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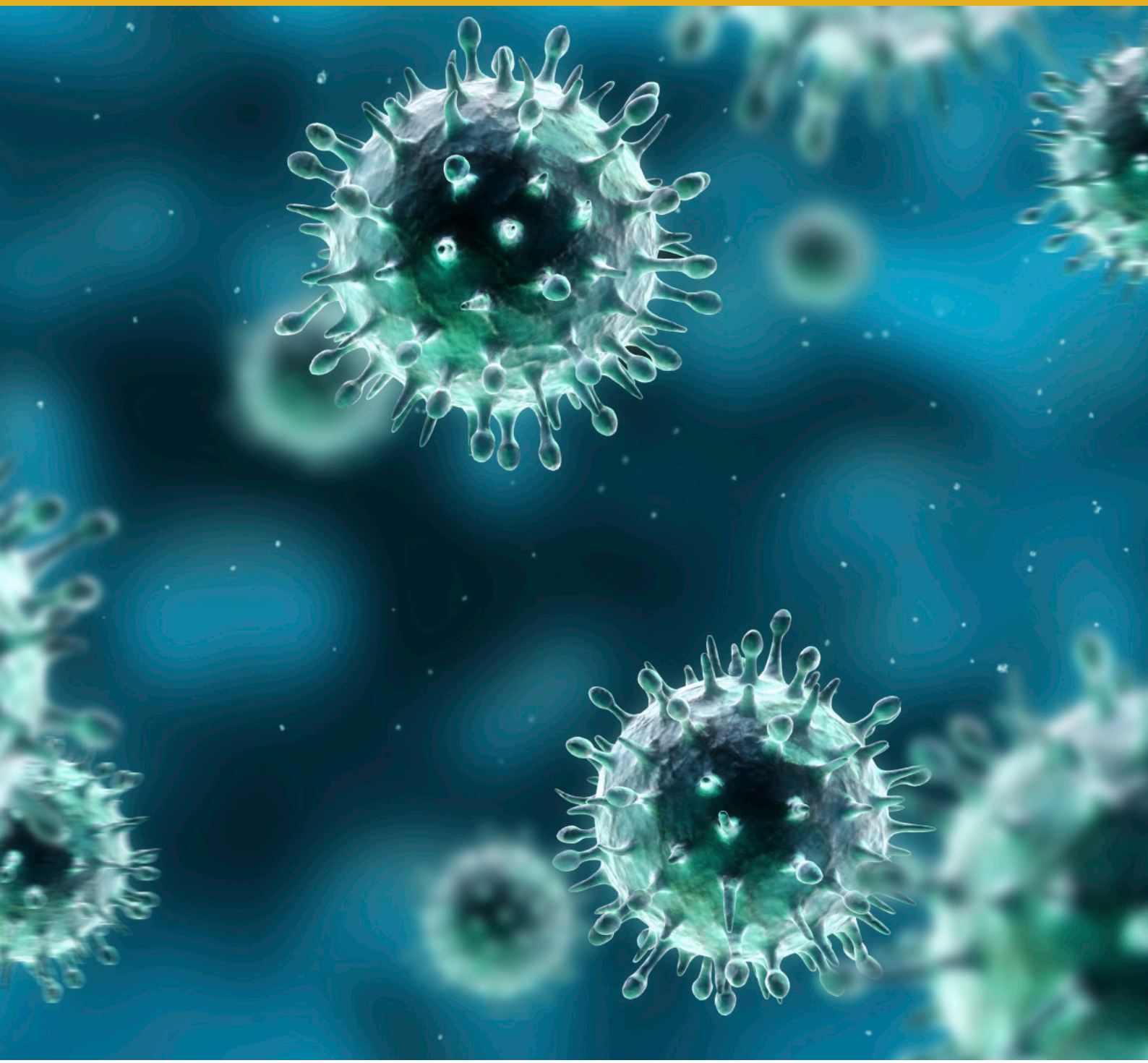

