**NEPHROTIC SYNDROME**

**Definition****-**The syndrome is characterized by

1. Proteinuria
2. Hypoalbuminemia
3. Edema
4. hyperlipidaemia
5. Lipiduria
6. Hypercoagulability

-Key component of the syndrome is Proteinuria

Defined as: > 3.5g/1.73m2/24 hrs

But in Practice: > 3.0 – 3.5g/24 hrs

-Other components of the syndrome and metabolic complications are all secondary to proteinuria :-

-The kidney function is often normal

-Hypoalbuminaemia (albumin **<25g/L**)

-Oedema

-EMU Protein: creatinine ratio (**>200mg/mmo**l) ***\* more accurate (EMU early morning urine)***

 **Pathogenesis**

**Proteinuria**

-Due to increase in glomerular permeability and not to a decrease in tubular reabsorption of filtered plasma proteins. Albumin is the main constituent of urinary protein

-By definition, the urinary protein excretion exceeds 3 g/1.73 m2/day

-This influenced by glomerular filtration rate, the plasma concentration of albumin, and dietary protein intake.

-Thus a high protein intake in nephrotic patients leads to an increase in proteinuria and albumin synthesis. Recently, it has been shown that nonsteroidal anti-inflammatory agents as well as angiotensin-converting enzyme inhibitors may decrease the proteinuria.

-Other plasma proteins lost in urine include-

* Peptide hormones
* Clotting inhibitors eg anti-thrombin factor III ,Protein C and S
* Transferrin
* Hormone-carrying proteins.-transporter protein.

-Highly selective proteinuria has been defined as clearance of molecules similar to albumin (66,000 daltons), transferrin (88,000 daltons), and small amounts of gamma globulins (150,000 daltons), and exclusion from urine of higher molecular weight plasma proteins.

 -In patients with lesser degrees of selectivity, there is clearances of larger globulins eg alpha 2-macroglobulin.

**Edema**

-The hypoalbuminemia leads to a decrease in plasma oncotic pressure, which results in an imbalance of Starling forces at the level of the peripheral capillaries.

-At the arteriolar end, the hydrostatic pressure within the capillary exceeds the oncotic pressure, leading to an egress of fluid into the interstitial space.

-Intravascular volume falls, thereby stimulating activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system and release of vasopressin (antidiuretic hormone), and suppressing atrial natriuretic peptide release. These neural and hormonal responses promote renal salt and water retention, thereby restoring intravascular volume and triggering further leakage of fluid to the interstitium

*-*However, primary renal salt and water retention may also contribute to edema formation in some cases.

-Ascitis may also occur due to the generalized fluid retention**:**

-It may be associated with:

* -Venous Dilation – of abdominal wall
* -Umbilical hernia
* -Rectal prolapse
* -↑ Respiratory difficulty
* -Scrotal/labial pain
* -Anasarca

**Hyperlipidemia**

-Due increased hepatic lipoprotein synthesis that is triggered by reduced oncotic pressure

 -LDL and cholesterol are increased in the majority of patients, whereas VLDL and triglycerides tend to rise in patients with severe disease.

–Abnormal lipid metabolism due to the loss of lipoprotein C may be contributor.

-Hyperlipidemia may accelerate atherosclerosis and progression of renal disease.

**Hypercoagulabilit*y***

*-*multifactorial in origin:-

1-Increased urinary loss of antithrombin III, proteins C and S (natural anti-coagulants)

2-Increased clotting factors synthesis by the liver- Fibrinogen and Factors V, VII, VIII, X

3-Impaired fibrinolysis

4-Increased platelet aggregability and thrombocytosis

5-Accelerated thromboplastin generation

6-Hypovolaemia

-As a consequence of these perturbations, patients can develop spontaneous peripheral arterial or venous thrombosis, renal vein thrombosis, and pulmonary embolism.

-Clinical features that suggest acute renal vein thrombosis include:-

* Sudden onset of flank or abdominal pain
* Gross hematuria
* Left-sided varicocele (the left testicular vein drains into the renal vein)
* Increased proteinuria
* Acute decline in GFR.

-Chronic renal vein thrombosis is usually asymptomatic. Renal vein thrombosis is particularly common (up to 40%) in patients with nephrotic syndrome due to membranous glomerulopathy, membranoproliferative glomerulonephritis, and amyloidosis.

**Other complications include:-**

1) **Protein calorie malnutrition** with Growth and developmental delays in children.

2) Iron-resistant **microcytic hypochromic anemia** due to transferrin loss and also due to decreased erythropoietin from kidneys.

