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An Overview on Nephrotic Syndrome

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Abstract:

Nephrotic syndrome is a clinical disorder characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and varying degrees of edema. It results from structural or functional disruption of the glomerular filtration barrier, particularly at the level of podocytes and the slit diaphragm. Nephrotic syndrome can be classified into primary (idiopathic) forms, such as minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), and secondary forms associated with systemic diseases including diabetes mellitus, lupus nephritis, infections, drugs, and malignancies.

In pediatric populations, minimal change disease is the most common and is typically steroid-responsive, whereas FSGS is more frequently associated with steroid resistance and higher risk of renal function decline. The pathophysiology involves immune dysregulation, podocyte injury, genetic susceptibility, and altered glomerular permeability. Persistent or poorly controlled disease can lead to complications such as infection, thrombosis, acute kidney injury, and progression to chronic kidney disease or end-stage renal disease (ESRD).

Management strategies depend on the underlying cause and treatment response, ranging from corticosteroids and immunosuppressive therapy to supportive measures such as diuretics, antiproteinuric agents, and lipid control. Recent advances in molecular and genetic studies have improved understanding of disease mechanisms, particularly in cases of steroid-resistant nephrotic syndrome (SRNS).

Keywords: Nephrotic Syndrome; Proteinuria; Hypoalbuminemia; Edema; Minimal Change Disease (MCD).

Introduction:

Nephrotic syndrome (NS) is a kidney condition caused by increased permeability in the glomerular filter as it affects the glomerular capillary wall, causing significant protein, fluid and nutrients loss through urination. Diagnosis is based on four main clinical signs: excess protein in urine, low blood albumin levels, swelling, and high blood lipid levels. Proper management through medication and nutrition is crucial to ensure normal growth and development in affected children while reducing the negative impacts of treatment (**1**).

NS can occur in people of any age, gender, or race. It may present in its classic form or alongside nephritic syndrome, which involves inflammation of the glomeruli, causing blood in the urine and reduced kidney function. In children, the initial sign of nephrotic syndrome is typically facial swelling, which then spreads throughout the body. Adults, on the other hand, may first notice swelling in lower parts of the body. Common symptoms also include tiredness and decreased appetite (**2**).

NS can be caused by primary kidney diseases or secondary systemic conditions. Primary causes often involve intrinsic kidney disorders such as membranous nephropathy, minimal-change nephropathy, and focal

glomerulosclerosis. Secondary causes may stem from systemic diseases like lupus erythematosus, diabetes mellitus, and amyloidosis. In some cases, focal glomerulosclerosis can be congenital or hereditary, resulting from genetic mutations affecting proteins in the podocytes, including podocin, nephrin, or the cation channel 6 protein (**3**).

NS is categorized based on the age of onset:

1. Congenital nephrotic syndrome (CNS) occurs within the first three months after birth. It's characterized by severe protein loss in urine, swelling, low blood albumin and gamma globulin levels, increased blood clotting tendency, and high blood lipids.

2. Infantile NS develops between 4 and 12 months of age.

3. Childhood NS is diagnosed when symptoms appear after the child's first birthday **(4)**.

The intricate structure and function of the kidney's filtration barrier, plays a crucial role in preventing protein leakage into urine, which is a hallmark of Congenital Nephrotic Syndrome (CNS). The barrier is a sophisticated three-layered system comprised of fenestrated endothelium, the glomerular basement membrane, and a podocyte layer with specialized foot processes and slit diaphragms **(5)**.

