Urological emergencies in the cancer patient – diagnosis and treatment

P.F. Keane*, H.F. O'Kane

Belfast City Hospital, Cancer Research Centre, Department of Urology, Belfast, Northern Ireland

Obstructive uropathy

Introduction

Obstructive uropathy is a common presenting feature of pelvic malignancy and infiltration from organs in proximity to the ureters or lymph node metastases can also lead to the development of obstruction (Table 1).

Obstruction can occur at any level along the urinary tract from as proximal as the calyces of the kidney to as distal as the penile meatus. Clinical presentation, diagnosis, treatment and prognosis will depend on the degree and nature of the obstruction.

Onset of obstruction may be acute with pain and anuria for example, in bladder outlet obstruction secondary to prostate cancer. Or it may have a more insidious onset being largely asymptomatic until symptoms of significant uraemia develop. The urgency to relieve diagnosed obstruction will depend on a number of factors. In particular, co-existent infection proximal to obstruction and the presence of hyperkalaemia secondary to impaired urine excretion require urgent intervention.

Table 1
Causes of obstructive uropathy in cancer patients

Malignant obstruction	
Urological	Non urological
Renal cell carcinoma	Colorectal
Transitional cell carcinoma	Cervix
renal pelvis	Ovarian
ureter	Uterine
bladder	Lymphoma
Prostate cancer	
Urethral cancer	
Penile cancer	
Lymph node metastasis	
Other causes of obstruction	
Blood clot	
Stone	
Sloughed papilla	

Obstruction of one or both kidneys results in complex pathophysiological responses, resulting ultimately in a reduction in renal blood flow and glomerular filtration rate. In patients with malignant obstruction, particularly ureteric obstruction not involving the bladder outlet, onset may be gradual with few symptoms. Patients may continue to produce urine in the presence of incomplete or unilateral obstruction. If unilateral obstruction occurs in the presence of a normally functioning contralateral kidney, normal plasma urea and creatinine levels may be maintained. Chronic obstruction will ultimately lead to irreversible renal damage.

Diagnosis

The vast majority of obstructive uropathy secondary to malignant disease will be initially discovered on routine blood testing with an elevated urea and creatinine. To confirm the diagnosis of obstruction, radiological imaging is required.

Ultrasound

Ultrasound is the most frequently used first line investigation. It is quick, non-invasive, readily available and accurate at detecting the presence of a dilated renal collecting system and ureter. Post-micturition residual bladder urine volume indicating bladder outlet obstruction is easily measured. Thinning of the renal cortex indicating longstanding obstruction is also readily quantified using ultrasound.

The key finding in suspected obstruction no matter at what level it occurs is that of hydronephrosis (Fig. 1). Correlation with other clinical findings is required, as although strongly suggestive of obstruction, hydronephrosis is not universally diagnostic. False positives can include longstanding vesicoureteric reflux or parapelvic and renal cysts. It should be remembered that hydronephrosis, following the onset of obstruction may in many cases take time to

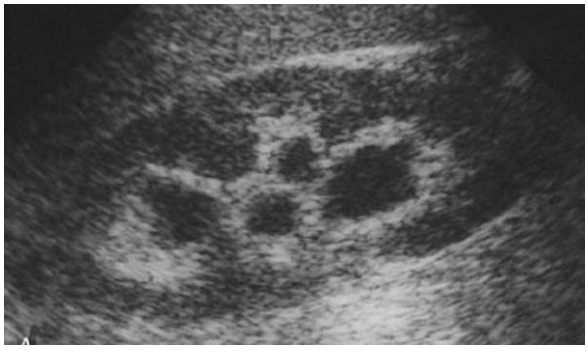

Fig. 1. Ultrasound demonstrating hydronephrosis.

develop [1]. A further measure of possible obstruction on ultrasound can be made with the addition of duplex Doppler scanning. A resistive index is calculated by measuring the velocity of flow within renal arterioles. It is defined as peak systolic velocity minus the lowest diastolic velocity divided by the peak systolic velocity. A value of >0.7 can be used to indicate obstruction [2].

Pyelography

For the investigation of acute obstructive pyelography the use of intravenous pyelography (IVP) is limited due to the nephrotoxicity of the intravenous contrast. However, it does provide useful functional and anatomical information regarding the degree and site of the obstruction (Fig. 2). Retrograde or antegrade pyelography are alternate but more invasive investigations.

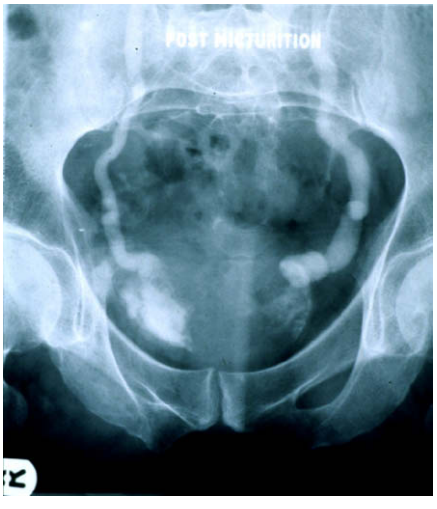

Fig. 2. IVP demonstrating a large bladder tumour partially obstructing both ureters.

Nuclear renography

Nuclear renography can provide useful information regarding the presence of obstruction and also split renal function without the requirement for iodinated contrast agents. Its role in the diagnosis of malignant obstruction is however limited.

