Urine Analysis

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Introduction

Formation of urine allows a cheap, noninvasive and novel insight into the pathological processes affecting the kidneys and urinary tract and has been shown to be an essential tool to the practising nephrologist [1, 2]. Urine analysis has evolved from 'the art of uroscopy', practised in medieval times [3], to detailed chemical analysis and microscopy, allowing early detection and differentiation of renal disease.

This chapter outlines the practical aspects of urine analysis and routine urine dipstick and aims to guide the interpretation of pathognomic features of urinary abnormalities on microscopy to relevant clinical situations.

Sample Collection

At the outset, it is important to optimise sample collection: poorly procured samples have little value and may result in inappropriate management (see Table 2.1 for guidance on sample collection). It is also important to ensure that samples are delivered without delay for processing; microscopy or cytology samples dispatched at the end of the day and left overnight are likely to be useless and waste lab resources. As a guideline, samples for cytology should ideally reach the laboratory within 2 h, whereas samples for culture may be refrigerated, if required, for 24 h at 4 °C. It is therefore worth ensuring that a system is in place for prompt sample delivery and that nursing staff routinely educate patients on how to reliably provide 'clean-catch' midstream urine (MSU) samples.

A variety of clean-catch systems are commercially available to reduce contamination, although to date there is very limited evidence of benefit. For those patients unable to cooperate, and in whom urine analysis is important, then alternatives include 'in-out' catheterisation or suprapubic aspiration (common in paediatrics) both of which may be contaminated by erythrocytes, but worth considering when urine analysis is critical.

Indwelling catheter specimens are invariably contaminated by blood and low-level proteinuria. Ileal conduits, urostomies and indwelling catheters are also very frequently (*universally*) colonised with bacteria, and there is little point obtaining samples in the asymptomatic patient except to exclude gross proteinuria or for analysis of electrolytes.

Physical Appearance

Prior to any testing of a urine sample, physical appearance should be assessed, particularly *colour*, *odour* and *turbidity* as certain circumstances result in specific appearances, as outlined in Table 2.2. Normal urine is clear when analysed in a transparent container against a white background, and colour ranges from light yellow to dark amber depending on the amount of urochromes present and solute concentration.

Urine Dipstick

Urine dipstick abnormalities are widely prevalent in both community and hospital practice and is most often the

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Table 2.1 Health Protection Agency standard method of MSU sample collection in men and women [4]

Midstream sample of urine is always preferential
Quality of urine sample determines accuracy of analysis
Clear instructions should be provided prior to voiding to avoid contamination
Males: *retract foreskin and clean glans*
Females: *clean labia and urethral meatus*
Place container midstream in the flow of urine
Analysis should be performed as soon as possible to avoid decomposition of cellular elements
As a general rule, samples should be exposed to minimal light and not be stored at room temperature for longer than 2 h
First morning urine provides a concentrated urine sample most likely to contain clinically important elements

Quick link: http://www.hpa-standardmethods.org.uk/documents/bsop/pdf/bsop41.pdf

Table 2.2 Physical characteristics of urine [5]

Colour	*Yellow/brown* – hyperbilirubinaemia, chloroquine, nitrofurantoin
	Orange – rifampacin, senna
	Red/brown – blood, myoglobin, phenytoin, beetroot (anthocyanins), blackberries, rhubarb, chronic lead or mercury poisoning
	Pink – propofol (especially in alcoholics)
	Blue – methylene blue, *Pseudomonas* infection, indicanuria
	Green – propofol, amitriptyline, indomethacin, phenergen
	White/milky – chyluria
	Black – ochronosis, porphyria (on standing, pink under UV light), melanomatosis, copper poisoning, chloroquine, primaquine, metronidazole, phenol poisoning, alkaptonuria, tyrosinosis
	Causes of urine darkening on standing – alkaptonuria, typically when left exposed to open air caused by oxidation and polymerisation of excess homogentisic acid, enhanced with alkaline pH
Odour	*Offensive* – consider bacterial infection
	'*Maple syrup*' – maple syrup urine disease
	Acetone – diabetic ketoacidosis
	'*Sweaty feet*' – isovaleric acidaemia
Turbidity	'*Cloudy*' – high concentration of either/or leucocytes, erythrocytes, epithelial cells, bacteria or crystals. Consider genital tract contamination (females), white cloudy can occur with phosphaturia (disappears with acetic acid)
	'*Milky*' – lipid-rich material (chyluria); consider abnormal connection between lymphatic and urinary systems
	'*Gas*' – termed pneumaturia, an important symptom that occurs in the presence of colovesical fistula or emphysematous pyelonephritis
	'*Frothy*' – indicative of nephrotic range proteinuria

first clue to the presence of renal disease. Careful interpretation of dipstick abnormalities is therefore important and should guide further appropriate investigations and specialist referral. Sample collection is an undervalued yet essential component of urinary examination and should be performed by standard methods as outlined in Table 2.1.