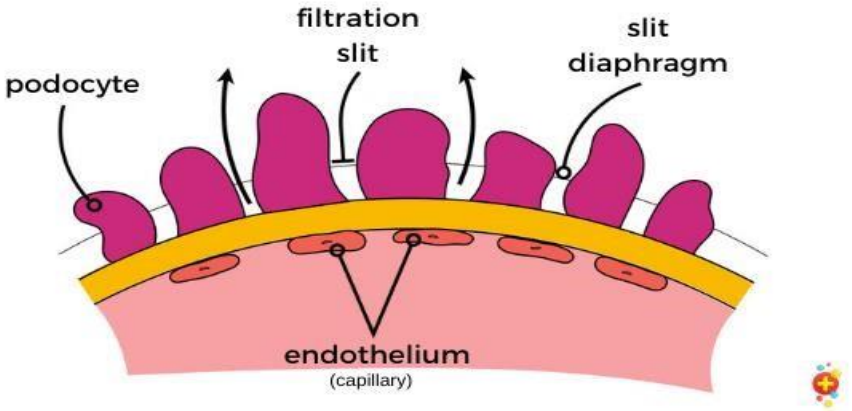

Figure-1 glomerular filtration border **(6)**

This filtration system operates like a precise molecular sieve, typically allowing only water and small plasma solutes to pass through while rigorously preventing larger molecules like albumin and other plasma proteins from entering the urine. The mechanism's effectiveness relies on the intricate interactions between the glomerular basement membrane and the slit diaphragms, which work together to maintain an extremely low protein content in the primary urine **(7)**.

Recent research has clarified that protein leakage can originate from primary defects in either the slit diaphragms or the glomerular basement membrane. These defects are often caused by genetic mutations in the proteins that constitute or regulate the filtration barrier. Such mutations can disrupt the barrier's delicate selectivity, leading to significant and potentially pathological protein excretion in urine, which is a defining characteristic of conditions like Congenital Nephrotic Syndrome **(8)**.

Percutaneous renal biopsy, while potentially diagnostic, carries inherent risks. Although the procedure can reveal histological features that are characteristic of CNS, the relationship between genetic mutations and tissue findings is not as conclusive as previously thought. This means that the histological appearance of kidney tissue does not always perfectly align with or definitively confirm the genetic mutations underlying the condition **(9)**.

When the diagnostic picture is not entirely clear, clinicians are advised to prioritize genetic analysis over immediately performing an invasive renal biopsy. The recommendation is to wait for genetic testing results, which can provide more precise information about the underlying genetic cause of the condition, rather than rushing to perform a potentially risky biopsy procedure **(10)**.

CNS management does not rely on steroids and other immunosuppressive agents, but rather on controlling edema and preventing underlying complications like thrombosis and infection. It is also crucial to maintain optimal nutrition for these children to thrive. Ultimately, renal transplantation could be the only therapeutic approach **(11)**.

In children, NS typically stems from two primary idiopathic diseases: minimal-change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Membranous nephropathy is a third type of NS but is uncommon in pediatric populations (**12**).

Minimal-change nephrotic syndrome (MCNS) is a distinct clinical and pathological condition characterized by selective protein loss in urine and low blood albumin levels. However, there is absence of cellular inflammation in the glomeruli and no detectable immunoglobulin deposits. The only observable microscopic abnormality is changes to the epithelial visceral cells, specifically the flattening or effacement of their foot processes. This unique presentation distinguishes MCNS from other forms of NS, making it a specific and identifiable kidney disorder (**13**).

Focal segmental glomerulosclerosis (FSGS) is a specific histological pattern that can arise from approximately six different underlying causes. Despite their diverse origins, these causes share a common pathological mechanism: damage to and reduction of podocytes, which are specialized cells in the kidney's filtering system (**14)**.

Differentiating between minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) is crucial because of their similarities. As both conditions share Proteinuria, Podocyte injury and Minimal immune deposits. To definitively rule out FSGS as the cause of NS and accurately evaluate the extent of kidney cortex involvement, a renal biopsy must include sufficient cortical tissue samples (**15**).

The classification of focal segmental glomerulosclerosis (FSGS) was originally proposed to have two main categories:

1. Primary (Idiopathic) FSGS

2. Secondary FSGS, which encompasses: familial or genetic forms, virus-associated forms, drug-induced forms and forms resulting from adaptive structural-functional responses, such as those occurring with congenital or acquired reduction of kidney mass or nephron count. This helps to distinguish between FSGS cases with unknown origins and those with identifiable underlying causes or contributing factors (**16**).

Primary FSGS is considered an immunological disorder triggered by an unidentified circulating factor that causes complete nephrotic syndrome. This form may respond to immunosuppressive treatments and is likely to recur rapidly after kidney transplantation, typically within days or weeks (**17**).

