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DEPARTMENT OF THERAPY AND FAMILY MEDICINE

UNDERSTANDING URINALYSIS
PART I

Methodological recommendations

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Methodological recommendations are purposed for medical students, clinical ordinators, therapeutics, family physicians and doctors of other specialties who may deal with urinalysis. Recommendations contain information about evaluation of the most common urine abnormalities.

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Table of contents

LIST OF ABBREVIATIONS

ACE - angiotensin-converting-enzyme
ACR - albumin-to-creatinine ratio
AMH - asymptomatic microhematuria
ANAs - antinuclear antibodies
ANCAs - antineutrophil cytoplasmic antibodies
a-NVH - asymptomatic non-visible hematuria
ARB - Angiotensin II receptor blocker
BUN - blood urea nitrogen
CT - computed tomography
eGFR - estimated glomerular filtration rate
GBM - glomerular basement membrane
GCW - glomerular capillary wall
HIV - human immunodeficiency virus
HPF - high-power field
IgA - Immunoglobulin A
IVU - intravenous urography
JVP - jugular venous pulse
KDIGO - Kidney Disease Improving Global Outcomes
KUB - kidneys, ureters and bladder
MPGN - Membranoproliferative glomerulonephritis
MRA - mineralocorticoid receptor antagonist
MRI - magnetic resonance imaging
MRU - magnetic resonance urography
NHANES - National Health and Nutrition examination Survey
NMP - nuclear matrix protein
NVH - non-visible hematuria
PAH - polycyclic aromatic hydrocarbons
PCR - protein-to-creatinine ratio
PCT - proximal convoluted tubule
PSA - Prostate-specific antigen
RAAS - renin-angiotensin-aldosterone system
RBCs - red blood cells
RPG - retrograde pyelogram
SLE - systemic lupus erythematosus
s-NVH - symptomatic non-visible hematuria
TGF - transforming growth factor
TURBT - transurethral resection of the bladder tumour

UACR - urinary albumin-to-creatinine ratio
USS - ultrasound scan
UTI - urinary tract infection
VEGF - vascular endothelial growth factor
VH - visible hematuria

WHAT IS URINARY SYNDROME?

The term “urinary syndrome” includes proteinuria and/or urinary sediment abnormalities (hematuria, leukocyturia (pyuria) and abnormal amount and/or type of urinary casts).

Urinary syndrome is the most constant symptom of renal and urinary tract disorders. Its diagnostic value is particularly high in the absence of extrarenal symptoms of kidney disease (edema, hypertension),when changes in the urine are the only diagnostic criterion for renal or urinary tract disease, such as glomerulonephritis with isolated urinary syndrome, chronic pyelonephritis, at the initial stage of renal amyloidosis etc.

PROTEINURIA

Proteinuria is the presence of excess proteins in the urine. Normal urinary protein excretion is <150 mg/24 hour, with majority consisting of secreted proteins such as Tamm-Horsfall protein. Daily albumin excretion in a healthy person is <30 mg. Proteinuria is divided into selective and nonselective. Proteinuria that is more than 85% albumin is selective proteinuria. Albumin has a net negative charge, and it is proposed that loss of glomerular membrane negative charges could be important in causing albuminuria. Nonselective proteinuria, being a glomerular leakage of all plasma proteins, would not involve changes in glomerular net charge but rather a generalized defect in permeability. This construct does not permit clear-cut separation of causes of proteinuria, except in minimal-change nephropathy, in which proteinuria is selective.

Proteinuria can occur in various forms and at different levels of severity. It can be classified on the basis of the amount of protein (nephrotic or non-nephrotic), the type of protein (albuminuria or low molecular weight proteinuria), or the underlying pathological damage (glomerular vs. non-glomerular). Most cases of proteinuria can be classified as tubular, overflow, or glomerular. Proteinuria could be functional (due to physiological or biological stress on kidneys) or organic (due to involvement of kidneys or other organs).

The functional proteinuria (albuminuria) is usually intermittent and not accompanied by any symptoms or evidence of kidney disease. It is of glomerular origin and occurs in patients with normal renal function, bland urine sediment, and normal blood pressure. The quantitative protein excretion is less than 1 g/day. The main causes of functional albuminuria are:

- fever;
- strenuous exercise (athletic proteinuria, effort proteinuria, march proteinuria);
- extreme cold;

- cardiac failure;
- seizures;
- emotional stress;
- orthostatic proteinuria (is diagnosed if the patient has no proteinuria in early morning samples but has low-grade proteinuria at the end of the day. It usually occurs in tall, thin adolescents or adults younger than 30 years (and may be associated with severe lordosis). Patients have normal renal function and proteinuria usually is less than 1 g/day with no hematuria);
- last two months of pregnancy (due to pressure on kidneys).

Organic proteinuria is of three types:

1) Pre-renal proteinuria – when the kidneys are affected secondarily to some other disease.

2) Renal proteinuria – when the cause is the kidney disease.

3) Post-renal proteinuria – when the protein is added to the urine after it has left the renal tubules.

Prerenal proteinuria. It is found in a variety of conditions exerting stress on the kidneys. The prerenal proteinuria usually disappears when the primary disease is cured. The most common conditions, which could lead to pre-renal proteinuria are impairment of renal circulation due to dehydration, diarrhea or vomiting, blood loss due to accidental injuries or anemia. Prerenal proteinuria can also be caused by overproduction of abnormal low molecular weight proteins (eg, light chains in multiple myeloma, myoglobin in rhabdomyolysis) that exceeds the tubular reabsorption capacity, leading to spilling of the protein into the urine (Overflow proteinuria). These low molecular proteins can be toxic to the tubules and can cause acute kidney injury.

Renal proteinuria. It is found in all forms of kidney disease. The cause of renal disorder or kidney disease may be inflammatory (infectious), degenerative (immunological) or destructive (toxic or malignant). The plasma globulin and red blood cells (RBCs) may also be excreted along with albumin during some renal disorders. The urine would be smoky in color if macroscopic hematuria is also associated with proteinuria. The cases of acute glomerulonephritis may excrete 0.5 to 2.0 percent (0.5 g to 2.0 g/dl) protein in the urine, whereas the cases affected by chronic glomerulonephritis generally excrete less than 0.5 percent (0.5 g/dl) protein in the urine. The amount of protein excreted daily would vary depending on the volume of urine voided daily. The ratio of albumin to globulin excreted in the urine may vary from 10:1 to 5:1. A routine and quantitative urine analysis is required to evaluate the extent of excretion of proteins in the urine.

