

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Thrombophilia of Nephrotic Syndrome in Adults

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H&O What are the causes and symptoms of nephrotic syndrome?

Nephrotic syndrome is the consequence of abnormal renal handling of protein due to a disruption of the glomerular filtration barrier, resulting in urinary loss and increased liver synthesis of plasma proteins. If the liver fails to fully compensate for urinary losses of albumin, hypoalbuminemia occurs, with consequent reduced plasma oncotic pressure and loss of intravascular fluid into the interstitium. Abnormalities of sodium and water retention also occur.¹ On occasion, a patient may notice frothy urine or develop eruptive xanthomata or xanthelasmata, but symptoms are usually the result of increasing edema (eg, leg, periorbital, pulmonary). The diagnosis of nephrotic syndrome is very rarely made after a thromboembolic event.

Causes of nephrotic syndrome are listed in Table 1. The profiles of most common glomerular diseases associated with nephrotic syndrome are changing, with focal segmental glomerulosclerosis (FSGS) becoming increasingly recognized, particularly in black patients, in whom it is the underlying etiology in more than half of cases.²

H&O What is the reported risk for venous thromboembolism in patients with nephrotic syndrome?

Thrombophilia is a prothrombotic state producing an increased risk of venous thromboembolism (VTE), which may be inherited or acquired. Among the numerous causes of nephrotic syndrome, only a few conditions are consistently associated with increased risk of VTE,

including membranous nephropathy, membranoproliferative glomerulonephritis, minimal change disease, and perhaps renal amyloidosis.³

Nephrotic syndrome has been associated with renal vein thrombosis (RVT). RVT may present acutely with severe flank pain, gross hematuria, and an acute deterioration in renal function, or can be asymptomatic. In a meta-analysis of several small studies, the incidence of RVT in patients with nephrotic syndrome appears to range from 5–62% with an overall incidence of 35%.⁴ The variation in risk is in part due to differing methods of RVT diagnosis and in patient selection for investigation (eg, routine screening, screening dependent on risk factors, or the presence of a pulmonary embolism [PE]). The greatest risk is reported in patients with membranous glomerulonephritis

Table 1. Causes of Nephrotic Syndrome

| Primary Causes | |
|---|--|
| <ul style="list-style-type: none"> • Focal segmental glomerulosclerosis • Membranous nephropathy • Minimal change disease • Membranoproliferative Nephropathy, eg IgA | |
| Secondary Causes | |
| <p>Congenital Causes</p> <ul style="list-style-type: none"> • Alport's syndrome • Congenital syndrome of the Finnish type • Pierson's syndrome • Nail-Patella syndrome • Denys-Drash syndrome | <p>Infections</p> <ul style="list-style-type: none"> • HIV • Hepatitis B and C • Mycoplasma • Syphilis • Malaria • Schistosomiasis • Filariasis • Toxoplasmosis |
| <p>Systemic Diseases</p> <ul style="list-style-type: none"> • Diabetes mellitus • Systemic lupus erythematosus • Amyloidosis | <p>Drugs</p> <ul style="list-style-type: none"> • Gold • Antimicrobial agents • Non-Steroidal anti-inflammatory drugs • Penicillamine • Captopril • Tamoxifen • Lithium • Anti-VEGF monoclonal antibodies |
| <p>Cancer</p> <ul style="list-style-type: none"> • Myeloma • Lymphoma | |

(37%), membranoproliferative glomerulonephritis (26%), and minimal change disease (24%).⁵

VTE other than RVT occur in 8.5–44% of patients with nephrotic syndrome.⁴ One study of 94 patients with nephrotic syndrome who underwent ventilation-perfusion scanning identified asymptomatic perfusion deficits in 12.8% of patients. In patients with acute and chronic RVT, the incidence of symptomatic PE was higher (25% and 20%, respectively) than those without RVT (10%).⁶ Another retrospective study of 89 patients with severe nephrotic syndrome (serum albumin <2.0g/dL) identified PE in 32% of patients who underwent pulmonary angiography if pretest probability was high, despite low or intermediate probability ventilation-perfusion scanning.⁷

High rates of VTE in patients with nephrotic syndrome were described in studies performed before 1980, whereas more recent evidence suggests a lower rate of events. A survey of all randomized therapeutic trials for membranous nephropathy during 1979–2001 reported clinical VTE in approximately 1 in 500 cases⁵; a retrospective analysis of coding data from the United States during 1979–2005 found that 1.5% of patients with nephrotic syndrome had DVT, and 0.5% had PE,⁸ although the follow-up period was short. A recent study from 1995–2004 of 298 patients with over 10 years follow-up suggests that the annual clinical incidence of VTE is 8 times higher than in the general population, and that the risk is 140 times higher in the first 6 months (9.85% annual incidence). Survival analysis showed that with over 25 years of observation, the probability of an arterial or VTE event was 48%.⁹

Other factors which are presumed to be associated with increased risk of VTE in patients with nephrotic syndrome include previous history of thromboemboli, corticosteroid treatment, volume depletion, diuretic therapy, venous stasis, or theoretical immune complex activation of coagulation.