Computed tomography (CT) and magnetic resonance imaging (MRI)

Both CT and MRI are accurate at demonstrating the presence of hydronephrosis. The use of contrast agents in both modalities and the cross sectional images obtained also allows evaluation of the nature of the obstructing lesion in many cases. The ability to asses the extent of local malignant disease and detect metastasis mean that these imaging modalities are more frequently used in disease staging.

Treatment

The treatment of malignant obstructive uropathy will depend on the patient and the nature and extent of the obstruction. In a minority of patients with advanced malignancy it may not be appropriate to carry out upper tract drainage if the prognosis is very poor. In the majority, however, obstructive uropathy may be the first presentation of a malignant disease or a sign of disease recurrence or progression following previous treatment.

Patients with significant pain, associated particularly with acute onset of obstruction, should be treated with caution with certain classes of analgesics. Non-steroidal anti-inflammatories inhibit synthesis of prostaglandins. Prostaglandins play an important role in maintaining renal blood flow, particularly in the presence of volume depletion. Their use should be avoided in the presence of significant renal impairment. Caution should also be exercised with patients taking angiotensin converting enzyme (ACE) inhibitors or opioid analgesics.

Hyperkalaemia

Hyperkalaemia caused by obstructive uropathy can induce potentially life threatening cardiac arrhythmias. Often it may require medical treatment prior to carrying out an attempted urine drainage procedure. It occurs as a result of the obstructed kidneys inability to excrete potassium, the raised serum potassium reducing the resting membrane potential of myocardial cells making them unstable and prone to arrhythmia. If the potassium rises above 6.5 mmol/L it can be potentially life threatening, although if the onset is

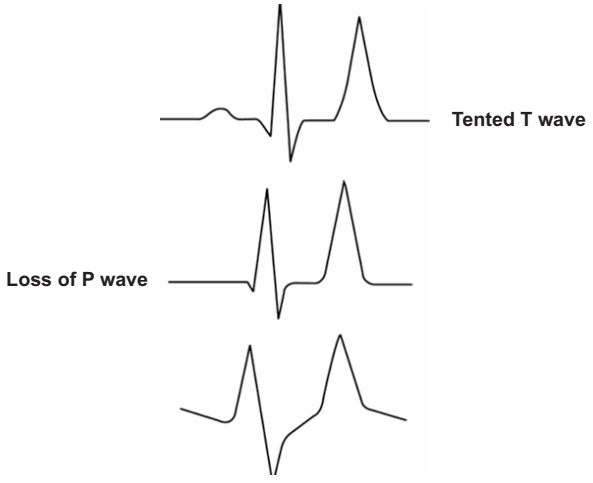

Fig. 3. Characteristic electrocardiogram changes induced by raised serum potassium include lengthening of the PR interval, increased QRS width and "tenting" of T waves. As hyperkalaemia worsens P waves disappear and the QRS complex merges with the T waves in a life threatening sine wave pattern.

gradual some patients may tolerate much higher serum levels.

If the serum potassium is elevated >6.0 mmol/L an ECG is done to look for cardiac changes (Fig. 3). If ECG changes are seen, 10 mL of calcium gluconate (10%) is given intravenously over 2 minutes. This increases the threshold potential of the cardiac myocytes and lasts for 30–60 minutes.

Insulin when administered with glucose can effectively lower potassium by driving extra cellular potassium into the cells. 10–20 units of insulin are added to 50 mL of 50% glucose and administered intravenously, the effect lasting up to six hours. Other drugs with similar, although less predictable effects, include nebulised β-adrenergic agonists such as salbutamol and the alkalinating agent sodium bicarbonate. Elimination of potassium may also be achieved via the gastrointestinal tract through the administration of chelating agents.

These medical therapies will usually allow enough time to affect a urine drainage procedure to allow urine excretion of retained potassium to begin. Occasionally when these conservative measures are not effective, a short period of haemodialysis may be required. Other indications for dialysis include volume overload, severe acidosis, pericarditis and symptomatic uraemia.

Relief of obstruction

Lower tract or bladder outlet obstruction can be easily treated by placement of urethral or suprapubic catheter. Where the obstructing lesion originates at or above the level of the vesicoureteric junction, upper tract drainage is carried out either by radiologically guided percutaneous insertion of nephrostomy tube via the lumbar approach or by endourological insertion of a double J stent.

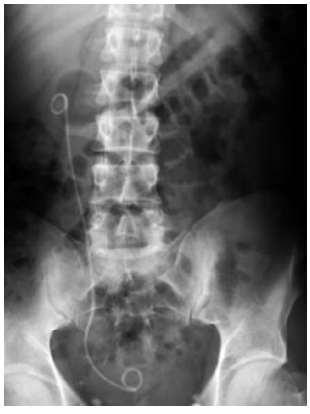

Fig. 4. Abdominal x-ray confirming position of JJ stent.

The choice of which procedure is most appropriate will depend on the clinical presentation and underlying aetiology of malignant obstruction. In patients with significant coagulopathy requiring urgent drainage e.g. patients taking warfarin, retrograde stenting is the procedure of choice (Fig. 4). Dependent on the malignant process however, stent insertion may not always be technically feasible. External ureteral compression secondary to malignancy e.g. ovarian cancer, may contribute to a failure rate of ureteral stents to relieve compression of between 42–54% [3,4]. It would appear to have more long term success for intraluminal malignant obstruction e.g. ureteric TCC. [4]

Percutaneous nephrostomy insertion is advocated by many as the drainage procedure of choice in the presence of malignant obstruction, particularly if co-existent infection proximal to the obstruction is present. It can be carried out under local anaesthetic with ultrasound guidance and conversion to ureteric stent via the antegrade route is also easily achieved later if required. It is not without problems however as it can be technically challenging in the absence of gross hydronephrosis or in the obese patient. In patients who are being considered for chemotherapy, internal ureteric stents are preferred to nephrostomy drainage prior to the start of treatment due to the lower risk of infective complications.