Renal proteinuria is divided into Glomerular and Tubular proteinuria. Glomerular proteinuria is caused by functional or structural modifications of the electronic glomerular base membrane charge, producing a disturbance of the filtration barrier. It can be observed in glomerulonephritis, infections, systemic lupus erythematosus, diabetes, hypertension, neoplasia, and congenital diseases. Glomerular proteinuria can be categorized according to whether pathological damage of the glomerulus is present. Types in which the patient has no pathological damage to the glomerulus include transient and orthostatic proteinuria.

Glomerular proteinuria associated with pathological damage to the glomerulus is categorized by protein quantity. In non-nephrotic proteinuria, the amount of proteinuria is <3.5 g/24h and is persistent. These patients require close follow-up and may need a kidney biopsy if they have abnormal urine microscopy results and/or impairment of kidney function.

Nephrotic-range proteinuria is defined as >3.5 g/24h. This finding denotes significant glomerular disease and requires a kidney biopsy for diagnosis and management.

Accompanying findings in patients with glomerular damage may include the following:

- active urine sediment – dysmorphic red blood cells and red cell casts;
- hypoalbuminemia;
- lipiduria;
- hyperlipidemia;
- edema;
- abnormal renal function;
- hypertension.

Tubular proteinuria: decreased reabsorption of the proteins usually filtered by the glomerulus caused by alterations of the tubular reabsorption mechanisms. Low-molecular-weight proteins appear in the urine, such as β2-microglobulin, α1-microglobulin, or retinol-binding protein. This kind of proteinuria can be observed in congenital or systemic diseases and in cases of toxicity caused by drugs and toxins.

Post-renal proteinuria. The proteinuria or albuminuria is termed as post-renal albuminuria if protein is possibly added to the urine as it passes along the urinary tract after leaving the urinary tubules of the kidneys. The major causes of the post-renal albuminuria are the lesions of the renal pelvis or urinary bladder. Lesions of the prostate (in male patients) and urethra also lead to post-renal albuminuria. Admixture of discharges from the vagina (in female patients) and semen (in male patients) may also give positive tests for protein.

Epidemiology of proteinuria

Race-related demographics

According to the National Health and Nutrition examination Survey (NHANES III), the prevalence of microalbuminuria (excretion of 30-300 mg of albumin daily) is greater in non-Hispanic blacks and Mexican Americans aged 40 to 79 years compared with age-matched non-Hispanic whites. Similar results were found in the NHANES survey from 2006, where even after adjusting for covariates and medication use, racial and ethnic minorities with and without diabetes had greater odds of albuminuria compared with whites without diabetes. The results were similar when the comparison was made in patients with eGFR (estimated glomerular filtration rate) < 60 mL/min.

Many causes of proteinuria are particularly common in African Americans and certain other groups. The primary glomerular disorder, focal segmental glomerulosclerosis, has a higher incidence as well as a worse prognosis in African Americans.

In a study by Friedman et al, nondiabetic chronic kidney disease was found to occur in more than 3 million African Americans who had genetic variants in both copies of APOL1, increasing their risk for hypertension-attributable end-stage renal disease and focal segmental glomerulosclerosis. However, African Americans without the risk genotype appear to have a risk similar to that of European Americans for developing nondiabetic chronic kidney disease.

Sex- and age-related demographics

Most primary glomerular diseases associated with proteinuria (eg, membranous glomerulonephritis) and secondary renal diseases (eg, diabetic nephropathy) are more common in males than in females. As a result, persistent proteinuria is at least twice as common in males as in females.

The incidence of hypertension and diabetes increases with age. In consequence, the incidence of persistent proteinuria (and microalbuminuria) also increases with age.

Etiology of proteinuria

The presence of abnormal amounts or types of protein in the urine may be due to:

- Systemic diseases that result in an inability of the kidneys to normally reabsorb the proteins through the renal tubules
- Overproduction of plasma proteins that are capable of passing through the normal glomerular basement membrane (GBM) and that consequently enter the tubular fluid in amounts that exceed the capacity of the normal proximal tubule to reabsorb them
- A defective glomerular barrier that allows abnormal amounts of proteins of intermediate molecular weight to enter the Bowman space.

Glomerular proteinuria. Glomerular diseases

Causes of glomerular disease can be classified as primary (no evidence of extrarenal disease) or secondary (kidney involvement in a systemic disease) and can then subdivided within these two groups on the basis of the presence or absence of nephritic/active urine sediment. In some cases, primary and secondary diseases can produce identical renal pathology.

Primary glomerular diseases associated with active urine sediment (proliferative glomerulonephritis):

- Immunoglobulin A (IgA) nephropathy;
- Membranoproliferative glomerulonephritis (MPGN);
- Mesangial proliferative glomerulonephritis;

Primary glomerular diseases associated with bland urine sediment (nonproliferative glomerulonephritis):

- Membranous glomerulonephritis;
- Minimal-change disease;
- Primary focal segmental glomerulosclerosis;
- Fibrillary glomerulonephritis;
- Immunotactoid glomerulopathy;

Secondary glomerular diseases associated with active urine sediment (proliferative glomerulonephritis, including rapidly progressive glomerulonephritis):

- Anti-GBM disease;
- renal vasculitis – including disease associated with antineutrophil cytoplasmic antibodies (ANCAs), such as granulomatosis with polyangiitis (formerly known as Wegener granulomatosis);
- lupus nephritis;
- cryoglobulinemia-associated glomerulonephritis;
- bacterial endocarditis;
- Henoch-Schönlein purpura;
- postinfectious glomerulonephritis.