Membranous nephropathy has recently shown to be associated with anti-enolase autoantibodies, which may interfere with fibrinolysis,¹⁰ the pathophysiological consequences of which needs further exploration. Pre-existing inherited thrombophilic tendencies such as Factor V Leiden may theoretically increase the risk of VTE in patients with nephrotic syndrome, studies so far have shown that there is no such association.¹¹

The relative risk of arterial thrombosis associated with nephrotic syndrome ranges from 1–5.5^{12,13} and, like VTE, arterial events are most common in the first 6 months following diagnosis (5.52% annual incidence in the first year, 1.49% thereafter).⁹ Classic risk factors for atherosclerosis are associated with arterial thrombosis in nephrotic syndrome including sex, age, diabetes, hypertension, smoking, previous arterial disease, and glomerular filtration rate (eGFR).⁹

H&O How does a physician determine whether a patient is at risk for VTE?

Currently there are no predictive tests to determine VTE risk in nephrotic patients. Some researchers have identified an association of serum albumin (<2.5 g/dL) with increased risk,¹⁵ with 40% of patients with albumin levels (<2.5 g/dL) having events, but only 2.7% of those with levels higher than 2.5 g/dL developing clinical VTE. Another study reports that the ratio of proteinuria to serum albumin predicts the risk of VTE.⁹ However, others believe that the level of hypoalbuminemia is not associated with increased VTE risk^{6,16,17} and perhaps surprisingly, unlike the general chronic kidney disease (CKD) population, the level of proteinuria is not a predictor of arterial thrombotic risk.⁹

The combined risk of VTE and/or RVT in patients with membranous nephropathy has been estimated in some studies to be as high as 45%, and therefore thromboprophylaxis has been suggested for patients with membranous glomerulonephritis.^{15,18} Routine screening for RVT for those at high risk is debatable, as a negative test does not exclude the subsequent development of an event.

H&O What is the underlying mechanism of thrombophilia in nephrotic syndrome?

The underlying mechanism of thrombophilia in nephrotic syndrome is poorly understood and mostly based on studies performed 2–3 decades ago. Although profound abnormalities in hemostasis (eg, increased levels of prothrombotic factors and impaired fibrinolytic activity) have been identified, a causal relationship between the hypercoagulable state and the development of thrombosis has yet to be understood.

It is commonly believed that antithrombin is lost in the urine due to increased glomerular permeability, which allows unregulated thrombin generation. Plasma antithrombin levels are reduced in some patients with nephrotic syndrome^{19,20}; particularly, those with hypoalbuminemia (<20 g/dL)²⁰ have been shown to correlate with proteinuria^{19,20} although this finding is not universal.^{21–24} Low plasma antithrombin has been associated with VTE in some studies,^{7,25} but not others²⁶ and levels have been shown to increase with the resolution of the nephrotic state after steroid therapy.²⁴ Plasma α_2 -macroglobulin levels are also elevated due to increased synthesis.²⁷ This may contribute to increased plasma viscosity but may have a beneficial role as an inhibitor of thrombin.

Protein C and S^{22,28} have been found to be elevated in patients with nephrotic syndrome and are inversely correlated with serum albumin levels.²² Two studies have shown that while total Protein S antigens are increased, functional levels of free protein S are reduced, due to increased C4b-binding protein.^{28,29} One study noted

urinary loss of circulating free Protein S,²⁹ but the other did not identify any urinary Protein S.²⁸

Various studies in nephrotic patients have reported urinary losses of factors VII, IX, XI, and XII, prothrombin and anti-plasmin, and increased production of Factors II, V, VII, VIII, IX, and X.^{4,19-21,23,30-35} Correlations between increased levels of Factors V and VIII and hypoalbuminemia have been observed.²³ Tissue factor pathway inhibitors have been shown to be increased in patients with nephrotic syndrome, particularly in those with steroid-resistant disease,³⁶ suggesting that compensatory anticoagulation mechanisms are also activated.³⁷ Despite these changes in coagulation factors, there is no evidence that any are associated with increased risk of thrombosis.²⁶ Hepatic coagulation factor synthesis is increased by interleukin 6, which is elevated in nephrotic syndrome,^{38,39} but the relationship between pro-inflammatory cytokines and thromboembolism in nephrotic syndrome has never been explored.

