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EDUCATIONAL REVIEW

The nephrotic syndrome: pathogenesis and treatment of edema formation and secondary complications

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Abstract Nephrotic syndrome is an important clinical condition affecting both children and adults. Studies suggest that the pathogenesis of edema in individual patients may occur via widely variable mechanisms, i.e., intravascular volume underfilling versus overfilling. Managing edema should therefore be directed to the underlying pathophysiology. Nephrotic syndrome is also associated with clinically important complications related to urinary loss of proteins other than albumin. This educational review focuses on the pathophysiology and management of edema and secondary complications in patients with nephrotic syndrome.

Keywords Nephrotic syndrome · Edema · Secondary complications · Underfill · Overfill

Introduction

Nephrotic syndrome is defined by proteinuria (>3–3.5 g/day in adults or >1 g/m^2/day in children), hypoalbuminemia (<3.0 g/dL), and edema. Hyperlipidemia is also present in many patients with nephrotic syndrome. Numerous glomerular conditions can result in nephrotic syndrome, and certain patients with glomerular disease may manifest nephrotic range proteinuria without significant hypoalbuminemia or edema. In the present review the pathogenesis and management of the edema and metabolic complications of nephrotic syndrome will be discussed.

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Pathogenesis of edema in nephrotic syndrome

Two major pathophysiologic mechanisms have been proposed to explain the development of edema in nephrotic syndrome, including the "underfilling" hypothesis [1] and the "overfilling" hypothesis [2]. In the underfill hypothesis (Fig. 1) [3], high-grade proteinuria results in hypoalbuminemia with an associated decrease in plasma oncotic pressure. This in turn leads to increased net capillary ultrafiltration and edema. In the early phase of this process, the edema may be attenuated by increases in interstitial hydrostatic pressure and lymphatic drainage which enhance the return of interstitial fluid into the intravascular compartment. Ultimately, however, this compensatory mechanism is overwhelmed, and edema forms. The diminished intravascular volume is exacerbated, resulting in clinical symptoms such as tachycardia, peripheral vasoconstriction, low blood pressure, oliguria, and urinary sodium retention. While the resultant fall in glomerular filtration rate (GFR) is generally of a prerenal nature, acute tubular necrosis may occur if these hemodynamic effects are prolonged. Such patients also manifest activation of the renin–angiotensin–aldosterone system (RAAS) and increased plasma norepinephrine and arginine vasopressin (AVP) concentrations [4, 5]. While activation of the RAAS or sympathetic nervous system is observed with both renal parenchymal disease and intravascular hypovolemia, the non-osmotic increase in plasma AVP suggests that the primary derangement is hypovolemia, particularly in the arterial component of the circulation, i.e., arterial underfilling [6]. Similarly, suppression of RAAS may indicate volume expansion but can also be observed with renal parenchymal disease