Urinary tract infection

Introduction

The urinary tract is the most common site of infection in humans. The pathogenesis involves bacterial invasion and subsequent induced inflammatory response

which result in a variety of symptoms and signs dependent on the site of infection. Disruption of normal defense barriers coupled with reduced immunity lead to urinary tract infection in the cancer patient. Patients with concomitant obstruction particularly in the presence of immuno-compromise may rapidly become critically ill therefore timely relief of obstruction is of paramount importance.

Pathogenesis

In the healthy individual, virulence factors possessed by the common uropathogens are required to cause significant infection. In the immuno compromised patient, normally innocuous bacteria are capable of causing significant infection and uropathogens which normally cause relatively benign infections are capable of causing significant sepsis and mortality. The presence of a foreign body such as urethral catheter will universally result in bacterial colonization of the catheter if left in for more than a few days. Colonisation can lead to infection in an immunocompromised patient.

The most common source of bacterial infection are bowel flora which gain access to the urinary tract via the urethra ascending into the bladder. Perineal soiling and insertion of urethral catheters significantly increase the rate of infection. Bacteria are capable of infecting the urinary tract via haematogenous spread but this is much less common.

Bacteria which commonly cause urinary tract infection possess a variety of factors which increase their virulence and ability to cause infection. Fimbriae or pili which are finger like projections on bacterial surface mediate adhesion to components of urothelial cells. Protease toxins secreted by bacteria are capable of damaging the urothelial surface allowing bacterial invasion. Other bacterial enzymes may increase the urine pH creating a more favourable environment in which bacteria will flourish.

Host defense

Several factors play a role in host defense against infection of the urinary tract. Probably the most import physiological defense factor relates to normal frequent micturition which flushes out bacteria which have gained entry to the bladder or urethra. Pathological conditions causing obstruction prevent the complete bladder emptying which markedly increases the rate of urinary tract infection. In addition complete eradication of bacteria in the presence of significant residual urine volumes is nearly impossible. For this reason, infection coupled with urinary tract obstruction posses a particular risk in the cancer patient. Other important host defense mechanisms include urine acidity, osmolality, urine urea and secreted urine factors such as TammHorsfall glycoprotein.

Diagnosis

The clinical manifestation of urinary tract infection will depend on the site and severity of infection. Simple cystitis, the commonest infection results in symptoms of urinary frequency, dysuria and suprapubic discomfort. Upper tract infection involving the renal parenchyma (pyelonephritis) will usually manifest with systemic features such as pyrexia, flank discomfort, vomiting and occasionally rigors. Immunocompromise or upper tract obstruction can lead to severe life threatening sepsis with hypotension, systemic inflammatory response syndrome and multiorgan failure. More serious upper tract infections include emphysematous pyelonephritis, renal abscesses and pyonephrosis.

In the male patient, local infection of the prostate known as acute prostatitis usually results in perineal discomfort which may radiate to the back, lower abdomen and rectum. Pyrexia is normally present but the presence of urinary symptoms are variable. Local infection of the male external genitalia is usually easily diagnosed with pain and swelling of the affected region – although diagnostic confusion can arise with testicular torsion if the history is short.

Urine collection

The diagnosis of most infections of the urinary tract will involve the collection of a urine sample for analysis by both direct and indirect methods. Identification of the causative organism is of prime importance. The correct technique of urine collection will minimize the possibility of contamination leading to diagnostic confusion. Suprapubic aspiration of urine offers the lowest risk of contamination – though clearly this is inappropriate in the majority of cases. In circumcised men, no preparation is required prior to the collection of a midstream urine specimen. In women and uncircumcised men, retraction of the labia or foreskin and a simple saline swab wash can reduce contamination risk.

If sending a collected urine sample for culture, it should be cultured immediately or stored in a refrigerator to prevent bacterial growth of the small number of contaminating bacteria which inevitably will be present.

Urinalysis

An initial direct (microscopy) and indirect (dipstick) examination of collected urine samples may suggest a diagnosis with confirmation achieved by urine culture of the infecting organism. Dipstick reagent strips which use chemicals to detect nitrites (converted from urine nitrates by bacteria) and leukocytes through detection of leucocyte esterase activity are 70% sensitive and 80% specific for infection when compared with urine culture [5]. Direct urine microscopy may confirm the presence of white blood cells, red blood cells and bacteria.

Urine culture

Urine culture should be carried out immediately following collection or the specimen refrigerated. After overnight incubation the number of colony forming units (cfu) is estimated per millilitre of urine. Historically a value of 10^5 colonies was considered likely to represent significant infection and is often used by laboratories to confirm infection [6]. This value should not be used didactically however, as around 30% of women with symptomatic urinary tract infections will have 10^2 to 10^4 cfu/ml of urine, therefore lower counts should be deemed significant in the presence of symptoms [7]. Conversely perineal or foreskin soiling can lead to contamination and false positive results. The presence of pyruria or red blood cells should help in the diagnosis.

Classification

Infection may be classified as uncomplicated or complicated. Uncomplicated infections occur in healthy patients with urinary tracts which are functionally and structurally normal. Complicated infections are associated with factors which make infection more likely, difficult to treat and potentially more serious. Such factors include male gender, old age, diabetes, immunosuppression, indwelling catheter, urinary tract instrumentation and hospital acquired infection.