Secondary FSGS forms present differently, with characteristics that distinguish them from the primary form. These variants usually involve proteinuria below nephrotic levels, demonstrate progressive kidney dysfunction, and do not respond effectively to immunosuppression. Treatment for secondary FSGS focuses on resolving the underlying cause, and these forms generally do not recur in kidney transplants unless the original triggering condition persists (**18**).

Currently, several morphological variants of FSGS have been identified, encompassing both primary and secondary forms. These variants include:

1. Focal segmental glomerulosclerosis not otherwise specified (FSGS-NOS)

2. Perihilar variant

3. Cellular variant

4. Tip variant

5. Collapsing variant

Each of these variants represents a distinct morphological presentation of FSGS, which can help in more precise diagnosis and potentially guide treatment approaches **(19)**.

Epidemiology of Nephrotic Syndrome

Annual Incidence rate: Nephrotic Syndrome is a prevalent childhood kidney condition, occurring in 2-7 out of every 100,000 children globally, and can emerge at any point during childhood or adolescence **(20)**.

Geographical variation: Research shows ethnic differences in nephrotic syndrome incidence and treatment response. In countries with large immigrant populations, South Asian populations show higher rates of NS, with incidence ranging from 7.4 to 16.9 per 100,000 people, compared to Europeans. Also, studies indicate that children of African descent have a higher incidence than those of European descent **(21)**.

In Egypt, specific nationwide incidence data are limited. However, a study conducted observed that among 170 pediatric NS patients, the mean age of onset was 4.66 ± 2.64 years, with a male predominance of 64.7%. In this study, 76.5% of patients responded to initial steroid therapy, while 23.5% were steroid-resistant. Among those who responded, 29.4% became steroid-dependent. Renal biopsies performed on 34.1% of the patients revealed that 69% had minimal change disease, 13.8% had membrano-proliferative glomerulonephritis, and 17.2% had focal segmental glomerulosclerosis (**22**).

These findings align with another Egyptian study, which reported a mean age of onset of 4.43 ± 2.7 years among 100 children with primary NS. In this group, 66% showed an initial response to steroids, while 34% were steroid-resistant. Renal biopsy results indicated that 30% had minimal change disease, 37.5% had mesangioproliferative glomerulonephritis, and 30% had focal segmental glomerulosclerosis **(23)**.

The rate of steroid resistance also varies among ethnic groups:

- Europeans: about 20%
- Africans: 16-27%
- Asians: 27-54%
- South Asians: 20-39% **(24)**.

Gender variation: Several studies among the pediatric population in Bangladiesh and others in Saudi Arabia show male patients to have increased likelihood of experiencing disease relapse after initial representation. They also report a male to female ratio of 2:1 in those experiencing their first attack **(25)**.

Age association was not statistically significant; however, studies found out that children diagnosed before the age of 5 were more likely to experience subsequent relapses **(26)**.

***Pathophysiology*:**

Albumin, a protein with a molecular weight of 66 kDa, is typically present in urine in very small amounts (less than 30 mg daily) in healthy people. However, certain physiological conditions can increase this loss, including: Fever, Exercise and Changes in posture **(27)**.

The amount of albumin in urine is regulated by two main processes: Glomerular filtration and tubular reabsorption. The balance between these two processes determines how much albumin appears in the urine. When the glomerulus (the kidney's filtering unit) is damaged, it allows more albumin to pass through, resulting in increased albumin loss in the urine, causing proteinuria **(28)**.

Proteinuria at nephrotic levels is defined as either losing 3 grams or more of protein through urine in a day, or having 2 grams of protein per gram of creatinine in a single urine sample. This high level of protein in urine isn't exclusive to nephrotic syndrome; it can also occur in other systemic conditions, like amyloidosis **(29)**.

Excessive proteinuria can have several harmful effects on the kidneys: It may trigger the formation of cellular or fibrous crescents, which can lead to progressive glomerulonephritis and focal glomerulosclerosis. Proteinuria can damage kidney tubules in several ways. It overloads and impairs the function of tubular epithelial cells, which

eventually leads to tubular atrophy. This process results in interstitial fibrosis, which is scarring that develops in the spaces between tubules leading to progressive kidney disease **(30)**.

