Urinary syndrome

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.

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

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 normal person is <30 mg.

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 has 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. Impairment of renal circulation due to dehydration, diarrhea or vomiting, blood loss due to accidental injuries or anemia are the most common conditions, which could lead to pre-renal proteinuria. Prerenal proteinuria can also be caused by over production of abnormal low molecular weight proteins (eg, light chains in multiple myeloma, myoglobin in rhabdomyolysis) that exceeds the reabsorption capacity of the tubules, 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.

Pathophysiology

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 result 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.

Etiology

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 glomerulonephritis;

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.

Epidemiology. 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 < 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.[11]

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.

Complications

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

Prognosis

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.

Microalbuminuria

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.

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 (EPIC-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 (CRIC) 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.

Patient examination. 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 antineutrophil cytoplasmic antibodies (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 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

ACE inhibitors and ARBs

The degree of proteinuria depends on the integrity (charge and size selectivity) of the glomerular capillary wall (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.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (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 Recommendation.s 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

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

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 (ie, 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

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
- Factitious (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% of the time, 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 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 fo rNeisseria gonorrhea and chlamydia are useful. An uncommon cause of emergent urethral bleeding is in the setting of traumatic Foley catheter manipulation or removal (eg, 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.

Assessment of hematuria

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 gynaecological 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:

- 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
- Plasma creatinine/eGFR (estimated glomerular filtration rate) to assess renal function
- Prostate-specific antigen (PSA) should be offered after counselling 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: creatinine ratio

(PCR) or albumin: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 (Silverman and Cohan, 2007). 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 visualisation of the kidneys.

Renal ultrasound scan (USS)

USS is able to identify bladder and renal tumours 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 tumours 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 recognised 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 pioglitozone are drugs that are associated with people being at increased risk of developing bladder cancer. Diabetics who have taken piogilitazone for 1-2 years have a 34% increased risk of developing bladder cancer and the risk is 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 (AMH) in Adults (according to American Urological Association guidline)

- 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. Expert Opinion.
- 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. Clinical Principle
- Once benign causes have been ruled out, the presence of asymptomatic microhematuria should prompt a urologic evaluation. Recommendation.
- At the initial evaluation, an estimate of renal function should be obtained (may include calculated eGFR, creatinine, and BUN) because intrinsic renal disease may have implications for renal related risk during

the evaluation and management of patients with AMH. Clinical Principle

- 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. Recommendation.
- 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. Recommendation.
- For the urologic evaluation of asymptomatic microhematuria, a cystoscopy should be performed on all patients aged 35 years and older. Recommendation.
- In patients younger than age 35 years, cystoscopy may be performed at the physician's discretion. Option
- 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. Clinical Principle
- The initial evaluation for AMH should include a radiologic evaluation. Multi-phasic computed tomography (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. Recommendation.
- 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. Option
- 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. Expert Opinion.
- 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. Expert Opinion.
- 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. Recommendation.
- 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. Option.
- Blue light cystoscopy should not be used in the evaluation of patients with asymptomatic microhematuria. Recommendation.
- 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. Expert Opinion.
- For persistent asymptomatic microhematuria after negative urologic workup, yearly urinalyses should be conducted. Recommendation.
- For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered. Expert Opinion.

Pyuria

Pyuria is defined as the presence of 10 or more white blood cells per cubic millimeter in a urine specimen, 10 or more white cells per high-power field of unspun urine, a positive result on Gram’s staining of an unspun urine specimen, or a urinary dipstick test that is positive for leukocyte esterase. Sterile pyuria is the persistent finding of white cells in the urine in the absence of bacteria, as determined by means of aerobic laboratory techniques (on a 5% sheep-blood agar plate and MacConkey agar plate). Pyuria is not a diagnosis; it is a laboratory finding in many diseases, most commonly urinary tract infections (UTI). Pyuria usually indicates that bacteria have invaded the upper or lower urinary tract, invoking an inflammatory response of the lining of the urinary tract (urothelium) in that location. When pyuria occurs secondary to UTI, it is usually accompanied by bacteriuria. Pyuria may also be found in the absence of infection (sterile pyuria) and is frequently