Imaging

In the majority of uncomplicated urinary infection cases radiological imaging is not required. If complicating factors are present imaging to exclude anatomical abnormalities or obstruction (hydronephrosis) can be quickly achieved with ultrasound.

Treatment

The aim of treatment is to eliminate bacteria from the urinary tract. The ability to do this will depend on the site of infection, the infecting organism and a variety of host related factors. Different antibiotics achieve differing serum and urine concentrations following administration. Successful treatment is dependent on achieving sufficient minimal inhibitory concentration in urine to achieve bacterial eradication. In the presence of bacteraemia or in parenchymal infection of the kidney or prostate, sufficient blood levels are essential. Decisions regarding the antibiotic of choice depend on the likely pathogen, the site of infection, the severity of infection and local patterns of antibiotic resistance.

Organisms and antimicrobials

The most common urinary tract pathogens are bowel flora derived Gram-negative facultative anaerobes. In uncomplicated urinary tract infection, the most common infecting organism is Escherichia coli which accounts for over 70% of infections. Other common Gram-ve infecting organisms include proteus mirabilis, klebsiella aerogenes and serratia marcescens. Gram positive organisms which cause urinary tract infections include Enterococcous faecalis and staphylococcus saprophyticus. Anaerobic bacteria rarely cause infections on their own but can contribute to polymicrobial infections related to abscess formation.

Fungal infections are extremely uncommon in the community. However, they are frequently seen in hospitalized patients with indwelling catheters. Tuberculosis infection of the urinary tract is rarely seen in western countries however it should be suspected in the presence of sterile pyuria or unexplained persistent pyrexia.

The common antimicrobials used in the treatment of urinary tract infection have a variety of mechanisms of action. These include Beta-lactams (penicillin's and cephalosporins) which inhibit bacterial cell wall synthesis, aminoglycosides which inhibit ribosomal protein synthesis, Trimethoprim which inhibits DNA folate metabolism and quinolones which inhibit bacterial DNA gyrase, an enzyme which contributes to bacterial DNA coiling and replication.

A table of the common sites of urinary tract infection, infecting organism and appropriate antibiotic treatment is outlined below (Table 2).

Atypical or resistant organisms

An increasing clinical problem in many western hospitals has been the emergence of bacteria with resistance to traditional antibiotic regimens. Meticillin Resistant Staphylococcus Aureus bacteria (MRSA) was first identified in the 1960's and now causes a significant

Table 2
Common urological infections and their treatment

Infection	Common organism	Antimicrobial and duration
Simple cystitis	E. coli (70–90%) Klebsiella, Proteus, Enterococcus, S. saprophyticus	Quinolone or Trimethoprim for 3 days
Complicated cystitis e.g. male, diabetes, symptoms >7 days	As above	Quinolone, trimethoprim or cephalosporin for 7 days
Complicated cystitis – systemically unwell	As above	Parenteral antibiotics Ampicillin and gentamicin, 3rd generation cephalosporin Complete course with oral antibiotics 14–21 days
Pyelonephritis	As above + occasionally S. aureus	Moderately ill – oral trimethoprim or quinolone 10–14 days Unwell – parenteral amicillin and gentamicin, quinolone or 3rd gen cephalosporin
Prostatitis	As above + St. epidermididis, St. saprophyticus Bacteroides	Quinolone 4–6 weeks
Epididymo-orchitis	Older ages – common uropathogens Younger sexual active – N. gonorrhoea, Chlamydia	Ofloxacin 2 weeks

number of hospital acquired infections. Patients at particular risk are those with immunocompromise due to systemic illness or those who have undergone surgery. If systemic sepsis occurs it carries a particularly grave prognosis. The most commonly used antibiotics used to treat MRSA include Vancomycin, Teicoplanin and linezolid.

Extended Spectrum Beta-Lactamases (ESBL) are enzymes which have developed resistance to penicillin or cephalosporin antibiotics. The enzymes are most commonly produced by the enterobacteria, e.coli or klebsiella. They can cause opportunistic infection in immunocompromised patients and can also spread easily through sub-optimal hygiene. They are resistant to most cephalosporins and usually require treatment with the carbapenem class of antibiotics.

Fournier's gangrene

Necrotizing fasciitis occurring around the male genitalia is termed Fournier's gangrene. It is characterised by a fulminant rapidly progressive gangrene which is frequently life threatening. It may originate in the skin, from the urethra or rectal regions, where perineal glands have been shown to be the cause in certain cases secondary to colorectal malignancy [8]. Bone marrow malignancies including myelocytic, non lymphoid and myeloblastic leukemia [9] have been implicated as a cause in a proportion of cases. Other medical co-morbities which are frequently seen include diabetes, obesity, steroid use and immunosuppression.

Pathophysiology

Pathomnemonic of the disease is necrosis of the superficial and deep fascial planes with a polymorphonuclear infiltrate with bacteria and air present within the tissues. Multiple organisms which are usually involved lead to the release of enzymes and toxins which result in coagulation of a number of small blood vessels. The thrombosis and resultant hypoxemia allows anaerobic bacteria to flourish, in turn producing enzymes such as collagenase which leads to digestion of fascial barriers and rapid extension of infection. The presence of tissue necrosis combined with infection invariably leads to severe systemic sepsis if left untreated.

