Nephrotic syndrome in adults

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The nephrotic syndrome is one of the best known presentations of adult or paediatric kidney disease. The term describes the association of (heavy) proteinuria with peripheral oedema, hypoalbuminaemia, and hypercholesterolaemia (box 1). Protein in the urine ("coagulable urine") was first described in 1821, 15 years before Richard Bright's celebrated series of descriptions of "albuminous urine."¹

Nephrotic syndrome has an incidence of three new cases per 100 000 each year in adults.² It is a relatively rare way for kidney disease to manifest compared with reduced kidney function or microalbuminuria as a complication of systemic diseases, such as diabetes and raised blood pressure.³

Why should I read this article?

Patients with nephrotic syndrome can present to primary or secondary care with diverse symptoms that reflect the primary process or with one of the many systemic complications of the syndrome.⁴ Although nephrotic syndrome is relatively common in renal practice, it is seen only rarely in primary or secondary care. This can result in a delayed or overlooked diagnosis, especially as many other conditions have similar symptoms. For example, severe peripheral (leg) oedema is seen in congestive cardiac failure, hypoalbuminaemia can be caused by severe liver disease or advanced malignancy, and periorbital oedema is seen in allergic reactions. This article deals with adults only, as the management of nephrotic syndrome is very different in children.

Owing in part to a lack of randomised trials, systematic reviews, and guidelines on the management of nephrotic syndrome, some uncertainty exists regarding its investigation and management. No high quality trials of treatment or interventions are available to inform the management of this rare condition, which has a complex and diverse aetiology. On the basis of the

Box 1 Diagnostic criteria for nephrotic syndrome

Proteinuria greater than 3-3.5 g/24 hour or spot urine protein:creatinine ratio of >300-350 mg/mmol

Serum albumin <25 g/l

Clinical evidence of peripheral oedema

Severe hyperlipidaemia (total cholesterol often >10 mmol/l) is often present

best available evidence and expert consensus, this article aims to provide an update on the causes, pathophysiology, relevant investigations, complications, and treatment of nephrotic syndrome in adults.

What conditions can cause nephrotic syndrome?

A wide range of primary (idiopathic) glomerular diseases and secondary diseases can cause the syndrome.

Pathophysiology of nephrotic syndrome

Increased glomerular permeability to large molecules, mostly albumin but other plasma proteins too, is the essential pathological process in nephrotic syndrome of any aetiology. Proteinuria causes a fall in serum albumin, and if the liver fails fully to compensate for urinary protein losses by increased albumin synthesis, plasma albumin concentrations decline, leading to oedema formation. Interstitial oedema forms either as a result of a fall in plasma oncotic pressure from urinary loss of albumin or from primary sodium retention in the renal tubules.^{5,6}

Primary (idiopathic) glomerular disease

Most cases of nephrotic syndrome are caused by primary glomerular diseases (table). Thirty years ago idiopathic membranous nephropathy was the most common primary cause of the syndrome.⁷ The incidence of other glomerular diseases, particularly focal segmental glomerulosclerosis, has increased and pronounced racial differences. Membranous nephropathy remains the most common cause in white patients, whereas focal segmental glomerulosclerosis is the most common cause in black patients (50-57% of cases).^{7,8}

Sources and selection criteria

We searched PubMed with the terms "nephrotic syndrome", "epidemiology", "glomerulonephritis, membranous", "glomerulosclerosis, focal", and "minimal change nephropathy". We also searched the Cochrane library for the limited number of systematic reviews on this subject and referred to the *Oxford Textbook of Clinical Nephrology* (3rd edition) for guidance on appropriate areas to cover for this article.

