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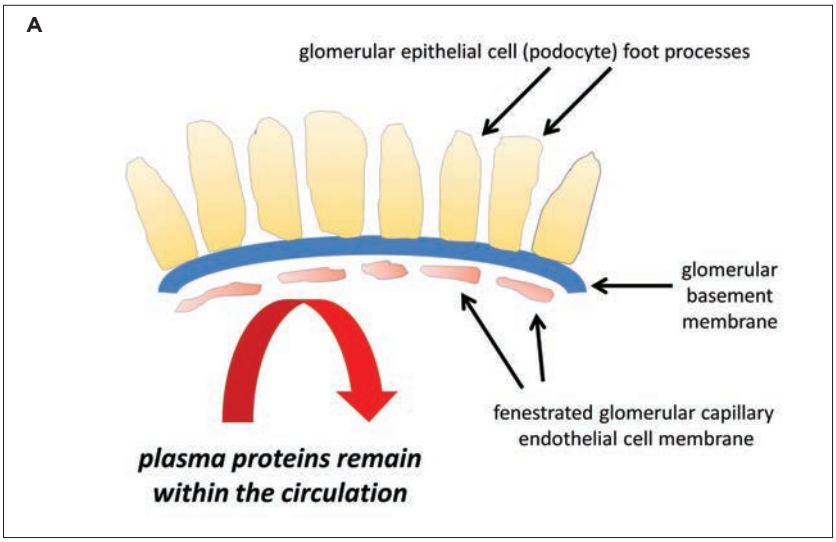
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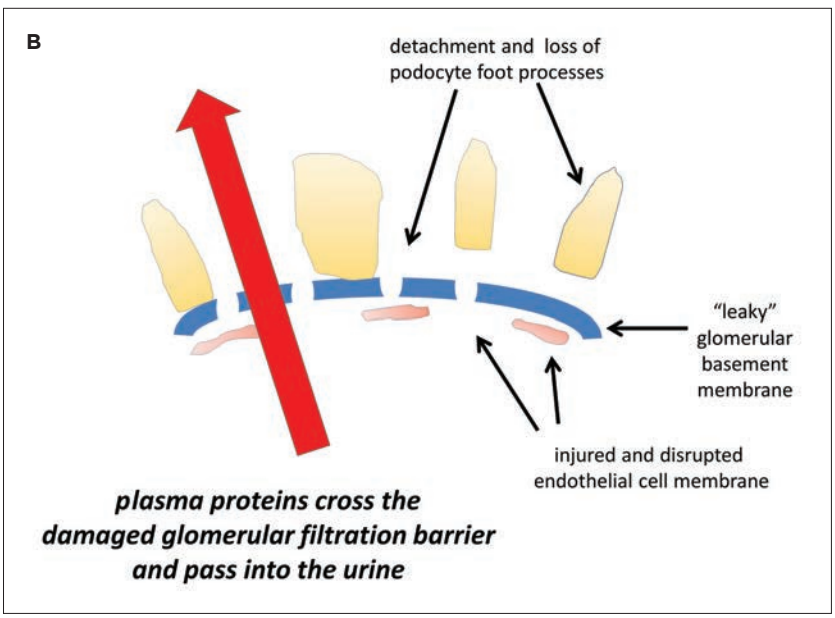


FIGURE 1
A Normal components of the intact glomerular filtration barrier: capillary endothelial cell; glomerular basement membrane; and glomerular epithelial cell (podocyte)

B Proteinuria in nephrotic syndrome resulting from loss of the normal glomerular filtration barrier: endothelial injury; glomerular basement membrane disruption; and loss of podocyte foot processes

What are the causes of nephrotic syndrome?

How do patients present in primary care?

What are the management approaches?

NEPHROTIC SYNDROME IS A WELL KNOWN PRESENTATION OF KIDNEY DISEASE WITH A TRIAD of clinical features namely oedema, substantial proteinuria (> 3.5 g/24 hours) and hypoalbuminaemia (< 30 g/L). It is often associated with hyperlipidaemia, thromboembolism and an increased risk of infection.

Nephrotic syndrome is uncommon in general practice. A GP may only see two or three adult cases in their career.

Nephrotic syndrome develops following pathological injury to renal glomeruli. This may be a primary problem, with a disease specific to the kidneys, or secondary to a systemic disorder such as diabetes mellitus.[1,2] The most common cause in children is minimal change glomerulonephritis.[3] In white adults, nephrotic syndrome is most frequently due to membranous nephropathy whereas in populations of African ancestry the most common cause of nephrotic syndrome is focal segmental glomerulosclerosis (FSGS).[1,2] Diabetic nephropathy is the most common multisystem disease that can cause nephrotic syndrome.

