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Nephrotic Syndrome: An Overview

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Abstract: Nephrotic syndrome (NS) is a clinical entity characterized by massive proteinuria (>3.5 g/day), hypoalbuminemia, edema, and hyperlipidemia, reflecting glomerular filtration barrier injury rather than a single disease. The condition is classified as either primary, due to intrinsic glomerular disease such as focal segmental glomerulosclerosis (FSGS), membranous nephropathy, and minimal change disease, or secondary, resulting from systemic disorders such as diabetes mellitus. Idiopathic nephrotic syndrome is increasingly understood as an immune-mediated process, with both T-cell and B-cell dysregulation contributing to podocyte injury and proteinuria. Complications include infection, thromboembolic events, and progressive renal dysfunction, with incidence rates varying between children (1.15–16.9/100,000) and adults (≈3/100,000 annually). Diagnosis is established through protein quantification (spot urine protein/creatinine ratio or 24-hour urine collection) and supported by biochemical findings including hypoalbuminemia and hyperlipidemia. Management is multifaceted, targeting reduction of proteinuria, control of edema, prevention of complications, and achievement of remission. Treatment strategies include sodium and fluid restriction, diuretics, immunosuppressive therapy, and renin–angiotensin system inhibitors. Evidence supporting routine use of ACE inhibitors or ARBs for improved clinical outcomes remains mixed, though their antiproteinuric effect is well recognized. Supportive care, including infection prevention, anticoagulation in high-risk patients, and management of dyslipidemia, is critical. Despite its rarity, NS poses significant morbidity and risk for progression to chronic kidney disease or end-stage kidney disease, highlighting the need for early diagnosis, individualized therapy, and long-term follow-up to optimize patient outcomes.

Keywords: *Nephrotic Syndrome, Proteinuria, Podocyte Injury, Edema, Diuretics, Immunosuppression, Renin–Angiotensin System Blockers.*

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I. INTRODUCTION

Nephrotic syndrome is a Massive proteinuria, usually defined as a urine protein excretion of more than 3.5 g per 24 hours, is a clinical symptom of nephrotic syndrome that causes hypoalbuminemia, edema, and hyperlipidemia. It is a collection of clinical and laboratory symptoms that indicate underlying glomerular injury and increased permeability of the renal filtration barrier rather than a disease in and of itself.(1)

Increased permeability of the glomerular filtration barrier causes nephrotic syndrome, a kidney disease. Proteinuria, hypoalbuminemia, edema, and hyperlipidemia are the four main clinical features that define it and are utilized to make the diagnosis.(2).

Idiopathic nephrotic syndrome (INS) is now understood to be primarily a T-cell-mediated illness, although recent developments in immunopathology have shown that B-lymphocytes are also essential. Through a variety of processes, such as the generation of autoantibodies, cytokine secretion, and T-cell response modulation, B cells play a role in the pathogenesis of disease. However, new research indicates that their dysregulation may even be more important than T-cell involvement in inducing podocyte damage and proteinuria.(3).

Additionally, a markedly hypercoagulable state that greatly increases the risk of venous and arterial thromboembolic events—particularly renal vein thrombosis, deep vein thrombosis, and pulmonary embolism—complicates nephrotic syndrome.

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Massive urinary loss of important anticoagulant proteins like antithrombin III and protein S, reactive hepatic overproduction of procoagulant factors like fibrinogen and coagulation factors V and VIII, platelet hyperreactivity, elevated blood viscosity from hyperlipidemia and hemoconcentration, and impaired fibrinolysis are some of the interrelated mechanisms that contribute to this prothrombotic milieu. Particularly in membranous nephropathy, where risk is particularly elevated, there is a substantial correlation between the degree of hypoalbuminemia and thrombotic risk.(4).

Despite being relatively rare, nephrotic syndrome has significant clinical implications, especially in children, where the annual incidence varies by area and ethnicity and averages between 1.15 and 16.9 cases per 100,000. About three out of every 100,000 adults are affected by the illness each year. Even though it is uncommon, its effects—which can range from severe edema to potentially fatal thrombotic episodes—call for caution and prompt identification in clinical practice.(5).

➢ *Incidence and Prevalence*

After diabetes mellitus and hypertension, glomerular illness—which includes nephrotic and nephritic syndrome—is the third most common cause of end-stage kidney disease (ESKD) in the US. Men are more likely than women to have nephrotic syndrome. Diabetic nephropathy, membranous nephropathy, and focal segmental glomerulosclerosis (FSGS) are the three most prevalent causes of nephrotic syndrome in North America. The primary cause of end-stage kidney disease (ESKD) and chronic kidney disease (CKD) is diabetes mellitus.(6).

➢ *Epidemiology*

Every year, there are three NS cases reported for every 100,000 adults. Adult NS cases are idiopathic in 80–90% of instances. Focal segmental glomerulosclerosis and membraneous nephropathy account for between 30% and 35% of adult cases of NS, with the former being more common in white individuals and the latter in black people. Immunoglobulin A nephropathy and minimal change disease account for about 15% of cases. In the other 10% of cases, the secondary cause is an underlying medical condition(7).

