191-196. doi: 10.2169/internalmedicine.56.7539.
34. **Park ES, Huh YS, Kim GH.** Is tolvaptan indicated for refractory oedema in nephrotic syndrome? *Nephrology* (Carlton) 2015;20:103-106. doi: 10.1111/nep.12348. PMID: 25619649.
35. **Kanzaki M, Wada J, Kikumoto Y, et al.** The

therapeutic potential of synthetic human atrial natriuretic peptide in nephrotic syndrome: a randomized controlled trial. *Int J Nephrol Renovasc Dis* 2012;5:91-96. doi: 10.2147/IJNRD.S32191.

36. **Ponticelli C, Glassock RJ.** Symptomatic therapy. In: *Treatment of primary glomerulonephritis.* Oxford University Press, 2019.
37. **Hoorn EJ, Ellison DH.** Diuretic Resistance. *Am J Kidney Dis* 2017;69:136-142. doi: 10.1053/j.ajkd.2016.08.027..
38. **Agarwal R, Gorski JC, Sundblad K, Brater DC.** Urinary protein binding does not affect response to furosemide in patients with nephrotic syndrome. *J Am Soc Nephrol* 2000;11:1100-1105. doi: 10.1681/ASN.V1161100.
39. **Kitsios GD, Mascari P, Ettunsi R, Gray AW.** Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care* 2014;29:253-259. doi: 10.1016/j.jcrc.2013.10.004.
40. **Neuhaus W, et al.** The effects of colloid solutions on renal proximal tubular cells in vitro. *Anesth Analg* 2012;114:371-374. doi: 10.1213/ANE.0b013e3182367a54.
41. **Solak Y, et al.** Renal artery embolization in severe nephrotic syndrome. *Hemodialysis International* 2016;20:407-413. doi: 10.1111/hdi.12397.
42. **Lin RM, et al.** A Systematic Review of Prophylactic Anticoagulation in Nephrotic Syndrome. *Kidney International Reports* 2019;5:435–447. doi: 10.1016/j.ekir.2019.12.001.
43. **Ismail G, Mircescu G, Ditoiu AV, et al.** Risk factors for predicting venous thromboembolism in patients with nephrotic syndrome: focus on haemostasis-related parameters. *Int Urol Nephrol* 2014;46:787-792. doi: 10.1007/s11255-013-0574-0.
44. **Kerlin BA, Blatt NB, Fuh B, et al.** Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. *J Pediatr* 2009;155:105-10 110.e1. doi: 10.1016/j.jpeds.2009.01.070.
45. **Kerlin BA, Ayoob R, Smoyer WE.** Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol* 2012;7:513-520. doi: 10.2215/CJN.10131011.
46. **Ismail G, Obrisca B, Jurubita R, et al.** Inherited Risk Factors of Thromboembolic Events in Patients with Primary Nephrotic Syndrome. *Medicina* (Kaunas) 2020;56:242. doi: 10.3390/medicina56050242.
47. **Singhal R, Brimble KS.** Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. *Thromb Res* 2006;118:397-407. doi: 10.1016/j.thromres.2005.03.030.
48. **Kauffmann RH, et al.** Acquired antithrombin III deficiency and thrombosis in the nephrotic syndrome. *The American Journal of Medicine* 1978;65:607-613. doi: 10.1016/0002-9343(78)90848-3.
49. **Vigano-D'Angelo S, D'Angelo A, Kaufman CE Jr, et al.** Protein S deficiency occurs in the nephrotic syndrome. *Ann Intern Med* 1987;107:42-47. doi: 10.7326/0003-4819-107-1-42.
50. **Citak A, Emre S, Sairin A, et al.** Hemostatic problems and thromboembolic complications in nephrotic children. *Pediatr Nephrol* 2000;14:138-142. doi: 10.1007/s004670050029.
51. **Gigante A, Barbano B, Sardo L, et al.** Hypercoagulability and nephrotic syndrome. *Curr Vasc Pharmacol* 2014;12:512-517. doi: 10.2174/15701611120314051817 2048.