PRESENTATION

Patients typically present with periorbital oedema (most noticeable in the morning) or dependent pitting oedema (more common later in the day). Facial oedema is rare in heart failure or liver cirrhosis as patients with these conditions are less able to lie flat. »

As the volume of peripheral oedema increases fluid accumulates in the limbs, trunk and genitals. Patients with nephrotic syndrome may also become breathless due to pleural effusion and ascites.

Individuals with substantial proteinuria may notice frothy or foamy urine, as protein in the urine acts like a detergent. Severe hypoalbuminaemia can result in white nails or if nephrotic syndrome has been transient the development of white bands in nails (Muerhrcke's lines).

The coincidental finding of a very elevated serum cholesterol concentration on a lipid profile may trigger assessment for other features of nephrotic syndrome.[4] If hyperlipidaemia has been present for a prolonged duration, then skin xanthomata may develop.

New onset of hypertension and renal impairment may also be secondary to the glomerular disease causing nephrotic syndrome. Occasionally the first presentation of nephrotic syndrome is a thromboembolic event (deep vein thrombosis or pulmonary embolus) associated with the hypercoagulable state found in this condition.[5]

CAUSES

Nephrotic syndrome is a direct consequence of glomerular pathology[1,2] and the precise cause can only be established by histological assessment of a kidney biopsy (see table 1, below, for pathological causes).

Proteinuria

Proteinuria results from structural or functional failure of the glomerular barrier between the blood and urinary space. Proteinuria is associated with injury to podocytes (glomerular epithelial cells), capillary endothelial cells and disruption of the glomerular basement membrane function, see figure 1, p11. Raised intraglomerular pressure may also contribute to proteinuria.

Hypoalbuminaemia

Massive urinary loss of protein leads to hypoalbuminaemia. Hepatic albumin synthesis increases but is insufficient to compensate for the urinary protein loss and a fall in serum albumin ensues. Hepatic synthesis of other proteins is also increased and accounts for the hyperlipidaemia and prothrombotic state associated with nephrotic syndrome.

Oedema

This may result from two mechanisms. The underfill hypothesis proposes that reduced oncotic pressure, due to hypoalbuminaemia, results in fluid shifts from the intravascular space to the interstitial compartment. This triggers salt and water retention, via the renin angiotensin aldosterone system and antidiuretic hormone release, and further promotion of fluid movement into the interstitial compartment.
The overfill hypothesis suggests that a defect in sodium excretion is the primary problem leading to fluid retention. This may be triggered by proteins lost in the urine that activate the epithelial sodium channel (ENaC) in the collecting duct promoting salt and water retention.[6]
Low oncotic pressure encourages movement of fluid into the interstitial compartment with resulting clinical signs of oedema.

Hyperlipidaemia

Hyperlipidaemia correlates inversely with the serum albumin level and extremely high serum cholesterol concentrations (> 10 mmol/L) may be seen in some patients.[4] An atherogenic lipid profile (low HDL/high LDL) is triggered by increased hepatic synthesis of VLDL and urinary loss of HDL.

'The precise cause can only be established by histological assessment of a kidney biopsy'

Hypercoagulability

Hypercoagulability is the net result of increased urinary loss of anticoagulant proteins, such as antithrombin III and protein C, increased hepatic synthesis of clotting factors, enhanced platelet aggregation and intravascular volume contraction.[5]

DIAGNOSIS

Nephrotic syndrome is recognised by the presence of oedema, proteinuria and hypoalbuminaemia. The initial diagnostic step is a dipstick urinalysis (3-4+ protein suggests the nephrotic range). Proteinuria should be documented by a quantitative measurement e.g. urine protein: creatinine ratio (PCR)

Table 1

Pathological causes of nephrotic syndrome

Kidney biopsy diagnosis	Nephrotic syndrome	Associations with risk factors	Possible treatment options	Risk of progression to end-stage renal disease
Minimal change disease	Common cause in children	Allergy, NSAIDs, Hodgkin's disease	Usually responds to steroids	Very low
Focal segmental glomerulosclerosis (FSGS)	Most common in patients of African ancestry	Obesity, HIV infection, heroin use	Primary FSGS may respond to steroids	High (if no response to steroids)
Membranous nephropathy	Most common in white adults	SLE, malignancy, hepatitis B, NSAIDs	May remit spontaneously	Moderate
Amyloidosis	More common in middle or older age	Chronic infection (AA amyloidosis); myeloma (AL amyloidosis)	Treatment directed to cause of amyloidosis	High

or albumin: creatinine ratio (ACR). PCR > 300-350 mg/mmol indicates nephrotic range proteinuria.[7] In practice, PCR and ACR measurements are as accurate as a 24-hour urine collection to quantify proteinuria.[7]

Hypoalbuminaemia is identified by measuring serum albumin (liver function tests or bone profile). It is essential to measure renal function (serum creatinine; eGFR) because nephrotic syndrome can be complicated by renal failure. A lipid profile will confirm the secondary hyperlipidaemia.