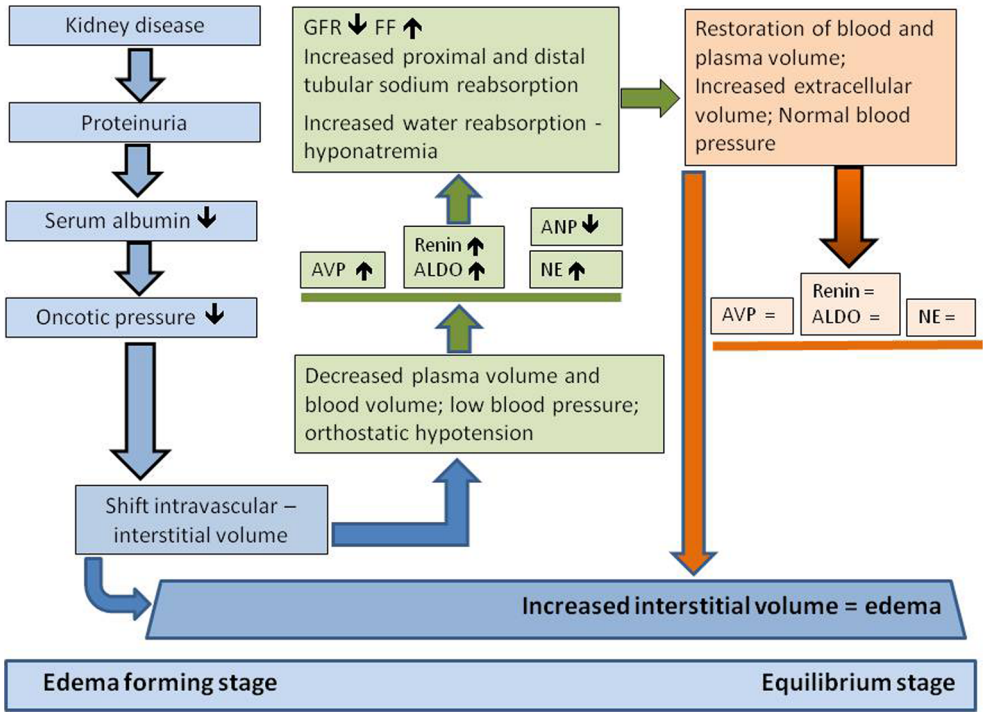

Fig. 1 The "Underfilling" theory of sodium retention in the nephrotic syndrome. *AVP* Arginine vasopressin, *ALDO* aldosterone, *ANP* atrial natriuretic peptide, *NE* norepinephrine, *GFR* glomerular filtration rate, *FF* filtration fraction. Reproduced with permission [3]

(e.g., diabetic nephropathy) independent of volume status [7, 8]. It should be emphasized that these characteristics of underfilling edema can occur in adults as well as children with nephrotic syndrome. This is believed to be the most common mechanism of edema formation in minimal change disease.

Usberti and colleagues studied 16 pediatric and adult patients with nephrotic syndrome who had normal renal function [9]. These patients had decreased plasma sodium concentration, increased plasma AVP concentration, impaired excretion of an acute water load, and elevation of plasma renin activity (PRA) and urinary norepinephrine levels as compared to controls. A highly significant inverse correlation between plasma AVP concentration and blood volume was demonstrated in these nephrotic patients (Fig. 2) [9]. Isotonic albumin infusion decreased plasma AVP concentration and increased water diuresis.

In contrast, Dorhout-Mees et al. have observed an overfill mechanism of edema formation in nephrotic syndrome (Reviewed in [10]). This interpretation necessitates an intrarenal mechanism of increased renal sodium and water reabsorption as the initiating factor in volume expansion and edema (Fig. 3) [3]. These authors observed that after prednisone-induced remission in 13 episodes of nephrotic syndrome in ten subjects with minimal change disease, blood pressure fell in 12 cases and plasma volume fell in ten cases. Gur et al. evaluated plasma and blood volume in 88 patients with nephrotic syndrome [11]. In support of vascular overfilling, they reported higher plasma and blood volumes corrected for estimated lean body mass as compared to controls. It should be emphasized, however, that the use of radioactive-labeled albumin to measure plasma or blood volume has an accuracy of ±10 % [12]. An additional source of variability comes from the correction of these volumes for body mass in the setting of significant edema. Nonetheless, it must be acknowledged that nephrotic syndrome, particularly when associated with various glomerulonephritides, may be characterized by hypertension, decreased kidney function, and volume expansion, i.e., vascular overfilling.