3) **Hypocalcaemia and secondary hyperparathyroidism** can occur as a consequence of vitamin D deficiency due to enhanced urinary excretion of cholecalciferol-binding protein

4) Loss of thyroxine-binding globulin can result in **depressed thyroxine levels.**

5) **An increased susceptibility to infection** may reflect low levels of IgG that result from urinary loss and increased catabolism.

6) Unpredictable changes in the **pharmacokinetics of therapeutic agents** that are normally bound to plasma proteins.

7) **Renal failure**- due do progression of the renal involvement or due to volume depletion and the inappropriate increase in angiotensin II

8) **Hypovolemia**-fluid loss into the interstitium

9) **Hypertensio**n-Renin angiotensin aldosterone system stimulated to hypovolemia

**Primary Nephrotic Syndrome(Idiopathic)**

1. Minimal change GN The most common cause (80%) of nephrotic syndrome in children

2. Membranous GN-The most common primary renal cause of nephrotic syndrome in adults in developing countries.

3. Focal segmental Glomerulosclerosis

4. Rapidly progressive GN

5. MembranoProliferative GN

6. IgA glomerulopathy

**Secondary Nephrotic Syndrome**

a). Metabolic diseases:

-[Diabetes mellitus](http://en.wikipedia.org/wiki/Diabetes_mellitus) is the most common cause of secondary nephrotic syndrome in adults in developing countries; [amyloidosis](http://en.wikipedia.org/wiki/Amyloidosis)

b). Autoimmune diseases:

-[SLE](http://en.wikipedia.org/wiki/Systemic_lupus_erythematosus), [Henoch-Schonlein purpura](http://en.wikipedia.org/wiki/Henoch-Schonlein_purpura), vasculitides, Sarcoidosis

C). Malignancies

1. Solid tumors (kidney malignancy, colorectal)

2. Lymphomas and leukemia

3. Multiple myeloma

d). Infections

1. Bacterial-Post streptococcal GN, Endocarditis, syphyllis, TB

2. Protozoal-malaria, toxoplasmosis

3. Viral-CMV, hepatitis B and C, HIV, EBV

4. Fungal-Candida

5. Helminthic-Schistosomiasis, Trypanisomiasis , leishmaniasis

e). Drugs

-Penicillamine, mephenytoin, Trimethadione, Probenicid

-Heavy metals- gold, mercury

f). Hereditary causes

-Alports syndrome

-Congenital nephritic syndrome

-Nail-patella syndrome

.-Sickle cell disease

**CLINICAL PRESENTATION**

**History**

-Swelling of the face; periorbital edema is a common presentation. Then other dependent areas as the feet and ankle.

-This is followed by swelling of the entire body-anasarca can be the presenting symptom.

-In certain instances, patients notice frothy urine, which leads to investigations that reveal evidence of nephrotic syndrome.

-A hypercoagulable state leading to thrombotic complications, such as deep vein thrombosis of the calf veins or the renal vein, may be the first clue indicating nephrotic syndrome.

History suggestive of predisposing factors

- History of acute or chronic infections, drugs, allergies, systemic symptoms (vasculitis, malignancy)

-HTN, DM

-Malaria treatment, risk for schistosomiasis

-Connective tissue disease-rash, joint pains and any pains in muscles

-Recurrent sore throat, or skin ulcers or swellings

-Wt loss, night sweat and general fatigue-malignancy

-Sickle cell disease

-Blood transfusions

-Any sexually transmitted infections.

Familial history

-DDX-R/ o hx suggestive Cardiac dz, liver dz.

**Physical:**

-Patients present with increasing edema over a few days or weeks, lethargy, poor appetite, weakness, and occasional abdominal pain.

-The initial episode and the subsequent relapses may follow an apparent viral upper respiratory tract infection.

-Edema is the predominant feature and initially develops around the eyes and lower extremities. With time, the edema becomes generalized and may be associated with an increase in weight, the development of an ascitic or pleural effusion, and a decline in urine output.

-Hematuria and hypertension are unusual but manifest in a minority of patients.

- Xanthelasma and Xanthomata - Widespread yellow nodules or plaques, especially of the skin, composed of lipid-laden histiocytes, especially on the *elbows and knees.*

**Investigations**

**a). Lab Studies:**

**1. Urinalysis**

* The ratio of urinary protein to urinary creatinine
* 24-hour protein excretion
* Hematuria
* UTI-Nitrites
* Determination of light-chain protein excretion.

-Proteinuria-Adults excrete up to 150 mg/d.

