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Management of patients with nephrotic syndrome

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Summary

Nephrotic syndrome is characterised by proteinuria >3.5 g/24h, oedema, hypoalbuminaemia and hyperlipidaemia.

Several glomerular diseases, either primary or secondary, may lead to nephrotic syndrome. Investigations for nephrotic syndrome include immunological and infectious evaluations. Renal biopsy is often mandatory, except in diabetes. Depending on aetiology specific treatment, often with immunosuppressive agents, may be implemented. In any cases nonspecific treatment should be started with ACE inhibitors or ARBs.

Urinary protein loss leads to several complications: water and sodium retention, hyperlipidaemia, increased risk of thromboembolism and infection, anaemia and alteration of mineral metabolism. Each of these complications must be identified and their treatment is discussed in this review.

Key words: nephrotic syndrome; proteinuria; kidney; oedema; hypertension

Introduction and definition

Nephrotic syndrome is defined by the association of a proteinuria higher than 3.5 g/24 hours, hypoalbuminaemia, oedema and dyslipidaemia.

The prevalence of this syndrome is high, mainly due to its frequency in diabetic patients. The aetiological causes of nephrotic syndrome are however miscellaneous, ranging from primary renal diseases to systemic illnesses with various histopathological presentations (tables 1 and 2).

Table 1

Primary glomerular diseases associated with nephrotic syndrome.

Primary glomerular diseases (frequent; rare)
Membranous glomerulopathy
Focal and segmental glomerulosclerosis
Minimal change disease (MCD) glomerulopathy
IgA nephropathy
Membranopoliferative glomerulonephritis
C1q glomerulopathy
Fibrillar glomerulopathy
Congenital podocyte anomaly

The renal disease revealed by nephrotic syndrome must be precisely characterised, since although many therapeutic strategies are common to all nephrotic patients, specific treatments exist and must be evaluated in each case.

Independently of the underlying disease, urinary protein loss may lead to several complications due either to the toxicity of proteinuria on the kidney, or to plasma depletion of specific proteins. The purpose of this review is to make recommendations for the evaluation of the nephrotic syndrome and the implementation of nonspecific treatment for nephrotic patients.

Aetiology and investigations

Nephrotic proteinuria, mainly albuminuria, involves a glomerular lesion since tubular lesions alone will not result in heavy albuminuria. Increased glomerular permeability may occur when a lesion is present, either in the endothelium, podocytes, basement membrane or a combination of these elements, resulting in leakage of albumin from the vascular to the tubular compartment.

Nephrotic syndrome may result from either primary glomerular or systemic disease leading to renal insult (tables 1 and 2). Aetiologies of nephrotic syndrome vary depending on the pa-

No conflict of interest.

Table 2

Causes of secondary nephrotic syndrome (most frequent).

Medications (non exhaustive) NSAIDs, pamidronate, rifampicin, IFN alpha, gold, lithium, interferon alpha	Allergens, immunisations Pollens, seric illness, vaccines, bee sting
Infections Bacterial: Endocarditis, syphilis, tuberculosis, mycoplasma infections Viral: HIV, HBV, HCV, EBV, CMV, VZV Protozoal: Toxoplasmosis, malaria Helminthic: Schisostomiasis, trypanosomiasis, filariasis	Systemic illnesses (most frequent) Systemic lupus erythematosus (SLE), Rheumatoid polyarthritis, Schonlein-Henoch purpura MGUS, amyloidosis
Neoplasia Solid tumours Haemo- or lymphopathies Multiple myeloma GVHD post marrow transplantation	Metabolic diseases and heredofamilial (non exhaustive) Type I and II diabetes Hypothyroidism Alport syndrome Graves disease Fabry disease
Miscellanous (examples) Pregnancy-associated Chronic allograft failure Nephronic reduction Renal artery stenosis Obesity Heart failure (right/left) and pericarditis	

tient's age. Among secondary causes, type I or II diabetes remain the most frequent aetiology in adults, although approximately 10% of nephrotic syndrome cases in diabetes are due to other renal diseases. Other systemic diseases, such as systemic lupus erythematosus (SLE), amyloidosis, hepatitis B and C, HIV, neoplasms or haematologic diseases may also be associated with glomerular disorders causing nephrotic syndrome. Finally, drugs or toxic substances must be considered (bisphosphonates, NSAIDs, heavy metals etc). Nephrotic syndrome patients require a thorough workup and our recommended initial evaluation of nephrotic patients is summarised in table 3. Evaluation of proteinuria can be done by 24-hour collections initially and then followed by iterative measurement of the protein-on-creatinine ratio. This ratio relies on the fact that adults excrete on average 1 g creatinine per day. It can safely be used to monitor the evolution of proteinuria and is a good renal prognosis factor [1].