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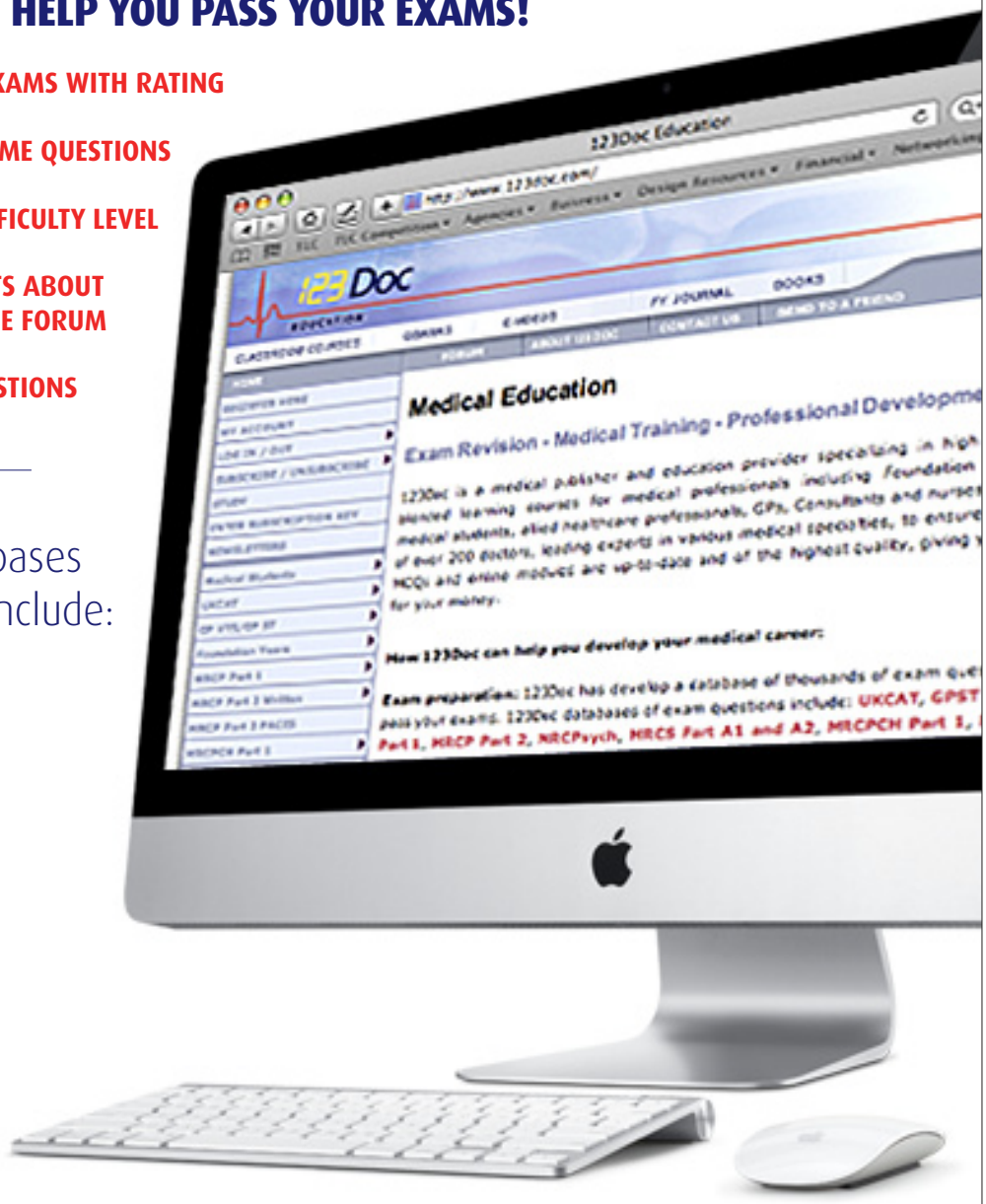

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Volume 9, Issue 5

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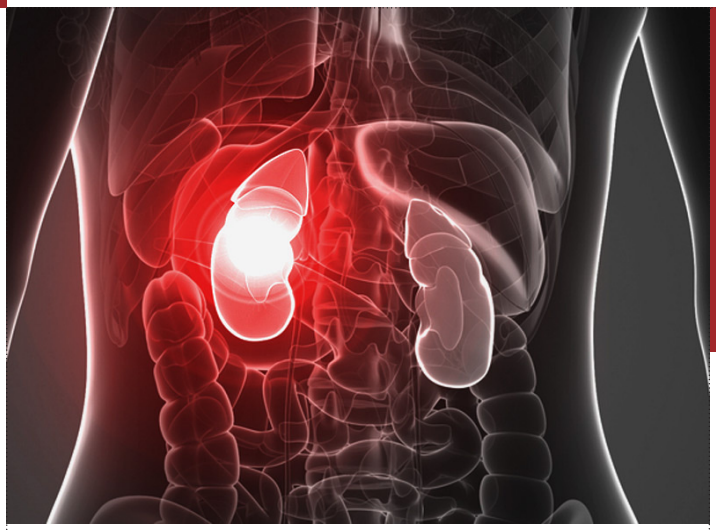
AN UNUSUAL CASE OF ACUTE KIDNEY INJURY

F Trimmer & J Taylor



Abstract

We present an unusual case of severe acute kidney injury in a young diabetic patient. The case highlights the severity and complexity of managing renal failure in obese diabetic patients.