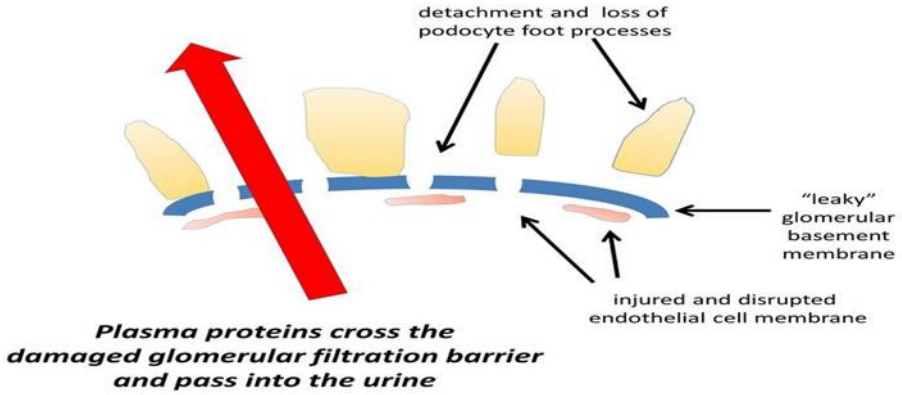

Figure-2 Proteinuria in Nephrotic Syndrome resulting from loss of glomerular filtration rate **(31)**

Edema, or swelling, is the primary clinical sign of nephrotic syndrome. The exact mechanisms causing edema in this condition have been a topic of ongoing research and debate. Two main hypotheses have been proposed:

1. The 'underfill' hypothesis:

- Decreased oncotic pressure causes excessive fluid movement from blood vessels to surrounding tissues, this leads to reduced blood volume and kidney perfusion
- The renin-angiotensin-aldosterone system is activated in response and the kidney then retains sodium as a secondary effect **(32)**.

2. The 'overfill' hypothesis:

NS directly causes the kidney to retain sodium. This sodium retention is the primary cause of edema **(33)**.

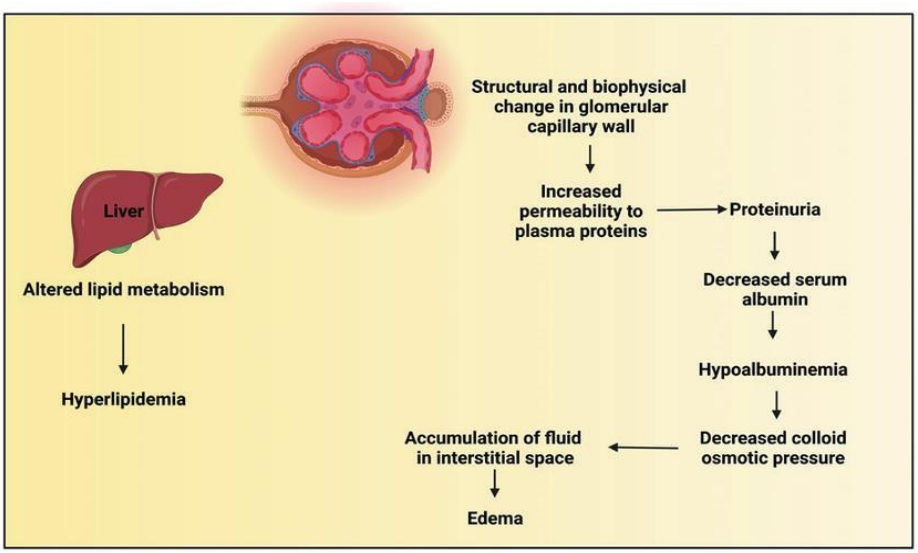

Figure-3: edema pathophysiology **(34)**

Hyperlipidemia and nephrotic syndrome

The metabolic disruption of serum lipids and lipoproteins in patients with nephrotic syndrome is primarily driven by impaired clearance mechanisms. This disruption is attributed to several factors:

1. Reduced Enzyme Activity: Decreased activity of enzymes such as hepatic lipase and lipoprotein lipase (LPL) in endothelial cells, adipose tissue, and muscle tissue hampers the clearance of lipids. This lead to the accumulation of VLDL and remnant lipoproteins such as intermediate-density lipoprotein (IDL). This accumulation is partly due to the loss of activating factors for these enzymes in the urine. These changes collectively result in significant disturbances in lipid and lipoprotein metabolism, contributing to the development of atherosclerosis and other cardiovascular diseases in patients with NS **(35)**.