➢ *Classification*

Nephrotic syndrome is classified according to the treatment response:

Steroid-resistant nephrotic syndrome: One month after starting treatment, a sufficient dosage of steroids does not result in either full or partial remission. Refractory nephrotic syndrome: Treatments for refractory nephrotic syndrome that either do not result in full or partial remission include immunosuppressive medications and steroids. After six months of beginning treatment, I. In steroid dependent nephrotic syndrome, relapses occur after reducing or stopping steroids more than twice, making it hard to stop medication. Frequent relapses In nephrotic syndrome, relapses happen more than twice every six months.

Nephrotic syndrome requires long-term treatment: For two years, nephrotic syndrome will be treated with steroids or immunosuppressive drugs.(8).

II. CAUSES

Most cases of nephrotic syndrome appear to be caused by primary renal disease. Both membraneous nephropathy and focal segmental glomerulosclerosis (FSGS) account for approximately one-third of primary nephrotic syndrome cases; however, FSGS is the most common cause of idiopathic nephrotic syndrome in adults. Minimal change disease and immunoglobulin A (IgA) nephropathy account for about 25% of cases of idiopathic nephrotic syndrome. One of the less common conditions is membranoproliferative glomerulonephritis. FSGS is responsible for around 3.3% of newly diagnosed instances of end-stage renal disease. The most common of the several secondary causes of nephrotic syndrome that have been identified is diabetes mellitus.(9).

➢ *Clinical and Laboratory Presentation*

A spot urine protein/creatinine value of 3.0 to 3.5 mg or a loss of 3.0 to 3.5 g of urine protein during a 24-hour period are considered indicators of nephrotic syndrome. Regular urinalysis is a good way to check for proteinuria, but it has drawbacks and isn't a good way to find out whether there is proteinuria in the nephrotic range. The most common early symptom of nephrotic syndrome is edema, particularly in the lower limbs.(6).

➢ *Clinical Features*

Fatigue, weight gain, and increasing edema in the lower extremities are common symptoms of nephrotic syndrome. Ascites, periorbital or vaginal edema, or pleural or pericardial effusion can occur in patients with severe illness. Patients who develop new edema or ascites without the typical congestive heart failure dyspnea or cirrhosis stigmata should be investigated for nephrotic syndrome.(10).Nephrotic-range proteinuria is the term used to describe a 24-hour urine collection that contains more than 3 to 3.5 g of protein; however, not all people with this range of proteinuria have nephrotic syndrome. Although a urine dipstick proteinuria value of 3+ is a useful semiquantitative means of diagnosing nephrotic-range proteinuria, the random urine protein/creatinine ratio is a more realistic quantitative test given the logistical hurdles of collecting a 24-hour urine sample. Since the numeric spot urine protein/creatinine ratio, in mg/mg, accurately calculates protein excretion in g per day per 1.73 m2 of body surface area, a ratio of 3 to 3.5 denotes nephrotic-range proteinuria.(11).Low serum albumin levels (below than 2.5 g per dL [25 g per L]) and severe hyperlipidemia are other prominent characteristics of nephrotic syndrome. According to one study, twenty-five percent of people with nephrotic syndrome had a total cholesterol level above 400 mg/dL (10.36 mmol/L), and fifty-three percent had a level above 300 mg/dL (7.77 mmol/L).(12).

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➢ *Diagnosis*

Diagnostic criteria for nephrotic syndrome:-

Table 1:- Shows Diagnostic Criteria for Nephrotic Syndrome (13)

Factor	*Criteria*
Heavy proteinuria	Spot urine showing a protein-to-creatinine ratio of > 3 to 3.5 mg protein/mg creatinine (300 to 350 mg/mmol), or 24-hour urine collection showing > 3 to 3.5 g protein
Hypoalbuminemia	Serum albumin < 2.5 g per dL (25 g per L)*
Edema	Clinical evidence of peripheral edema
Hyperlipidemia (not required for diagnosis)	Severe hyperlipidemia, total cholesterol is often > 350 mg per dL (9.06 mmol per L)

➢ *Pathophysiology*

Damage to or malfunction of the glomerulus's structural components, such as the basement membrane, endothelium surface, or epithelial cells (podocytes), results in the loss of urine proteins, primarily albumin. Due to limitations on the size of the pore in the basement membrane and the charges of the implicated barriers, only a subset of proteins can be eliminated in the urine.(14) NS symptoms include edema, protein loss in the urine, hypoalbuminemia, and hyperlipidemia. Numerous conditions damage the glomerular podocytes, resulting in NS. These specialized epithelial cells form a filter that captures plasma proteins in the bloodstream in conjunction with the basal membrane and the glomerular capillary endothelial cells. Proteinuria is the outcome of an issue with this filter. Primary focal segmental glomerulosclerosis, membranous glomerulonephritis, and minimal change are the three most prevalent primary glomerular diseases.Despite the rarity of the well-known varieties, the identification of significant gene anomalies has significantly increased our understanding of podocyte function and the etiology of NS.(15) The development of edema in NS has no known cause. The primary issue seems to be increased glomerular permeability to albumin and other plasma proteins. Edema is caused by increased fluid drainage in the vascular zone between blood vessels, primarily as a result of kidney salt absorption, and decreased flow because of a drop in blood albumin levels. Although it is still unclear, the biological relationship between normal saline and thrombus formation seems complex and includes increased liquid outflow in the vascular area between blood vessels. If a patient also has NS and prothrombotic genetic variations, their risk of thrombosis is significantly increased .(16)