Table 3

Initial evaluation of nephrotic patients (except diabetes).

Complete medical history	Blood tests
	Blood count, electrolytes (CRP, Na, K, BUN, creatinine, albumin, serum proteins, calcium, phosphate, bicarbonates, chloride) Urinary spot and sediment
	24-hour proteinuria and/or protein/ creatinine ratio
	Serum and urinary electrophoresis and immuno-electrophoresis
	Lipid profile
	Liver tests
	HBV, HCV, HIV serology
	Immunological profile (ANA, RF)
	glycaemia
	TSH
	Coagulation tests
Complete physical examination	Additional tests
	Renal duplex echography
	ECG et chest x-ray
	Renal biopsy

Renal biopsy plays a major role in the evaluation of nephrotic patients, since several histological lesions are associated with nephrotic syndrome. Diabetic glomerulosclerosis, membranous glomerulopathy, focal segmental glomerulosclerosis and minimal change glomerulopathy are the most common in adults. The three latter may be either primary or a component of a systemic disease. The sharing and variability of clinical manifestations among these different glomerular diseases do not allow accurate diagnosis based on clinical and laboratory features alone. Renal biopsy is therefore mandatory for every nephrotic patient except the diabetic patient, in order to define the disorder accurately and optimise treatment. In diabetic patients atypical features such as a rapidly progressive nephrotic syndrome or acute renal failure, presence of glomerular haematuria and/or absence of associated microvascular lesions (retinopathy, neuropathy) are indications for renal biopsy.

Prognosis

Vital prognosis is mainly influenced by the disorder causing nephrotic syndrome. However, nephrotic proteinuria confers per se a higher cardiovascular risk, and nephrotic patients are at risk of several systemic complications to be detailed later.

Renal prognosis is dependent on non-modifiable variables such as the cause of nephrotic syndrome, renal function and age at presentation, as well as the extent of renal interstitial lesions on the biopsy. Prognostic factors are not similar for all nephrotic syndromes. A well studied example is

membranous nephropathy, where the best parameters for predicting the evolution of renal function are creatinine clearance at diagnosis, the extent of proteinuria (< or >4 g/day) and the slope of creatinine clearance over a six months' observation period. Partial or complete remission of proteinuria at six months accurately predicts the risk of progression in this disease [2, 3]. Several studies have also demonstrated that either partial or complete elimination of proteinuria results in renal function preservation, in diabetic or non-diabetic patients [4]. The magnitude of proteinuria and its correction is therefore a major modifiable risk factor for progression to end-stage renal failure. The main therapeutic goal in nephrotic patients is to reduce proteinuria to the lowest possible level.

Specific treatments

In diabetes, metabolic control is the mainstay of treatment. In other secondary causes of nephrotic syndrome specific treatment varies depending on the causative illness, e.g. curative or palliative treatment of a neoplastic disease, antiviral treatment of hepatitis or immunosuppressive therapy of a systemic disease.

Among primary renal diseases the most frequently encountered are membranous glomerulopathy, focal segmental glomerulosclerosis and minimal change glomerulopathy. An underlying immunological disorder is suspected in these three diseases. Immunosuppressive or immunomodulatory drugs are therefore the mainstay of treatment, therapeutic strategies depending on the clinical and histological features. The decision to treat and how to treat the patients cannot be detailed here and many options are possible. Several regimens which generally include corticosteroids have been studied and are not detailed here. However, irrespective of these specific treatments, nonspecific protective therapies must be implemented in patients with nephrotic syndrome.