Clinical presentation

Patients characteristically present with intense pain, tenderness and oedema of the affected tissues. Bronzing of the skin is the earliest sign but tissues become dusky and crepitus develops leading to clinically obvious gangrene and purulent drainage (Fig. 5). The spread of infection characteristically follows certain fascial planes not infrequently advancing onto the

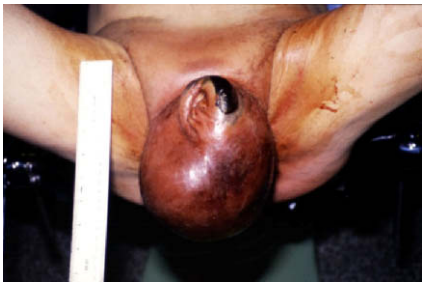

Fig. 5. Fournier's gangrene

abdominal wall and onto the thigh. The scrotal contents, penile corpora, urethra and spermatic cord are rarely affected.

Treatment

The mainstay of treatment is aggressive re-section of affected tissues preceded by a short period of resuscitation and administration of broad spectrum antibiotics. Hyperbaric oxygen has been shown in some studies to bring some benefit but should not delay surgery if necessary [10]. Surgical re-section can be extensive and may require more than one operation but should attempt to remove all the affected tissue. Colonic diversion, suprapubic catheterization and placement of testis in subcutaneous pockets may be necessary. Skin grafts and flaps may be necessary to cover any skin defect. Overall the prognosis is poor, approaching 50% in many cases.

Antibiotic prophylaxis prior to genito-urinary procedures

Antibiotic prophylaxis is commonly used to prevent infection associated with a variety of genitourinary diagnostic and therapeutic procedures. Certain procedures associated with a high rate of infection mandate obligatory prophylaxis for all patients. Less invasive procedures require prophylaxis in higher risk patients. Ideally prophylaxis should be initiated 30–60 minutes prior to the procedure either as a single dose or in certain cases, continued for a short time after the procedure.

Host factors

Host factors which may increase susceptibility to infection include advanced age, urinary stasis or obstruction, poor nutrition, smoking, malignancy and systemic disease such as diabetes. Indwelling catheters, ureteric stents are quickly colonized with bacteria and may initiate infection when manipulated or changed. Patients with other distant prosthetic implants such as artificial heart valves are also at risk of bacterial seeding during these procedures and more intensive prophylaxis regimes are required.

Uretheral catherisation

Routine prophylaxis is not generally indicated before urethral catheterization. In women, the risk of infection after a single catheterization is between 1–2%. If host factors are present, a single dose of trimethoprim or a fluoroquinolone is all that is necessary. Good evidence is limited, however, a single dose of antibiotic is reasonable in higher risk patients prior to catheter removal.

Transrectal biopsy of prostate

Prostate cancer is most commonly diagnosed by ultrasound guided transrectal biopsies. Not unsurprisingly given the nature of the procedure, antibiotic prophylaxis is necessary in all patients. The definitive regime has not been described. In our department the regime used is i.v. gentamicin 120 mg, flagyl suppository 500 mg and oral ciproxin 500 mg b.d. for 5 days.

Urinary tract haemorrhage

Introduction

Haematuria can be the presenting feature of benign or malignant urological tumours, or as a result of direct invasion of another tumour into the urinary tract. Cancer treatment with radiotherapy or cyclophosphamide may induce hemorrhagic cystitis. Coagulopathies due to the systemic manifestation of a cancer or as a result of treatment may also produce significant urinary tract haemorrhage.

Resuscitation and clot retention

The initial management of any patient presenting with significant haematuria involves an assessment of haemodynamic status, coagulation profile and if necessary fluid resuscitation. Most significant cases require the passage of a large bore 22–24ch irrigating catheter. A bladder syringe can be used to remove smaller blood clots via the catheter. If the patient's bladder contains significant residual blood clot which cannot be removed via the irrigating catheter, this may require a cystoscopy and clot evacuation under anaesthetic. In the majority of cases, an initial attempt of continuous bladder irrigation via a 3-way catheter will in most cases at least temporarily stop bleeding without the need for more invasive intervention.

Table 3
conservative methods for treating significant haematuria originating from the bladder

Treatment	Mode of action	Response rate	Complications
Intravesical alum 1% [18] Aluminium ammonium/ potassium sulphate	Protein precipitation, decreased capillary permeability, contraction of intercellular space, vasoconstriction	60–95%	Mild Aluminium toxicity, lethargy, confusion, acidosis seizures
Intravesical formalin [19]	Protein precipitation – occlusion of capillary bed	>80%	Significant Bladder fibrosis/contraction, incontinence, ureteric reflux, ATN, bladder rupture, small number of deaths reported
Hydrostatic pressure [20]	Hydrostatic pressure to 10–20cm H_2O above diastolic pressure	50–99% tends to be short-lived response	Significant Bladder rupture Pulmonary embolus
Embolisation [21]	Embolisation of internal iliac artery or super selective embolisation of vesical arteries		Significant Bladder gangrene Gluteal pain if superior gluteal artery occluded
Hyperbaric oxygen [22]	Reverse radiation induced vascular damage. Induce neovascularistion	70–80%	Mild Decompression, sickness

Bladder cancer

Haematuria is the primary presenting symptom in the majority of patients with bladder cancer. Transitional cell carcinoma (TCC) of the bladder or invasion of the bladder wall by other pelvic malignancies can cause significant haematuria. In addition, bladder cancer treatment can induce intractable haemorrhagic cystitis.