A variety of dipstick testing kits are available, but standard combination strips routinely include five or seven of the following tests: *protein*, *blood*, *glucose*, *ketones*, *pH*, *bilirubin* and *urobilinogen*. Other characteristics detected on urine dipstick are *specific gravity* and the presence of *leucocytes* and *nitrites*. Table 2.3 outlines common abnormalities, possible causes and important false positive situations to consider. Specific urine dipstick tests are also available in specialist practice with the most widely available tests including Micral-Test II® or Microbumintest® (microalbuminuria), Ictotest® (bilirubin), Acetest® (ketones) and Clinistix® (glycosuria only).

Urine Microscopy

> Urine…… can provide us day by day, month by month and year by year with a serial story of the major events going on within the kidney.
>
> Thomas Addis (1948) [6]

Urine microscopy performed by a nephrologist is a cheap, noninvasive and educational test that, in the right setting, can substantially aid the diagnosis. Before investing in resources, it is worth approaching local laboratories for used centrifuges and microscopes. The requirements are:

1. A centrifuge capable of taking 10 ml samples at 1,500 rpm
2. Centrifuge tubes
3. Disposable pipettes
4. Microscope slides
5. Cover slips
6. Microscope (with phase contrast)
7. Appropriate bench space (usually dirty utility room)
8. Individual with responsibility for maintaining equipment (*Draconian penalties for leaving the microscope on or in a mess – optional*)

Suitably preparing urine for microscopy is essential to obtaining informative results. A midstream sample should be obtained by the method outlined (Table 2.1) and at least 10 ml of urine should be collected and analysed *within 2 h*. Table 2.4 shows how to prepare a urine sample for light microscopy, and Table 2.5 shows technical information on analysing the urine sediment.

The urine sediment may contain a vast number of cellular elements. This section is not an exhaustive atlas, but rather a summary of the important components which should be recognised on examination in association with the relevant clinical syndromes, helping guide the practising nephrologist in the pursuit of diagnosis.

Table 2.3 Urinary dipstick abnormalities (*for haematuria and proteinuria see below*)

Specific gravity	Polyuria associated with low SG <1.010
Normal range 1.002–1.035 NB: varies according to urine concentration	Low with polydipsia (psychogenic, beer drinking) and diabetes insipidus Tends to be fixed (c.1.010) in acute tubular injury or CKD High levels (≥1.035) seen in shock and dehydration (appropriately concentrated) Artificially high with glycosuria, proteinuria and following IV contrast *Useful cheap measure of fluid intake for patients with recurrent UTI or stone disease if renal function is normal*
pH	Low pH in acidosis and high-protein diet and promotes uric acid and cysteine stone formation
Normal range 5–8, Western diet pH = ~6	High pH in (1) renal tubular acidosis (inappropriately alkaline urine (>5.5) in face of acidosis) (pH <5.4 excludes distal RTA), (2) low-protein/low-vegetarian diet and (3) urinary tract infection, particularly from urease-producing organisms such as *Proteus mirabilis* High pH promotes calcium-phosphate deposition
Glucose	Freely filtered at glomerulus, but almost completely reabsorbed at the proximal tubule
In normal homeostasis, glucose is not present in urine	Causes of glycosuria Pregnancy (normal physiological response) Hyperglycaemia (diabetes mellitus) Impaired proximal tubular reabsorption in isolation (SGLT2 defect)
Ketones	Ketones are produced following increased metabolism of fat. Ketone bodies (acetoacetic acid, acetone and 3-hydroxybutyrate *not detected*) are freely filtered in the glomerulus
In normal homeostasis, ketones are not present in the urine	Causes of ketonuria Type 1 diabetes mellitus (diabetic ketoacidosis) Starvation states (prolonged fasting, anorexia nervosa)
Bilirubin	Bilirubin is normally conjugated and excreted into the gastrointestinal tract as a water-soluble molecule. Small bowel bacterial metabolism converts bilirubin to urobilinogen which is then reabsorbed at the distal small bowel lumen and partially excreted in the urine
Urobilinogen gives urine its 'normal' physical appearance	*Positive bilirubin dipstick test* – suggests failure of hepatic conjugation of bilirubin preventing excretion and conversion of urobilinogen *Negative urobilinogen dipstick test* – indicates failure of hepatic excretion of conjugated bilirubin (biliary obstruction)
Nitrites	Most bacteria convert nitrates to nitrites during growth and replication. Positive nitrite test is suggestive of infection, but a negative test is not exclusive. A minimum time period is required for bacterial transformation
In health, nitrites are excreted in variable amounts, although are undetectable in the majority	Bacteria that do not reduce nitrate compounds include *Enterococcus* *Pseudomonas species* *Streptococcus faecalis* *Staphylococcus albus* *Neisseria gonorrhoea*
Leucocytes	Urine dipstick detects the enzymatic reduction of a synthetic ester substrate by urinary neutrophil esterase to a blue derivative in the presence of air
The presence of leucocytes in the urine suggests inflammation or infection *NB*: *may be absent in neutropenia*	Leucocyte esterase reaction has a reported better sensitivity than nitrite testing for the diagnosis of urinary tract infection, but false negatives can occur in the presence of tetracyclines, cephalosporins, glucose, albumin and ketones

Isolated Haematuria

Haematuria on dipstick should *always* be confirmed by microscopy to exclude false positives (pigment nephropathy, hypochlorite solutions, oxidising agents, bacterial peroxidase) and false negative results (vitamin C, gentisic acid).