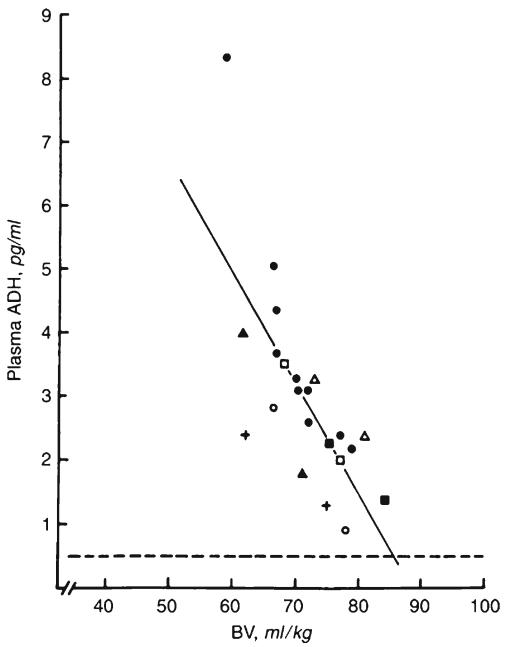

Fig. 2 Relationship between plasma antidiuretic hormone (*ADH*) and blood volume (*BV*) in nephrotic syndrome. *Solid circles* Basal values of nonexpanded patients, *other symbols* individual patients who underwent the BV expansion with 20 % plasma albumin. Reproduced with permission [9]

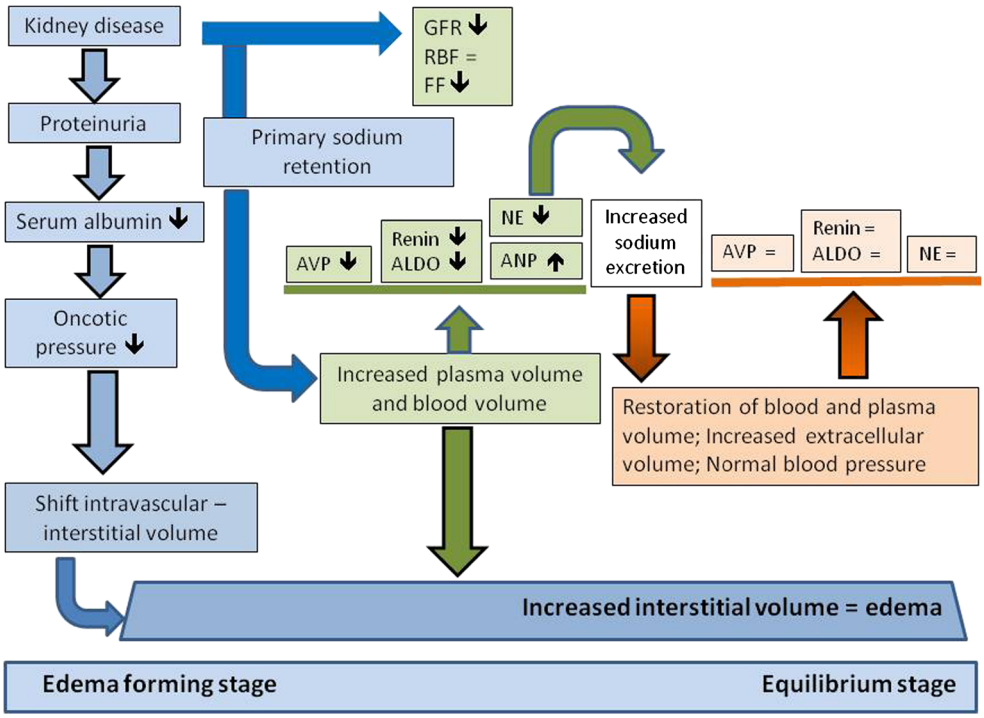

Fig. 3 The "Overfilling" theory of sodium retention in the nephrotic syndrome. Reproduced with permission [3]

Studies in which an angiotensin-converting enzyme inhibitor (ACEI) decreased plasma aldosterone concentration without inducing negative sodium balance have been used to support the overfilling hypothesis [13]. It is important to note, however, that blood pressure and thus renal perfusion pressure decreased with ACEI treatment which could have obscured any natriuretic response. In this regard, the mineralocorticoid receptor antagonist spironolactone has been shown to induce natriuresis in nephrotic patients in the absence of a fall in blood pressure [14].