Secondary glomerular diseases associated with bland urine sediment (nonproliferative glomerulonephritis):

- diabetic nephropathy;
- amyloidosis;
- hypertensive nephrosclerosis;
- light-chain disease from multiple myeloma;
- secondary focal glomerulosclerosis.
- secondary focal glomerulosclerosis may result from the following:
- the healing phase of other glomerulonephritides;
- as a nonspecific result of reduced nephron mass from any cause, including nonglomerular diseases such as reflux nephropathy;

- from other causes of glomerular hyperfiltration, such as hypertensive nephrosclerosis and obesity.

Unlike primary focal segmental glomerulosclerosis, the secondary type usually is gradual in onset and is not usually associated with hypoalbuminemia or other manifestations of nephrotic syndrome, even in the presence of nephrotic-range proteinuria.

MPGN is usually a pattern of injury seen on light microscopy. The current classification divides MPGN further into immunoglobulin- and complement-positive MPGN versus complement-positive MPGN. The latter is due to dysregulation of complement pathway and includes C3 glomerulonephritis and dense-deposit disease.

Pathophysiology of proteinuria

The glomerulus provides a charge- and size-selective barrier to albumin. The small amount of albumin and non-albumin protein that is filtered is very well reabsorbed in the proximal convoluted tubule (PCT). Damage to this intricate selectivity to albumin has detrimental effects and contributes to sclerosis.

Podocytes are the terminally differentiated epithelial cells of the glomerulus. Crosstalk among podocytes, mesangium, and endothelium maintains the normal filtration barrier. As all three are interlinked, damage to any one of them affects the functioning of the others.

Endothelium activation and loss of selectivity leads to prolonged exposure of podocytes to proteins. This results in the activation of renin-angiotensin in podocytes and alteration of size selectivity. Damage to podocytes in turns leads to decrease in vascular endothelial growth factor (VEGF) required for endothelial fenestrae formation.

The filtration of proteins across the abnormal glomerular capillary wall (GCW) exposes mesangial and tubular cells to these proteins. Mesangial cells lie close to capillary lumen and play an important role in glomerular hemodynamics and immune complex clearance. However, cytokine generation with podocyte damage can lead to mesangial cell activation and proliferation.

The protein-mediated cytotoxicity causes endothelial damage, with podocyte loss leading to the production of chemokines and cytokines that initiate an inflammatory response. The end point is sclerosis and fibrosis of the glomerulus.

Complications of proteinuria

Complications of proteinuria include the following:

- Pulmonary edema due to fluid overload;
- Acute renal failure due to intravascular depletion;
- Increased risk of bacterial infection, including spontaneous bacterial peritonitis;

- Increased risk of arterial and venous thrombosis, including renal vein thrombosis;
- Increased risk of cardiovascular disease.

Cardiovascular outcomes and proteinuria

In a study of 2310 patients, Jackson et al. concluded that spot urinary albumin-to-creatinine ratios (UACRs) have significant prognostic value in persons with heart failure. These authors determined that, compared with patients with normoalbuminuria, those with an elevated UACR tended to be older, had higher rates of cardiovascular comorbidity and diabetes mellitus, and suffered from worse renal function. Even after adjustment for variables such as renal function and diabetes, it was determined that an increased UACR was associated with a greater mortality risk.

In the European Prospective Investigation into Cancer in Norfolk population study, the incidence of myocardial infarction was higher in patients with microalbuminuria than in those with normal urinary albumin levels. In a study by Rein et al., albuminuria was an important predictor of cardiovascular mortality even after adjusting for conventional risk factors. Analysis of 1208 hypertensive, normoalbuminuric patients with type 2 diabetes from the BENEDICT trial also showed increased cardiovascular problems with any degree of measurable urinary albumin.

Vascular calcification

Results from a study by Chiu et al of 225 proteinuric patients with type 2 diabetes mellitus indicated that vascular calcification, which can be particularly severe in nondialyzed patients with coexisting proteinuria and diabetes, is a prognostic indicator in early-stage type 2 diabetic nephropathy.

In the study, 86% of patients were found to have coronary artery calcification, the degree of which was associated with older age, white ethnicity, and male sex. Fifty-four patients died during the follow-up period, which averaged 39 months. Univariate and multivariate analyses indicated that the degree of coronary artery calcification was, in relation to the calcification's severity, an independent predictor of all-cause mortality in the study's patients, with a 2.5-fold greater mortality risk found in subjects with a calcification score in the highest quartile.

Stroke risk

A study of 3939 subjects enrolled in the Chronic Renal Insufficiency Cohort study, a prospective observational cohort, found that proteinuria and albuminuria are better predictors of stroke risk in patients with chronic kidney disease than estimated glomerular filtration rate. In patients with albuminuria, treatment with renin-angiotensin blockers did not decrease stroke risk.

Prognosis of proteinuria

The prognosis for patients with proteinuria depends on the cause, duration, and degree of the proteinuria. Young adults with transient or orthostatic proteinuria have a benign prognosis, while patients with hypertension and microalbuminuria (or higher degrees of albuminuria) have a significantly increased risk of cardiovascular disease.

Proteinuria has been associated with progression of kidney disease, increased atherosclerosis, and left ventricular abnormalities indirectly contributing to cardiovascular morbidity and mortality. In addition to being a predictor of outcome in patients with renal disease, microalbuminuria also is a predictor of morbidity and mortality in patients who do not have evidence of significant renal disease. In patients with hypertension, the presence of microalbuminuria is correlated to the presence of left ventricular hypertrophy. In hypertensive patients and normotensive patients, the presence of microalbuminuria predicts an increased risk of cardiovascular morbidity and mortality.

Examination of patient with proteinuria

History taking

Mild to moderate proteinuria may be asymptomatic. The majority of patients will not report any symptoms, and proteinuria will be detected in the course of routine laboratory testing conducted to evaluate systemic disease, such as hypertension or diabetes, or as part of a well-person examination.