Box 2 Secondary causes of nephrotic syndrome**Other diseases**

Diabetes mellitus

Systemic lupus erythematosus

Amyloidosis

Cancer

Myeloma and lymphoma

Drugs

Gold

Antimicrobial agents

Non-steroidal anti-inflammatory drugs

Penicillamine

Captopril

Tamoxifen

Lithium

Infections

HIV

Hepatitis B and C

Mycoplasma

Syphilis

Malaria

Schistosomiasis

Filariasis

Toxoplasmosis

Congenital causes

Alport's syndrome

Congenital nephrotic syndrome of the Finnish type

Pierson's syndrome

Nail-patella syndrome

Denys-Drash syndrome

Secondary glomerular disease

A wide range of diseases and drugs can cause nephrotic syndrome (box 2). Diabetic nephropathy is a common cause, reflecting the increasing prevalence of diabetes. Amyloid is also an important cause, with immunoglobulin light chain amyloid nephropathy accounting for 10% of cases in one series.⁷

How do I assess patients who present with nephrotic syndrome?

The aims are to assess the current clinical state of the patient—to ensure that no complications of the disease are present—and to start formulating whether a primary or secondary cause underlies the syndrome, as this informs referral. Almost all patients should be referred to a nephrologist for further management. In children, a paediatric nephrologist will supervise investigation and treatment.

What are the key points in the patient's history?

The history is key in pinpointing the cause of nephrotic syndrome. It is important to note any features suggestive of systemic disease, the drug history (especially newly prescribed or “over the counter” drugs), and any acute or chronic infections. Membranous nephropathy has an association with cancer, particularly of the lungs and large bowel. Although rare in clinical practice, suspicion should be raised, especially in elderly patients. It is useful to take a family history because the syndrome has several congenital causes, such as Alport's syndrome (box 2).

What clinical signs accompany nephrotic syndrome?

Nephrotic syndrome should be part of the differential diagnosis for any patient with new onset oedema. Oedema associated with nephrotic syndrome is often first noticed periorbitally and can become severe—patients may develop oedema of the lower leg and genitals as well as ascites, pleural effusions, and pericardial effusions (box 3).

Which investigations should be performed?

No guidelines are available for the investigation of nephrotic syndrome. The sequence of investigations in box 4 is typical of those used to assess the patient's current clinical status and identify the underlying cause of the syndrome. Assessing the patient's renal function

is a key part of this; serum urea and creatinine should be measured and an estimated glomerular filtration rate calculated. Dipstick testing of the urine for haematuria (which would suggest glomerulonephritis) and proteinuria (3-4+ protein indicates the nephrotic range) is essential, as is measuring the amount of protein loss. We recommend using a spot (preferably early morning) urine sample for a protein:creatinine ratio or an albumin:creatinine ratio as these tests are less prone to error, give quicker results, and have been shown, in cross sectional longitudinal studies, to be as accurate as 24 hour urine collections.^{3,10} A protein:creatinine ratio value greater than 300-350 mg/mmol indicates nephrotic range proteinuria. Renal ultrasound is used to assess renal size and morphology and may need to be performed urgently if signs of renal vein thrombosis are present (such as flank pain, haematuria, renal impairment—using, for example, Doppler examination of the renal veins).

Complications of nephrotic syndrome

The nephrotic syndrome has systemic consequences (box 5). They result, in part, from significant changes in the protein environment of the body as a result of overproduction of proteins in the liver and loss of low molecular weight proteins in the urine.

Is there a significant risk of thromboembolism?

Patients with nephrotic syndrome are at increased risk for thromboembolic events. Imbalances of prothrombotic and antithrombotic factors as well as impaired thrombolytic activity occur.¹¹ Intravascular volume depletion; the use of diuretics; immobilisation; and procoagulant diatheses, such as protein C and protein S deficiencies, or antiphospholipid antibodies, are important contributing factors. The most common sites of thrombosis in adults are in the deep veins of the lower limb. Thrombosis can also occur in the renal veins and can cause pulmonary embolism. Arterial thrombosis can also rarely occur in patients with nephrotic syndrome.¹² Historical case series reported that deep vein thrombosis of the lower limb occurred in 8% and renal vein thrombosis occurred in up to 22% of patients.^{11,13-15} Modern data differ, however. A recent retrospective study reviewing coding data from discharged patients in the United States found deep vein thrombosis occurred in 1.5% and renal vein thrombosis in 0.5% of patients with nephrotic syndrome.¹⁶ Another recent retrospective cohort study found an eight times higher absolute risk of venous thromboembolism, with the greatest risk occurring in the first six months after diagnosis.¹⁷ Case series have shown that membranous nephropathy is particularly associated with venous thrombosis,¹¹⁻¹⁵ and the risk of venous thrombosis is higher when serum albumin is <20-25 g/l.¹³

Should all patients receive prophylactic anticoagulation?