➢ *Goals*

The goals of treating patients with nephrotic syndrome are to:

- Prevent relapses;
- Identify and treat acute complications of persistent nephrotic syndrome;
- Prevent and treat long-term complications related to drug side effects; and
- Achieve complete remission of nephrotic syndrome.(17)

➢ *Management*

Few high-quality research and no clinical guidelines exist for the treatment of adult nephrotic syndrome. The main sources of recommendations are expert opinion, additional observational research, and early case series.(18).

III. FLUID AND NUTRITION

Edema will be lessened by establishing a negative sodium balance, most likely while the underlying condition is being treated or while the renal inflammation gradually goes away. Patients may need to limit their fluid consumption (to less than roughly 1.5 L per day) and limit their sodium intake to 3 g per day.(10)

➢ *Diuretics*

Despite being the mainstay of medical treatment, there is little evidence to support the choice or dosage of diuretics. Experts recommend diuresis to prevent acute renal failure or electrolyte imbalances by achieving a daily weight loss of 1 to 2 pounds (0.5 to 1 kilogram). Bumetanide and furosemide (Lasix) are the two most often used loop diuretics. Large doses (e.g., 80–120 mg of furosemide) are often required14 because to intestinal edema's low absorption of oral medicines, and these drugs are typically delivered intravenously.(19).Furthermore, low serum albumin levels make diuretics less effective and necessitate higher dosages. Metolazone (Zaroxolyn), potassium-sparing diuretics, or thiazide diuretics may be useful as additional or synergistic diuretics.(20)

➢ *Antibiotic Therapy*

Although the use of cytostatic medication may change our approach in the future, we do not currently administer prophylactic antibiotic treatment to patients who are under proper supervision. The risk of infection by an organism resistant to the particular antibiotic used does not go away with prolonged usage of antibiotics. If an infection develops, immediate, vigorous antibiotic treatment is required. With the exception of pyelonephritis, penicillin is the recommended antibiotic for pyrexia of unclear cause or infection. Effective antibiotics and the unique effects of steroid therapy are undoubtedly equally responsible for the decline in the mortality rate of idiopathic nephrosis. Concomitant bacterial

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pyelonephritis is not overlooked; it is by no means uncommon and requires intensive treatment for at least six months.(20)

➢ *Treating Edema*

Nephrotic patients are resistant to diuretics, even when their glomerular filtration rate is normal. For loop diuretics to work in the renal tubule, they need to be protein-bound. Loop diuretics are less effective when NS lowers serum proteins, therefore patients may require higher-than-normal prescriptions. Other possible mechanisms of diuretic resistance exist. Oral loop diuretics are usually advised to be taken twice day due to their extended duration of action. However, intestinal wall edema may make it impossible for the diuretic to be absorbed through the gastrointestinal tract in situations of severe NS and edema, requiring IV diuretic treatment. Diuresis should aim for 2 to 4 pounds (1 to 2 kilograms) every day, be reasonably progressive, and be controlled . (21).

40 mg of furosemide (Lasix) or 1 mg of bumetanide administered orally twice a day is a suitable starting dosage. The dosage should be approximately doubled every one to three days if edema or other symptoms of fluid overload do not go away..(21)

The maximum dosage of furosemide is approximately 240 mg per dose, or 600 mg per day.(22) However, there is no compelling evidence or rationale for this limit. If the clinical response remains insufficient, patients may be treated by switching to intravenous loop diuretics, adding oral thiazide diuretics, or providing an intravenous bolus of 20% human albumin prior to an intravenous diuretic bolus.(21)

➢ *Treating and Preventing Infection*

Up to 20% of individuals with NS have been documented to have an infection; however, it is unclear if NS is the cause of the infection or whether it results from hospitalization, corticosteroid usage, or other causes(18). A Cochrane review reported that there is insufficient evidence to support any particular intervention for preventing infections in adults with nephrotic syndrome(23).

➢ *Antiproteinuric Treatment*

Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers seems to lower the risk of venous thrombosis, but this effect has not been definitively proven(24).Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are commonly advised for patients with nephrotic syndrome due to their established antiproteinuric action. Nonetheless, their effectiveness in improving specific outcomes—such as preventing renal failure, promoting recovery, reducing edema, or decreasing the need for dialysis—remains uncertain, and the available evidence on their routine use is inconsistent.(25)

IV. CONCLUSION

Heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia are the characteristics of nephrotic syndrome, a clinical condition that commonly results from primary glomerular disease or other systemic issues. Early detection, timely management of complications, and personalized medication are critical for lowering morbidity and preventing the progression of chronic kidney disease or end-stage renal disease. The cornerstone of treatment to achieve remission and improve patient outcomes is comprehensive care, which includes supportive management, immunosuppressive medicine, diuretics, and dietary changes.

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