52. **Ozkayin N, Mir S, Kavakli K.** Hypercoagulability risk factors in children with minimal change disease and the protective role of protein-C activity. *Int Urol Nephrol* 2004;36:599-603. doi: 10.1007/s11255-004-0868-3.
53. **Ocak G, Vossen CY, Lijfering WM, et al.** Role of hemostatic factors on the risk of venous thrombosis in people with impaired kidney function. *Circulation* 2014;129:683-691. doi: 10.1161/circulationaha.113.002385.
54. **Soff GA, Sica DA, Marlar RA, et al.** Protein C levels in nephrotic syndrome: use of a new enzyme-linked immunoadsorbent assay for protein C antigen. *Am J Hematol* 1986;22:43-49. doi: 10.1002/ajh.2830220107.
55. **Vaziri ND, Gonzales EC, Shayestehfar B, Barton CH.** Plasma levels and urinary excretion of fibrinolytic and protease inhibitory proteins in nephrotic syndrome. *J Lab Clin Med* 1994;124:118-124.
56. **de Sain-van der Velden MG, Rabelink TJ, Reijngoud DJ, et al.** Plasma alpha 2 macroglobulin is increased in nephrotic patients as a result of increased synthesis alone. *Kidney Int* 1998;54:530-535. doi: 10.1046/j.1523-1755.1998.00018.x.
57. **Colle JP, Mishal Z, Lesty C, et al.** Abnormal fibrin clot architecture in nephrotic patients is related to hypofibrinolysis: influence of plasma biochemical modifications: a possible mechanism for the high thrombotic tendency? *Thromb Haemost* 1999;82:1482-1489.
58. **Eneman BL, et al.** Platelet abnormalities in nephrotic syndrome. *Pediatric Nephrology* 2015;31:1267-1279. doi: 10.1007/s00467-015-3173-8.
59. **Bernard BD, et al.** Extrarenal complications of the nephrotic syndrome. *Kidney International* 1988;33:1184-1202.
60. **Rovin BH, Adler SG, Barratt J, et al.** KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney International* 2021;100:S1-S276.
61. **Sexton DJ, et al.** Direct-Acting Oral Anticoagulants as Prophylaxis Against Thromboembolism in the Nephrotic Syndrome. *Kidney International Reports* 2018;3:784-793. doi: 10.1016/j.ekir.2018.02.010.
62. **Glassock RJ.** Prophylactic Anticoagulation in Nephrotic Syndrome: A Clinical Conundrum. *Journal of the American Society of Nephrology* 2007;18:2221-2225. doi: 10.1681/asn.2006111300.
63. **Cattran DC, et al.** Kidney disease: Improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl 2* 2012:139-274.
64. **Ganeval D, Fischer AM, Barre J, et al.** Pharmacokinetics of warfarin in the nephrotic syndrome and effect on vitamin K-dependent clotting factors. *Clinical Nephrologyi* 1986;25:75-80.
65. **Holford NH.** Clinical Pharmacokinetics and Pharmacodynamics of Warfarin. *Clinical Pharmacokinetics* 1986;11:483-504. doi: 10.2165/00003088-198611060-00005.
66. **Zou P, Li H, Cai J, et al.** The role of prophylactic use of low molecular weight heparin or aspirin in thromboembolic events in primary membranous nephropathy. *Renal Failure* 2019;41:623-628. doi: 10.1080/0886022X.2019.1635030.
67. **Medjeral-Thomas N, Ziaj S, Condon M, et al.** Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. *Clin J Am Soc Nephrol* 2014;9:478-483. doi: 10.2215/CJN.07190713.
68. **Hofstra JM, Wetzels JFM.** Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? *Kidney Int* 2016;89:981-983. doi: 10.1016/j.kint.2016.01.019.
69. **Pokorney S.** Renal hemodialysis patients allocated apixaban versus warfarin in atrial fibrillation—RENAL-AF. Presented at the American Heart Association Annual Scientific Sessions 2019.