Because proteinuria occurs frequently in the absence of serious underlying renal disease, considering the more common and benign causes of proteinuria first is important. Questions to ask include the following:

- Is this transient proteinuria? If yes, this may be associated with physical exertion and fever.
- Is this orthostatic proteinuria? – It typically is observed in tall, thin adolescents or adults younger than 30 years; it may be associated with severe lordosis; renal function is normal, and albuminuria usually is less than 1 g/day.
- Is this due to a nonrenal disease (eg, severe cardiac failure, sleep apnea)? If yes, renal function is normal and proteinuria usually is less than 1 g/day; microalbuminuria frequently is observed in association with hypertension and the early stages of diabetic nephropathy.
- Are symptoms present that suggest nephrotic syndrome or significant glomerular disease?
- Have changes occurred in the urine's appearance (eg, red/smoky, frothy); did this occur in relation to an upper respiratory tract infection.
- Is edema (eg, ankle, periorbital, labial, scrotal) present?
- Has the patient ever been told that his or her blood pressure is elevated?
- Has the patient ever been told that his or her cholesterol is elevated?

- Is a history of multisystem disease or of another cause of glomerular disease present?
- Is a past or family history of kidney disease (including pregnancy related) present?
- Does the patient have diabetes mellitus? If so, for how long; are eye diseases or other complications present?
- Is a family history of diabetes mellitus present; does it include kidney disease?
- Is any chronic inflammatory disease (eg, systemic lupus erythematosus [SLE]) or rheumatoid arthritis present?
- Does the patient have any joint discomfort, a skin rash, eye symptoms, or symptoms of Raynaud syndrome?
- Is the patient taking any medication, including over-the-counter or herbal remedies?
- Are any past health problems, such as jaundice, tuberculosis, malaria, syphilis, or endocarditis, present?
- Are any other systemic symptoms, such as fever, night sweats, weight loss, or bone pain, present?
- Does the patient have any risk factors for human immunodeficiency virus (HIV) or hepatitis?
- Are symptoms present that suggest complication(s) of nephrotic syndrome?
- Does the patient have any loin pain, abdominal pain, breathlessness, pleuritic chest pain, or rigors?

Physical Examination

The physical examination should include the following:

- Assess intravascular volume status – examine the jugular venous pulse (JVP), erect and supine pulse and blood pressure, and heart sounds;
- Assess extravascular volume status – look for edema (eg, ankle, leg, scrotal, labial, pulmonary, periorbital), which may or may not be pitting, depending on the duration of edema; massive weight gain due to fluid is very common, especially in patients with nephrotic syndrome; patients may also have decreased breath sounds due to pleural effusions;
- Examine the patient for signs of systemic disease – eg, retinopathy, rash, joint swelling or deformity, stigmata of chronic liver disease, organomegaly, lymphadenopathy, and cardiac murmurs;
- Examine the patient for complications such as venous thrombosis and peritonitis.

Laboratory studies

To determine whether patients have transient proteinuria, perform the following:

- Urinalysis and microscopic examination on at least three separate occasions;
- Albumin-to-creatinine or protein-to-creatinine ratio in random urine sample;
- Urinalysis on early morning sample, before the patients is involved in physical activity;

To determine whether patients have orthostatic proteinuria, perform the following:

- Urine microscopy;
- Split urine collection - Daytime (7 am to 11 pm) and overnight (11 pm to 7 am);

To determine whether proteinuria may be glomerular in origin, perform the following:

- Urine microscopy – To search for dysmorphic red blood cells and casts;
- Urine collection (24 h) for quantification of albumin (or protein) excretion and creatinine clearance – Especially if the patient is muscular or cachectic; spot protein/creatinine ratio can be used for subsequent assessments;
- Serum creatinine, albumin, cholesterol, and blood glucose determinations;
- Autoantibody determinations. If indicated, including antistreptolysin O titers, antinuclear antibodies (ANAs), anti-DNA antibodies, complement levels, and cryoglobulins;
- Hepatitis B, hepatitis C, and HIV serologies (if indicated);
- Urine and plasma protein electrophoresis (if indicated);
- Anti–glomerular basement membrane (anti-GBM) antibodies and ANCA – If there is a suspicion of pulmonary renal syndrome.

Imaging studies

Imaging studies in proteinuria can include the following:

- Renal ultrasonography – If glomerular disease is being considered;
- Chest radiography or computed tomography (if indicated).

Renal Biopsy

Renal biopsy should be considered in adult patients with persistent proteinuria, because the diagnostic and prognostic information yielded is likely to guide the choice of specific therapy.

In children, most cases of nephrotic syndrome are due to steroid-sensitive minimal-change disease. The clinician may reasonably assume this to be the diagnosis and give a trial of therapy, reserving biopsy for unresponsive cases.

In adult patients who have isolated proteinuria of less than 1 g/day and no other indicators of renal disease, the renal prognosis is good and the need for specific treatment is unlikely. these patients are treated with nonspecific measures and biopsy

is needed only if the degree of proteinuria increases or if the patient undergoes progressive renal decline.

Medical management of proteinuria

Medical management of proteinuria has the following two components:

- Nonspecific treatment – Treatment that is applicable irrespective of the underlying cause, assuming the patient has no contraindications to the therapy.
- Specific treatment – Treatment that depends on the underlying renal or nonrenal cause and, in particular, whether or not the injury is immune mediated.

If a patient is not being monitored by a nephrologist, transfer to a nephrologist is indicated if he or she develops proteinuria, any adverse prognostic markers (eg, rise in albumin excretion of > 1 g/day), or any worsening in renal function.

Pharmacologic Therapy in Nonspecific Treatment

angiotensin-converting-enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs)

The degree of proteinuria depends on the integrity (charge and size selectivity) of the (GCW) and the intraglomerular pressure. Intraglomerular pressure is controlled by the afferent arteriole, which transmits systemic blood pressure to the glomerulus, and the efferent arteriole.

ACE inhibitors and ARBs reduce intraglomerular pressure by inhibiting angiotensin II– mediated efferent arteriolar vasoconstriction. These groups of drugs have a proteinuria-reducing effect independent of their antihypertensive effect. Other hemodynamic and nonhemodynamic effects of ACE inhibitors may partly explain the renoprotective properties of this group of drugs, such as reduced breakdown of bradykinin (an efferent arteriolar vasodilator), restoration of size and charge selectivity to the GCW, and reduced production of cytokines that promote glomerulosclerosis and fibrosis, such as transforming growth factor (TGF)–beta.

Target blood pressure is less than 125/75 mm Hg. The dose of ACE inhibitor should be increased as tolerated until this blood pressure is achieved.