Radiation

Irradiation of the bladder in the treatment of bladder or other pelvic malignancy may result in cystitis and haemorrhage. Radiotherapy results in small vessel endarteritis leading to vessel occlusion, cellular hypoxia and necrosis which may lead to fibrosis and ulceration [11]. Radiation cystitis has a reported incidence of 2–47% after radical radiotherapy treatment of bladder cancer [12]. It is also seen following irradiation of other pelvic malignancies including prostate (9–21%) and cervix (3–6.7%) [13,14]. The majority of cases are self limiting however radiation cystitis may occasionally lead to severe life threatening haemorrhage. Interestingly hypofractionated low dose radiation can be used to treat troublesome haematuria in patients with muscle invasive bladder cancer [15].

Cyclophosphamide

The alkylating agent Cyclophosphamide is used in the treatment of malignant B-cell lymphoma and certain solid tumours. Acrolein a metabolite of cyclophosphamide is excreted in the urine, causing oedema, ulceration and haemorrhage [16]. Haemorrhagic cystitis is a well described complication of cyclophosphamide treatment with an incidence of 2–40% [17].

Treatment

In the majority of cases bleeding caused by bladder cancer or cancer treatments may be controlled by catheter or cystoscopic evacuation of residual clot from bladder followed by continuous bladder irrigation. If this fails to control the bleeding cystoscopy and fulguration or laser ablation of any bleeding points is carried out under anaesthetic. If unsuccessful a number of other conservative treatment strategies have been described (Table 3). Ultimately, if significant haematuria fails to respond to these conservative measures the only option may be palliative cystectomy and urinary diversion.

Prostate cancer

Most patients with prostate cancer do not suffer from problematic haematuria. However if advanced prostate cancer invades the base of the bladder or urethra it may occur. Radical radiotherapy treatment for prostate cancer may result in haemorrhagic cystitis and significant bleeding. Historically, as an initial step a palliative TURP was carried out in an attempt to control bleeding however, there is little evidence to support this practice. Other possible strategies are outlined in Table 4.

Table 4
Methods to control haematuria secondary to malignant prostatic bleeding

Treatment	Evidence
Hormone therapy	5α-reductase inhibitors have been used effectively in haematuria in benign prostatic hypertrophy [23] The effect in prostate cancer is unknown Antiandrogens reduce prostate vascularity in animals [24]
Radiotherapy	Evidence mainly for use in bladder cancer – see below One study demonstrated benefit [25]
Antifibrinolytics	Tranexamic acid – plasminogen activator inhibitor. Used in menstrual bleeding and orthopaedic surgery, benefit demonstrated following TURP [26]
Potential novel treatments	Novel treatments include – high-intensity focused ultrasound (HIFU) and cryotherapy [27]

Kidney cancer

Renal carcinoma bleeding can manifest with bleeding into the renal collecting system resulting in haematuria or clot colic/ureteric obstruction. If the bleeding is extra-renal most will present with flank pain. The management will depend on a number of factors including severity and recurrence of bleeding and symptoms, the stage of disease and the patients overall fitness.

In patients with localised disease, in most cases radical nephrectomy will resolve the symptoms and cure the patients. Patients with metastatic disease should also be considered for nephrectomy. Randomized trials have demonstrated a survival advantage of cytoreductive nephrectomy when combined with immunotherapy for patients with metastatic renal cell carcinoma [28,29].

In patients with symptomatic bleeding and extensive metastasis, or those with significant medical co-morbidity, tumour embolisation may be sufficient to palliate bleeding without the need for open surgery in the majority of cases [30–32].

Penile cancer

Penile cancer characteristically metastasises to the inguinal lymph nodes. If left untreated they tend to ulcerate and erode into nearby tissues. Erosion into the femoral vessels can lead to massive haemorrhage and is usually terminal in penile cancer.

Coagulopathies

Significant coagulopathies directly related to urological cancers are uncommon. Rare examples include the paraneoplastic syndrome of non-metastatic hepatic dysfunction or Stauffer's syndrome associated with renal cancer which may result in a prolonged prothrombin time [33]. More commonly, coagulopathies are caused by chemotherapeutic agents affecting bone marrow production of platelets leading to thrombocytopaenia. Bone marrow replacement with tumour is also possible and results in coagulopathy. Thrombocytopaenia typically occurs between 6–10 days after treatment and may require temporary platelet transfusion.

Priapism

Priapism is defined as a pathologically persistent erection lasting longer than 4 hours in the absence of sexual stimulus [34]. It is a urological emergency which without prompt treatment may result in long term permanent corpora cavernosa fibrosis and impotence [35].

There are two types of priapism, low flow ischaemic and high flow non-ischaemic. Low flow priapism is characterised by absence of cavernosal blood flow preventing venous drainage of the penis and detumescence and is associated with pain due to ischaemia of the corporeal tissue. High flow priapism which is less common and also painless, is caused by uncontrolled inflow of blood to the cavernosal tissue. In contemporary urological practice the most common cause of priapism is the result of increased usage of intracavernosal pharmacotherapy for treatment of erectile dysfunction. However malignancy is a causative factor in certain cases.

Priapism has a bimodal age distribution with peaks at 5–10 years and 20–50 years. In particular haematological dyscrasias such as sickle cell disease and chronic granulocytic leukaemia are a more common cause in the younger age groups [36]. Neurological malignancies with an association with priapism include brain tumours and malignancies causing spinal cord compression. Cancers of the urethra [37], bladder [38], primary and metastatic cancers to the penis [39]. and rectosigmoid tumours have also been associated with priapism. In malignant cases it is

likely that malignant infiltration and occlusion of the corporeal venous outflow is the cause.