No randomised control trials are available to guide the decision of who is given prophylactic anticoagulation and for how long.^{13,18,19} A Cochrane review protocol,

Primary glomerular diseases that can cause nephrotic syndrome^{7,9}

Disease	Frequency of disease (%) as a cause of nephrotic syndrome		
	1960s and 1970s		1990s to the present
	Patients <60 years	Patients >60 years	
Focal segmental glomerulosclerosis	15	2	35
Membranous glomerular disease	40	39	33
Minimal change glomerular disease	20	20	15
Membranoproliferative glomerular disease (for example, IgA)	7	0	14
Other glomerular disease	18	39	3

Box 3 Clinical signs of nephrotic syndrome**Oedema**

Periorbital oedema

Lower limb oedema

Oedema of the genitals

Ascites

Low albumin

Tiredness

Leuconychia

Breathlessness

Pleural effusion

Fluid overload (high jugular venous pressure)

Acute renal failure

Breathlessness with chest pain

Thromboemboli

Dyslipidaemia

Eruptive xanthomata

Xanthelasmata

Other

Frothy urine

published in 2006, reviewed this subject, but the paucity of trials means that the authors used only a pooled meta-analysis of the available data and non-randomised evidence for their study.²⁰ Screening for thrombosis is not thought to add value to the decision making process and was not recommended in a recent expert commentary.¹⁹ General factors such as immobility, oedema, coexisting prothrombotic tendency, and a previous history of thromboembolic events need to be taken into account, but no “threshold” of proteinuria or hypoalbuminaemia has been identified as a trigger for the use of anticoagulation. Common practice among nephrologists is to anticoagulate with heparin and then warfarin if serum albumin is less than 20 g/l and proteinuria is within the nephrotic range.²¹ The decision of when and how to anticoagulate a patient with nephrotic syndrome should be made after careful consultation with a nephrology team (because, for example, a renal biopsy cannot safely or easily be done with systemic anticoagulation).

Is infection an important problem?

Infection has been reported in up to 20% of adult patients with nephrotic syndrome.²² Patients have an increased susceptibility to infection because of low serum IgG concentrations, reduced complement activity, and depression of T cell function.²³ A variety of infectious complications, particularly bacterial infections, such as cellulitis, can occur. Views on the use of antibiotic and vaccine prophylaxis are conflicting. No trials have assessed the use of prophylactic antibiotics in adults. A Cochrane review in 2004 was not able to recommend any interventions for preventing infection.²⁴

Can nephrotic syndrome cause acute renal failure?

Acute renal failure (acute kidney injury) is a rare spontaneous complication of nephrotic syndrome.²⁵ It can also be caused by excessive diuresis, interstitial nephritis related to the use of diuretics or non-steroidal anti-inflammatory drugs, sepsis, or renal vein thrombosis. Renal impairment of a more chronic nature can reflect damage to the kidneys from systemic or primary renal conditions (such as amyloidosis or diabetes). Reviews of case reports suggest that older patients (and children), and those with heavier protein loss, are most at risk. Patients may need dialysis and can take weeks to recover.²⁵

How can nephrotic syndrome be treated?**What is the best way to treat oedema?**

No guidelines or randomised trials are available on this subject. The underlying cause of the oedema is sodium retention, but the underlying process is complex, controversial, and not fully understood. The key to treatment is to create a negative sodium balance. Patients often need to limit their dietary sodium intake (<100 mmol/day; 3 g/day), restrict their fluid intake (1.5 litres/day), and take diuretics. We recommend reversing the oedema slowly, with a target weight loss

of 0.5–1 kg a day, because aggressive diuresis can cause electrolyte disturbances, acute renal failure, and thromboembolism as a result of haemoconcentration.

