REVIEW

Uroscopic rainbow: modern matula medicine

C L Foot, J F Fraser

Postgrad Med J 2006;82:126-129. doi: 10.1136/pgmj.2005.037598

Visual inspection of a patient's urine has long been used by physicians, with colour recognised as having important clinical implications. In this review the authors will revisit this ancient pastime with relevance to contemporary medical practice.

In the Middle Ages doctors inspected their patients' urine with grandiosity and reverence using the matula, a transparent bulbous urine glass held up to the light.¹ This unsophisticated, low cost investigation may provide doctors practising in diverse environments with valuable information. A comprehensive coverage of the rainbow of urine discolouration, of practical medical importance will be presented in this article with reference to the colour chart provided (fig 1).

1. YELLOW

The normal yellow colour of urine is attributable to the presence of the pigment urochrome.² This substance is excreted at a constant rate in a steady state and was characterised by Thudicom in the 19th century.³ Deviations from this characteristic colour arise when the concentration of urochrome is increased, decreased, or other pigments are excreted in the urine.

2. PALE YELLOW-CLEAR

Some data show that urine colour is as good an indicator of hydration as plasma or urinary osmolality or urine specific gravity.⁴ Pale urine is associated with increased production of dilute urine, while darker yellow, concentrated urine arises with dehydration with free water conservation. In the critically ill, a weak but statistically significant correlation between urine colour and urine output, and between urine colour and urine:plasma sodium ratio has been reported.⁵ Dilute urine is also caused by diuretic substances including loop, thiazide, potassium sparing, and osmotic diuretics including alcohol consumption, mannitol, glycosuria, and hypercalcaemia.⁵ Diabetes insipidus classically causes large volumes of clear urine. In this condition there is impaired synthesis and release of vasopressin from the hypothalamic-pituitary unit (neurogenic) or renal insensitivity to circulating vasopressin (nephrogenic).⁶ Factitious, pale urine is also seen after catheters are flushed and sterile water drains into the catheter collecting chamber. This is usually as a test for patency when oliguria is encountered.

3. MILKY

A milky appearance may arise with lipiduria, chyluria, and urinary tract infection with neutrophilia.³

Small amounts of lipid normally appear in the urine, however, in nephrotic syndrome there are large amounts of high density lipoprotein as well as smaller amounts of other lipoproteins.⁸ Chyle may enter the urinary tract through a traumatic communication between lymphatic vessels and the urinary system.⁹

Inconsequential, milky white urine has been noticed in a small number of people during prolonged general anaesthetics with propofol, a popular sedative and anaesthetic agent. It has been attributed to excretion of the intralipid vehicle, with lipiduria causing the discolouration. Lipiduria, however, was not confirmed with urine analysis in these cases.¹⁰ Some authors suggest that the milky colour is most probably related to uric acid excretion and is the same phenomenon as the propofol associated pink urine syndrome.¹¹ Phosphates excreted in an alkaline urine may also cause turbidity of urine with a cloudy appearance arising from amorphous phosphate crystals.¹² The consequence of this is unclear. Non-pathological causes of milky urine to consider are contamination from creams or powders applied to the perineal area in non-catheterised patients.⁷

4. PINK

A range of pink coloured pigments may discolour urine. Low concentrations of red blood cells may produce haematuria of varying intensity. As little as one millilitre of blood per litre may cause a visible colour change. Blood may originate anywhere along the urinary tract system, from the kidneys to the urethra. Abnormal causes may be categorised into glomerular and non-glomerular, coagulopathy related, trauma and factitious aetiologies. Glomerular bleeding classically causes red cell casts and dysmorphic red cells from mechanical deformation resulting from passage through the renal tubules.¹² Urine in glomerulonephritis may range from red to a more tea coloured hue. Renal colic is a commonly feigned factitious disorder whereby the deception is facilitated by adding the patients own blood to the urine or by a self inflicted bleeding urethral wound.¹³ Macroscopic haematuria should always be investigated.¹⁴