Diagnosis

The diagnosis of priapism is usually self evident from clinical examination. In order to manage patients correctly it is important to differentiate between low flow ischaemic and high flow non-ischaemic priapism. Key to the diagnosis is cavernosal blood sampling. The venous stasis of low flow priapism leads to characteristic metabolic changes of hypoxia and acidosis within the corporeal blood (Table 5).

Table 5
cavernosal blood gas analysis in priapism

	Ischaemic (low flow)	Non ischaemic (high flow)	Normal
PO2	<30 mmHg	>90 mmHg	40 mmHg
PCO2	>60 mmHg	<40 mmHg	50 mmHg
pH	<7.25	7.4	7.35

Other basic investigations include full blood picture including white cell and platelet counts. In particular, reticulocyte count should be carried out to screen for sickle cells disease. Doppler ultrasound is accurate at differentially diagnosing causes of priapism with reduced flow in ischaemic priapism and the presence of a fistula or pseudoaneurysm in high flow [40], however is usually not necessary.

Treatment

The treatment of patients with priapism proceeds in a stepwise manner following diagnosis. This is well described in the guidelines of the American urological association [34] summarized in Fig. 6.

For ischaemic priapism the primary step involves insertion of a 19 gauge butterfly needle directly into the corpora cavernosa. Aspiration of blood with or without irrigation with normal saline will achieve success in 30% of cases [34]. Where this fails the next step involves instillation of a sympathomimetic agent directly into the cavernosa leading to contraction of the cavernosal tissue. Phenylephrine is the safest agent and should be diluted in normal saline to a concentration of 100–500 mcg/ML. 1 ml injections are given every 3–5 minutes for up to one hour. All patients should be monitored closely for signs of toxicity such as headache, arrhythmia and hypertension.

When conservative measures fail, a number of surgical operations have been described. They all involve the creation of artificial shunts between the corpora cavernosa either to the glans distally, blood subsequently draining via the corpora spongiosum or proximally to the corpora spongiosum or saphenous vein.

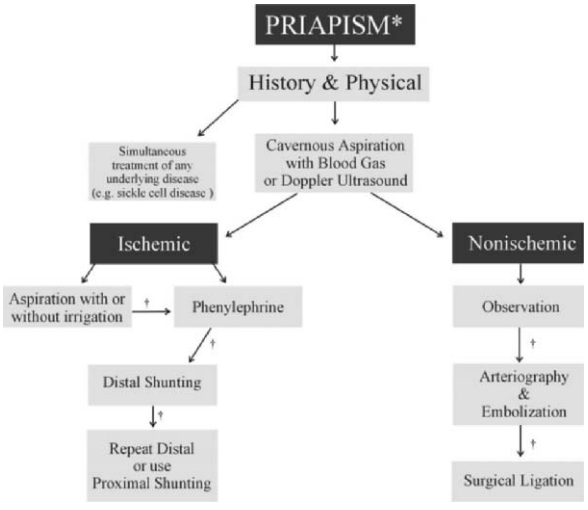

Fig. 6. American Urological association algorithm for management of priapism [34].

For an initial period non ischaemic priapism is usually managed conservatively with observation to allow for spontaneous resolution. In certain cases however, selective arterial embolisation will be required. Patients with resolved priapism should be followed up and counseled regarding the risk of long term erectile dysfunction.

Conflict of interest statement

None declared.

References

1 Jeffrey RB, Laing FC, Wing VW, Hoddick W. Sensitivity of sonography in pyonephrosis: a reevaluation. *AJR Am J Roentgenol* 1985, **144**, 71–73.
2 Rawashdeh YF, Djurhuus JC, Mortensen J, Horlyck A, Frokiaer J. The intrarenal resistive index as a pathophysiological marker of obstructive uropathy. *J Urol* 2001, **165**, 1397–1404.
3 Chung SY, Stein RJ, Landsittel D, *et al.* 15-year experience with the management of extrinsic ureteral obstruction with indwelling ureteral stents. *J Urol* 2004, **172**, 592–595.
4 Yossepowitch O, Lifshitz DA, Dekel Y, *et al.* Predicting the success of retrograde stenting for managing ureteral obstruction. *J Urol* 2001, **166**, 1746–1749.
5 Pfaller MA, Koontz FP. Laboratory evaluation of leukocyte esterase and nitrite tests for the detection of bacteriuria. *J Clin Microbiol* 1985, **21**, 840–842.
6 Kass EH. Asymptomatic infections of the urinary tract, 1956. *J Urol* 2002, **167**, 1016–1019.

7 Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med* 1993, **329**, 1328–1334.

8 Gamagami RA, Mostafavi M, Gamagami A, Lazorthes F. Fournier's gangrene: an unusual presentation for rectal carcinoma. *Am J Gastroenterol* 1998, **93**, 657–658.

9 Faber HJ, Girbes AR, Daenen S. Fournier's gangrene as first presentation of promyelocytic leukemia. *Leuk Res* 1998, **22**, 473–476.

10 Dahm P, Roland FH, Vaslef SN, Moon RE, Price DT, Georgiade GS, *et al.* Outcome analysis in patients with primary necrotizing fasciitis of the male genitalia. *Urology* 2000, **56**, 31–35.

11 Antonakopoulos GN, Hicks RM, Berry RJ. The subcellular basis of damage to the human urinary bladder induced by irradiation. *J Pathol* 1984, **143**, 103–116.

12 Duncan W, Williams JR, Kerr GR, *et al.* An analysis of the radiation related morbidity observed in a randomized trial of neutron therapy for bladder cancer. *Int J Radiat Oncol Biol Phys* 1986, **12**, 2085–2092.