Usberti et al. have described two groups of adult nephrotic patients differentiated by their plasma albumin concentration [15]. Those with plasma albumin concentrations of <1.7 g/dL had low blood volume, low plasma atrial natriuretic peptide (ANP) concentration, increased plasma angiotensin II concentration, and increased proximal tubule sodium reabsorption as estimated by lithium clearance. Alternatively, nephrotic patients with a plasma albumin concentration of >1.7 g/dL exhibited normal blood pressure and hormone concentrations. An analysis of all patients demonstrated that plasma albumin concentration was positively correlated with blood volume, while PRA was inversely correlated with blood volume and plasma albumin concentration. In children with nephrotic syndrome and severe edema, Kapur et al. [16] were able to differentiate underfilled and overfilled subjects by the fractional excretion of sodium (FENa). Those with a FENa of <0.2 % appeared to be volume contracted with significantly elevated blood urea nitrogen (BUN), elevated BUN/creatinine ratio, decreased urine sodium concentration, and increased plasma renin activity, serum aldosterone and plasma antidiuretic hormone concentrations as compared to the group with a FENa of >0.2 %.

Several mechanisms have been proposed to explain primary renal sodium and water retention in nephrotic patients with overfilling of the intravascular compartment, leading to edema. Such patients show resistance to ANP which has been attributed to increased activity of cyclic guanosine 3′,5′-monophosphate (cGMP) phosphodiesterase. This enzyme catabolizes the second messenger cGMP which is normally formed when ANP interacts with its biologically active natriuretic peptide A receptors, thereby leading to blunted ANP responsiveness [17–19]. It has also been suggested that intrarenal sodium retention in overfilled nephrotic patients is due to activation of the epithelial sodium channel (ENaC) in the collecting duct. Modification of extracellular loops of ENaC by proteinases such as plasmin is known to enhance channel activation [20, 21]. In this regard, Svenningsen et al. have shown that nephrotic urine activates ENaC channels expressed in cell culture and that such activation can be prevented by inhibitors of plasmin [22]. More recently, Andersen et al. studied 20 children with idiopathic nephrotic syndrome, reporting that urine obtained during relapsed nephrotic syndrome contains an increased amount of plasminogen–plasmin compared with urine collected during remission and that the relapse urine activated ENaC in a collecting duct cell line while remission urine did not [23].

Management of edema in nephrotic syndrome

Treatment of nephrotic syndrome should be directed at the primary disease. Guidelines for treatment in specific conditions

are detailed elsewhere [24–26]. When there are no specific evidence-based therapies, treatments aimed at mechanisms common to a variety of glomerular diseases can be considered. For example, proteinuria is considered to be an important risk factor for progression of chronic kidney disease [27]. Thus, inhibition of the RAAS with either an ACEI or angiotensin receptor blocker (ARB) is often utilized in order to decrease proteinuria and to hopefully delay the progression of chronic kidney disease.

Diet

Many of the symptoms in patients with nephrotic syndrome relate to the edema caused by renal sodium and water retention. Thus dietary sodium intake should be restricted to 2 g per day in adults or 35 mg/kg/day in children. Restriction of water intake can be reserved for patients with hyponatremia. If edema persists, diuretic treatment should be considered.

Diuretics

It is important to distinguish the potential contributions of underfilling versus overfilling in individual patients prior to the initiation of diuretic therapy (Table 1) [3]. Aggressive use of high-dose diuretics in "overfilled" nephrotic patients is indicated for management of edema and intravascular volume excess. In contrast, the use of diuretics in nephrotic syndrome with vascular underfilling should be undertaken judiciously with careful monitoring of renal and systemic hemodynamics given the potential to exacerbate intravascular hypovolemia. In this regard, Kapur et al. have demonstrated that diuretic therapy alone is safe and effective for the management of severe edema in nephrotic children who are overfilled while underfilled nephrotics may require both albumin and diuretics [16].

The extent of diuretic support required depends on the degree of edema and the individual's clinical response. In nephrotic patients with mild edema and normal GFR, an oral thiazide diuretic may be a reasonable first choice. With more severe edema, a loop diuretic should be considered, with intravenous administration more effective than oral administration [28]. When using oral loop diuretics, bioavailability of the drug must be considered (Table 2). While furosemide is the most commonly used loop diuretic, particularly in children, it has the greatest variation in oral bioavailability. In one study the oral bioavailability of furosemide in nephrotic children was found to be 58 % [29]. Because of the short duration of action of loop diuretics they must be administered at least twice per day. Poor diuretic response may be overridden by increasing the oral dose of the loop diuretic and/or by administering the agent intravenously. One study in nephrotic children demonstrated that 1 mg/kg of intravenous furosemide was twice as effective as 2 mg/kg of oral furosemide [28]. Torsemide and ethacrynic acid are less commonly utilized in children. As ethacrynic acid is the only loop diuretic which does not contain a sulfhydryl moiety, it may be useful in patients with significant sulfa allergy.