asymptomatic. When pyuria lacks the presence of bacteria, its cause is unclear, although "silent" or unrecognized kidney infection may be suspected as well as tuberculosis, renal stones, Kawasaki disease, or cancer. Almost half of chronically incontinent individuals or those with indwelling catheters (primarily elderly long-term care patients), exhibit asymptomatic pyuria. However, urinary tract infection can also be asymptomatic in the elderly. In the absence of infection, asymptomatic pyuria is not usually treated.

Incidence and Prevalence: Urinary tract infection (UTI) is the most common bacterial infection found in people of all ages. Consequently, the incidence of pyuria corresponds to the large numbers of people diagnosed with UTI, which is far more common among women than men under the age of 70 and increases in both men and women as they age. Among the elderly, the rate of UTI is only slightly higher among women compared to men. The overall prevalence of asymptomatic infection among the general population is estimated at 3.5%, and the prevalence increases with age in a linear trend. Other risk factors for asymptomatic infection include parity, diabetes in women, a history of UTI, and lower education. An estimated 4% to 10% of pregnant women are diagnosed with asymptomatic UTI.

Causation and Known Risk Factors

Urinary tract infection, especially urethritis, has an almost certain risk of being accompanied by pyuria. There are no known risk factors for asymptomatic pyuria other than chronic incontinence or urinary catheterization.

Diagnosis

History: Pyuria itself may be asymptomatic. The individual may, however, seek medical attention because of cloudy and foul-smelling urine or symptoms of UTI such as a frequent and/or urgent need to urinate (frequency and/or urgency) or discomfort on urination (dysuria).

Physical exam: Physical findings in pyuria depend on the underlying cause of the condition. Bladder infection (cystitis) can usually be diagnosed from the individual's history and symptoms. In general, there are no abnormal findings on physical examination. Individuals with a kidney infection (pyelonephritis) may have fever, tenderness in the region of the back over the kidneys (costovertebral angle), and kidney enlargement.

Tests: Pyuria is detected by urinalysis. The microscopic examination of urine as part of a routine urinalysis may actually be the first sign of pyuria in asymptomatic individuals. If pus is found, a urine culture is performed to determine whether bacterial infection is the underlying cause and to identify the causative organism. Symptoms will help determine whether the site of infection is the urethra, bladder, or kidney. Additional diagnostic tests may include a contrast study such as intravenous pyelogram (IVP), computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound imaging of the kidneys to help identify possible kidney abnormalities or underlying infection.

Treatment

Treatment, if any, depends on the underlying condition. Asymptomatic pyuria in the absence of infection (sterile pyuria) does not usually require treatment. Urinary tract infections are treated with antibiotics. Individuals who do not respond to a course of appropriate antibiotics (depending upon the infective organism identified in urine culture) may need further evaluation and treatment.

Prognosis

The probable outcome depends on the underlying cause of the pyuria. Asymptomatic pyuria may disappear spontaneously or remain without causing problems. Urinary tract infections generally clear promptly when treated with appropriate antibiotics; they can resolve without antibiotic therapy, but not as quickly, and recurrence and/or complications are more likely.

Complications

Potential complications depend on the underlying condition causing the pyuria. In cases of bladder infection, possible complications include progression of the infection to the upper urinary tract (ureters and kidneys). In cases of a kidney infection (pyelonephritis), generalized infection (sepsis) and kidney damage can result due to the infection.

Ability to Work (Return to Work Considerations)

Asymptomatic pyuria requires no restrictions or accommodations. In cases of pyuria due to UTI, necessary accommodations may include frequent restroom breaks.

Risk: If a benign condition or simple UTI, then no job would pose a risk to the individual.

Capacity: If a benign condition or simple UTI, then there would be no impact on a person's capacity.

