For the full versions of these articles see bmj.com

CLINICAL REVIEW

# Nephrotic syndrome in adults

Richard P Hull, David J A Goldsmith

Guy's Hospital Renal Unit, London SE1 9RT

Correspondence to: D J A Goldsmith
david.goldsmith@gstt.nhs.uk

BMJ 2008;336:1185-9
doi:10.1136/bmj.39576.709711.80

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 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.

**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

**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.

## 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]

**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).

**Primary glomerular diseases that can cause nephrotic syndrome[7 9]**

| | Frequency of disease (%) as a cause of nephrotic syndrome | | |
|---|---|---|---|
| | 1960s and 1970s | | |
| Disease | Patients <60 years | Patients >60 years | 1990s to the present |
| 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 |

## 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,

**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, immunofluoresence 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.

RPH and DJAG contributed equally to the design, writing, and editing of this article. DJAG is guarantor.

**Competing interests:** None declared.

**Provenance and peer review:** Commissioned; externally peer reviewed.

1 Cameron JS, Hicks J. The origins and development of the concept of a "nephrotic syndrome." *Am J Nephrol* 2002;22:240-7.
2 Llach F. Thromboembolic complications in the nephrotic syndrome. Coagulation abnormalities, renal vein thrombosis and other conditions. *Postgrad Med* 1984;76:111-4, 116-8, 121-3.
3 National Collaborating Centre for Chronic Conditions. *Chronic kidney disease: early identification and management of adults with chronic kidney disease in primary and secondary care.* Draft for consultation: full guideline published 10 March 2008. www.nice.org.uk/nicemedia/pdf/CKDConsFullGuideline.pdf.
4 Jayawardene SA, Scoble JF, Goldsmith DJ. Nephrotic syndrome: more than just oedema. *Int J Clin Pract* 2002;56:129-31.
5 Ichikawa I, Rennke HG, Hoyer JR, Badr KF, Schor N, Troy JL, et al. Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. *J Clin Invest* 1983;71:91-103.
6 Buerkert J, Martin DR, Trigg D, Simon EE. Sodium handling by deep nephrons and the terminal collecting duct in glomerulonephritis. *Kidney Int* 1991;39:850-7.
7 Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. *Am J Kidney Dis* 1997;30:621-31.
8 Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. *Am J Kidney Dis* 1996;27:647-51.
9 Orth SR, Ritz E. The nephrotic syndrome. *N Engl J Med* 1998;338:1202-11.
10 Ruggenenti P, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. *BMJ* 1998;316:504-9.
11 Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. *Thromb Res* 2006;118:397-407.
12 Parag KB, Somers SR, Seedat YK, Byrne S, Da Cruz CM, Kenoyer G. Arterial thrombosis in nephrotic syndrome. *Am J Kidney Dis* 1990;15:176-7.
13 Bellomo R, Atkins RC. Membranous nephropathy and thromboembolism: is prophylactic anticoagulation warranted? *Nephron* 1993;63:249-54.
14 Llach F, Papper S, Massry SG. The clinical spectrum of renal vein thrombosis: acute and chronic. *Am J Med* 1980;69:819-27.
15 Wagoner RD, Stanson AW, Holley KE, Winter CS. Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome: incidence and significance. *Kidney Int* 1983;23:368-74.
16 Kayali F, Najjar R, Aswad F, Matta F, Stein PD. Venous thromboembolism in patients hospitalized with nephrotic syndrome. *Am J Med* 2008;121:226-30.
17 Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L, et al. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation* 2008;117:224-30.
18 Sarasin FP, Schifferli JA. Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. *Kidney Int* 1994;45:578-85.
19 Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. *J Am Soc Nephrol* 2007;18:2221-5.
20 Kulshrestha S, Grieff M, Navaneethan SD. Interventions for preventing thrombosis in adults and children with nephrotic syndrome (protocol). *Cochrane Database Syst Rev* 2006;(2):CD006024.
21 Charlesworth JA, Gracey DM, Pussell BA. Adult nephrotic syndrome: non-specific strategies for treatment. *Nephrology (Carlton)* 2008;13:45-50.
22 Li YJ, Xie C, Xia ZM. Risk factors for infection in adult nephrotic syndrome. *Chinese J Nephrol* 1996:12:76-8.
23 Ogi M, Yokoyama H, Tomosugi N, Hisada Y, Ohta S, Takaeda M, et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. *Am J Kidney Dis* 1994;24:427-36.
24 Wu HM, Tang JL, Sha ZH, Cao L, Li YP. Interventions for preventing infection in nephrotic syndrome. *Cochrane Database Syst Rev* 2004;(2):CD003964.
25 Koomans HA. Pathophysiology of acute renal failure in idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2001;16:221-4.
26 Dorhout Mees EJ. Does it make sense to administer albumin to the patient with nephrotic oedema? *Nephrol Dial Transplant* 1996;11:1224-6.
27 Ruggenenti P, Perusa A, Mosconi L, Pisone R, Remuzzi G. Urinary protein excretion is the best predictor of ESRF in non-diabetic chronic nephropathies. *Kidney Int* 1998;53:1209-16.
28 Locatelli F, Marcelli D, Cornelli M, Alberti D, Graziani G, Buccianti G, et al. Proteinuria and blood pressure as causal components of progression to end-stage renal failure. Northern Italian Cooperative Study Group. *Nephrol Dial Transplant* 1996;11:461-7.
29 Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, de Jong PE. Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials. *Nephrol Dial Transplant* 1995;10:1963-74.
30 Randomised controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997;349:1857-63.
31 Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003;361:117-24.
32 Tsouli SG, Liberopoulos EN, Kiortsis DN, Mikhailidis DP, Elisaf MS. Combined treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: a review of the current evidence. *J Cardiovasc Pharmacol Ther* 2006;11:1-15.
33 Wheeler DC, Bernard DB. Lipid abnormalities in the nephrotic syndrome: cause, consequences and treatment. *Am J Kid Dis* 1994;23:331-46.
34 Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. *Kidney Int* 1993;44:638-42.
35 Crew RJ, Radhakrishnan J, Appel G. Complications of the nephrotic syndrome and their treatment. *Clin Nephrol* 2004;62:245-59.
36 Fried LF, Orchard TJ, Kasiske BL; for the Lipids and Renal Disease Progression Meta-analysis Study Group. Effect of lipid reduction on the progression of renal disease: a metanalysis. *Kidney Int* 2001;59:260-9.
37 Tonelli M, Moyé L, Sacks F, Cole T, Curham G. Effect of pravastatin on loss of renal function in patients with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol* 2003;14:1605-13.
38 Guarneiri GF, Toigo G, Situlin R, Carraro M, Tamaro G, Lucchesli A, et al. Nutritional status in patients on long term low-protein diet or with nephrotic syndrome. *Kidney Int Suppl* 1989;27:S195-200.