New patients over 40 years of age (or younger for those with risk factors for urinary tract malignancy, e.g. previous cyclophosphamide or aristolic acid exposure) with proven micro- or macroscopic haematuria should be screened for urinary tract malignancy [7] or another cause of lower urinary tract bleeding. There is a strong argument for an integrated uro-nephrology approach to haematuria in this

Table 2.4 Preparation of urine for microscopy

Collect 10 ml midstream urine sample in sterile universal container
Centrifuge 10 ml at 1,500 rpm
Discard supernatant (9.5 ml)
Resuspend 500 µl sediment using *Pasteur* pipette
Transfer 50 µl of urinary sediment to slide
Apply cover slip (24×32 mm)

Table 2.5 Technical aspects of urine microscopy

Microscope	Indications
Phase contrast	Allows best identification of cellular elements, less need for special stains
Light	Poor visualisation of contents with low refractive index
Polarised light	Positive birefringence allows detection of crystalluria
Stains	
Wright's	Lymphocytes
Papanicolaou's	'Decoy cells' pathognomic of Bk viruria
May-Grünwald-Giemsa	Eosinophils
Hansel's	Haemosiderin
Prussian blue	

group of patients (Table 2.6). Perhaps the most patient-orientated approach is a '*haematuria one-stop shop*' where patients are seen and assessed by urologists with urine microscopy, renal blood tests, same-day ultrasound of kidneys and bladder and cystoscopy when appropriate. Those deemed not to have a urological cause for haematuria can then be assessed by a nephrologist in reserved slots on the same day. This takes a bit of organising, but the dividends for the patient and the clinician are obvious in terms of providing an efficient and joined-up approach.

Lower urinary tract bleeding is indicated by erythrocytes (RBC) with essentially normal and homogenous morphology. In haematuria due to glomerular disease, RBC presumably become distorted as they pass through the glomerular basement membrane and down the tubule resulting in heterogenous and dysmorphic shapes including acanthocytes, best seen with phase-contrast microscopy (Fig. 2.1a). A large quantity of dysmorphic red blood cells is suggestive of an aggressive glomerular lesion, whereas scanty dysmorphic RBC are more indicative of a subacute GN. The presence of a red blood cell cast is highly suggestive of an aggressive glomerulonephritis and, to paraphrase the old adage, '*one RBC cast makes a Summer*'. As this is one of the most important and specific findings in urine microscopy, it is extremely helpful to train the nephrologist's eye with the urine of patients known to have acute renal vasculitis/lupus.

Isolated Proteinuria

The detection of protein on urine dipstick is affected by (1) concentration (consider specific gravity), (2) macroscopic haematuria and (3) urine pH >8.0. Urine dipstick testing does, however, provide a semi-quantitative measurement of proteinuria as outlined in Table 2.7, but whilst dipstick reagent testing is sensitive to albumin, it has low sensitivity to other proteins, such as tubular proteins and light chain immunoglobulins. Proteinuria should therefore be confirmed by additional testing, and for the vast majority of patients, a random urine protein:creatinine ratio (uPCR) or urine albumin:creatinine ratio (uACR) (monitoring of choice in diabetes) is sufficient for diagnosis and monitoring. Table 2.8 outlines different types of proteinuria with important clinical considerations.