Tolerance: If a benign condition or simple UTI, no work adjustments to enhance tolerance are needed.

Sterile Pyuria

Sterile pyuria is a highly prevalent condition, and population-based studies show that 13.9% of women and 2.6% of men are affected. Specific populations have a higher risk of this condition; for example, the frequency of detection of sterile pyuria was 23% among inpatients in one study (excluding those with urinary tract infection), and sterile pyuria is more common among women than among men because of pelvic infection. Subsequent to initial detection, the costs of laboratory, radiographic, and invasive evaluation in such large populations can have a considerable effect on health care expenditures.

Although colony counts greater than 100,000 colony-forming units (CFU) per milliliter in voided urine have historically been used to distinguish bacterial urinary tract infection from colonization, many U.S. laboratories currently report bacterial colony counts of more than 1000 CFU per milliliter in urine as being diagnostic of bacteriuria. It is important to consider that lower bacterial counts can be associated with urinary tract infection. Contemporary studies indicate that a colony count of 100,000 CFU per milliliter would differentiate clinically significant from clinically nonsignificant infections and thus reduce the number of positive cultures by 38% relative to the number of cultures that would be considered positive with the 1000 CFU per milliliter cutoff point. Use of the higher cutoff point as the "level to treat" could also decrease the use of antibiotics.

Causes of sterile pyuria

Causes related to infection

- Current use of antibiotics.
- Recently treated urinary tract infection (within past 2 wk).
- Gynecologic infection.
- Urethritis due to chlamydia, Neisseria gonorrhoeae, mycoplasma, or ureaplasma.
- Prostatitis.
- Balanitis.
- Appendicitis (if the appendix lies close to a ureter or the bladder).
- Viral infection of the lower genitourinary tract Genitourinary tuberculosis Fungal infection.
- Parasitic disease such as trichomoniasis or schistosomiasis.

Causes not related to infection.

- Presence or recent use of a urinary catheter.
- Recent cystoscopy or urologic endoscopy.
- Urinary tract stones.
- Foreign body such as surgical mesh in the urethra or a retained stent.
- Urinary tract neoplasm.
- Pelvic irradiation.
- Urinary fistula.
- Polycystic kidney.
- Rejection of a renal transplant.
- Renal-vein thrombosis.
- Interstitial nephritis or analgesic nephropathy Papillary necrosis Interstitial cystitis.
- Inflammatory disease such as systemic lupus erythematosus or Kawasak disease.

Sexually Transmitted Infections

In 2008, it was estimated that 500 million people worldwide were infected with sexually transmitted viruses such as herpes simplex virus type 2 (HSV-2) and human papillomavirus (HPV) or had sexually transmitted infections such as gonorrhea, chlamydia, syphilis, mycoplasma, and trichomoniasis. More than 300,000 U.S. cases of infection with *Neisseria gonorrhoeae* are reported to the Centers for Disease Control and Prevention each year.

In men, the majority of sexually transmitted infections cause symptomatic urethritis and, less commonly, epididymitis or disseminated gonococcal infection. Many women may be asymptomatic initially, and pelvic inflammatory disease may develop without symptoms.

Gonorrhea and Chlamydia

Historical and current studies indicate that gonorrhea is a cause of sterile pyuria. In asymptomatic men, urine tests to detect leukocyte esterase have a sensitivity of 66.7% for the diagnosis of gonorrhea and 60.0% for

the diagnosis of chlamydia. Commercially available nucleic acid hybridization tests provide rapid detection of *N. gonorrhoeae* and *Chlamydia trachomatis*.