Normotensive patients with proteinuria also should be given ACE inhibitors, because low doses usually are well tolerated and do not usually cause symptomatic hypotension.

Patients who develop adverse effects from ACE inhibitors, such as cough, should be given an ARB. Patients also may develop angioedema, due to the increase in bradykinin levels that accompany the use of ACE inhibitors. This adverse effect also warrants cessation of treatment. An ARB may be used instead. Patients with mild hyperkalemia should receive dietary counseling. Those with significant hyperkalemia

should have the medication immediately discontinued and should be treated with a potassium-binding resin.

When treatment with an ACE inhibitor or ARB does not adequately control proteinuria in a patient with chronic kidney disease (eg, diabetic nephropathy), a further reduction in proteinuria can be achieved by adding a mineralocorticoid receptor antagonist (MRA) such as eplerenone or spironolactone. However, MRA is associated with a three- to eightfold increased risk for hyperkalemia.

Diuretics

Patients with moderate to severe proteinuria are usually fluid overloaded and require diuretic therapy along with dietary salt restriction. In spite of good kidney function, these patients may not respond to normal doses of diuretics and may require increased doses for the drug to be delivered to renal tubule.

If fluid overload becomes refractory to therapy with a single diuretic agent, a combination of diuretics acting at different sites of the nephron can be tried. If the edema is due to marked hypoalbuminemia, aggressive diuresis may put the patient at risk of acute renal failure due to intravascular volume depletion.

The routine use of albumin infusion combined with diuretics is not advocated in patients with nephrotic syndrome. Treatment with a loop diuretic or a combination of diuretics produces diuresis in most patients. The addition of albumin may improve natriuresis in patients with refractory salt and water retention, but the potential benefits must be weighed against the cost and risks of albumin infusion, which include the possibility of exacerbating fluid overload.

Anticoagulants

Patients with proteinuria tend to be hypercoagulable due to urinary losses of coagulation inhibitors, such as antithrombin III and protein S and C. The risk of thrombosis appears to be highest in patients with membranous glomerulonephritis. Numerous case reports have described renal vein thrombosis (which usually presents as acute onset of gross hematuria and back pain) in patients with membranous glomerulonephritis.

There are no randomized controlled trials supporting the use of prophylactic anticoagulation in patients with nephrotic syndrome. However, guidelines published by Kidney Disease Improving Global Outcomes (KDIGO) in 2012 recommend treatment with warfarin in patients with nephrotic syndrome who have a low serum albumin level (<2.5 g/dL), especially if the patient has other risk factors for thrombosis.

Vitamin D and proteinuria

In animal studies, vitamin D and vitamin D analogues decrease inflammatory mediators and may act as immunosuppressive agents. Vitamin D may play a role in down-regulating prorenin gene expression and thereby enhancing renin-angiotensin-aldosterone system (RAAS) blockade.

A randomized controlled trial showed a reduction in proteinuria of around 20% in diabetic patients with paricalcitol.

Treatment of Lipid Abnormalities

Lipid abnormalities are quite common in patients with nephrotic syndrome. No evidence-based recommendations are available for the treatment of hyperlipidemia associated with nephrotic syndrome. Since, the presence of proteinuria and hyperlipidemia may increase the risk for atherosclerotic disease, it should be treated in the same way as general population.

Dietary measures are usually not very effective and most of these patients do require medication. The treatment of choice is statin therapy. Some studies have reported statins to be renoprotective. Dyslipidemia usually improves once the proteinuria resolves or immunosuppression is started.

Diet in patients with proteinuria

Sodium restriction

Patients with nephrotic syndrome and fluid overload should have a salt-restricted diet. A "no-added-salt" diet usually is sufficient, although some patients may need restrictions of up to 40 mmol/day.

It was found that for nondiabetic patients with chronic kidney disease, high dietary salt (>14 g daily) appeared to blunt the antiproteinuric effect of ACE-inhibitor therapy and increase the risk for end-stage renal disease, independent of blood pressure control.

Protein restriction

The issue of dietary protein restriction is controversial. Evidence indicates that protein restriction may slow the rate of deterioration in the GFR in patients with glomerular diseases, including diabetic nephropathy. The presumed mechanism is a reduction in intraglomerular pressure.

However, concern exists that protein-restricted diets may increase the risk of protein malnutrition. Other methods of reducing intraglomerular pressure, such as the use of ACE inhibitors, may be safer than protein restriction. Most nephrologists recommend no restrictions or only mild restriction in protein intake (0.8-1 g/kg daily).

Inpatient care

Inpatient care is necessary only if the patient develops complications of severe nephrotic syndrome.

Follow-up of patients with proteinuria

Patients may require regular follow-up care by a family physician, general internal medicine specialist, or nephrologist, depending on the cause and setting of proteinuria. Monitoring of proteinuria, the presence or absence of other indicators of renal disease, complications of nephrotic syndrome, treatment effectiveness, and adverse effects is required.

HEMATURIA

Generally, hematuria is defined as the presence of 5 or more red blood cells (RBCs) per high-power field in 3 of 3 consecutive centrifuged specimens obtained at least 1 week apart. Hematuria can be either gross (i.e., overtly bloody, smoky, or tea-colored urine) or microscopic. It may also be either symptomatic or asymptomatic, either transient or persistent, and either isolated or associated with proteinuria and other urinary abnormalities.

Pathophysiology of hematuria

The etiology and pathophysiology of hematuria vary. For instance, hematuria of glomerular origin may be the result of a structural disruption in the integrity of glomerular basement membrane caused by inflammatory or immunologic processes. Chemicals may cause toxic disruptions of the renal tubules, whereas calculi may cause mechanical erosion of mucosal surfaces in the genitourinary tract, resulting in hematuria.

Possible causes of hematuria

- Prostate cancer.
- Renal, ureteric or bladder calculi.
- Bladder cancer.
- Renal cancer.
- Ureteric cancer.
- Prostate cancer.
- Urinary tract infection; bacterial, mycobacterial (i.e. tuberculosis) or parasitic (e.g. schistosomiasis).
- Inflammation, e.g. intersitial cystitis.
- Benign prostatic hyperplasia.
- Glomerulonephritis (urine may resemble cola in colour when acute).
- Trauma, e.g. traumatic urethral catheterisation or pelvic fracture.
- Endometriosis.
- Exercise induced.
- Artificial (added by patient or carer).