Nonspecific treatments of proteinuria

These treatments are therefore either complementary to a specific treatment or the sole therapy available to lower proteinuria. In contrast to specific treatment, complete remission of proteinuria cannot be expected with these treatments. A reasonable goal is to aim at a 50% reduction in proteinuria, or, even better, at proteinuria below 1g/day, which seems to be a critical threshold for long term renal survival.

Antihypertensive treatment

Tight blood pressure control is critical to renal function preservation in all cases of proteinuric renal diseases, aiming at upper systolic and diastolic values of 125 and 75 mm Hg respectively. It should also be mentioned that low blood pressure likewise appears to be detrimental and lowering blood pressure below 110 mm Hg systolic should be avoided [5]. All classes of antihypertensive drugs can be used to meet these targets, and a combination of 2–4 different drugs is often necessary. 24-hour ambulatory blood pressure measurement is often needed to assess optimal control and optimise treatment. Association of a low salt diet (6 g/day) is mandatory to optimise the action of antihypertensive drugs.

Angiotensin conversion enzyme (ACE) inhibitors and angiotensin type 1 receptor antagonists (ARBs)

Stimulation of the renin-angiotensin-aldosterone (RAA) system is critical to the genesis of glomerular lesions leading to proteinuria. RAA system blockade has been shown to be successful in reducing proteinuria in both animal and human studies. ACE inhibitors and ARBs are therefore recommended as first line treatment in proteinuric diseases, even in the absence of hypertension. Their antiproteinuric effect relies on the decrease in glomerular pressure due to their preferential vasodilatory effect on the glomerular efferent arteriola, rather than on their antihypertensive effect per se. There is also experimental evidence of a direct protective effect of these drugs on the glomerular filtration barrier [6].

Both drugs have exhibited their nephroprotective action in either type I (ACE inhibitors) or type II (ARB) diabetes or in the nondiabetic population [6–9]. This favourable effect on renal survival is well correlated to the extent of proteinuria reduction [7].

Introduction of ACE inhibitors or ARBs may be risky in nephrotic patients, in particular when renal dysfunction is present. Plasma creatinine often rises after treatment initiation and a 30% increase should be tolerated. If plasma creatinine rises more than 30% transient interruption of the treatment is recommended and a search for a precipitating condition such as renal artery stenosis or relative hypovolaemia (diuretics, severe hypoalbuminaemia <20 g/L) should be conducted. It should be borne in mind that proteinuria per se stimulates tubular creatinine secretion and therefore induces overes-

timation of renal function. Proteinuria correction will therefore decrease this secretion and increase plasma creatinine levels without actually altering renal function.

Hyperkalaemia may also be a limiting factor. Plasma potassium up to 5.5 mmol/L is tolerated. Above this level, ACE inhibitors or ARB should be decreased in dosage or even stopped. Importantly, concomitant medications, such as beta blockers, spironolactone, potassium sparing diuretics and cyclosporine may potentiate a rise in plasma potassium level.

When starting a patient on ACE inhibitors or ARBs, serum creatinine and potassium levels must be checked with a second blood test within five days after the start of the treatment and after each dose modification. Once stable, monthly blood testing is recommended in nephrotic patients.

Finally, if clinical and biological tolerance of the medication is good, dosage should be increased to the maximum recommended level to maximise the antiproteinuric effect. Small studies have demonstrated that supramaximal doses of ARBs (e.g. irbesartan 900 mg) could further reduce proteinuria. We recommend however targeting only maximum doses, except in very limited situations.

In the event of persistent heavy proteinuria despite maximal doses of either one treatment (ACE inhibitors or ARBs), dual blockade of the RAA system may be useful.

Recently, however, the "On Target" trial [10] has raised issues regarding the validity of this association. This multicentric study comparing three groups of high risk cardiovascular patients (a group treated with ACE, a group treated with ARB or a combination of ACE and ARB) failed to demonstrate a beneficial role of the combination with respect to survival and hard renal endpoints, such as renal failure progression and beginning of dialysis, despite an additive effect on proteinuria reduction. The association even appeared deleterious in some patients, with an increased rate of hypotensive episodes, hyperkalaemia and acute renal dialyses.