In the setting of propofol exposure, pink urine has been attributed to the presence of uric acid crystals. It is thought to arise in the setting of uric acid excretion and crystallisation. Propofol appears to be a uricosuric agent, with low urinary pH and core temperature favouring crystal formation.^{15 16}

5. RED

Gross haematuria causes deep red urine staining, is always pathological and haematuria has been

See end of article for authors' affiliations

Correspondence to:
Dr C L Foot, The Critical
Care Research Group, The
Prince Charles Hospital,
Rode Road, Chermide,
Australia 4032;
Carole_Foot@health.qld.
gov.au

Submitted 22 May 2005
Accepted 6 June 2005

Figure 1 Colour chart of urine discolouration.

discussed under pink urine. Common causes include renal calculi, urinary tract infection, and malignancy.¹⁴ Fresh blood arising from perineal sources (for example, haemorrhoids, menstrual blood) should be distinguished from renal causes.

Less commonly, red urine may arise from ingestion of foods that result in excretion of substances causing pH dependant red urinary discolouration such as beetroot and blackberries in acidic urine and rhubarb in alkaline urine.³ Beeturia, the passage of pink or red urine after the ingestion of beetroot, is said to occur in 10%–14% of the population, is more common in iron deficiency and malabsorption, and is caused by the presence of betacyanins.¹⁷ Medications implicated in causing red urine include senna, anthraquinone and phenolphthalein-containing laxatives, doxorubicin, and phenothiazines.³

6. TEA COLOURED

Haemoglobin and myoglobin yield dark oxidation products, particularly in acidic urine.³ Haemolysis may be classified as hereditary and acquired disorders as well by the site of haemolysis, which may be intravascular or extravascular. Features common to these conditions include a reduced serum haptoglobin, increased lactate dehydrogenase, and increased plasma free haemoglobin.¹⁸ Muscle injury, causing myoglobinuria, may result from insults ranging from direct muscle injury (for example, crush syndrome, electric shock, excessive exercise), sepsis, metabolic disorders (for example, hypothyroidism, diabetic crises, hypokalaemia, hypophosphataemia), and inflammatory myopathies to hereditary disorders, drugs and toxins (for example, cholesterol lowering agents, snakebite).¹⁹

Urine dip sticks turn positive when haemoglobin (free or bound to intact red cells) or myoglobin, with peroxidase-like activity, catalyses the oxidation of a chromogen indicator.²⁰ Haematuria will be distinguished by detecting red blood cells on urine microscopy. Haemoglobinuria and myoglobinuria may be differentiated by examining a centrifuged, anticoagulated blood specimen. Patients with myoglobinuria have a normal appearing plasma, whereas those with haemoglobinuria have a dark reddish plasma.¹⁸

Metronidazole therapy is also a cause of dark brown urine.²¹ Povidone-iodine perineal contamination should also be considered in patients having surgical procedures.²² In the porphyrias, inherited or acquired disorders of enzymes involved in haem synthesis, a range of urine colours may be seen. Porphyria is derived from the Greek word for purple and originally referred to the red to purple colour of the urine of patients with acute intermittent porphyria. The colours seen depend on the individual disorder and the fluorescence pattern of the excreted porphyrins and range from pink, red, purple to brown.^{23–24} Freshly passed urine may be normal in colour and only darken upon standing in light and air.²

7. ORANGE

Rifampicin therapy causes a characteristic orange-red discolouration of body secretions including urine. Interestingly this characteristic has been used as a marker of compliance with treatment.²⁵

Conjugated bilirubin not only causes yellowish-orange urine but also yields yellow foam when the specimen is

shaken.³ It is excreted into urine in the presence of biliary tract obstruction after leaking from hepatocytes into blood. Conjugated bilirubin is missing from the intestinal tract in these circumstances. Stercobilin, the pigment that colours faeces, is thus also absent resulting in pale stools. Urobilinogen, another conversion product from bilirubin, which normally forms in the intestine and reabsorbed into blood, is also characteristically absent from urine in biliary obstruction.