Kidney and Ureter

Specifically from the kidney, hematuria can be of glomerular origin, including medical renal disease, and nonglomerular origin, which includes urologic disorders. Urologic sources of hematuria from the kidney and ureter may include masses, both benign and malignant, infection, urolithiasis, arteriovenous malformation, and trauma. Kidney masses may represent metastasis or be primary renal tumors. Although

infrequent, the most common malignancies to metastasize to the kidneys include lung, colorectal, head and neck, breast, and gastrointestinal tumors. Renal tumors can be intraparenchymal or urothelial. Upper tract urothelial tumors can be found anywhere along the ureters and in the renal pelvis. Infection of the kidney, or pyelonephritis, may cause microscopic or gross hematuria. Pyelonephritis often results from ascending infection from the bladder (cystitis) and can lead to high fevers and lateralizing flank pain. These symptoms can also be present in patients with renal or ureteral calculi. Thus, if the suspicion is high (known history of nephrolithiasis, chronically bed bound patient, strong family history of kidney stone formation), there should be a low threshold to image the patient with noncontrast computed tomography (CT). Blunt, penetrating, or iatrogenic trauma can lead to hematuria from anywhere along the urinary tract. The kidneys are the most frequently injured genitourinary organ, in up to 5% of civilian traumas and 24% of traumatic abdominal solid organ injuries. The kidneys are especially at risk of deceleration injuries owing to their relatively fixed position by the renal pelvis and vascular pedicles in the retroperitoneum. Accounting for only 1% of urologic injuries, ureteral injuries are infrequent. Iatrogenic ureteral injury during gynecologic, urologic or colorectal surgeries accounts for 80% of ureteral injuries.

Bladder

Bladder sources of hematuria include trauma, infection, hemorrhagic cystitis (from radiation and/or chemotherapy exposure), and tumors. Bladder ruptures are categorized as intraperitoneal (about 30%), extraperitoneal (60%), and both in the remaining (10%). Although more than 85% of blunt bladder injuries are associated with pelvic fractures, less than 10% of blunt pelvic fracture patients are found to have bladder injuries. They occur rarely in blunt abdominal trauma owing to the location of the bladder in a relatively protected position in the pelvis. The typical site of intraperitoneal rupture is at the dome of the bladder, often in setting of a full bladder. Extraperitoneal bladder ruptures often occur at the bladder neck or the base of the bladder. Blood at meatus in the setting of trauma and pelvic fractures should make the clinician suspicious of urethral or bladder injury. Cystitis refers to any inflammation of the bladder, whether infectious or noninfectious in origin. Infectious causes can be bacterial, viral, and fungal. Uropathogenic Escherichia coliis the most common cause of urinary tract infections (UTIs). These bacteria have unique properties that allow them to bind to the outermost layer of the urothelium, enter the cells, replicate, and eventually lead to cell lysis. Less common, viral cystitis is typically seen in immunosuppressed patients owing to adenovirus and BK virus. Noninfectious etiologies of cystitis include radiation and chemical cystitis, which can lead to hemorrhagic cystitis. Radiation-induced cystitis can be seen at any time after

treatment, and there are no known risk factors for who will develop this complication. Radiation cystitis leads to damage of urothelium via apoptosis initiated by DNA damage and can also affect the muscular layers of the bladder as well as the vasculature. Chemical cystitis can be from various medications, for example, cyclophosphamide and/or ifosfamide chemotherapy. These medications are metabolized by the liver, resulting in the formation of a harmful metabolite acrolein, which is filtered into the urine, inducing urothelial damage. Bladder tumors are a common cause of gross and microscopic hematuria; approximately 80% to 90% of patients with bladder cancer present with painless gross hematuria. Transitional cell carcinoma (or urothelial carcinoma) accounts for 90% of bladder cancers and develops in the inner layer (urothelium) of the bladder. It is described as a field change defect, meaning that it can affect the entire urothelium, with significant potential for recurrence owing to highly malignant tumor biology. The remaining 10% of bladder cancers include but are not limited to squamous cell, adenocarcinoma, and small cell.

Prostate

Prostatic causes of hematuria can largely be attributed to prostatic hyperplasia. The prostatic hyperplastic process is owing to an imbalance between cell death and cell proliferation, which eventually leads to cell accumulation. In this process, there is also expression of vascular endothelial growth factor, which makes the prostate an extremely vascular organ prone to bleeding. Prostatic malignancy and infection of the prostate, or prostatitis, are other contributors to hematuria of prostatic source. Bacterial prostatitis is the result of focal uropathogenic bacteria residing in the prostate gland. The most common cause of bacterial prostatitis, both acute and chronic, is the Enterobacteriaceae family of Gram-negative bacteria. Locally advanced prostate cancer may also cause hematuria.

Urethra

Urethral causes of hematuria include infection (urethritis), urethral masses, and trauma. Urethritis is inflammation of the urethra, and is usually infectious in origin. As with any infection, a urinalysis and culture as well as testing for Neisseria gonorrhea and chlamydia are useful. An uncommon cause of emergent urethral bleeding is in the setting of traumatic Foley catheter manipulation or removal (e.g., by a demented or delirious patient or during transfers). After traumatic catheter removal, reinsertion of the catheter is recommended. If resistance is met on reinsertion, there should be further evaluation of urethral integrity, either with bedside cystoscopy or retrograde urethrogram.

Hematuria in patients taking anticoagulants and antiplatelet medication

Blood in urine, either visible or non-visible, in people taking anticoagulants (for example, warfarin) or antiplatelet medication (such as aspirin), should be investigated in the same way as in people not taking these medications. Research has shown that up to 25% of people with visible hematuria (VH) and 10% of people with non-visible hematuria (NVH) taking these medications had an underlying abnormality, including bladder cancer. The incidence of NVH in anticoagulated people is similar to non-anticoagulated people, and therefore cannot be blamed entirely on these medications.