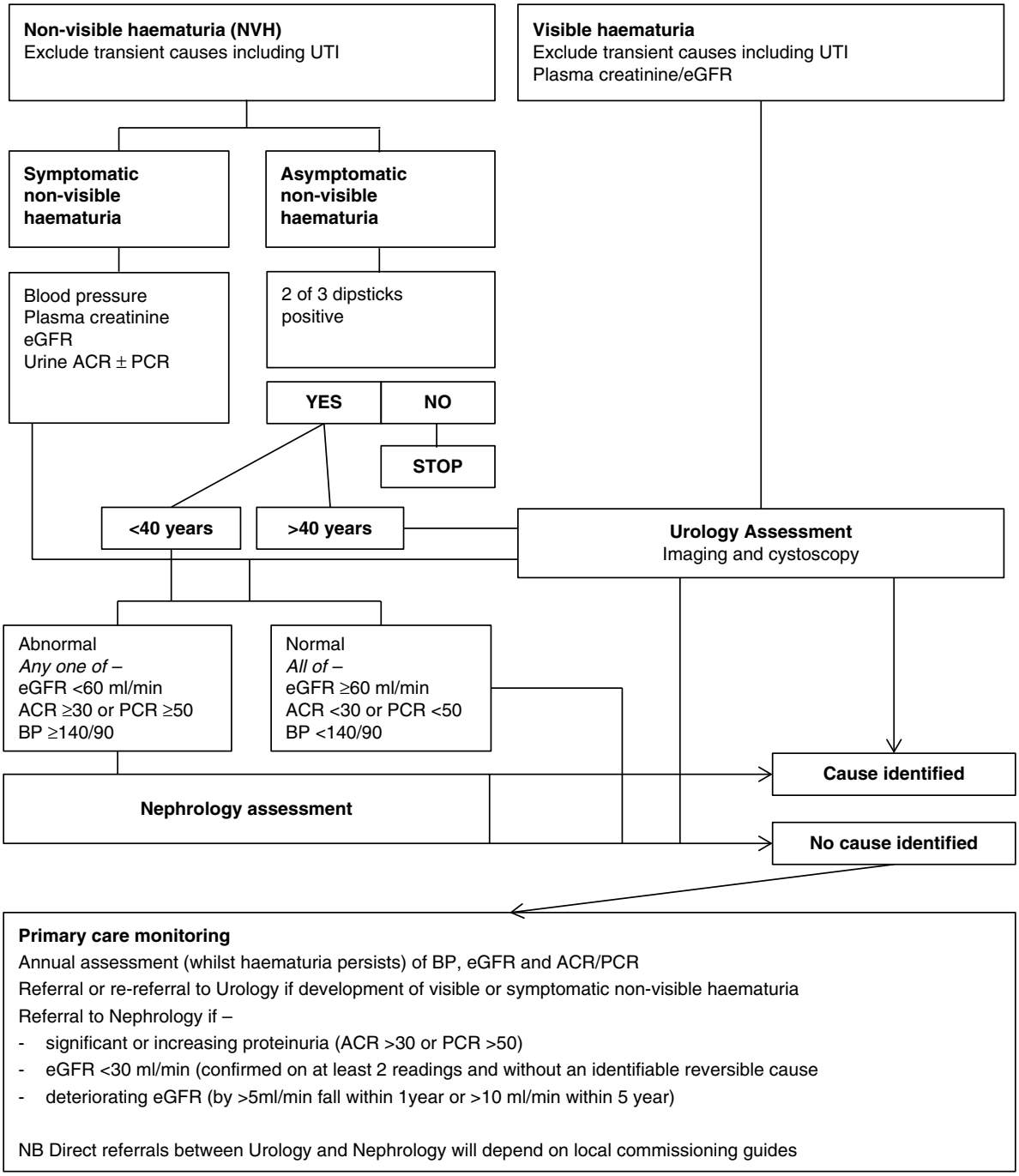
Although largely superseded by simpler tests, occasionally 24 h collections may be helpful for the assessment of proteinuria particularly if combined with other diagnostic tests such as 24 h sodium, urine volume, creatinine clearance and Bence-Jones proteinuria. It is noteworthy that the value of such tests is diminished if incomplete collection is performed. For 24 h collections, patients should be given clear guidance and a pre-labelled large volume container and instructed to empty their bladder first thing in the morning (ideally a nonworking day with no heavy exercise) and then collect all urine until the following morning including finishing with an empty bladder on rising.

Acute Kidney Injury

Urine analysis is absolutely critical in guiding the diagnosis and initial management of patients with AKI, and although the clinical picture is often complex, there are several scenarios when urine analysis can substantially guide or cleverly make the diagnosis. It is important that your referring wards and emergency departments try, where possible, to obtain a fresh urine prior to catheterisation (and reliably record residual urine volume on catheterisation):

1. *Acute tubular injury*: The majority of AKI is secondary to hypoperfusion-induced acute tubular injury, and, in the absence of an intrinsic renal disease, the urine is likely to have minimal haematuria or proteinuria, and urine microscopy therefore reveals large numbers of renal epithelial cells (Fig. 2.1b) and granular casts (not specific) and limited numbers of erythrocytes with no red cell casts. Urine festooned with tubular cells is highly suggestive of acute tubular injury, but more often it is the exclusion of an active glomerular lesion that is critical.

Table 2.6 Decision algorithm for the investigation and referral of haematuria



Adapted from the UK Renal Association Clinical Guidelines [7]

2. *Pigment nephropathy*: This is a great opportunity to make a rapid diagnosis in that myoglobinuria and haemglobinuria both result in a dark urine and positive haemstix test, but microscopy will show an absence of RBC. Thus, +++ haematuria but no RBC on microscopy is highly suggestive of a pigment nephropathy. If sent rapidly enough, rhabdomyolysis may be confirmed by the presence of myoglobin in the urine, but this is evanescent. Although not strictly urine analysis, intravascular haemolysis can then be cunningly distinguished from rhabdomyolysis by spinning the

