Interpretation and management of abnormal dipstick urinalysis

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Abstract

For centuries, physicians have attempted to use urine as a non-invasive means of assessing disease. Today, urinalysis and, in particular, identification and measurement of proteinuria underpin the routine assessment of patients with renal disease. Urine dipstick analysis can also be used to screen for urinary tract infections (nitrites and leucocyte esterase), diabetes mellitus (glucose) and confirm pregnancy (β-hCG; human chorionic gonadotropin). Apart from intrinsic renal disease, an abnormal urine dipstick result may indicate malignancy in the genitourinary tract, so it is important to be clear when and who to refer for further investigation. Included in this section are guidelines for the initial assessment and referral of patients with haematuria and proteinuria. Formal assessment of the patient with renal disease is described later in this issue.

Keywords glomerulonephritis; haematuria; leucocyte esterase; nitrites; proteinuria; urinalysis

What's new?

- Updated management of haematuria: it is important to appreciate that any adult over the age of 40 years with repeated invisible haematuria requires urological investigation and all patients with visible haematuria in the absence of a urinary tract infection should be referred to the urologists
- New guidelines for assessing proteinuria: recently published National Institute for Health and Clinical Excellence guidelines for Chronic Kidney Disease have clearly defined the level of proteinuria and albuminuria which should trigger nephrological review. These guidelines also recommended the use of an ACR (albumin–creatinine ratio) for the initial identification of proteinuria
- The future of urine dipsticks: it is likely that over the next 5 years dipstick testing for specific proteins such as KIM-1 (kidney injury molecule 1) and NGAL (neutrophil gelatinase-associated lipocalin) will be used to stratify patients who are acutely unwell for the risk of developing acute kidney injury

Historically, urine examination involved assessment of the appearance, smell and, on occasion, taste of urine, and physicians, known as Pisse Prophets, carved out lucrative careers based on urine examination (uroscopy) and its interpretation (uromancy).[1,2] Today, the commonest method of urinalysis is the more prosaic use of urine dipsticks, which test the urine for the presence of a range of chemical constituents (Table 1).

The macroscopic appearance of urine can, occasionally, be useful (Table 2). The urine of patients presenting with acute porphyria (unexplained abdominal pain, mental dysfunction or peripheral neuropathy) is dark, reddish brown (urinary porphobilinogen) and the colour becomes more pronounced if the urine is left standing. The urine will be dipstick negative for blood. In alkaptonuria, a defect in tyrosine metabolism associated with cartilage degeneration and black pigmentation of the sclera, the urine turns black on standing. In chyluria, which results from development of a fistula between the lymphatics and urinary tract, most commonly because of lymphatic obstruction by the parasite *Wuchereria bancrofti (filariasis)*, the urine has a 'milky' appearance due to the presence of lipids, especially triglycerides.

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Blood

Dipsticks detect the presence of both haemoglobinuria (free haemoglobin in the urine) and haematuria (intact red blood cells in the urine). Isolated haemoglobinuria is usually seen only with extensive haemolysis (a false-positive result will be seen in patients with myoglobinuria secondary to rhabdomyolysis, and in some cases of bacteriuria where the bacteria contain hydroperoxidase). Isolated haematuria usually indicates bleeding somewhere in the urinary tract, is often associated with haemoglobinuria and should trigger a urological review because of the risk of urological malignancy (Figure 1). Invisible (microscopic) haematuria in combination with proteinuria suggests glomerular disease.

Protein

Normal urinary protein excretion is less than 150 mg/24 hours, of which less than 30 mg is albumin. Whereas transient

Substances tested for by using urine dipsticks

Commonly assessed	Less commonly assessed
Blood	Ketones
Protein	Urobilinogen
Glucose	Bilirubin
Leucocyte esterase	Specific gravity
Nitrites	pH
Albumin	
β-human chorionic gonadotropin	

Table 1

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Common causes of changes to the macroscopic appearance of urine

Colour	Pathological causes	Food and drug causes
Cloudy	Phosphaturia	
	Pyuria	
	Chyluria	
Brown/black	Bilirubinuria (obstructive jaundice)	Levodopa
	Melanuria (malignant melanoma)[a]	Methyldopa
	Homogentisic acid (alkaptonuria)[a]	Senna
	Methaemoglobinuria	Metronidazole
		Fava beans
Green/blue	*Pseudomonas* spp urinary tract infection	Amitriptyline
		Intravenous cimetidine
		Promethazine
		Methylene blue
		Asparagus
Red	Erythrocyturia	Phenothiazines
	Haemoglobinuria	Beetroot (in acidic urine)
	Myoglobinuria	Blackberries (in acidic urine)
	Porphyria[a]	Rhubarb (in alkaline urine)
Orange/yellow		Rifampicin
		Carrots

[a] Urine darkens on standing.