Box 4 Sequence of investigations for a person presenting with nephrotic syndrome**Confirm proteinuria present**

Urine dipstick positive (2/3/4+)

Check for concomitant invisible (microscopic) haematuria

Urine dipstick positive (1/2/3+)

Exclude urine infection

Midstream urine to exclude active urinary tract infection—microscopy, culture, and sensitivity

Measure amount of proteinuria

Early morning urinary protein:creatinine ratio or albumin:creatinine ratio (mg/mmol)

Typically >300–350 mg/mmol in nephrotic syndrome

Basic blood testing

Full blood count and coagulation screen

Renal function including plasma creatinine and estimated glomerular filtration rate

Liver function tests to exclude concomitant liver pathology

Bone profile—corrected (for albumin) plasma calcium

Check for other systemic diseases and causes of nephrotic syndrome

C reactive protein and erythrocyte sedimentation rate

Glucose

Immunoglobulins, serum and urine electrophoresis

Autoimmune screen if an underlying autoimmune disease is suspected—antinuclear antibody (ANA), antidouble stranded DNA antibody (dsDNA), and complement values (C3 and C4)

Hepatitis B and C and HIV (after obtaining informed consent)

Chest x ray and abdominal or renal ultrasound scan (especially if renal function is abnormal)

To check for pleural effusion or ascites

To check for the presence of two kidneys, their size and shape, and the absence of obstruction

Be vigilant for complications such as thromboembolism

Doppler ultrasound of leg veins in suspected deep vein thrombosis

Abdominal ultrasound, renal vein Doppler scan, venography of the inferior vena cava, computed tomography and magnetic resonance imaging of the abdomen if renal vein thrombosis is suspected

V/Q nuclear medicine lung scan, computed tomography pulmonary angiography for pulmonary embolism

Investigate the underlying renal and systemic cause of nephrotic syndrome

Renal biopsy under ultrasound

Make histological preparations for light microscopy, immunofluorescence or immunoperoxidase, electron microscopy

Box 5 Complications of nephrotic syndrome**Thromboembolism**

Deep vein thrombosis or renal vein thrombosis, which can lead to pulmonary embolism

Arterial thrombosis (very rare)

Infection

Cellulitis

Bacterial infections, such as pneumonia and cellulitis

Bacterial peritonitis (rare)

Viral infections in immunocompromised patients

Other complications

Hyperlipidaemia

Loss of vitamin D (via binding protein) leading to bone disease

Acute renal failure

Loop diuretics like furosemide are usually used, but drug absorption may be affected by oedema of the gut wall, so large doses of intravenous diuretic are often used for refractory cases. Common diuretics are mostly protein bound so their activity may be affected by heavy proteinuria once filtered across the glomerulus. Thiazide diuretics or potassium sparing diuretics are often added to try to improve the poor responses sometimes found with loop diuretics. They are synergistic for distal inhibition of sodium reabsorption. Intravenous albumin has been used to improve diuresis, and it probably acts by increasing delivery of the diuretic to its site of action and by expanding the plasma volume. It is often used in hypotensive patients in whom conventional treatment is failing. However, its use is not supported by evidence from (albeit small and limited) studies, and it can have harmful effects, such as anaphylaxis, hypertension, and pulmonary oedema.²⁶

Does proteinuria need specific treatment?

Proteinuria is one of the most important adverse prognostic factors for progression to end stage renal failure in chronic renal disease.^{27,28} One of the main

goals of treating nephrotic syndrome is to reduce or eliminate proteinuria. In some patients, this can be achieved by treating the underlying pathology, but additional measures are needed in most. Strategies to limit protein excretion also help correct oedema.