Urgent referral to a nephrologist (ideally within 2 weeks) is necessary and a renal biopsy is usually performed. This will establish what form of glomerular disease is responsible. Additional tests may be undertaken to assess if nephrotic syndrome is secondary to another disorder e.g. systemic lupus erythematosus (SLE) or amyloidosis, see table 2, below.

Table 2

Investigations for nephrotic syndrome

To diagnose nephrotic syndrome	
Urinalysis	Identify proteinuria
Urinary ACR or PCR	Quantify proteinuria
Serum albumin	Confirm < 30 g/L
Urea and electrolytes	Determine renal function
Cholesterol	Usually elevated (may be > 10 mmol/L)
To identify cause	
HbA_{1c} and fasting glucose	Exclude diabetes mellitus
CRP, ESR	Markers of inflammation and infection ● If longstanding associated with AA amyloidosis
Bone profile	Hypercalcaemia ● Multiple myeloma potentially causing AL amyloidosis ● Malignancy associated with secondary membranous nephropathy
Free light chains, paraprotein electrophoresis	Multiple myeloma potentially causing AL amyloidosis
Urinary Bence Jones protein	Multiple myeloma potentially causing AL amyloidosis
Anti-PLA2R antibodies	Associated with idiopathic membranous nephropathy
Hepatitis B, hepatitis C serology	Infection causes secondary membranous nephropathy
Anti-nuclear antibody; anti-dsDNA antibody, complement levels	Lupus nephritis may present with membranous nephropathy
HIV	Infection associated with focal segmental glomerulosclerosis
Renal tract ultrasound	Identify two kidneys, exclude scarring or obstruction
Renal biopsy	Tissue diagnosis to determine cause and inform prognosis

POTENTIAL COMPLICATIONS

Deteriorating renal function

Deteriorating renal function may be an acute insult or represent kidney disease progression. Acute kidney injury (AKI) is commonly due to a prerenal insult from intravascular volume depletion secondary to aggressive diuresis and/or sepsis. The risk of AKI is also increased by concurrent use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) as part of the general management of nephrotic syndrome. Pragmatic advice to reduce the risk of AKI would be to have 'sick day rules' for patients asking them to stop ACEi /ARB temporarily in the setting of acute illness, e.g. vomiting and diarrhoea.[8] Other causes of AKI include drug-induced interstitial nephritis or renal vein thrombosis.[1]

Chronic kidney disease (CKD) may develop as most causes of nephrotic syndrome are associated with progressive loss of renal function (with the exception of minimal change disease). The risk of CKD is directly correlated with the severity of proteinuria and there is evidence that proteinuria itself is directly associated with chronic injury and fibrosis of the renal tubulointerstitium.

Thromboembolism

The annual incidence of venous thromboembolism is ten times higher in patients with nephrotic syndrome than the general population and up to 10% of adults with nephrotic syndrome have a clinical thrombotic event.[5] The risk of thrombosis also correlates inversely with serum albumin concentration. There is no clear evidence on how this risk should be minimised. In clinical practice many would consider anticoagulation with low molecular weight heparin or warfarin if serum albumin was < 20 g/L.

Infection

Nephrotic patients are prone to bacterial infection. Loss of circulating immunoglobulins and complement factors in the urine impairs the immune response to encapsulated organisms. In addition zinc and transferrin are required for lymphocyte function and these are lost in the urine.

There is no evidence to support the use of routine antibiotic prophylaxis in nephrotic syndrome,[9] but a recent trial indicates that vaccinating against pneumococcus may be of benefit.[10]

Nutritional deficiency

Patients with nephrotic syndrome are in marked negative protein balance. »

key points

SELECTED BY

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Nephrotic syndrome is defined by a triad of clinical features namely oedema, substantial proteinuria (> 3.5 g/24 hours) and hypoalbuminaemia (< 30 g/L). It is often associated with hyperlipidaemia, thromboembolism and an increased risk of infection.

Nephrotic syndrome develops following pathological injury to renal glomeruli. This may be a primary problem, with a disease specific to the kidneys, or secondary to a systemic disorder such as diabetes mellitus. The most common cause in children is minimal change glomerulonephritis. In white adults, nephrotic syndrome is most frequently due to membranous nephropathy whereas in populations of African ancestry the most common cause of nephrotic syndrome is focal segmental glomerulosclerosis. Diabetic nephropathy is the most common multisystem disease that can cause nephrotic syndrome.

Patients typically present with periorbital oedema (most noticeable in the morning) or dependent pitting oedema (more common later in the day). Proteinuria should be documented by a quantitative measurement e.g. urine protein: creatinine ratio (PCR) or albumin: creatinine ratio (ACR). PCR > 300-350 mg/mmol indicates nephrotic range proteinuria.