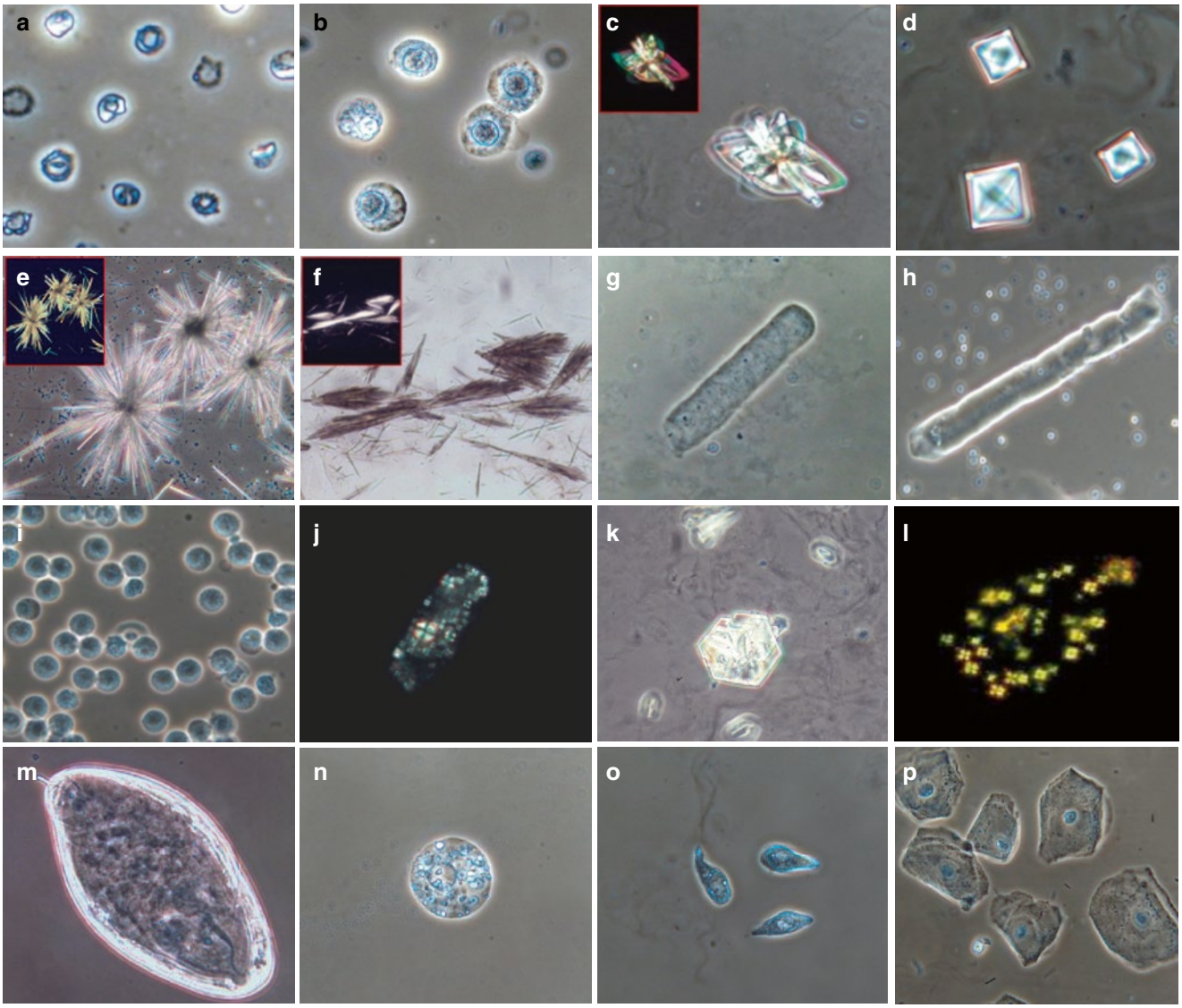


Fig. 2.1 Magnification ×400. (**a**) Dysmorphic erythrocytes; (**b**) proximal renal tubular epithelial cells – round shape, large nucleus and granular cytoplasm; (**c**) rhomboidal uric acid crystal with polychromatic birefringence under polarised light; (**d**) bipyramidal appearance of bihydrated calcium oxalate crystals; (**e**) ciprofloxacin crystals with birefringent star-like shape; (**f**) amoxicillin crystals appearing as needles, strong birefringence; (**g**) hyaline granular cast; (**h**) waxy cast; (**i**) leucocyturia; (**j**) 'Maltese cross' crystals on polarised light; (**k**) hexagonal crystals of cysteine; (**l**) 2,8-dihydroxyadenine crystals; (**m**) *Schistosoma haematobium* eggs; (**n**) granular macrophage; (**o**) deep urothelial cells; (**p**) squamous cells [8, 9] (Reprinted with permission from Fogazzi et al. [8] and Bouzidi et al. [9])

patient's blood and demonstrating pink serum. Myoglobin and haemoglobin can stain granular and epithelial casts orange/brown, and this can be a late useful clue.

3. *Rapidly progressive glomerulonephritis* (*RPGN*): The presence of a classical 'active urine', i.e. significant blood and protein and dysmorphic RBC in large numbers (and ideally a RBC cast), is extremely helpful contributory evidence for RPGN. Similarly, the absence of any dysmorphic RBC may be very reassuring in a complex patient with AKI.
4. *Acute interstitial nephritis* (*AIN*): There are no truly discriminatory findings in the urine of patients with AIN, but patients often have low to moderate levels of haematuria/proteinuria but can occur with neither, emphasising the importance of urine microscopy for white blood cells; large amounts of either blood or protein tending to make the diagnosis less likely (e.g. urine PCR >200). Classically AIN is associated with a sterile pyuria and eosinophiluria* is common, but neither particularly specific nor sensitive (**visible on Giemsa staining*). Of note, simultaneous measurement of urinary albumin and protein to creatinine ratio allows determination of urinary albumin to total protein ratio, and it has been shown that a measurement of <0.40 is highly sensitive and specific for the diagnosis of AIN [10].
5. *Crystal nephropathy*: The rhomboid shapes of uric acid crystals in otherwise 'quiet' urine may be indicative of

tumour lysis syndrome (Fig. 2.1c). Bipyramidal crystals of calcium oxalate may be extensive in acute oxalosis secondary to ethylene glycol ingestion or hyperoxalosis of any cause, although they can occur in normal urine (Fig. 2.1d). Occasionally it may be possible to heroically make the diagnosis of drug-induced crystal nephropathy relating to aciclovir, antiretroviral therapy or antibiotics, such as ciprofloxacin and amoxicillin (Fig. 2.1e, f).