Table 2

proteinuria is usually benign and associated most often with urinary tract infection, exercise or fever, persistent proteinuria is always abnormal. The exception to this is orthostatic proteinuria, a benign condition where protein is found in the urine only after a period of time spent in the standing position. Proteinuria is the single most important indicator of renal disease (Figure 2) and risk factor for progression of chronic kidney disease (CKD).[3] Proteinuria is also an independent risk factor for cardiovascular disease and death.

Dipsticks detect protein by production of colour with an indicator dye, tetrabromophenol blue, which binds proteins in a pH-dependent manner.[4] Albumin binds optimally at pH 5–7; other proteins bind only at a pH lower than 5 and with an affinity that is lower than that of albumin; Bence Jones protein fails to bind at any pH. Since urinary pH is usually 5–6, urine dipsticks can be regarded as albumin-specific. The limit of sensitivity for urine dipsticks is approximately 300 mg/litre, so they do not detect microalbuminuria. Albumin-specific dipsticks are available that can detect albumin at 10 mg/litre and are therefore capable of detecting microalbuminuria.

Standard urine dipsticks cannot be used accurately to quantify proteinuria. In patients with dipstick-positive proteinuria, urinary protein excretion must be quantified, usually by measuring the protein–creatinine ratio (PCR) or albumin–creatinine ratio (ACR) on a single spot urine sample. The ACR has higher sensitivity and specificity than the PCR, especially at lower protein concentrations, and is recommended for the initial identification of proteinuria. In patients undergoing monitoring for CKD (National Institute for Health and Clinical Excellence (NICE) Guideline 73; Table 3), the ACR should be used routinely without the prior use of standard dipsticks.[5] It is also recommended that an ACR should be used for the monitoring of patients with diabetes. A PCR can be used in those patients with established proteinuria and high ACR readings.

Nitrites and leucocyte esterase

Specific groups of bacteria, particularly Gram-negative rods such as *Escherichia coli*, generate nitrites; when present in significant numbers, they can be detected by screening for urinary nitrite.[6] Some bacteria (e.g. *Pseudomonas* spp., *Staphylococcus albus* and *Enterococcus* spp.) do not produce nitrites, so a negative dipstick does not exclude a urinary tract infection (UTI) without additional studies. A weakly positive dipstick (indicating the presence of only a few bacteria) should be interpreted with caution and further corroborative evidence sought before treatment is started.

Leucocyte esterase testing is specific for the presence of intact or lysed neutrophils and macrophages in the urine (pyuria).[7] A negative leukocyte esterase test makes a UTI unlikely, although high glucose or protein concentrations can cause false-negative results. A urine sample that tests positive for both nitrites and leucocyte esterase is highly likely to be infected and should be retained for microscopy and culture and sensitivity testing.[8,9] Sterile pyuria, in which there are leucocytes but no growth on culture, should always raise the suspicion of renal tuberculosis, transitional cell carcinoma, nephrolithiasis and chlamydial infection.

Glucose and ketones

Testing for glucose is most commonly used to confirm a diagnosis of diabetes mellitus and/or monitor the effectiveness of diabetic control. Glycosuria is not necessarily abnormal and further testing must always be performed to establish a diagnosis of diabetes mellitus.

Ketones are produced as a consequence of fatty acid metabolism when the body cannot use carbohydrate as a source of energy, and ketonuria is therefore mainly associated with insufficient insulin availability in type I diabetes mellitus or some form of calorie deprivation (anorexia, prolonged vomiting, diarrhoea, fever, starvation, Atkins diet). Each of these underlying causes should be readily apparent on clinical assessment of the patient and ketonuria rarely requires independent evaluation.

Urine pH and specific gravity

Depending on the plasma acid–base status, urinary pH can range from as low as 4.5 to as high as 8.0. In isolation, urine pH cannot be reliably interpreted and therefore should be used in assessing the patient only in specific circumstances (for example, renal tubular acidosis). If a urine sample is strongly alkaline one should, however, consider a UTI with a urease-producing bacteria (urease catalyses the conversion of urea to ammonia).

Specific gravity is directly proportional to urine osmolality or urine solute concentration. A low specific gravity (1.001–1.010) can be seen in intrinsic renal disease, diabetes insipidus and

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