Examination of the patient with hematuria

History taking

Clinical history can identify possible causes and help to rule out possible benign reasons for hematuria. The following should be considered when assessing the condition:

- At what point during voiding does blood appear? Blood at the beginning of the stream, for example, would indicate a prostatic or urethral cause, whereas blood on the toilet tissue in females could have a gynecological cause.
- Symptoms, e.g. pain, fever, urinary frequency urgency, that could indicate a urinary tract infection or possible renal calculi.
- Presence of clots; this would be conclusive of visible blood in urine (red urine with clots in is hematuria as opposed to coloured by other causes, and occasionally patients describe having passed clots only without discolouration of their urine).
- Recent vigorous exercise, in particular running.
- Diet/foods that could discolour urine, e.g. beetroot.
- Medications that could discolour urine, for example, prochlorperazine.
- Identification of risk factors for urological malignancy, e.g. smoking history.

Physical examination

There are a number of different physical examinations that can be conducted in order to assess for hematuria:

- The urine three-glass test is used to roughly determine the source of urinary hematuria and assist in identifying the site of urinary tract bleeding. In the three-glass test, patients leave urine in 3 test tubes, the first tube contains the washings from the anterior urethra, the second, material from the bladder, and the last, material from the posterior urethra, prostate, and seminal vesicles.
- Examination of abdomen to exclude e.g. renal pain, tenderness or masses.
- In men, rectal examination of the prostate to identify any abnormality suggestive of benign enlargement or prostate cancer.

- In women, vaginal examination to exclude gynaecological causes of hematuria e.g. vaginal bleeding, prolapse or urethral caruncle (benign tumour visible at the urethral meatus).

Investigations

There are a number of investigations that should be undertaken when hematuria is present:

- Urine culture to exclude a urinary tract infection. Once any urine infection has been treated the urine should be dipstick tested to ensure that the hematuria has resolved. This is because people can present with a urine infection as the first symptom of significant urinary tract pathology.
- eGFR to assess renal function.
- Prostate-specific antigen (PSA) should be offered after counseling to male patients (once urinary tract infection has been excluded). Raised PSA would prompt further investigation to exclude prostate cancer.

In addition people who have asymptomatic non-visible hematuria (a-NVH) should also have:

- Blood pressure recorded.
- Proteinuria measured on a random urine sample. Send urine to the laboratory for protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR) on a random sample (according to local practice). Raised blood pressure and proteinuria may indicate glomerelonephtitis proteinuria.

Referral to hematuria clinics

Between 20% and 25% of people with VH and 5-10% of people with NVH will be found to have a urological malignancy, therefore, all people with a single episode of VH, symptomatic non-visible hematuria (s-NVH), all people aged over 40 years with hematuria and persistent or recurrent urinary tract infection and all people over 50 years with a-NVH should be referred to a hematuria clinic for investigation within 2 weeks as instructed in the NICE (2005) guidelines.

People who have hematuria are often very anxious, not only about what might be the cause of their hematuria but also about the tests they will need to have. The 2-week wait guideline ensures that people who have symptoms that may be caused by cancer are seen within 14 days. Cancer must then be diagnosed or excluded within 31 days and if it is diagnosed, the patient should be treated within 62 days of referral.

People under 50 years of age with a-NVH, no proteinuria and normal serum creatinine should be referred to the hematuria clinic for non-urgent investigation.

Referral to a nephrologist

Referral to a nephrologist may be considered more appropriate if acute glomerulonephritis is clinically suspected, i.e. some people under the age of 40 years who have a-NVH with cola-coloured urine and an inter-current (usually upper respiratory tract) infection. Raised serum creatinine and/or hypertension or proteinuria may indicate renal disease, therefore, people with persistent a-NVH and proteinuria (ACR 30 mg/mmol or more, or urinary protein excretion 0.5 g/24 hours or more) should also be referred to a nephrologist.

Investigations

People referred to a hematuria clinic for further investigation will usually have a flexible cystoscopy to exclude bladder and urethral pathology and a renal ultrasound scan, to exclude upper tract pathology, a CT intravenous urography, intravenous urogram (IVU) or a kidneys, ureters and bladder (KUB) X-ray.

Flexible cystoscopy

A flexible cystoscope is a fine fibre optic tube that is inserted into the bladder through the urethra to examine the bladder urothelium, ureteric orifices and urethra. If the image is transmitted to a monitor, the person performing the procedure can show the patient and explain their results to them either during or at the end of the procedure. A local anaesthetic lubricant gel containing lidocaine and chlorhexidine is inserted into the urethra to minimise discomfort and reduce the risk of causing trauma and a urinary tract infection. The risk of urinary tract infection is approximately 5% following cystoscopy.

It may be possible for patients who do not wish to undergo flexible cystoscopy under local anaesthetic to have the procedure performed under sedation or general anaesthetic, according to local policy.

It is possible to biopsy abnormal areas via a flexible cystoscope. However, these biopsies will not be sufficient to accurately stage cancer. Biopsies therefore, are not usually performed if cancer is suspected, or even if a urothelial malignancy is diagnosed and the patient will be asked to return to have a cystoscopy and biopsies of any abnormal areas, or transurethral resection of the bladder tumour (TURBT) under general anaesthetic within 31 days.

Flexible cystoscopy may be omitted if radiological investigations conclusively demonstrate the presence of a bladder tumour, in which case TURBT will be performed.

CT intravenous urography (IVU)

CT IVU provides an assessment of all of the major urological structures except for the prostate and urethra and is becoming the standard X-ray procedure for radiological

investigation of VH replacing IVU because of its increased diagnostic accuracy. It can identify 80% of upper tract cancers and 60% of bladder cancers and rarely gives false positive results (Silverman and Cohan, 2007).

IVU

IVU has for many years been the gold standard radiological procedure for investigation of hematuria, able to identify bladder and renal masses and renal calculi. However, it is unable to differentiate between solid or cystic masses and is poor at identifying small renal masses. The procedure involves an injection of intravenous contrast and several X-rays being taken as the contrast is eliminated by the kidneys. A compression band may be fastened tightly around the patients' waist to improve visualization of the kidneys.

Renal ultrasound scan (USS)

USS is able to identify bladder and renal tumors and renal calculi. It can also differentiate between renal cysts and renal cancers. It is not, however, as sensitive as CT, identifying only 26% of small masses that measure <1 cm, 60% of masses measuring 2—3 cm and 85% of masses measuring >3 cm.