In summary whilst many cases of AKI result from multiple insults, sometimes, careful assessment of the urine can cheaply and noninvasively hone the differential diagnosis that significantly or reassuringly excludes some important disease groups.

Chronic Kidney Disease (CKD)

The kidney loses the ability to substantially regulate urine concentration (beyond 1.010) or control pH in CKD. The concentration of creatinine in the urine tends to remain stable with worsening renal function as GFR falls but plasma creatinine rises. Low levels of proteinuria are very common in CKD, but substantial proteinuria (3+), especially if combined with haematuria, suggests a primary glomerular lesion. Microscopy of urine in CKD is usually dominated by signs of progressive tubular damage including tubular cell casts, waxy casts, coarse granular casts and leucocytes (Fig. 2.1g–i).

Table 2.7 Semi-quantitative correlation of dipstick proteinuria

	Protein concentration (mg/dl)	Estimated daily protein excretion (g/day)
Trace	5–20	
1+	30	<0.5
2+	100	0.5–1
3+	300	1–2

Is There Any Value in Urine Analysis in Suspected CKD?

The role of urine analysis in chronically damaged kidneys is rather more limited than in AKI. However, when faced with a new patient who has marked renal impairment, it is critical to distinguish between AKI and CKD. This is often resolved by detailed clinical history, historical creatinine results or renal ultrasound; however, urine microscopy demonstrating granular and tubular cell casts with an *absence* of acute cellular casts, dysmorphic red cells or features of an 'active urine deposit' may be helpful confirmatory evidence of CKD and exclusion of a rapidly progressive glomerulonephritis or urinary tract infection.

A significant proportion of patients with ESRF have no definite renal diagnosis, and occasionally thoughtful urine analysis in CKD can narrow down the differential diagnosis and sometimes achieve a diagnostic coup and is worth considering in new patients, for example:

- The identification of '*Maltese cross*' on polarised light microscopy (Fig. 2.1j) in a patient with CKD and low-level proteinuria is highly suggestive of Anderson-Fabry disease, although it can occur in any heavily nephrotic state. In Anderson-Fabry's disease, these represent myelin bodies free within the urine or within hyaline casts and can be definitively distinguished by electron microscopy.
- Extremely broad *hyaline casts* are said to be indicative of medullary cystic disease or reflux nephropathy and maybe helpful in early CKD but can occur in any advanced CKD.
- The oval or bipyramidal crystals of *calcium oxalate* (Fig. 2.1d) may indicate either acute or chronic hyperoxalaemia, although oxalate crystals are a fairly nonspecific finding.

Table 2.8 Types of proteinuria with important clinical considerations

Glomerular proteinuria	*Physiological* – ACR <30 mg/24 h (but raised acutely if febrile, see below)
Predominantly albumin and an early, important indicator of glomerular injury. Standard dipsticks sensitive	*Microalbuminuria* – ACR >30–300 mg/24 h (not detectable with standard dipstick)
	Overt proteinuria – ACR > PCR
	Nephrotic range proteinuria – ACR > PCR>
Tubular proteinuria	Rarely greater than 100 mg/mmol or 1 g/l
Suspect with low-level proteinuria especially if uPCR out of proportion to dipstick/uACR or accompanied by other features of tubular injury/inflammation such as sterile pyuria or features of Fanconi syndrome	Indicated by normal ACR but raised PCR
	Specific tests for tubular proteins include retinol binding protein (RBP), α-1 microglobulin and N-acetyl β glucosamine (NAG)
	Causes include drug toxicity (eg. cisplatin, tenofovir etc.), causes of acquired tubulointerstitial nephritis, heavy metal poisoning and Dent's disease
Overflow proteinuria	Overproduction of proteins, most commonly light chains
	Not detected by standard urine dipsticks
	Negative or low-level dipstick with disproportionate urine PCR may suggest overflow or tubular proteinuria
Benign proteinuria	'Physiological': febrile proteinuria, post-exercise proteinuria
	Orthostatic proteinuria: isolated low-level proteinuria, often in young males, possibly associated with 'nutcracker kidney' (arterial compression of renal veins occasionally with loin pain). Proteinuria is absent on rising sample, present after being ambulant so easily diagnosed with paired rising and ambulant uPCRs

- Hexagonal crystals of *cysteine* (Fig. 2.1k) are always pathological and thus indicate cystinosis if not already identified or isolated cystinuria as a cause of stones.
- *2,8-Dihydroxyadenine crystals* (Fig. 2.1l) are indicative of the rare adenine phosphoribosyltransferase deficiency – an important diagnosis to make in terms of treatment and risk of recurrence.
- Urine microscopy (of early morning sample) is a cheap and widely used method for diagnosis of *Schistosoma haematobium* (Fig. 2.1m) in endemic areas and may give the diagnosis in CKD secondary to obstructive uropathy.
- In the setting of CKD, significant blood and glomerular range proteinuria is suggestive of a *subacute glomerular disorder* (such as IgA or Alport's syndrome).