Case presentation

The patient was a 42 year old female with a history of insulin dependent diabetes, hypertension, obesity, and deliberate self-harm. She initially developed Type 2 diabetes in association with obesity, and then subsequently required insulin therapy.

She presented to accident and emergency after being found on the floor by a relative. She was very drowsy with a 3 day history of diarrhoea and vomiting. She had not taken her insulin for 6 weeks, and on arrival was very confused and unwell with an arterial pH of 7.3, lactate 2.1 mmol/l, blood glucose level of 35 mmol/l, ketones of 5, and a severe acute kidney injury (AKI) - urea 27.1 mmol/l, creatinine 482 umol/l, eGFR 9 ml/min/m2 (baseline creatinine 100 mmol/l, eGFR 53 ml/min/m2, 6 months earlier). CRP was 750 mg/l, haemoglobin 13.6 g/dl, white cell count 17.4, platelet count 190, potassium 4.8 mmol/l, and creatinine kinase 354 iu/l (upper limit 190 iu/l).

She became haemodynamically unstable and required intubation, ventilation, inotropes, and admission to the intensive care unit. Intravenous antibiotics for presumed chest sepsis were administered before her urine sample result was available. This showed a mixed growth, mainly E.coli and contaminants, and blood cultures grew Klebsiella. She required haemofiltration for severe AKI (anuria and fluid overload).

An unusual case of acute kidney injury
Patient Management

A computed tomography scan demonstrated "severe left emphysematous pyelonephritis and poor corticomedullary differentiation of the left kidney" (Figure 1). A nephrostomy tube was inserted into the left kidney. This was described as a 'difficult procedure with several passes' and no immediate complications.

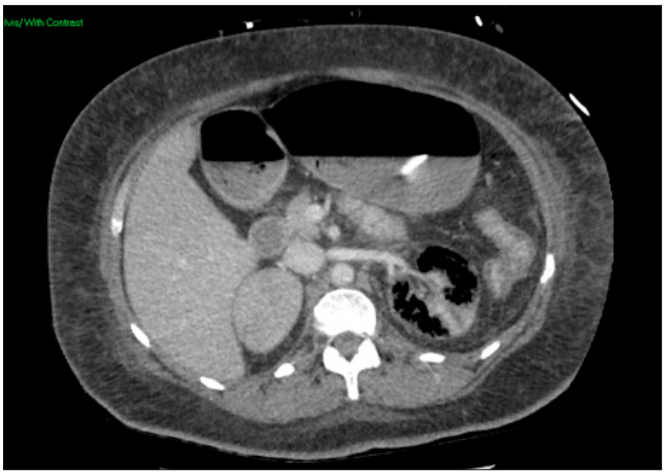


Figure 1: Initial CT demonstrating emphysematous pyelonephritis in the patient's left kidney.

On microbiology advice oral Cefalexin was commenced initially, however 15 days after admission, her inflammatory markers increased and intravenous Piperacillin/Tazobactam and Metronidazole were started. The nephrostomy tube was flushed with minimal output noted. Oral Ciprofloxacin was subsequently commenced 18 days after admission.

She was seen by the urologists and a repeat CT scan undertaken. This showed the nephrostomy tube to be situated incorrectly in the descending colon. Review by colorectal surgeons suggested leaving the tube in situ with surgical removal in 4-6 weeks' time after the tract had epithelialised. An interval left nephrectomy was initially planned, however urology MDT review decided against this unless there were further septic episodes.

AN UNUSUAL CASE OF ACUTE KIDNEY INJURY

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Her renal function recovered to the point where she no longer required dialysis, however she was left in stage 4 CKD with an eGFR of 19 ml/min/m^2.

Discussion

Acute Kidney Injury is seen in 13 – 18% of hospital admissions, with a cost to the NHS estimated at 434 – 620 million per year. 20 – 30% cases are partially or fully preventable, and if preventable cases were reversed, the NHS could save up to 185 million and prevent 12,000 unnecessary deaths (1). It is estimated that 10% of cases of AKI are due to obstruction (2).