2. Altered LCAT and CETP Activities: The activity of lecithin-cholesterol acyltransferase (LCAT) is reduced, while plasma cholesteryl ester transfer protein (CETP) is activated. This leads to the generation of immature HDL and reduced cholesterol efflux. CETP facilitates the exchange of cholesterol esters from HDL to VLDL and triglycerides from VLDL to HDL, further contributing to dyslipidemia **(36)**.

3. PCSK9 Involvement: The serine protease proprotein convertase subtilisin kexin type 9 (PCSK9) plays a crucial role in hyperlipidemia by regulating hepatic LDL receptor expression. Increased PCSK9 expression in NS leads to the degradation of LDL receptors, resulting in decreased LDL uptake by the liver **(37)**.

4. Hypercholesterolemia and Hypertriglyceridemia: Enhanced LDL production and impaired catabolism, along with increased expression of liver acetyl-CoA acetyltransferase 2 (ACAT2), contribute to hypercholesterolemia. Hypertriglyceridemia arises due to dysregulated fatty acid metabolism in the liver, involving increased expression of synthetic enzymes and downregulation of fatty acid catabolism **(38)**.

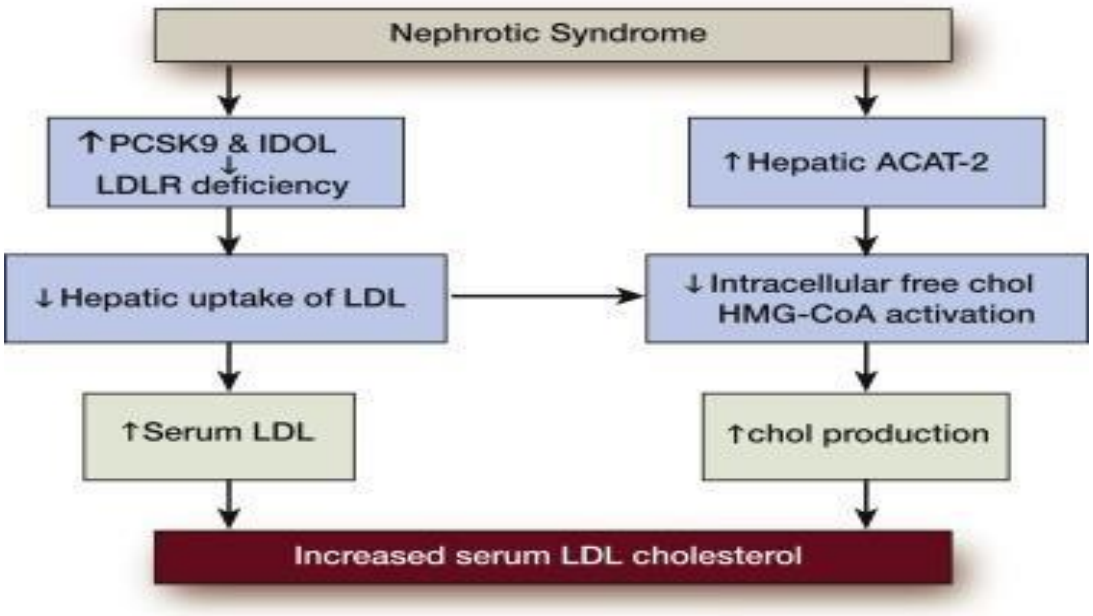

Figure-4: process of increasing LDL cholesterol **(38)**

Clinical approach to Nephrotic Syndrome:

Investigations:

Urine analysis: The diagnostic process begins with confirming proteinuria through a urine dipstick test, where a result of 2+ to 4+ indicates significant protein presence. This is followed by checking for microscopic hematuria and ruling out urinary tract infections through midstream urine analysis **(39)**.

Quantification of proteinuria is then performed using early morning urinary protein: creatinine or albumin:creatinine ratios, with values above 300-350 mg/mmol indicating nephrotic-range proteinuria **(40)**.