-Spot proteinuria >1g/L

-Urinary protein to urinary creatinine ratio >200mg/mmol or ratio of urinary protein to urinary creatinine of greater than 2 when using creatinine in mg/dl.

-A quantitative estimation of 24-hour urine protein excretion is the standard method, but EMU testing and determining the ratio of urinary protein to urinary creatinine is the method of choice for proteinuria quantification.

**2. Blood**

-FBC and ESR

-U/E/C

-LFT-serum albumin

-Fasting Serum lipids and differential and

-Random Blood sugar.

3. **Screen**

-Hepatitis B and hepatitis C testing

-HIV screening

-VDRL

-Serum complements values,

-Varicella serology.

-Malaria slide

- Antinuclear antibodies

-Antistreptolysin O titers

**Others**

**-**Performing serum protein electrophoresis or urine protein electrophoresis can be useful for detecting the etiology of nephrotic syndrome.

-Serum protein electrophoresis or immunofixation for light-chain proteins

**b). Imaging Studies:**

-Renal ultrasonography is an essential tool to help establish the presence of 2 kidneys that are of normal size and architecture.

-The presence of hydronephrosis or cysts in the kidney that will undergo biopsy mandates caution.

- Similarly, small kidneys may not yield enough information and may be associated with an increased incidence of RF

**c). Renal biopsy**

- Before attempting a renal biopsy, ensure that a renal ultrasound scan is ordered to confirm:-

* that the patient has 2 functioning kidneys
* that the kidneys are of normal size
* The kidney architecture is normal (ie, devoid of cysts and vascular malformations).

- A renal biopsy is indicated in the following circumstances:

1)-Steroid resistance

2)-Frequent relapses or steroid dependency

3)-Significant chronic nephritic manifestations

4)-Adult nephrotic syndrome:

-Probably even paediatrics locally

-30 – 45% minimal change disease (MCD)

5)-Confirm the etiology of nephrotic syndrome

6)-Guiding therapy and assessing prognosis

NB-Renal biopsy is not indicated in adults when the nephrotic syndrome is due to an obvious cause such as diabetes mellitus, ie, when the patient has other diabetes-related overt complications

**MANAGEMENT**

**Aims**

* Induce prompt remission
* Minimize complications and subsequent mortality
* Treat underlying disease

**General supportive measure**

1. Monitor **vital signs**-4 hourly

2**. Restrict salt intake**

3. **Restrict fluids** in severe edema –give fluids as previous day output + 400ml

4. Mantain a **Daily fluid input/out** chart

5. **Daily weight** measurement and abdominal girth measurement incase of ascitis

6. **Bed rest in acute phase** and **ambulation as soon as possible** as its hypercoagulable state

7.? **Normal protein diet**. Severe protein loss consider protein rich diet Vs risk of more glomerular injury

-If patient obese due to steroid restrict the calorie intake

**Symptomatic treatment**

**Edema**

-Diuretics and intravenous albumin may be needed.

-Furosemide (1 mg/kg/d)

-spironolactone (2 mg/kg/d) Achieving a satisfactory Diuresis is difficult when the patient's serum albumin level is less than 1.5 g/dL.

-An effective regimen is to give salt-poor albumin at 1 g/kg, followed by intravenous furosemide.

-Close monitoring is obligatory to prevent pulmonary edema. Some evidence suggests that albumin may delay the response to steroids and may even induce more frequent relapses, probably by causing severe glomerular epithelial damage.

-The time required for remission is prolonged with a longer duration of administration and larger volumes of infused albumin.

-Fluid removal and weight loss remain transient unless proteinuria remits.

**2. Infection**

-Care taken with puncture sites and procedures should observe aseptic techniques

-Prophylactic Antibiotics

-? Immunizations- influenza, pneumococcal, HBV, varicella

-Immunoglobulin

**3. Hyperlipidaemia**

-“Statins” – lipid lowering agents

-HMGCoA reductase inhibitors

**4. Hypercoagulable State**

-Anticoagulants

* Heparin may be ineffective as loss of anti thrombin III
* Warfarin

5. **Bone Disease**

-Vit D, Ca++ supplements

-Bisphosphonates (osteoporosis).

**6. Proteinuria**

**-**Angiotensin Converting Enzyme (ACE) inhibitors

**-**Angiotensin2 Receptor blocker (ARB)

**-**[\*NSAIDs \*nephrectomy]

**Treatment of underlying cause**

1. Treatment of infections

2. Control of metabolic syndrome and autoimmune conditions eg DM, SLE

3. Management of malignancies-reduce the tumor mass

4. Withdraw any drug culprits