Before citing additional information on more detailed analyses of subgroups of patients from this large study (25 000 patients), we need to integrate these results into our practice. In a patient aged over 55 with diabetes and/or vascular problems and nephrotic syndrome, the aim will be to normalise blood pressure and reduce proteinuria. Either an ACE inhibitor or an ARB will then be chosen and the dosage adjusted according to clinical and biological tolerability. Other antihypertensive drugs may be added to achieve optimum blood pressure control. The combination of ACE inhibitors and ARB is not recommended in this case.

In a young (<55 years old) or older patient with no increased cardiovascular risk (no hypertension, no diabetes), presenting with nephrotic syndrome secondary to a systemic or primary glomerular disease, the therapeutic strategy may differ, a recent meta-analysis having shown that dual RAA blockade was safe and had an additional antiproteinuric effect despite a tendency to increase plasma potassium levels [11]. The dual blockade can therefore be recommended if proteinuria persists despite a maximum dose of either ACE inhibitors or ARB, conditional on careful renal and electrolyte monitoring.

Diuretics

Diuretics are an integral part of the treatment of nephrotic syndrome, given the presence of oedema. In addition to their effect on oedema, discussed later in more detail, diuretics are also critical for blood pressure control, potentiating the effect of either ACE inhibitors or ARBs. This synergistic effect is also observed on proteinuria reduction.

Aldosterone antagonists

Spironolactone is a mineralocorticoid receptor antagonist which possesses a diuretic effect, particularly in cases or primary or secondary stimulation of the RAA system. It also has potential antiproteinuric effects, small studies having demonstrated that addition of spironolactone to either ACE inhibitors, ARBs or both in nondiabetic proteinuric patients may have an additive effect on proteinuria reduction. In diabetic patients similar results are observed with the association of spironolactone to maximum doses of either an ACE inhibitor or an ARB [12]. These studies, however, were short-term and not designed to assess preservation of renal function.

The triple association (ACE, ARB and spironolactone) can therefore be considered in specific patients with refractory proteinuria despite optimal ACE and ARB treatment. The risks of hyperkalaemia well documented with spironolactone must be carefully considered [13]. Eplerenone, another mineralocorticoid receptor antagonist, can be regarded as equivalent to spironolactone although not yet accepted in this indication.

Direct renin inhibitors

Aliskiren, a direct renin inhibitor, is now commercially available in Switzerland. This drug directly inhibits the enzymatic activity of renin. A recent study showed that addition of aliskiren to an ARB in diabetic proteinuric patients was beneficial in reducing albuminuria [14]. These results are interesting, but the short follow-up (six months) and the specific type of population studied require additional studies to define the exact place of this new class of drugs compared to ACE inhibitors and ARB in nephrotic patients.

There are no data regarding the triple association of ACE inhibitors, ARBs and aliskiren, and hence this combination cannot be recommended.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) reportedly decrease proteinuria [15]. This effect is essentially mediated by a decrease in glomerular filtration rate consecutive to inhibition of vasodilatory prostaglandins and the treatment is restricted to very limited cases of symptomatic nephrotic syndrome refractory to other classical treatments. In these cases iatrogenic reduction of glomerular filtration rate may play a beneficial symptomatic role.

Calcium channel blockers

Calcium channels blockers are potent antihypertensive drugs. They are therefore useful in meeting blood pressure targets and hence may contribute to decreasing proteinuria. This is observed with both verapamil, diltiazem or dihydropiridine calcium channel blockers. The latter may have a synergistic vasodilatory effect with ACE inhibitors or ARB on the efferent artery, and may have cardioprotective effects [16].

These drugs are therefore useful in nephrotic syndrome, their major drawback being the occurrence or aggravation of peripheral oedema.

Dietary factors

Sodium intake should imperatively be reduced to less than 6 g/day in order to minimise oedema and hypertension, and to potentiate the effect of ACE inhibitors and ARBs.

Protein intake has been a subject of debate in nephrotic syndrome. Various studies have demonstrated that a high protein diet (to correct for the urinary losses) was ineffective in correcting hypoalbuminaemia [17]. Moreover, the increased protein intake tends to further increase proteinuria and glomerular hyperfiltration, and is therefore probably deleterious. Conversely, low protein diets (<0.8 g/kg/d) have a slight anti-proteinuric effect which might be valuable [18]. Vegetable proteins appear to be beneficial compared to animal proteins in reducing proteinuria. However, muscle wasting being a major problem in nephrotic patients, and a low protein intake diet increasing the risk of malnutrition, it is not recommended.