Plasma fibrinogen levels increase in proportion to urinary protein loss.⁴⁰ Fibrinogen is synthesized at the same rate as serum albumin⁴¹ and may be as high as 10 g/L. There is a direct correlation between fibrinogen levels and total cholesterol and an inverse relationship with serum albumin.¹⁴ In vivo experiments in which blood from nephrotic patients is circulated over a matrix of tissue-factor rich cultured endothelial cells have demonstrated increased fibrin formation at lower venous shear rates compared with normal blood.⁴¹ Increased fibrinopeptide A and high molecular weight fibrin complexes suggest elevated fibrin deposition in nephrotic patients,⁴³ significantly in the renal vein, suggesting intraglomerular fibrin deposition, which may contribute to the downstream development of RVT.⁴⁴

Fibrinolysis: In general, plasminogen levels are low in patients with nephrotic syndrome and correlate with low serum albumin and severe proteinuria.^{45,46} Alpha-1 antitrypsin is reduced²¹ but alpha-2 antiplasmin levels are increased.^{31,47} Both plasma and urine tissue plasminogen activator (tPA) are elevated in nephrotic patients when compared to normal controls, but urinary excretion and intraglomerular expression of plasminogen activator inhibitor-1 are increased.⁴⁸ Hypoalbuminemia may also contribute to reduced fibrinolysis because albumin is a cofactor for binding plasminogen to fibrin and subsequent interaction with tPA.⁴⁹

Platelet Function: Patients with nephrotic syndrome have been shown to have normal to increased platelet counts.^{21,50} Platelet hyperaggregability is increased in response to stimulation with adenosine diphosphate, epinephrine, collagen, or arachidonic acid⁵¹⁻⁵⁴ and has been shown to significantly correlate with hypoalbuminemia, hyperfibrinogenemia, and hypercholesterolemia.⁵⁴ Markedly elevated levels of LDL cholesterol may affect plate-

let aggregability, as spontaneous aggregation has been shown to resolve with lipid-lowering therapy.⁵⁵ Decreased negative surface charge of isolated platelets with possible increased binding of von Willebrand factor (vWF) to glycoprotein Ib has also been demonstrated.⁵⁶

Levels of plasma β -thromboglobulin, P-selectin expression and CD62P/CD63-positive platelets are usually increased in nephrotic patients compared to healthy controls.⁵⁷ β -thromboglobulin may return to baseline with clinical remission.⁵⁸ Circulating arachidonic acid, which is usually albumin-bound, is elevated, and in the presence of hypoalbuminemia it has been shown to lead to increased platelet generation of thromboxane A₂^{59,60} and thromboxane B₂,⁶⁰ although this has not been found by all groups.⁵⁴ Platelet hyperaggregability as a result of thromboxane generation is corrected with an increase in albumin concentration.⁵²

Increased vWF levels may contribute to hypercoagulability,⁴¹ but in vivo studies of platelet-vessel wall interactions have shown normal platelet adhesion and only moderate increases in aggregate formation in de-endothelialized or collagen type I sprayed human umbilical artery segments.⁴¹ It is hypothesized that platelet hyperaggregability is reduced in vivo by fibrinogen binding to glycoprotein IIb-IIIa, thereby interfering with vWF-glycoprotein IIb-IIIa mediated vessel wall adhesion. Modulation of fibrinogen concentrations in normal blood has been shown to demonstrate the same properties of platelet aggregability in vivo as nephrotic blood (ie, platelet aggregation in suspension increased), while platelet adhesion and aggregate formation under flow conditions decreased with rising concentrations of fibrinogen.⁴¹