Blood testing: includes full blood count, coagulation screening, renal and liver function tests, and bone profile with corrected calcium levels. Further testing checks for systemic diseases through inflammatory markers (CRP and ESR), glucose levels, immunoglobulin analysis, and autoimmune screening. With consent, patients are also tested for Hepatitis B, C, and HIV **(41)**.

Imaging studies: include chest X-rays and renal ultrasound to check for complications like pleural effusion and ascites, and to assess kidney structure. Special attention is paid to potential thromboembolic complications, using various imaging techniques including Doppler ultrasound for deep vein thrombosis, and specialized scans for suspected renal vein thrombosis or pulmonary embolism **(42)**.

Finally, a renal biopsy under ultrasound guidance is performed to investigate the underlying cause, with tissue samples prepared for light microscopy, immunofluorescence or immunoperoxidase, and electron microscopy examination **(43)**.

Nutritional management of Nephrotic Syndrome patients:

Fluid intake: If edema is being presented, moderate fluid restriction is recommended, especially if the patient is hyponatremic.

Sodium restrictions and recommendations:

Age	Sodium
0-6 months	120 mg/d or 1-2 mEq/kg
7-12 months	370 mg/d
1-3 years	1000 mg/d
4-8 years	1200 mg/d
9-18 years	1500 mg/d

Table 1: sodium requirements**(44)**

Energy requirements:

Patients with NS and edema have the same energy needs as healthy children of the same age **(45)**.

Protein intake:

Recommended intake is 1-2 g/kg/day for most children.

An alternative recommendation suggests 130%-140% of the recommended dietary allowance.

Historical high-protein diets (3-4 g/kg/day) are no longer recommended due to concerns about accelerating glomerulonephritis. A study in rats showed no effect on serum albumin levels when comparing 8.5% vs 21% protein calories **(46)**.

Diet after edema resolution:

- Children should follow a healthy, age-appropriate diet meeting energy requirements and recommended protein intake.
- If catch-up growth is needed, energy intake may increase to 120%-140% of the recommended dietary allowance **(47)**.

Dietary restrictions:

- Continue to limit sodium intake.
- Restrict saturated and trans fats due to their link with inflammation **(44)**.

Pharmacological management of Nephrotic Syndrome:

1. Primary treatment:

o Corticosteroids are the main treatment for idiopathic nephrotic syndrome in children **(48)**.

2. Alternative treatments for frequently relapsing or steroid-dependent cases:

o Cyclophosphamide o Mycophenolate mofetil (MMF) o Calcineurin inhibitors o Levamisole **(49)**.

3. Treatment for steroid-resistant cases:

o First-line: Calcineurin inhibitors

o If no response: MMF or extended/intravenous pulse corticosteroids **(50)**.

4. Rituximab (anti-B cell antibody):

o Effective steroid-sparing agent in pediatric cases

o May not achieve drug-free remission in children dependent on both calcineurin inhibitors and steroids

o Potentially useful in steroid-resistant cases **(51)**.

5. Extended use of Rituximab:

o It was found that giving additional rituximab at B cell recovery may maintain longer remission in children with complicated steroid resistant nephrotic syndrome who initially responded to rituximab **(52)**.

In managing nephrotic syndrome, particularly when severe fluid retention is present, diuretics are a crucial component of treatment. Here are some key points regarding the use of diuretics and additional measures to manage complications:

1. Diuretic Therapy:

- Loop Diuretics: Furosemide is commonly used as the first-line treatment for edema in nephrotic syndrome. It is often started at a low dose and increased as needed to achieve satisfactory diuresis. High doses (e.g., 80-120 mg) may be required, especially if given intravenously due to poor oral bioavailability and intestinal edema **(53)**.
- Combination Therapy: If furosemide alone is insufficient, combination therapy with other diuretics such as thiazide-like metolazone or potassium-sparing diuretics like spironolactone or amiloride can be beneficial. Amiloride, an epithelial sodium channel (ENaC) inhibitor, has shown promise in overcoming diuretic resistance **(54)**.

2. Challenges with Low Serum Albumin:

- Achieving satisfactory diuresis can be difficult when serum albumin levels are low (less than 1.5 g/dL). In such cases, administering albumin infusions may be necessary to enhance diuretic efficacy **(55)**.