13 Boersma LJ, van den BM, Bruce AM, *et al.* Estimation of the incidence of late bladder and rectum complications after high-dose (70–78 Gy) conformal radiotherapy for prostate cancer, using dose-volume histograms. *Int J Radiat Oncol Biol Phys* 1998, **41**, 83–92.

14 Dewan AK, Mohan GM, Ravi R. Intravesical formalin for hemorrhagic cystitis following irradiation of cancer of the cervix. *Int J Gynaecol Obstet* 1993, **42**, 131–135.

15 Duchesne GM, Bolger JJ, Griffiths GO, *et al.* A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. *Int J Radiat Oncol Biol Phys* 2000, **47**, 379–388.

16 Brock N, Stekar J, Pohl J, Niemeyer U, Scheffler G. Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sufosfamide. *Arzneimittelforschung* 1979, **29**, 659–661.

17 Choong SK, Walkden M, Kirby R. The management of intractable haematuria. *BJU Int* 2000, **86**, 951–959.

18 Ostroff EB, Chenault OW, Jr. Alum irrigation for the control of massive bladder hemorrhage. *J Urol* 1982, **128**, 929–930.

19 Kumar S, Rosen P, Grabstald H. Intravesical formalin for the control of intractable bladder hemorrhage secondary to cystitis or cancer. *J Urol* 1975, **114**, 540–543.

20 Helmstein K. Treatment of bladder carcinoma by a hydrostatic pressure technique. Report on 43 cases. *Br J Urol* 1972, **44**, 434–450.

21 Jenkins CN, McIvor J. Survival after embolization of the internal iliac arteries in ten patients with severe haematuria due to recurrent pelvic carcinoma. *Clin Radiol* 1996, **51**, 865–868.

22 Weiss JP, Mattei DM, Neville EC, Hanno PM. Primary treatment of radiation-induced hemorrhagic cystitis with hyperbaric oxygen: 10-year experience. *J Urol* 1994, **151**, 1514–1517.

23 Delakas D, Lianos E, Karyotis I, Cranidis A. Finasteride: a long-term follow-up in the treatment of recurrent hematuria associated with benign prostatic hyperplasia. *Urol Int* 2001, **67**, 69–72.

24 Kaya C, Ozyurek M, Turkeri LN. Comparison of microvessel densities in rat prostate tissues treated with finasteride, bicalutamide and surgical castration: a preliminary study. *Int J Urol* 2005, **12**, 194–198.

25 Gibbons RP, Mason JT, Correa RJ Jr., *et al.* Carcinoma of the prostate: local control with external beam radiation therapy. *J Urol* 1979, **121**, 310–312.

26 Rannikko A, Petas A, Taari K. Tranexamic acid in control of primary hemorrhage during transurethral prostatectomy. *Urology* 2004, **64**, 955–958.

27 Barrass BJ, Thurairaja R, McFarlane J, Persad RA. Haematuria in prostate cancer: new solutions for an old problem. *BJU Int* 2006, **97**, 900–902.

28 Flanigan RC, Salmon SE, Blumenstein BA, *et al.* Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001, **345**, 1655–1659.

29 Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001, **358**, 966–970.

30 Nurmi M, Satokari K, Puntala P. Renal artery embolization in the palliative treatment of renal adenocarcinoma. *Scand J Urol Nephrol* 1987, **21**, 93–96.

31 Onishi T, Oishi Y, Suzuki Y, Asano K. Prognostic evaluation of transcatheter arterial embolization for unresectable renal cell carcinoma with distant metastasis. *BJU Int* 2001, **87**, 312–315.

32 Kalman D, Varenhorst E. The role of arterial embolization in renal cell carcinoma. *Scand J Urol Nephrol* 1999, **33**, 162–170.

33 Sufrin G, Chasan S, Golio A, Murphy GP. Paraneoplastic and serologic syndromes of renal adenocarcinoma. *Semin Urol* 1989, **7**, 158–171.

34 Montague DK, Jarow J, Broderick GA, *et al.* American Urological Association guideline on the management of priapism. *J Urol* 2003, **170**, 1318–1324.

35 El Bahnasawy MS, Dawood A, Farouk A. Low-flow priapism: risk factors for erectile dysfunction. *BJU Int* 2002, **89**, 285–290.

36 Morano SG, Latagliata R, Carmosino I, Girmenia C, Dal Forno S, Alimena G. Treatment of long-lasting priapism in chronic myeloid leukemia at onset. *Ann Hematol* 2000, **79**, 644–645.

37 Hettiarachchi JA, Johnson GB, Panageas E, Drinis S, Konno S, Das AK. Malignant priapism associated with metastatic urethral carcinoma. *Urol Int* 2001, **66**, 114–116.

38 Guvel S, Kilinc F, Torun D, Egilmez T, Ozkardes H. Malignant priapism secondary to bladder cancer. *J Androl* 2003, **24**, 499–500.

39 Chan PT, Begin LR, Arnold D, Jacobson SA, Corcos J, Brock GB. Priapism secondary to penile metastasis: a report of two cases and a review of the literature. *J Surg Oncol* 1998, **68**, 51–59.

40 Berger R, Billups K, Brock G, Broderick GA, Dhabuwala CB, Goldstein I, *et al.* Report of the American Foundation for Urologic Disease (AFUD) Thought Leader Panel for evaluation and treatment of priapism. *Int J Impot Res* 2001, **13**, S39–S43.