In practice we recommend a protein intake of 0.8–1 g/kg/d, with a preference for vegetable and fish proteins. Intravenous supplementation of albumin is not beneficial and is not recommended, except in cases of very severe hypovolaemia.

A nutritionist consultation is recommended to every nephrotic patient.

Complications of nephrotic syndrome

Oedema

Pathophysiological mechanisms resulting in water and sodium retention are still a subject of debate. There are two theories in the field. The first is that decreased oncotic pressure and relative hypovolaemia are the triggers for renal water and sodium retention due to subsequent activation of the RAA and vasopressin systems. The second theory is in favour of primary renal dysfunction with inappropriate sodium retention by the cortical collecting duct [19]. Globally, both mechanisms are probably active at different phases of the disease and both participate in water and sodium retention in this disease.

In children presenting with pure nephrotic syndrome without hypertension and with normal renal function, amiloride, an inhibitor of the sodium epithelial channel (ENaC) which blocks sodium reabsorption in the collecting duct, is often very efficient.

In adults, sodium retention is frequently associated with a decrease in glomerular filtration rate and hypertension. In this situation diuretics should be associated with ACE inhibitors or ARBs. If renal function is relatively preserved, either amiloride or thiazides or spironolactone can be chosen as the first alternative. A loop diuretic is usually necessary to obtain efficient natriuresis. Indeed, given the intensity of sodium retention and the diversity of causal mechanisms, a sequential blockade of the nephron is habitually needed, the collecting duct being an interesting target in view of its probable physiopathological role. Maintenance of a low salt diet is crucial for the effectiveness of antihypertensive drugs and diuretics, together with periods of bed rest (with antithrombotic prophylaxis). In severe cases intravenous administration of loop diuretics may be necessary. In the event of profound hypoalbuminaemia (plasma levels <15 g), especially in the acute setting and associated with hypovolaemia, intravenous desalted albumin may be administered. The weight loss should approximate 1 kg per day and both renal function and electrolytes must be carefully monitored during diuretic treatment.

Lipid metabolism

Dyslipidaemia may be marked, with an increase in total cholesterol, LDL, triglycerides and lipoprotein (a).

Dyslipidaemia in nephrotic syndrome contributes to the increased cardiovascular mortality in these patients, and may also be involved in renal disease progression. Screening and treatment of dyslipidaemia are therefore of critical importance.

The pathogenesis of dyslipidaemia in nephrotic patients is not yet totally understood. Decreased plasma oncotic pressure stimulates hepatic synthesis of different proteins and may contribute to the increase in LDL. Acquired HDL me-

Table 4
Summary of recommendations.

Complication	Recommendations
Proteinuria	Specific treatment according to primary disease
	In all cases: ACE inhibitors or ARBs increased to maximum dose depending on biological and clinical tolerance
	If age <55 or no comorbidities: evaluate ACE and ARB combination
	If refractory proteinuria, consider spironolactone
Oedema	Low salt diet
	Amiloride in children
	Sequential diuretic blockade in adults (loop diuretics, thiazide, spironolactone or amiloride)
Hyperlipidaemia	Lipid profile
	Statin if pathological or severe long lasting nephrotic syndrome
Hypertension	ACE inhibitors or ARBs as first choice
	Thiazides or calcium channel blockers in association
	Low salt diet
Hypoalbuminaemia	High protein diet not indicated
	0.8–1 g/kg/day
Thromboembolic risk	Prophylactic anticoagulation if immobilisation
	Full-dose anticoagulation if thrombotic event or membranous nephropathy and severe hypoalbuminaemia (alb <20 g/l)
	In other cases of NS: to be discussed depending on bleeding risk
Anaemia	Anaemia evaluation
	Erythropoietin if required
	Target haemoglobin 11–12 g/l
Infections	High index of suspicion
	Antipneumococcal and influenza vaccinations
Bone metabolism	Vitamin D and calcium
	Bisphosphonates if steroids and/or pathological osteodensitometry

ACE: Angiotensin conversion enzyme / ARB: Angiotensin receptor blocker

tabolism abnormalities resulting in increased triglycerides and decreased HDL synthesis have also been observed [20].