In an Australian study, 1295 symptomatic men with nongonococcal urethritis and pyuria were evaluated for sexually transmitted diseases. *C. trachomatis* was detected in 401 men (31%), and *Mycoplasma genitalium* was diagnosed in 134 men (10%). A Japanese study involving 51 men showed that the 16S ribosomal RNA gene of *Ureaplasma urealyticum* (quantified by means of a real-time polymerase-chain-reaction [PCR] assay) was associated with the presence of symptoms of urethritis and higher leukocyte counts in first voided urine.13

Genital Herpes and Herpes Zoster

Genital vesicular eruption, which is characteristic of HSV-2 infection, extrudes white cells into urine. Pyuria may be associated with HSV-2–associated urethritis and cervicitis. The diagnosis of genital herpes is determined by means of HSV PCR, an antigen-detection immunofluorescence test, or an enzyme immunoassay.

In a 12-year study involving 423 patients with herpes zoster, 17 patients (4%) manifested changes in lumbosacral dermatomes and voiding dysfunction. Twelve patients with cystitis-associated symptoms (3% of all the patients with herpes zoster) had pyuria.

HPV and Human Immunodeficiency Virus Infections

In one study, among 114 patients with biopsy-proven HPV infection, 14 patients (12.3%) had an intraurethral lesion. A British survey tested 3123 urine samples obtained from male and female respondents who were 18 to 44 years of age. HPV DNA was detected in 29.0% of samples obtained from women and in 17.4% of samples obtained from men. The respondents were not screened by means of measurement of leukocytes. However, one study showed that male patients with HPV infection can have urethral discharge containing inflammatory cells.

Pyuria is associated with advanced human immunodeficiency virus (HIV) infection. In one study, among 104 patients with untreated HIV infection, 13% had pyuria.

Other Viral Infections

Viral infections such as adenovirus, BK polyomavirus, and cytomegalovirus may cause hemorrhagic cystitis in immunocompromised children. However, these infections are typically not associated with pyuria.

Genitourinary Tuberculosis

Nearly 10,000 tuberculosis infections are reported in the United States each year. Genitourinary tuberculosis, the most common form of nonpulmonary tuberculosis after lymphadenopathy, accounts for 27% of cases (range, 14 to 41). Hematuria and pyuria are typical findings in genitourinary tuberculosis. This condition can infect the kidneys, ureters, bladder, prostate, and genitalia. Genitourinary tuberculosis can cause renal calyceal destruction, calyceal obstruction, or hydronephrosis, or all of these conditions.

Since the incidence of tubercular infection is 13 to 26 times as high among foreign-born persons and recent immigrantsas among non-Hispanic whites, clinical suspicion of tuberculosis infection should be higher in these patients when they present with sterile pyuria. In the United States, the incidence of tubercular infection is also higher among Asians, Hispanics, and blacks than among whites. In addition, nonpulmonary tuberculosis is more common in ethnic minority groups.

The tuberculin skin test is helpful in determining whether a person has been exposed to tuberculosis, but false positive results often occur in patients who have received the*Mycobacterium bovis bacilli* Calmette–Guérin (BCG) vaccine, and a false negative skin test may occur in patients with impaired T-cell function. Interferon-γ–release assays are whole-blood tests that are not affected by BCG immunization.

M. tuberculosis may also be identified on urine culture. However, in a study involving 42 patients in whom there was suspicion of genitourinary tuberculosis on the basis of radiologic abnormalities, mycobacteria were isolated in the urine acid-fast bacilli culture in only 13 of 35 patients (37%) and bladder biopsy was positive in 11 of 24 patients (46%), whereas urinary PCR for *M. tuberculosis*was positive in 33 of 35 patients (94%).

Fungal Infections

Candida infections are a common source of urosepsis in hospitalized patients, especially those who are immunocompromised. *Candida albicans* is the most prevalent species; however, *C. glabrata, C. tropicalis, C. krusei*, and other candida species can also cause infection.

Speciation is important because of differences in antifungal susceptibility.30 Notably, patients with diabetes are prone to candida infections, patients who have received transplants are vulnerable to aspergillosis, and patients with HIV infection may be susceptible to cryptococcuria. Blastomycosis, coccidioidomycosis, and histoplasmosis are associated with intense environmental exposures (e.g., disruption of the environment by

construction, sandstorms, or tornadoes or exposure to a high concentration of bird excrement). All these fungal infections may cause genitourinary infection with associated pyuria.