Loop diuretics are highly protein bound and must be secreted into the lumen of the nephron in order to block the Na-K-2Cl cotransporter in the thick ascending limb of the loop of Henle. Thus, it has been suggested that insufficient tubular secretion of the loop diuretic occurs in nephrotic patients with severe hypoalbuminemia, , resulting in a need for higher doses to achieve the desired effect. In fact, however, urinary protein binding of loop diuretics does not appear to be a major mechanism of diuretic resistance in nephrotic syndrome [30]. Poor compliance with prescribed medications and/or dietary salt intake should be excluded as causes of apparent resistance to loop diuretics. True resistance to loop diuretics in edematous disorders is multifactorial (Fig. 4) [31]. Diuretic-induced intravascular volume depletion and negative sodium balance stimulate neurohormonal systems, including RAAS, the sympathetic nervous system, and AVP, leading to renal vasoconstriction and sodium and water retention. The associated decrease in distal sodium delivery leads to loop diuretic resistance. Resistance by this mechanism can be addressed with concomitant use of a thiazide or amiloride. Chronic administration of loop diuretics in animals has also been shown to cause hypertrophy and hyperplasia in epithelial cells of the distal convoluted tubule with increased expression of the sodium chloride cotransporter, thereby blunting the natriuretic effect [32, 33]. Resistance by this mechanism can be overcome by concomitant use of a mineralocorticoid receptor antagonist. Limited data suggest that similar adaptations also occur in humans [34].

Combination therapy with loop and thiazide or thiazide like-diuretics (e.g., metolazone) can enhance diuresis as compared to a loop diuretic alone—but the patient needs to be carefully monitored to avoid severe hypokalemia and alkalosis. The administration of amiloride or a mineralocorticoid receptor antagonist with the loop diuretic can minimize hypokalemia although the diuretic effect of these

Table 1 Factors which help to differentiate overfill and underfill edema in nephrotic syndrome[a]

Factors	Overfill	Underfill
GFR <50 % of normal	+	–
GFR >75 % of normal	–	+
Serum albumin >2 g/dL	+	–
Serum albumin <2 g/dL	–	+
Minimal change histology	–	+
Hypertension	+	–
Postural hypotension	–	+

GFR, Glomerular filtration rate

[a] Table is reproduced from reference [12] with permission

Table 2 Pharmacology of loop diuretics

Pharmacology parameters	Furosemide	Bumetanide	Torsemide
Relative IV potency (mg)	40	1	20
Bioavailability (%)	10–100 (50)	80–100	80–100
Average effect duration (h)	6–8	4–6	6–8
Oral to IV conversion	2:1	1:1	1:1
30-day cost (USD $)	4	4	19–23

IV, Intravenous

medications alone at routine doses appears to be minimal [35, 36]. However, high-dose spironolactone (200 mg twice a day) has been shown to induce significant natriuresis in nephrotic adults as compared to controls [14]. Although it has been suggested that increased activity of ENaC may be a mechanism of primary sodium retention in nephrotic syndrome, there is no current clinical evidence to support the use of amiloride as a first-line diuretic in nephrotic syndrome. Whether the diuretic effect of amiloride is blunted by enhanced distal sodium delivery secondary to the frequent concomitant use of a loop diuretic is not known.