KUB X-ray

KUB is a plain X-ray of the kidneys, ureters and bladder and may be used with USS in younger patients or for patients who have contraindications to radiological contrast media, (e.g. allergy or renal failure) to exclude renal calculi as the cause of NVH. However, approximately 15% of renal calculi are not radiopaque, and phleboliths (deposits of calcium in blood vessels) may cause false-positive diagnosis of renal calculi which then requires further investigation.

Urine cytology

The epithelial lining of the bladder sheds cells that are voided in urine. These cells are centrifuged from the urine and examined microscopically to identify abnormal cells. Ideally the second void of the day should be collected in a clean container and sent to the laboratory promptly. Degeneration of cells means an early morning sample of urine is unsuitable for cytological examination. Urine cytology is not sensitive enough to diagnose low- grade urothelial tumors and false positive results can be found in people with benign conditions including urinary calculi, chronic infection and inflammation, and in people who have received radiotherapy or chemotherapy.

Voided markers

Bladder cancer cells release higher levels of nuclear matrix protein (NMP22) than normal cells. Voided urine can be tested for NMP22 at the hematuria clinic and the result be available in 30 minutes, meaning patients can be informed at the same time as their cystoscopy result. Like urine cytology, false-positive results can also be found in people who have a urine infection, renal calculi, hematuria, etc.

Risk factors for urological malignancy

Smoking history. It is estimated that cigarette smoking is the cause of bladder cancer in 38% of men and 34% of women diagnosed. Current smokers have two to three times the risk of people who have never smoked with the risk increasing with the number of years people have smoked and the number of cigarettes smoked each day. Smoking cessation reduces the risk, but the risk of developing bladder cancer remains higher in people who have quit smoking than in people who have not smoked for more than 20 years.

Occupational risks. It is estimated that approximately 7-10% of bladder cancer diagnoses in the UK are associated with occupational exposures. Bladder cancer is therefore a recognized industrial disease. People who work in occupations that are at increased risk of developing bladder cancer include painters, people who are highly exposed to diesel fumes or polycyclic aromatic hydrocarbons (PAH), a by-product of combustion processes and people who work with or have worked with aniline dyes.

Medication history. Cyclophosphamide and pioglitazone are drugs that are associated with people being at increased risk of developing bladder cancer. Diabetics who have taken pioglitazone for 1-2 years have a 34% increased risk of developing bladder cancer and the risk doubles when people have taken it for 2 years or more.

Previous pelvic radiotherapy. People who have previously been treated with radiotherapy to the pelvic area e.g. for testicular, cervical or prostate cancer have approximately twice the risk of developing bladder cancer.

Medical history. People who are paraplegic have an increased risk of squamous cell bladder cancer. This is likely to be because of their increased risk of urinary tract infections and renal calculi.

Diagnosis, evaluation and follow-up of asymptomatic microhematuria in adults

- Asymptomatic microhematuria (AMH) is defined as three or greater RBC/HPF on a properly collected urinary specimen in the absence of an obvious benign cause. A positive dipstick does not define AMH, and evaluation should be based solely on findings from microscopic examination of urinary sediment and not on a dipstick reading. A positive dipstick reading merits microscopic examination to confirm or refute the diagnosis of AMH.
- The assessment of the asymptomatic microhematuria patient should include a careful history, physical examination, and laboratory examination to rule out causes of AMH such as infection, menstruation, vigorous exercise, medical renal disease, viral illness, trauma, or recent urological procedures.
- Once benign causes have been ruled out, the presence of asymptomatic microhematuria should prompt a urologic evaluation.

- At the initial evaluation, an estimate of renal function should be obtained (may include calculated eGFR, creatinine and blood urea nitrogen [BUN]) because intrinsic renal disease may have implications for renal related risk during the evaluation and management of patients with AMH.
- The presence of dysmorphic red blood cells, proteinuria, cellular casts, and/or renal insufficiency or any other clinical indicator suspicious for renal parenchymal disease warrants concurrent nephrologic workup but does not preclude the need for urologic evaluation.
- Microhematuria that occurs in patients who are taking anti-coagulants requires urologic evaluation and nephrologic evaluation regardless of the type or level of anti-coagulation therapy.
- For the urologic evaluation of asymptomatic microhematuria, a cystoscopy should be performed on all patients aged 35 years and older.
- In patients younger than age 35 years, cystoscopy may be performed at the physician's discretion.
- A cystoscopy should be performed on all AMH patients who present with risk factors for urinary tract malignancies (e.g., history of irritative voiding symptoms, current or past tobacco use, chemical exposures) regardless of age.
- The initial evaluation for AMH should include a radiologic evaluation. Multi-phasic CT urography (without and with IV contrast), including sufficient phases to evaluate the renal parenchyma to rule out a renal mass and an excretory phase to evaluate the urothelium of the upper tracts, is the imaging procedure of choice because it has the highest sensitivity and specificity for imaging the upper tracts.
- For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy, pregnancy), magnetic resonance urography (MRU) (without/with intravenous contrast) is an acceptable alternative imaging approach.
- For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy, pregnancy) where collecting system detail is deemed necessary, combining magnetic resonance imaging (MRI) with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tracts.
- For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy) and MRI (such as presence of metal in the body) where collecting system detail is deemed necessary, combining non-contrast CT or renal ultrasound with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tracts.

- The use of urine cytology and urine markers (NMP22, BTA-stat, and UroVysion FISH) is NOT recommended as a part of the routine evaluation of the asymptomatic microhematuria patient.
- In patients with microhematuria present following a negative work up or those with other risk factors for carcinoma in situ (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures), cytology may be useful.
- Blue light cystoscopy should not be used in the evaluation of patients with asymptomatic microhematuria.
- If a patient with a history of persistent asymptomatic microhematuria has two consecutive negative annual urinalyses (one per year for two years from the time of initial evaluation or beyond), then no further urinalyses for the purpose of evaluation of AMH are necessary.
- For persistent asymptomatic microhematuria after negative urologic workup, yearly urinalyses should be conducted.
- For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered.

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