Urine microscopy may show budding yeast forms or hyphae, but identification of fungus requires special culture medium and from 3 days to 3 weeks for speciation. In patients with candida or aspergillus infections, imaging studies may reveal filling defects in the collecting system or bladder caused by fungal materials that are referred to as "fungal balls."

Parasitic Infections

Trichomonas vaginalis is one of the most common human parasitic infections in the United States and the most prevalent nonviral sexually transmitted infection. Infection can be diagnosed by identification of the motile parasite during microscopic examination of a wet-mount preparation of cervicovaginal secretions in women and urethral discharge in men, but PCR is more sensitive. In one study, 46 of 205 male partners of women with confirmed trichomonas infection (22%) had culture-detected infection, whereas 201 of 205 male partners (98%) had infection detected by means of PCR.

An estimated 119 million people in the world are infected with *Schistosoma haematobium*.34Transmission requires the contamination of water by egg-containing feces or urine, a specific freshwater snail as intermediate host, and human contact with water inhabited by the intermediate host snails.35 The urogenital system is affected in 75% of infected persons. Radiographic studies may show calcification of the bladder wall or ureter. Diagnosis has been based on microscopic examination of urine, but this method is dependent on the skill of the observer and is known for low sensitivity. A recent study showed that real-time PCR has 100% sensitivity as an indicator of infection intensity.

In a 10-year study involving more than 25,000 ill travelers from endemic areas, 410 cases of schistosomiasis were identified; 83% of the infections were acquired in Africa. A total of 63% of the patients with schistosomiasis presented within 6 months after travel.

Inflammatory and Autoimmune Conditions

The cause of the combination of interstitial cystitis and the painful bladder syndrome, which occurs primarily in women, is unclear. In an evaluation of 122 patients in whom this condition was suspected, 22 (18%) had detectable leukocyte esterase with a negative nitrite indicative of sterile pyuria and prodromal inflammatory changes in the bladder.

Kawasaki's disease often manifests with sterile pyuria, microscopic hematuria, and proteinuria associated with renal involvement. In one study, sterile pyuria, which is typically associated with more severe systemic inflammation, was identified in 40 of 133 patients (30%). In another study, sterile pyuria was identified in 215 of 946 patients with systemic lupus erythematosus (23%). In addition, analgesic nephropathy can cause sterile pyuria in association with chronic interstitial nephritis and renal papillary necrosis.

Inflammation outside the Urinary Tract and Other Urologic Conditions

One study involving 210 patients who were hospitalized for infections outside the urinary tract (e.g., pneumonia, bacterial septicemia, intraabdominal infection, enteritis, and female genital tract infections) identified 31 patients (15%) with sterile pyuria.3 In addition, pyuria may be associated with radiation cystitis, urinary stones, foreign bodies, stents, transvaginal mesh, urinary fistulae, polycystic kidney disease, renal-transplant rejection, and intrinsic renal disease.

Evaluation of patients with sterile pyuria

As noted above, the differential diagnosis of sterile pyuria is broad. A complete history and physical examination with consideration of the factors are required to identify the potential causes of genitourinary inflammation. Specific evaluation for sexually transmitted infections is warranted. Evaluation to detect bacterial, fungal, and parasitic infections is indicated in patients with a clinical history that suggests specific infections.

Abdominal, renal, and bladder imaging should be considered for evaluation of febrile or otherwise symptomatic patients. Inflammatory conditions near the urinary tract as well as systemic diseases should be included in the differential diagnosis. Sterile pyuria has historically been considered to be suggestive of genitourinary tuberculosis, but a wide variety of other causes must be considered.

Criteria for successful treatment of conditions that cause sterile pyuria include curtailment or resolution of symptoms, a negative culture, or a negative PCR assay. Pyuria may persist because of underlying inflammatory changes.