Current guidance advises that renal ultrasound should be performed within 24 hours unless the cause of AKI is clear cut and the patient is improving. When there is suspected obstruction and infection (pyonephrosis) diagnosis needs to be made quickly, and ideally renal ultrasound performed within 6 hours, because these patients are at high risk of deterioration and death. There are no studies determining how quickly renal obstruction should be relieved, and the current recommendation is within 12 hours. This may not always be possible if the patient requires stabilisation by dialysis or transfer to another centre where interventional radiology is available (1).

Emphysematous Pyelonephritis is a severe gas-producing necrotizing bacterial infection involving the renal parenchyma and peri-renal tissue. It is potentially fatal and carries a high mortality. The main risk factor is diabetes (80-96% of cases). The main causative bacteria are E.coli, and occasionally Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. It is uncommon for anaerobic bacteria to cause emphysematous pyelonephritis (3,4).

An ultrasound scan is very useful in diagnosing an obstruction and is non-invasive and reliable. A non-contrast CT scan is however the preferred method in this condition, and shows gas formation, the extent of the infection, and can identify any obstruction (5). Initial treatment focuses on resuscitation; correcting electrolyte imbalances and glucose levels; and antibiotics to target gram-negative bacteria. If there is obstruction this must be managed with either a percutaneous nephrostomy or stent, and if there has been extensive renal destruction, a nephrostomy, as these patients may be obstructed due to the pyelonephritis (4).

This case also highlights the difficulties in dealing with young obese diabetic patients with a history of compliance problems. Obesity hinders the ability to gain good vascular access for monitoring and provision of therapy. Our patient defaulted from renal follow up. Her most recent renal function (12 months after her illness) indicates that she has advanced chronic renal failure and is likely to progress towards the need for long term dialysis. Any single episode of AKI doubles mortality risk, increases the likelihood of developing chronic renal failure by almost 9-fold, and the need for future dialysis 3-fold (6).

Multiple choice questions

1. An unwell patient arrives in A&E and is found to have renal failure – creatinine 1007 umol/l, urea 43 mmol/l, and K+ 7 mmol/l. What is the next most important blood test?

1. FBC

2. Blood cultures

3. Blood gases

4. Coagulation

5. CRP

2. A patient presenting with AKI has symptomatic hyperkalemia and ECG changes. The patient has difficult veins. What is the best management strategy?

1. Nebulised salbutamol followed by insulin/dextrose

2. Calcium gluconate followed by insulin/dextrose

3. Calcium chloride followed by insulin/dextrose

4. Calcium gluconate followed by nebulised salbutamol

5. Calcium chloride followed by nebulised salbutamol

3.A patient presenting with AKI is clinically found to be very dehydrated. Their potassium is 7.4 mmol/l, pH 7.1, and BP 90/65. What is your plan for intravenous rehydration for the next 72 hours?

1. Normal saline

2. Plasmalyte/Hartmann's

3. 5% dextrose

4. Colloid starch

5. 1.26% sodium bicarbonate

6. None of the above

AN UNUSUAL CASE OF ACUTE KIDNEY INJURY

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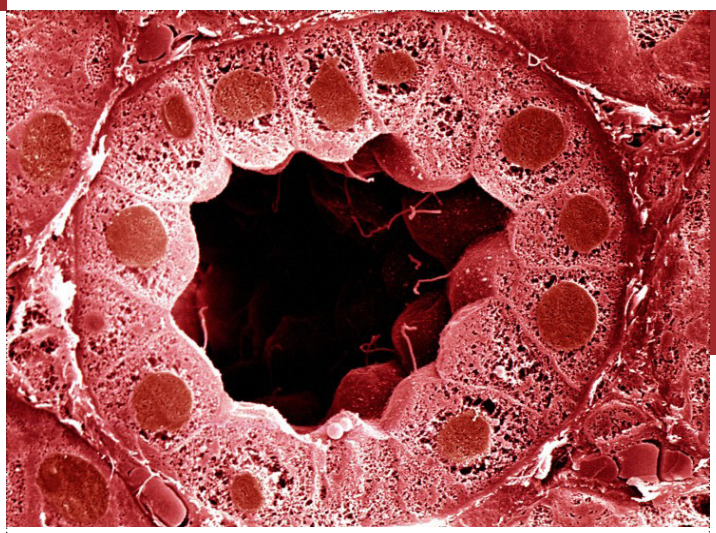