Albumin support

If diuretic therapy has not been effective, the intravenous administration of loop diuretics in combination with albumin may induce an effective although short-lived and relatively expensive diuresis [37]. The transient increase in blood volume associated with improved oncotic pressure is anticipated to improve renal hemodynamics and increase diuresis. With such treatment it is particularly important to determine the patient's intravascular volume status. In nephrotic patients with underfilling associated with severe hypoalbuminemia (<2 g/dL), an enhanced diuresis can be obtained with intravenous co-administration of 1 g/kg of 25 % albumin and furosemide. Alternatively, the administration of 25 % albumin to nephrotic patients who are overfilled may further exacerbate hypervolemia, contributing to systemic hypertension and generation or exacerbation of pulmonary edema. A 25 % solution of albumin must also be used with caution in patients with oliguria or significantly impaired renal function due to increased risk of pulmonary edema, while 5 % albumin is not helpful for management of edema due to the large volume required to provide a significant colloid load in an already edematous patient.

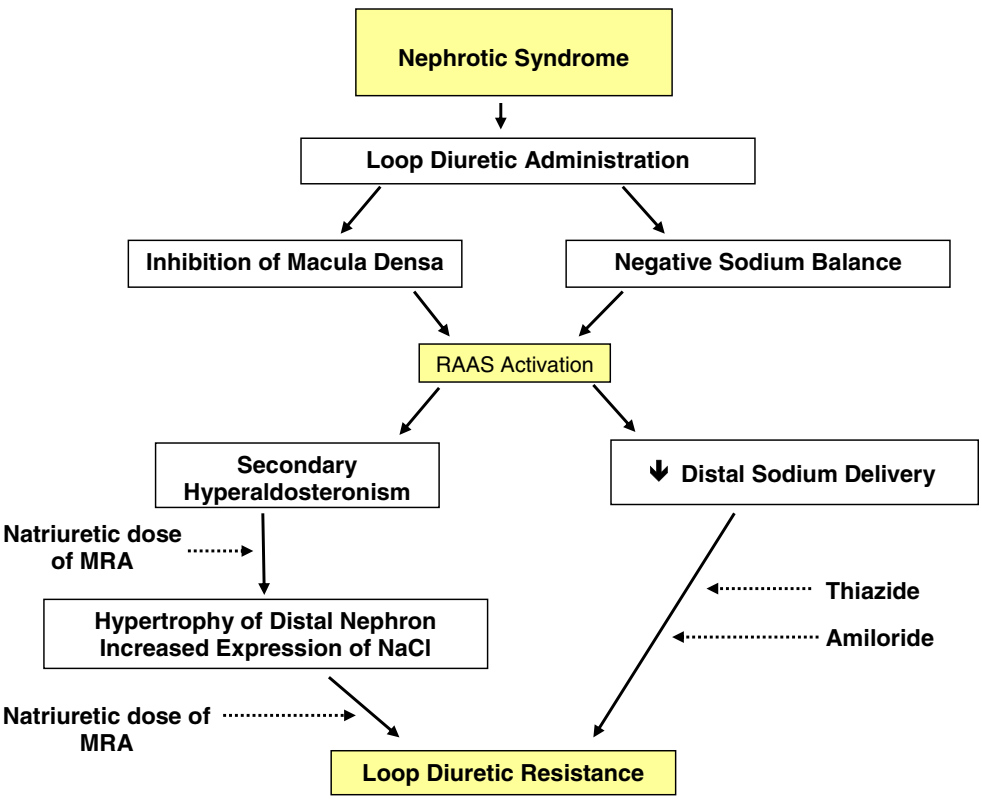

Fig. 4 Mechanisms of loop diuretic resistance in nephrotic syndrome. Loop diuretic administration induces intravascular volume depletion and negative sodium balance which result in activation of the renin–angiotensin–aldosterone system (*RAAS*). Loop diuretics also block sodium chloride transport at the macula densa, which directly stimulates RAAS independent of renal sodium loss. Elevated serum aldosterone concentration also results in hypertrophy of the distal nephron and increased expression of the sodium chloride cotransporter. These effects can be addressed with the use of a mineralocorticoid receptor antagonist (*MRA*). Decreased distal sodium delivery also contributes to resistance to loop diuretics. This effect can be mitigated with use of a thiazide or amiloride. Reproduced with permission [31]

Secondary complications of nephrotic syndrome

Increased urinary losses of protein and protein-bound molecules contribute to several complications in patients with nephrotic syndrome. The loss of albumin and thyroid binding globulin may reduce the binding capacity for total triiodothyronine and thyroxine. However, due to a rise in thyroid stimulating hormone (TSH), overt hypothyroidism is only rarely observed [38, 39]. Both subclinical and overt hypothyroidism may be more prevalent among treatment-resistant nephrotic children [40, 41]. Therefore, this subpopulation may warrant routine monitoring of thyroid function tests although no specific guidelines are available.