Urgent referral to a nephrologist (ideally within 2 weeks) is necessary and a renal biopsy is usually performed. This will establish what form of glomerular disease is responsible. Additional tests may be undertaken to assess if nephrotic syndrome is secondary to another disorder e.g. systemic lupus erythematosus or amyloidosis.

Oedema is managed by fluid and dietary salt restriction (< 80 mmol/day; < 2 grams salt/day) coupled with loop diuretics (furosemide or bumetanide). Close monitoring of the patient's weight, electrolytes and renal function is essential since a rapid diuresis can result in hypokalaemia and acute kidney injury (AKI).

Proteinuria may be partly reduced by altering glomerular haemodynamic pressure with prescription of an ACEi (or ARB). Use of an ACEi (or ARB) will also help control hypertension if present. However, the risk of AKI is increased by use of these drugs.

Immunosuppressive medications may be used to target the underlying glomerular pathology causing the nephrotic syndrome. Steroids are used alone or in combination with a variety of other drugs including cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil and rituximab.

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Loss of muscle mass is often masked by oedema. Loss of binding proteins in the urine can lead to copper, zinc and iron deficiency. Dietetic input is invaluable.

Other metabolic effects

Thyroid binding globulin is lost in the urine and total circulating thyroxine is reduced but free thyroxine and thyroid stimulating hormone are normal. Usually this causes no clinical change in thyroid status. Protein binding of drugs may be altered by low serum albumin necessitating dose modification.

TREATMENT

All patients with nephrotic syndrome should be referred to a nephrologist to help establish the underlying diagnosis and advise on further management.

General management principles

Oedema is managed by fluid and dietary salt restriction (< 80 mmol/day; < 2 grams salt/day) coupled with loop diuretics such as furosemide or bumetanide. Patients with nephrotic syndrome may be relatively resistant to oral loop diuretic treatment and stepwise addition of a thiazide diuretic may be needed to trigger an effective diuresis.

If these measures are insufficient to improve oedema, then hospital admission for daily intravenous loop diuretics may be necessary.

Close monitoring of the patient's weight, electrolytes and renal function is essential since a rapid diuresis can result in hypokalaemia and AKI. Daily measurement of the patient's weight is a simple method of gauging response to diuretics with a maximum target weight loss of 0.5-1.0 kg/day.

Proteinuria may be partly reduced by altering glomerular haemodynamic pressure with prescription of an ACEi (or ARB). Use of ACEi (or ARB) will also help control hypertension if present.

Statins are often coprescribed for the secondary hyperlipidaemia but there is limited evidence for efficacy of these agents in nephrotic syndrome.[4]

Disease specific treatments

Immunosuppressive medications may be used to target the underlying glomerular pathology causing the nephrotic syndrome. Steroids are used alone or in combination with a variety of other drugs including cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil and rituximab.[11,12] Treatment involves two phases; induction of remission (absence of proteinuria and resolution of oedema), followed by maintaining remission. The total duration of treatment varies, depending on the disease activity and clinical response.

Induction regimens are briefly described for the three most common renal diseases that cause nephrotic syndrome in adults.[12,13,14]

Minimal change disease

Induction: Prednisolone 1 mg/kg per day (maximum 80 mg daily).[13] If unsuccessful by 16 weeks consider alternatives such as cyclophosphamide or calcineurin inhibitors. If frequently relapsing or steroid dependent, then consider cyclophosphamide or calcineurin inhibitors.

Focal segmental glomerulosclerosis

Induction: Prednisolone 1 mg/kg per day (maximum 80 mg daily). If unsuccessful at 16 weeks KDIGO guidelines recommend ciclosporin.[12] If this fails to induce remission within 4-6 months, high-dose dexamethasone and mycophenolate mofetil are recommended.

Membranous nephropathy (idiopathic)

As this glomerular disease may spontaneously remit in approximately one third of patients, it is common practice to manage patients conservatively for six months (i.e. no immunosuppression, but the treatment defined under 'general management principles' above). Immunosuppression may be commenced earlier in the case of severe, life-threatening symptoms of nephrotic syndrome.[14]

Induction: Options include a regimen of monthly alternating steroids and cyclophosphamide for a total of six months, or calcineurin inhibitors.

MONITORING AND FOLLOW-UP

Patients with active nephrotic syndrome should be under regular nephrology clinic follow-up to ensure treatment regimens are adjusted and monitor progression of renal disease.

GPs may be asked to check renal function, blood count and liver function particularly for those patients receiving immunosuppression. Any new abnormalities or complications of nephrotic syndrome should be discussed with the nephrologist.

Long-term nephrology clinic follow-up is appropriate for most patients with nephrotic syndrome particularly if the cause is associated with progressive CKD.

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