Figure 2.1 also shows additional frequent findings on urine microscopy which are important to recognise including granular macrophage (Fig. 2.1n), deep urothelial cell (Fig. 2.1o) and squamous cells (Fig. 2.1p).

Tubular Disorders

The causes of tubular and interstitial disease are numerous, but there are less pathognomic signs on urine microscopy than that found in the context of glomerular injury. Nevertheless, the presence of isolated mild proteinuria should always raise the possibility of a tubular disorder and may be supported by the detection of granular or 'waxy' casts on urine microscopy. In addition, the diagnosis of tubular clinical syndromes is often heralded by urinary abnormalities. Tubular syndromes result from abnormal handling of waste products, electrolytes and hydrogen ions and bicarbonate compounds without a necessary change in GFR:

1. *Renal tubular acidosis* may be associated with either a consistently elevated urine pH (distal RTA, type 4) or may be variable (proximal RTA, type 1) according to changes in bicarbonate reabsorption.
2. *Fanconi syndrome* is associated with reduced urine pH, but rather than an isolated bicarbonate reabsorption defect being present, additional proximal tubular function is impaired. Characteristic urinary abnormalities are phosphaturia, glycosuria (normoglycaemia), uricosuria and aminoaciduria. These abnormalities may be found in association with 'tubular' proteinuria.
3. *Tubular proteinuria* is a term used interchangeably with low molecular weight proteinuria and usually implies chronic proximal tubular dysfunction with the abnormal presence of β2-microglobuin, α-microglobulin, retinol binding protein and Clara cell protein within the urine. It is rarely more than 1 g/l and may be indicated by minimal protein on dipstick (detecting albumin) or normal ACR with a raised PCR.
4. *Acute and chronic tubulointerstitial nephritis* as mentioned above tend to be associated with low levels (<1.5 g/l) of proteinuria (PCR ≫ ACR), pyuria (more common in AIN than chronic TIN), occasionally eosinophiluria (nice to see but very low sensitivity and uncertain specificity) and sometimes microscopic haematuria.

Urinary Tract Infection (UTI)

The initial appearance of cloudy, offensive urine (especially in a symptomatic patient) may convincingly make a rapid diagnosis of UTI. It is often helpful to see urine at presentation, and it is important to get fresh samples to the laboratory swiftly for culture in order to confirm the diagnosis and guide antimicrobial chemotherapy. Urine analysis findings both in favour and against of a significant/clinically relevant UTI in a MSU specimen are shown in Table 2.9. Sterile pyuria has to be considered in the differential diagnosis prior to confirmation of bacterial culture as the hallmark 'nonspecific' features on initial urine analysis may also be

Table 2.9 Considerations in the diagnosis of a significant/clinically relevant UTI

	Features suggestive of UTI	Features against clinically relevant UTI
Appearance	Cloudy/turbid/offensive	Clear urine in asymptomatic patient
Urine dipstick	*Leucocyte esterase* positive (sensitive and very specific for pyuria) *Nitrites* (helpful if present but low sensitivity) *Low-level proteinuria/haematuria* (sometimes macroscopic), particularly if not previously present	Negative *leucocyte esterase* and *nitrite* dipstick have a strong negative predictive value (caveats above)
Microscopy	*White cell casts* (rare but important finding, very strong evidence of pyelonephritis) *Pyuria* (for other causes of sterile pyuria see Table 2.10) *Bacteruria* (if present on high-power field in clean catch, unspun urine, correlates with 10^5 or more bacteria/ml). Two clean-catch specimens in asymptomatic woman with 10^5 or more bacteria/ml represent a 95 % probability of true bacteruria	Absence of pyuria (NB: pyuria may be absent in neutropenic patients)
Culture	Pure growth of single organism with $>10^5$ cfu/ml	Bacteruria in the absence of pyuria and or multiple squamous cells contaminating sample Mixed growth of organisms (bona fide in 5 % of UTIs)

explained by the causes of sterile pyuria as outlined in Table 2.10.

Considerable thought also needs to be applied to the interpretation of urine from patients with indwelling catheters, ileal conduits and urostomies in that these frequently demonstrate all the features of a urinary tract infection as a result of chronic colonisation, and these samples frequently do not represent clinically relevant UTI.

Table 2.10 Causes of sterile pyuria

Urinary tract infection during or immediately post-antibiotics
Children with pyrexia of non-urinary tract origin
Urinary tract infection with fastidious organism
Symptomatic patient but no bacteria: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*
Asymptomatic tuberculosis, fungal infections
Interstitial nephritis
Chronic prostatitis
Papillary necrosis
Radiation or chemical cystitis
Renal stones
Solvent abuse

Urinary Electrolytes

Measurement of urinary electrolytes and osmolality is often performed in clinical practice in an attempt to guide diagnosis. However, interpretation is complex, compounded by the intricate mechanisms regulating solute excretion and osmolality. It is useful to remember that urinary electrolytes and osmolalities do not have fixed 'normal' values but rather parameters, based on the clinical setting.