Both transferrin and erythropoietin (EPO) may be lost in the urine of nephrotic patients. Since transferrin transports iron to red blood cells, severely decreased transferrin levels can produce a microcytic anemia which is poorly responsive to iron supplementation [42]. EPO therapy has been shown to increase hemoglobin levels in anemic nephrotic patients with normal renal function and iron repletion[43].

Patients with nephrotic syndrome also may have reduced 25-hydroxy-vitamin D levels secondary to urinary loss of vitamin D binding protein [44]. In this setting, decreased serum ionized calcium levels may occur secondary to decreased free serum calcitriol, possibly leading to secondary hyperparathyroidism and only rarely to severe complications such as osteitis fibrosis and osteomalacia [45]. Vitamin D supplementation as cholecalciferol or ergocalciferol should be instituted when vitamin D deficiency is documented.

Patients with nephrotic syndrome have an increased risk of thromboembolic events [46]. Such events are associated with increased procoagulants, such as fibrinogen, factor VIII, and plasminogen activity factor-1, and decreased anticoagulants due to urinary losses of antithrombin III, plasminogen, and protein S [47]. A procoagulant state is favored and is further exacerbated by low intravascular volume observed in underfilled nephrotic patients or induced by diuretic therapy. A retrospective review reported that 9 % of 326 children with nephrotic syndrome of any cause had experienced at least one thromboembolic event, with a median time to the first event of 70.5 days following the diagnosis of nephrotic syndrome [48]. This is similar to adults in whom the majority of venous thromboembolism events occur within the first 6 months after diagnosis of nephrotic syndrome [46]. Independent predictors of thromboembolic events in the children of this study included age at onset of nephrotic syndrome of over 12 years, severity of proteinuria, and history of thromboembolic event prior to diagnosis of nephrotic syndrome [48]. Children with congenital nephrotic syndrome and membranous nephropathy are known to have a higher risk of thrombotic events [48]. The role of prophylactic anticoagulation in this setting is still debated [49]. Some have suggested primary pharmacologic prophylaxis with appropriately dosed low-molecular-weight heparin or other anticoagulant for nephrotic patients at the highest risk of thromboembolic events, such as those with additional thrombotic risk factors including surgery, malignancy, or pregnancy, those with a prior history of thromboembolism, or patients with membranous nephropathy [50]. However, there are no controlled clinical trials to support this recommendation.

Patients with nephrotic syndrome are prone to serious bacterial infection, notably pneumonia, sepsis, and peritonitis secondary to *Streptococcus pneumoniae*, *Escherichia coli*, and *Hemophilus* bacteria. Infection was the major cause of death in nephrotic children prior to the introduction of prednisone and antibiotics. The predisposition to infections with nephrotic syndrome has been associated with urinary immunoglobulin losses leading to low serum immunoglobulin G levels [51]. Treatment with intravenous immunoglobulin may be considered in the setting of acute serious bacterial infection or recurrent severe bacterial infections, but the protective effects are short-lived and routine administration is costly. Vaccination against pneumococcus with 13-valent conjugate vaccine and 23-valent polysaccharide vaccine is indicated and should be provided according to patient age and prior immunization history [52]. Studies suggest that an adequate serologic response can be induced in many subjects despite high-dose corticosteroid treatment [53, 54].