Statins are efficient and safe for the treatment of dyslipidaemia in patients with nephrotic syndrome. Statins reduce cardiovascular risk in moderate renal failure patients [21] and should be implemented as long as nephrotic syndrome is ongoing. Proteinuria reduction is however the best treatment for dyslipidaemia correction.

Thromboembolism

Nephrotic syndrome is a risk factor for thromboembolic events, mainly in young patients and at the beginning of the nephrotic syndrome. The risk can be as high as 40% in particular forms of renal disease such as membranous nephropathy. Thromboembolic events remain highly suspect in nephrotic patients.

The pathophysiology of thromboembolic events is related to imbalance between pro- and anticoagulant factors. Urinary loss of antithrombotic factors (mainly antithrombin III) and synthesis of procoagulant factors are implicated in the pathogenesis of this complication. The higher incidence observed in some glomerular disorders (e.g. membranous nephropathy), is unexplained.

Treatment of an incidental thromboembolic event is similar to a standard event, with the difference that full dose anticoagulation should be maintained as long as the nephrotic syndrome is present. Primary prophylaxis is a much more difficult problem [22]. Markov risk benefits analyses have demonstrated a higher expected benefit than risk from full dose prophylactic anticoagulation in severe membranous-associated nephrotic syndrome (plasma albumin <20 g/l) [23]. This is however not applicable to secondary nephropathies such as diabetic nephropathy.

In practice, except for diabetic nephrotic syndrome, institution of primary prophylaxis by full dose anticoagulation should be discussed according to the type of disease, its severity and individual haemorrhagic risk, but is usually indicated as long as proteinuria is ongoing and serum albumin below 20 g/l.

Infections

Nephrotic patients present a high risk of infection. Encapsulated pathogens (e.g pneumococcus) are frequently encountered in children (pneumonia, spontaneous peritonitis, dermohypodermitis) and are associated with severe disease. In adults the bacterial susceptibility extends to gram-negative rods. This susceptibility is probably related to loss of various immunoglobulins and alternate complement pathway dysfunctions in part due to urinary loss. Immunosuppressive treatments further increase susceptibility to other pathogens such as CMV, PCP, etc., usually if nephrotic syndrome persists.

Anti-influenza and antipneumococcal vaccina-

tion is therefore recommended with plasma monitoring of antibodies (for pneumococcus) after six months, given the high risk of immunity loss. A high degree of suspicion should be entertained regarding infections in these patients.

Anaemia

Anaemia of chronic renal disease is related to inadequate erythropoietin production by the kidneys (endocrine failure). In nephrotic patients this can be aggravated by urinary losses of erythropoietin, transferrin and iron. The association of nephrotic syndrome with anaemia in the absence or renal dysfunction is still a subject of debate [24].

In cases of anaemia a standard evaluation should be performed (reticulocytes count, B12, folate, iron status). In the absence of renal dysfunction and with an unexplained aregenerative anaemia, erythropoietin measurement is useful. If the erythropoietin level is low, administration of erythropoiesis synthesis agents (ESA) is indicated, targeting a haemoglobin level of 11–12 g/l.

Bone metabolism

Renal failure is associated with secondary hyperparathyroidism and hypovitaminosis D. In nephrotic patients this may be further complicated by urinary loss of albumin and globulins that are vitamin D transporters. Monitoring of serum calcium and phosphates as well as vitamin D and PTH measurement is warranted in these patients. Steroid treatments will also alter bone density.

If possible, supplementation with calcium and vitamin D is recommended in all patients. Depending on the clinical context and associated medications, mostly corticosteroids, a dual absorption densitometry and/or bisphosphonate therapy may be indicated [25].

Conclusion

In conclusion, diagnosis and follow up of nephrotic patients require close cooperation between general practitioners and nephrologists to ensure the best possible care.

Evaluation and treatment of complications are crucial in order to minimise mortality and morbidity associated with nephrotic syndrome.

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