From a practical perspective, testing is now routinely performed on a 'random' 10 ml clean-catch MSU sample, although certain circumstances require 24-h collection. Common indications and clinical scenarios when testing of urinary electrolytes and osmolality is appropriate are outlined in Table 2.11. However, the physiological principles underpinning water and solute excretion need to be continually considered; for example, urine osmolality assesses the action of ADH in the collecting ducts and hence water excretion, whilst urinary sodium is a measure of tubular function with the majority of freely filtered sodium being reabsorbed by the renal tubules. Table 2.11 is intended to be a helpful guide to interpreting urinary electrolytes, rather than an exhaustive atlas.

Table 2.11 Guide to interpretation of urine electrolytes [11]

	Urinary abnormalities	Considerations
Acute kidney injury		
'Prerenal' volume-depleted AKI	UNa^+ <20 mmol/l, *UOsm* ↑, FE_{Na}^+ <1 %, FE_{urea} <35 %	Abnormalities in urinary electrolytes in AKI reflect disease/damage to renal tubules with concentrating ability usually preserved in 'prerenal' volume-depleted AKI
Acute tubular necrosis (ATN)	UNa^+ >20 mmol/l, *UOsm* ↔, FE_{Na}^+ >3 %, FE_{urea} <35 % (*Hepatorenal syndrome* – UNa^+ *<20 mmol/l*, FE_{urea} ↓)	UNa^+ in post-obstructive uropathy is *not* reliable despite volume depletion
Contrast nephropathy Pigment nephropathy	FE_{Na}^+ typically <1 % (*Also seen in cardiac failure*)	In any post-operative patient, vasopressin release alters urine concentration ability
Interstitial nephritis	Usually 'salt-wasting' state – UNa^+ >20 mmol/l, FE_{Na}^+ >3 %	
Chronic kidney disease		
Crystal nephropathy	24-h urine collection most useful. Need to measure:	Risk factors for calcium stone formation:
Renal stone disease	Volume, calcium (acid preservative), phosphate, oxalate (acid preservative), uric acid (alkaline preservative), sodium, citrate, creatinine (ensure adequate collection), pH	Hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, RTA (*see also* Chap. 36)
Nephrocalcinosis	In addition, random urine sample to measure:	
Fanconi syndrome	Amino acids, β2-microglobulin, glucose Phosphaturia, glycosuria (normoglycaemia), uricosuria and aminoaciduria	

UNa^+ urine sodium, *UOsm* urine osmolality, *FE_{Na}^+* fractional excretion of sodium, *FE_{Urea}* fractional excretion of urea

$$\mathrm{FE}_{\mathrm{Na}^+} = \frac{\text{urine Na}^+ \times \text{plasma creatinine}}{\text{plasma Na}^+ \times \text{urine creatinine}} \times 100, \quad \mathrm{FE}_{\mathrm{Na}^+} = \frac{\text{urine urea} \times \text{plasma creatinine}}{\text{plasma urea} \times \text{urine creatinine}} \times 100$$

Summary

Urine analysis remains an important tool available to all clinicians and offers particularly useful information to the practising nephrologist. From initially inspecting the urine to performing routine urine dipstick and microscopy, clinical information is available at each stage and should therefore always be considered as an extension of the physical examination.

References

1. Bagshaw SM, Haase M, Haase-Fielitz A, Bennett M, Devarajan P, Bellomo R. A prospective evaluation of urine microscopy in septic and non-septic acute kidney injury. Nephrol Dial Transplant. 2012; 27(2):582–8.
2. Kanbay M, Kasapoglu B, Perazella MA. Acute tubular necrosis and pre-renal acute kidney injury: utility of urine microscopy in their evaluation – a systematic review. Int Urol Nephrol. 2010;42(2): 425–33.
3. Connor H. Medieval uroscopy and its representation on misericords – part 1: uroscopy. Clin Med. 2001;1(6):507–9.
4. HPA. Investigation of Urine. Health Protection Agency. National Standard Method BSOP 41. 2009. http://www.hpa-standardmethods.org.uk/documents/bsop/pdf/bsop41.pdf. Accessed 1 Feb 2012.
5. Berman LB. Urine in technicolor. JAMA. 1974;228(6):753.
6. Addis T. Glomerular nephritis. Diagnosis and treatment. New York: Macmillan; 1948. p. 2.
7. BAUS/RA Guidelines. Joint Consensus Statement on the Initial Assessment of Haematuria. Renal Association. 2008. http://www.renal.org/Libraries/Other_Guidlines/Haematuria_-_RA-BAUS_consensus_guideline_2008.sflb.ashx.
8. Fogazzi GB, Verdesca S, Garigali G. Urinalysis: core curriculum 2008. Am J Kidney Dis. 2008;51(6):1052–67.
9. Bouzidi H, Lacour B, Daudon M. 2,8-dihydroxyadenine nephrolithiasis: from diagnosis to therapy. Ann Biol Clin (Paris). 2007;65(6): 585–92.
10. Smith ER, Cai MMX, McMahon LP, Wright DA, Holt SG. The value of simultaneous measurements of urinary albumin and total protein in proteinuric patients. Nephrol Dial Transplant. 2012;27(4): 1534–41.
11. Winter SD, Gabow PA. Measurement of urine electrolytes: clinical significance and methods. Clin Rev Clin Lab Sci. 1981;14(3): 163–87.