Nephrotic patients have abnormalities of lipid metabolism which predispose to cardiovascular disease [55, 56]. Adults with nephrotic syndrome have a significantly increased relative risk of myocardial infarction (5.5; 95 % confidence interval 1.6–18.3) as compared to controls despite adjustment for hypertension and smoking status [57]. The lipid abnormalities which occur with nephrotic syndrome include: (1) an increase in low-density lipoprotein (LDL) cholesterol due to reduced hepatic cholesterol uptake associated with acquired LDL-receptor deficiency; (2) increased lipoprotein(a) concentration due to increased rate of synthesis; (3) hypertriglyceridemia secondary to an inability to clear very low density lipoprotein, chylomicrons, and remnant particles. The defect in triglyceride clearance involves reduced endothelial lipoprotein lipase (LPL) and decreased ability of lipoproteins to bind to LPL. Acute myocardial infarction has been rarely reported in children with chronic nephrotic syndrome [58, 59]. Although previous data suggest no increased risk of cardiovascular events in adulthood associated with resolved childhood steroid-responsive nephrotic syndrome [60], concern for premature atherosclerosis and associated early cardiovascular events still exists. Adults with a history of steroid-responsive childhood nephrotic syndrome demonstrate increased total cholesterol, LDL, homocysteine, and apolipoprotein B and A1 levels as compared to controls, and there is a significant correlation between carotid intima-media wall thickness (IMT) and the number of recurrences of nephrotic syndrome [61]. In adults with childhood onset systemic lupus erythematosus, nephrotic range proteinuria has been associated with significantly higher levels of total cholesterol, LDL,

apolipoprotein B, and fibrinogen as well as higher IMT as compared to patients with lupus and lesser degrees of proteinuria or with controls [62]. Further study in this area is needed. Decreasing proteinuria and hypoalbuminemia with ACEI or ARB therapy may improve lipid abnormalities as well as control blood pressure in nephrotic patients (reviewed in [63]). In chronic nephrotic syndrome with persistent hyperlipidemia, statin therapy should be considered in both children and adults.

In adults, if proteinuria in nephrotic patients remains ≥1 g per day, a blood pressure goal of ≤125/75 mmHg is recommended, whereas with a decrease to <1 g per day a goal of ≤130/80 mmHg is satisfactory. In children with nephrotic syndrome, the goal blood pressure should be at or below the 90th percentile for age, sex, and height with a maximum for teenagers of 120/80 mmHg. Moderate protein restriction (0.8–1 g/kg per day) is recommended in adults with nephrotic syndrome while affected children require normal caloric and protein intake for their age to allow for appropriate growth. High dietary protein intake should be avoided in both pediatric and adult nephrotic patients.

In conclusion, in addition to treatment of the underlying glomerular disease, management of edema should include assessment of an underfilled versus overfilled intravascular space. This assessment may guide clinical decision-making with respect to diuretic and albumin support. Given the urinary losses of multiple proteins in addition to albumin, it is important to monitor affected patients for secondary metabolic complications and to treat these complications appropriately. Children with treatment-resistant nephrotic syndrome are at particular risk for these secondary complications. Further study into the long-term effects of childhood nephrotic syndrome on adult kidney and cardiovascular health are needed.

Multiple choice questions (answers are provided following the Reference list)

1) The following are more suggestive of underfilling than overfilling in nephrotic syndrome EXCEPT:
   a. Serum albumin concentration below 2 g/dL
   b. Minimal change histology
   c. Hypertension
   d. Postural hypotension
2) The following should be considered in the management of severe anasarca and mild pulmonary edema in a hypertensive nephrotic child with serum albumin concentration 2.7 g/dL and other findings consistent with the overfill hypothesis EXCEPT:
   a. Loop diuretics
   b. Addition of a thiazide or metolazone to enhance diuresis
   c. Daily intravenous administration of 25 % albumin
   d. Fluid restriction
3) The following are commonly known secondary complications of active nephrotic syndrome EXCEPT:
   a. Subclinical hypothyroidism
   b. Thromboembolism
   c. Hypogammaglobulinemia
   d. Hepatitis
4) A teenage girl with membranous nephropathy presents with left flank pain, gross hematuria, and thrombocytopenia. The most likely etiology related to her nephrotic syndrome is:
   a. Urolithiasis
   b. Left renal vein thrombosis
   c. Urinary tract infection
   d. Wilms tumor

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Answers

1. C
2. C
3. D
4. B