8. BLUE-GREEN

Green urine arises when blue compounds are excreted by the kidneys and mix with normal yellow urochrome pigments. A number of agents have been known to cause green urine (for example, indomethacin, amitriptyline, triamterene, Listerine, flutamide, and injectable formulations containing phenol such as some preparations of promethazine).²⁶ Propofol is excreted in the urine mainly as the 1-glucuronide, 4-glucuronide and 4-sulfate conjugates of 2,6 di-isopropylphenol. These are phenol derivatives, which cause a pH dependent green urine discolouration that is more prominent in alkaline urine. There are abundant case reports describing green urine in patients with the propofol infusion syndrome, a potentially fatal disorder marked by severe metabolic acidosis, rhabdomyolysis, renal and cardiac failure particularly in association with prolonged high dose propofol infusions, in patients with brain injury.^{27–28} Case reports may also be identified that record green urine in the context of low doses of propofol, administered for sedation in intensive care units and even after single anaesthetic induction doses, unassociated with adverse complications.^{29–30}

The addition of dyes to enteral formulas is a bedside technique for detecting aspiration in mechanically ventilated patients. Blue dyes known to cause green urine discolouration with their excretion include food drug and cosmetic blue number 1, indigo blue, indigo carmine and methylene blue.³¹ Intravenous infusion of methylene blue has been suggested in the treatment of refractory septic shock.³² Conversely, in recent times, concern regarding systemic absorption and toxicity of these agents has been raised, particularly in

Five key references

- Wittern-Sterzel R. Diagnosis: the doctor and the urine glass. *Lancet* 1999;**354**(suppl):SIV13.
- Cone TE. Diagnosis and treatment: some syndromes, diseases, and conditions associated with abnormal coloration of the urine or diaper. *Pediatrics* 1968;**41**:654–8.
- Raymond JR, Yarger WE. Abnormal urine color: differential diagnosis. *South Med J* 1988;**81**:837–41.
- Ernest D, French C. Propofol infusion syndrome—report of an adult fatality. *Anaesth Intensive Care* 2003;**31**:316–19.
- Noll WW, Glass DD. Causes of dark urine. *JAMA* 1980;**243**:2398.

critically ill patients. Food drug and cosmetic dye number 1 may inhibit mitochondrial oxidative phosphorylation resulting in lactic acidosis and impaired organ function. Recommendations to stop using these agents for this purpose have been issued.³³

Urinary tract infection caused by *Pseudomonas aeruginosa* can cause green urine through the liberation of the pigment pyocyanin.³ In chronic obstructive jaundice green and blue urine may arise attributable to biliverdin excretion, an oxidation product of bilirubin.²

9. PURPLE

Purple discolouration of urine drainage bags has been described in long term catheterised patients. This has been attributed to a violet discolouration of the plastic tubing by indirubin and fine blue crystals of indigo in urine. These coloured pigments arise from the substrate indoxyl sulfate (indican). Indican is derived from bacterial oxidation of tryptophan by the bacterial flora of the gut.³⁴ Purplish-blue urine has long been described with malabsorption and bacterial overgrowth syndromes and classically Hartnup disease, a rare specific defect of tryptophan transport.³

Intestinal stasis attributable to constipation may be an explanation for the high prevalence of purple urine bags in elderly nursing home patients. Bacterial fermentation of indican by organisms such as *Klebsiella* and *Providencia* species, well known producers of blue colonies on urine enriched agar, appear to be the final necessary pathophysiological step in the purple urine bag syndrome.³⁴

10. GREY-BLACK

Blackening of urine on exposure to air is characteristic of homogentisic acid, caused by alkaptonuria. Discolouration results from oxidation of the homogentisic acid, a reaction that is accelerated when urine is alkalinised. This is a rare genetic disorder in which the enzyme homogentisic oxidase is deficient, resulting in accumulation of homogentisic acid in various bodily tissues. This manifests as a multisystem disorder with blue-black discolouration of skin and cartilage, termed ochronosis. Arthropathy and cardiac valvular disease are the primary disabilities.³⁵