Angiotensin converting enzyme inhibitors, either on their own or together with angiotensin II receptor antagonists, have become the mainstay of treatment as a result of evidence from randomised controlled trials and meta-analyses.²⁹⁻³¹ Proteinuria can be reduced without a change in blood pressure and combined treatment reduces proteinuria more effectively than single agents alone.^{29,31,32} The use of these agents mandates regular monitoring of plasma electrolytes and their full antiproteinuric effect can take some weeks to manifest. Several older treatments, such as high dose non-steroidal anti-inflammatory drugs, have appreciable side effects and are rarely used now. In severe and uncontrollable proteinuria with incapacitating symptoms, especially with complications such as renal dysfunction and malnutrition, patients may need single or bilateral nephrectomy or renal embolisation. In practice this is a rare outcome.

Should we treat dyslipidaemia?

Hyperlipidaemia of nephrotic syndrome is characterised by increases in low density lipoprotein cholesterol and triglyceride and alterations in high density lipoprotein concentrations.³³ Increased cardiovascular events in nephrotic patients could be related to lipid abnormalities.³⁴ No prospective trials have shown that treatment improves survival, but a meta-analysis and post hoc subgroup analyses show that statins have a small protective effect on the progression of renal damage.³⁴⁻³⁷ Of note, many patients spontaneously remit or go into remission with treatment. Treating the underlying cause of nephrotic syndrome and thereby reducing proteinuria will improve or resolve the dyslipidaemia.

Do patients need a special diet?

Muscle wasting is a major problem in severe nephrotic syndrome and patients have a greatly increased albumin turnover. Because of a lack of evidence, the optimal protein intake for such patients is not clear. A low protein diet runs the risk of negative nitrogen balance and malnutrition and so is not recommended.³⁸

Who should be referred for targeted investigation and treatment?

We recommend that all new cases are discussed urgently with local kidney specialists with a view to urgent referral for investigation and treatment. Only rarely is this not necessary (for example, a patient with established diabetic nephropathy, whose protein loss increased to the nephrotic range, might initially be managed by further titration of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists).

ADDITIONAL EDUCATIONAL RESOURCES**Resources for healthcare professionals**

Goldsmith DJ, Jayawardene S, Ackland P, eds. *ABC of kidney disease*. Oxford: Blackwell Publishing, 2007

Davison AMA, Cameron JS, Grunfeld JP, Ponticelli C, Ypersele CV, Ritz E, et al, eds. *Oxford textbook of clinical nephrology*. 3rd ed. Oxford: Oxford University Press, 2005

Burden R, Tomson C. Identification, management, and referral of adults with chronic kidney disease: concise guidelines. *Clin Med* 2005;5:635-42. www.renal.org/eGFR/eguide.html

Resources for patients

Renal Unit of the Royal Infirmary of Edinburgh (<http://renux.dmed.ed.ac.uk/edren/index.html>)—Excellent source of information about renal disease for patients and non-specialist practitioners

National Kidney Federation UK (www.kidney.org.uk)—A collection of disease resources under the "medical information" heading

SUMMARY POINTS

Nephrotic syndrome is a relatively rare but important manifestation of kidney disease

It has serious complications and must be part of the differential diagnosis for any patient presenting with new onset oedema

It can be caused by a wide range of primary (idiopathic) and secondary glomerular diseases

All patients should be referred to a nephrologist for further investigation, which (often) includes a renal biopsy

Initial management should focus on investigating the cause, identifying complications, and managing the symptoms of the disease

Conclusions

Nephrotic syndrome can present in diverse ways in multiple healthcare settings and has important complications. Investigating and managing the syndrome is made more challenging by the lack of a guiding evidence base, but strategies derived from expert consensus are available for its initial management. All patients presenting with nephrotic syndrome should be discussed with local kidney specialists before embarking on further investigations and management. Large randomised trials in the management of the nephrotic syndrome, and in glomerular disease in general, are urgently needed to achieve further progress.

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