Endothelial Function: Endothelial derived nitric-oxide mediated vasodilation has been found to be impaired in nephrotic patients.⁶¹ Endothelial perturbation due to hypoalbuminemic-associated increases in lysophosphatidylcholine in circulating LDL has been proposed to be important.³⁸ Patients with nephrotic syndrome have been shown to have endothelial dysfunction to the same degree as patients with primary hyperlipidemia, although no significant relationship between serum lipids and lipoproteins has been demonstrated.⁶² L-arginine, which improves nitric oxide (NO)-mediated vasodilation in patients with familial hypercholesterolemia has no effect in patients with nephrotic syndrome,⁶³ and increased blood pressure⁶² and homocysteine,⁶⁴ which are correlated with endothelial function in patients with hyperlipidemia, has no relationship with endothelial function in those with nephrotic syndrome, suggesting that other mechanisms may also be important. Circulating nonesterified fatty acids (NEFA) are predominantly bound to albumin, and NEFA:albumin is a marker of cardiovascular risk in non-nephrotic individuals.⁶⁵ NEFA:albumin has also been shown to be associated

with endothelial dysfunction in patients with nephrotic syndrome; free NEFA may cause direct endothelial toxicity or decrease endothelial NO synthesis.³⁸ Others have proposed that hypoalbuminemia itself may disturb endothelial function by affecting the configuration of the cell membrane, or by directly affecting Gi-protein-dependent signal transduction.⁶³

Localized activation of coagulation has also been suggested to be responsible for the finding of RVT in patients with nephrotic syndrome because increased glomerular tissue factor activity has been identified downstream in animal models of glomerulonephritis and tissue biopsies of patients with crescentic glomerulonephritis,³⁴ but has never formally been assessed.

H&O What are the treatment options for VTE in patients with nephrotic syndrome?

In the event of a VTE in a patient with nephrotic syndrome, treatment usually consists of intravenous unfractionated heparin (UFH) maintaining an activated partial thromboplastin time (APTT) of 2.0–2.5, followed by warfarin. Low molecular weight heparin is safe in patients with eGFR higher than 30 mL/min/1.73 m² and has been used successfully for the treatment of RVT.⁶⁶ However, as it is renally excreted, UFH use is recommended in those who have severe renal impairment. Higher doses of UFH are usually required to achieve adequate anticoagulation in patients with nephrotic syndrome,⁶⁷ which appears to be an acute phase response and unrelated to antithrombin deficiency. As UFH has unpredictable pharmacokinetics, dosing must be guided by standard nomograms and APTT. Anticoagulation should be continued until nephrotic syndrome resolves and further events subside,⁵ although RVT has been reported after treatment withdrawal.⁶⁸ Prescribing oral vitamin K antagonists in patients with chronic kidney disease for VTE (eGFR <30 mL/min/1.73 m²) is associated with increased bleeding than those with normal renal function,⁶⁹ particularly in the setting of altered pharmacokinetics in the presence of hypoalbuminemia, and therefore should be monitored carefully.

Alternative approaches include thrombolysis and mechanical thrombectomy for RVT, but these methods have never been directly compared with conventional anticoagulation.

Thromboprophylaxis

There are no randomized controlled trials assessing the use of thromboprophylaxis in patients with nephrotic syndrome. Due to the higher risk of VTE, it has been recommended by some authors that patients with membranous nephropathy and nephrotic syndrome should receive thromboprophylaxis^{14,18}; it should be given for patients with other underlying etiologies when serum albumin is less than 20 g/dL and proteinuria is in neph-

rotic range.⁷⁰ Using a Markov-based decision analysis model, it has been estimated that “for a hypothetical 50-year-old patient with membranous nephropathy who remained nephrotic for 2 years, prophylactic anticoagulation yielded a gain representing 2.5 months of quality adjusted life expectancy.”¹⁸ For patients with other underlying etiologies of nephrotic syndrome, until further studies establish the VTE risk, each patient needs to be assessed on an individual basis according to underlying disease, renal function, and additional risk factors.

The utility of aspirin for the primary and secondary prevention of arterial atherothrombosis for patients with nephrotic syndrome has not been explored; however, treatment of hypercholesterolemia with pravastatin has been demonstrated to reduce platelet hypercoagulability in 11 patients, possibly mediated by suppression of TXA₂, but this has not been assessed in larger numbers.⁷¹

Children, due to their hypocoagulable state, have a lower incidence of VTE than adults⁷²; events are usually precipitated by intravascular lines. The management of VTE in pediatric renal disease is the same as in adults.

The arrival of new oral anticoagulants with predictable pharmacokinetics heralds a new era in anticoagulation. However, the first 2 licensed for short term use after orthopedic surgery are renally excreted. Apixiban, a synthetic anti-Xa agent that is not excreted renally, is currently in clinical trials and its utility in patients with renal disease is much anticipated. The next 5 years heralds many changes in the prevention and management of VTE.

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