Melanogens are substances that spontaneously polymerise to form melanin, which may be found in the urine of patients with disseminated melanoma and rarely with Addison's disease. Normal metabolism of the antihypertensive agent α -methyldopa also produces a variety of melanogens, of which the best defined is α -methyldopamine. Urinary discolouration usually manifests when urine is alkaline.³⁶

CONCLUSION

Inspection of a patient's urine continues to provide valuable clinical information. Exposure to exogenous agents and the presence of specific medical disorders or infections may cause characteristic changes in the colour of urine. Knowledge of these patterns is of relevance for clinicians practising both in primary care, as well as critical care environments.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT THE END OF THE REFERENCES

- The potentially lethal propofol infusion syndrome is associated with which urine discolouration?
 - Red
 - Green
 - Pink
 - Brown
 - Orange

- Pale yellow-clear urine is associated with which of the following drugs?
 - Mannitol
 - Digoxin
 - Furosemide
 - Enalapril
 - Rifampicin
- Which of the following drugs used to treat tuberculosis classically causes urine to turn orange?
 - Ethambutol
 - Isoniazid
 - Pyrazinamide
 - Rifampicin
 - Streptomycin
- The purple urine bag syndrome is associated with the staining of plastic tubing by which pigment?
 - Indirubin
 - Pyocyanin
 - Urochrome
 - Urate
 - Betacyanin
- Which of the following conditions are associated with black urine?
 - Graves' disease
 - Diabetes insipidus
 - Addison's disease
 - Disseminated melanoma
 - Alkaptonuria

Authors' affiliations

C L Foot, J F Fraser, The Critical Care Research Group, The Prince Charles Hospital, Queensland, Australia

Funding: none.

Conflicts of interest: none.

REFERENCES

- Wittern-Sterzel R. Diagnosis: the doctor and the urine glass. *Lancet* 1999;**354**(suppl):SIV13.
- Cone TE. Diagnosis and treatment: some syndromes, diseases, and conditions associated with abnormal coloration of the urine or diaper. *Pediatrics* 1968;**41**:654-8.
- Raymond JR, Yarger WE. Abnormal urine color: differential diagnosis. *South Med J* 1988;**81**:837-41.
- Kavouras SA. Assessing hydration status. *Curr Opin Clin Nutr Metab Care* 2002;**5**:519-24.
- Fletcher SJ, Slaymaker AE, Bodenham, et al. Urine colour as an index of hydration in critically ill patients. *Anaesthesia* 1999;**54**:189-92.
- Blevins LS, Wand GS. Diabetes insipidus. *Crit Care Med* 1992;**20**:69-79.
- Cooper C. What color is that urine specimen? *Am J Nurs* 1993;**93**:37.
- Streather CP, Varghese Z, Moorhead JF, et al. Lipiduria in renal disease. *Am J Hypertens* 1993;**6**:353-7S.
- Nielsen HK, Lybecker H. Lipiduria after intralipid infusion of a lipid emulsion in a boy with an abdominal trauma. *J Parenter Enteral Nutr* 1991;**15**:572-3.
- Nates J, Avidan A, Gozal Y, et al. Appearance of white urine during propofol anesthesia. *Anesth Analg* 1995;**81**:210.
- Masuda A, Hirota K, Satone T, et al. Pink urine during propofol. *Anesthesia* 1996;**83**:666-7.
- Sokolosky MC. Hematuria. *Emerg Med Clin North Am* 2001;**19**:621-32.
- Banerjee A. Factitious disorders presenting as acute emergencies. *Postgrad Med J* 1994;**70**:68-73.
- Carroll PR. Evaluation of the patient with hematuria. *Med Clin N Am* 2004;**88**:329-43.
- Masuda A, Asahi T, Sakamaki M, et al. Uric acid excretion increases during propofol anesthesia. *Anesth Analg* 1997;**85**:144-8.
- Kato N, Ogawa R. Does use of propofol in heavy alcohol drinkers tend to discolor their urine? *Acta Anaesthesiol Scand* 1999;**43**:868-9.