3. Prevention and Treatment of Infections:

- Prophylactic Antibiotics: In children with overt edema, penicillin can be started to prevent infections.
- Abdominal Paracentesis: Recommended for patients showing signs of peritonitis to manage potential bacterial infections.

- Immunoglobulin and Acyclovir: Non-immune patients exposed to chickenpox should receive immunoglobulin therapy, and acyclovir should be started if the patient develops chickenpox **(56)**.

4. General Management:

- Sodium and Fluid Restriction: Patients should limit sodium intake to 3g per day and restrict fluid intake to less than 1.5 L per day to help to reduce edema. ACE Inhibitors: Angiotensin-converting enzyme (ACE) inhibitors are recommended to reduce proteinuria and slow the progression of renal disease **(57)**.

Classification of Nephrotic Syndrome according to response to treatment

The staging and classification of nephrotic syndrome particularly in the context of its clinical course and response to treatment are crucial for managing the condition effectively. Here are the key definitions and criteria:

1. Remission:

Definition: Remission is achieved when there is no significant albuminuria. Specifically, it is defined as urine albumin being nil or trace for three consecutive early morning specimens **(58)**.

2. Relapse:

Definition: A relapse occurs when there is a significant increase in albuminuria after a period of remission. This is defined as urine albumin 3+ or 4+ (or proteinuria greater than 40 mg/m^2 /h) for three consecutive early morning specimens, having been in remission previously **(59)**.

3. Frequent Relapses:

Definition: Frequent relapses are characterized by two or more relapses in the initial six months or more than four relapses in any 12 months **(60)**.

4. Steroid Dependence:

Definition: Steroid dependence is diagnosed when there are two consecutive relapses while on alternate-day steroids or within 14 days of its discontinuation **(61)**.

5. Steroid Resistance:

Definition: Steroid resistance is defined as the absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for four weeks **(62)**.

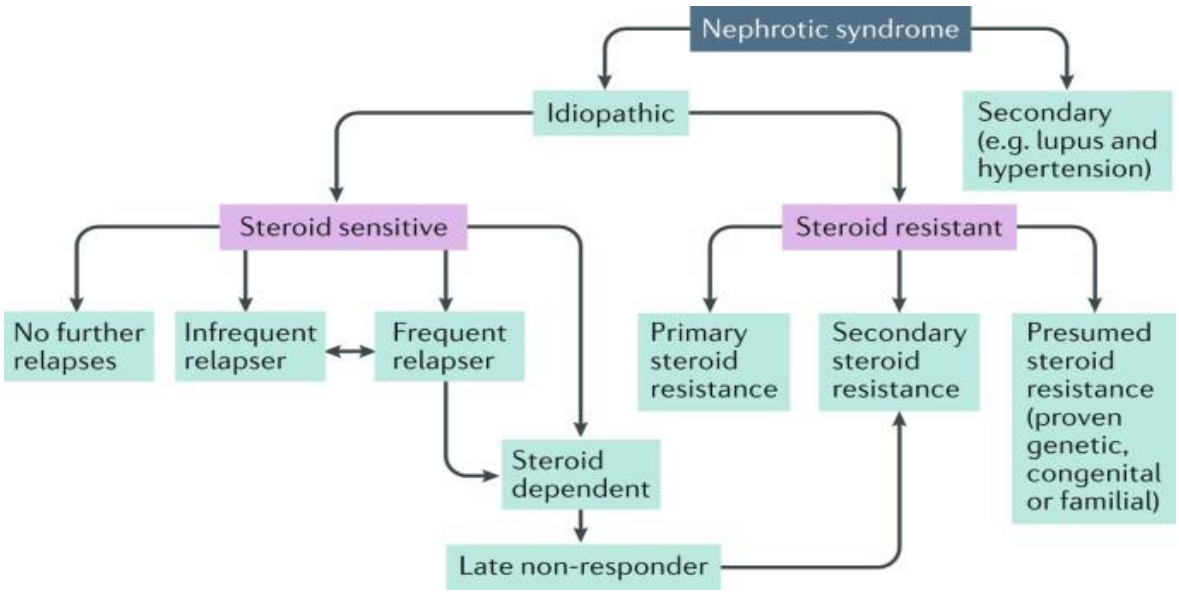

Figure-5: steroid sensitive and steroid resistant NS (**63**)

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