- 17 **Watts AR**, Lennard MS, Mason SL, *et al*. Beeturia and the biological fate of beetroot pigments. *Pharmacogenetics* 1993;**3**:302–11.
- 18 **Tabbara IA**. Hemolytic anemias—diagnosis and management. *Med Clin North Am* 1992;**76**:649–68.
- 19 **Zager RA**. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int* 1996;**49**:314–26.
- 20 **Yun EJ**, Meng MV, Carroll PR. Evaluation of the patient with hematuria. *Med Clin North Am* 2004;**88**:329–43.
- 21 **Bruce TA**. Dark urine related to metronidazole therapy. *JAMA* 1971;**218**:1832.
- 22 **Noll WW**, Glass DD. Causes of dark urine. *JAMA* 1980;**243**:2398.
- 23 **Nuttall KL**. Abnormal chromatographic patterns of porphyrins in urine. *Ann Clin Lab Sci* 2001;**31**:259–64.
- 24 **Rich MW**. Porphyruria cutanea tarda. *Postgrad Med* 1999;**105**:208–14.
- 25 **Harries AD**, Chilemba PE, Greya D, *et al*. Monitoring rifampicin compliance by visual inspection of urine colour. *Trop Doct* 1999;**29**:243–4.
- 26 **Ananthanarayan C**, Fisher JA. Why was the urine green? *Can J Anaesth* 1995;**42**:87–8.
- 27 **Ernest D**, French C. Propofol infusion syndrome—report of an adult fatality. *Anaesth Intensive Care* 2003;**31**:316–19.
- 28 **Cremer OL**, Moons KG, Bouman EA, *et al*. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001;**357**:117–18.
- 29 **Bodenham A**, Culank LS, Park GR. Propofol infusion and green urine. *Lancet* 1987;iii:740.
- 30 **Tirosh R**, Barzilay Z, Almog S, *et al*. Propofol and green urine. *Paediatr Anaesth* 1996;**6**:244.
- 31 **Carpenito G**, Kurtz I. Green urine in a critically ill patient. *Am J Kid Dis* 2002;**39**:E20.
- 32 **Kirov MY**, Evgenov OV, Egorina EM, *et al*. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med* 2001;**29**:1860–7.
- 33 **Lucarelli MR**, Shirk MB, Julian MW, *et al*. Toxicity of food drug and cosmetic blue no 1 dye in critically ill patients. *Chest* 2004;**125**:793–5.
- 34 **Dealler SF**, Belfield PW, Bedford M, *et al*. Purple urine bags. *J Urol* 1989;**142**:769–70.
- 35 **Albers SE**, Brozena SJ, Glass F, *et al*. Alkaptonuria and ochronosis: case report and review. *J Am Acad Dermatol* 1992;**27**:609–14.
- 36 **Altmann P**, Mansell MA. Black urine. *Postgrad Med J* 1980;**56**:877–8.

ANSWERS

1. (B); 2. (A) and (C); 3. (D); 4. (A); 5. (C), (D), and (E).

Committee on Publication Ethics – Seminar 2006

9.30am–5pm Friday 10th March 2006, BMA House, London, UK

This year's seminar takes an international perspective and addresses publication ethics and research in several European countries and beyond, with interactive workshops on common ethical and editorial dilemmas. The manipulation of impact factors, and whether unethical, will also be considered.

The seminar is for editors, authors, and all those interested in increasing the standard of publication ethics. The seminar will include:

- Professor Michael Farthing – the Panel for Research Integrity (UK)
- Publication ethics and research in other countries, including those in Northern Europe, Turkey, and China
- Publication ethics in animal research
- Making the COPE website work for you – real time demonstration on how to use the website
- New indexing services
- Interactive workshops – common ethical and editorial dilemmas for editors
- Opportunities to network with other editors and share your experiences and challenges

The seminar is free for COPE members and £30.00 + VAT for non-members. Numbers are limited and early booking is advisable. For registrations or more information please contact the COPE Secretary at cope@bmjgroup.com or call 020-7383-6602

For more information on COPE see www.publicationethics.org.uk