	Na^+ mmol/L	Cl^- mmol/L	K^+ mmol/L	Ca^{2+} mmol/L	HCO_3^- mmol/L	pH	Osmol mosmol/L
Plasma	140	100	4	2.4	24	7.4	280
0.9% NaCl	154	154	-	-	-	5	308
Hartmann's Solution (CSL)	131	111	5	2	29 as lactate	6-7.5	278
Plasma Lyte	140	98	5	-	27 as acetate	4 – 6.5	294
$NaHCO_3$ 1.2%	150	-	-	-	150	8.17	300
Dextrose 5% (50g/L)	-	-	-	-	-		252
8.4% $NaHCO_3$	1000	0	0	0	1000	14	2000
Gelofusine	154	120	-	-	-	7.1–7.7	290

Table: Management of AKI: Type Of Fluids

4.A patient with AKI is initially hydrated with intravenous fluid but remains oliguric. Some peripheral oedema is noted. What is your strategy to manage their fluid status?

1. Continue to rehydrate but slow down the rate of infusion

2. Use oral furosemide

3. Urgent dialysis

4. Stop IV fluids and adopt a "conservative" fluid management strategy

5. Use intravenous furosemide

5. A patient with known stable chronic renal failure requires a CT scan with contrast. Their eGFR is 38 ml/min/m2 and they are known to have Type 2 diabetes. How would you minimise the risk of this patient developing contrast nephropathy?

1. Prescribe either intravenous saline or 1.26% sodium bicarbionate

2. Advise the patient to drink plenty of fluid prior to and after the CT

3. Prescribe intravenous saline and N-acetylcysteine.

4. Prescribe intravenous 1.26% sodium bicarbonate and N-acetylcysteine

5. Prescribe intravenous saline plus intravenous 1.26% sodium bicarbonate

Answers

1. Answer: Blood gases

Hyperkalemia, uraemic inflammation, pulmonary oedema, and acidosis are the most life threatening complications of AKI that usually necessitate acute dialysis.

2. Answer 2

Calcium stabilises cardiac membranes against the toxic effects of hyperkalemia. Usually use 10 – 30 mls of calcium gluconate, or 10 mls of calcium chloride. Calcium gluconate contains a third of the calcium concentration of calcium chloride and can be give peripherally. Follow this with 10 units of short acting insulin in either 250 ml 20% dextrose over 30 minutes, or 500 ml 10% dextrose over 1 hour, or 50 ml 50% dextrose IV via syringe driver over 15 minutes.

Use of more dilute insulin/dextrose combinations may be preferable when the patient is not fluid overloaded, as they are less likely to damage veins which may subsequently be required for arteriovenous fistula formation for long term dialysis if the patient does not recover renal function. Insulin dextrose is effective within 10 minutes, and will reduce serum potassium by 0.5 – 1 mmol/l for a period of 4 – 6 hours which offers time to stabilise and prepare the patient for dialysis if required.

AN UNUSUAL CASE OF ACUTE KIDNEY INJURY

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Do not use nebulised salbutamol if possible. It is less effective and exacerbates any underlying ischaemic heart disease, and may cause arrhythmias. The most common group of patients with AKI are the acute on chronic patients who are more likely to have underlying heart disease. This group are also most likely to die or require long term dialysis.

3. Answer: None of the above

Normal saline has an acidotic pH and theoretically may exacerbate acidosis (thus reducing renal blood flow) if used solely causing a hyperchloremic acidosis. Plasmalyte and Hartmann's contain potassium, and colloid starch based fluids may exacerbate AKI. Current recommendation is to balance a crystalloid fluid regimen according to daily U&Es – remember to request bicarbonate (and chloride) on blood tests.

4. Answer 4

Fluid overload significantly worsens prognosis and increases the risk of multisystem dysfunction. Loop diuretics block sodium transport in the thick ascending limb of the Loop of Henle in animal studies. Sodium is filtered at the glomerulus and passes into the tubular filtrate to get to the Loop of Henle. Human evidence suggests that loop diuretics may not be of benefit, and may delay referral for dialysis and cause ototoxicity through use of high dose infusions rapidly administered.

They also can lead to renal hypoperfusion and excessive diuresis thus exacerbating and prolonging AKI. They should never be used in hypovolaemic patients. Apart from urgent indications for dialysis (hyperkalemia, pulmonary oedema, acidosis, and uremic inflammation), the best time to initiate dialysis is not fully determined from available studies. Early dialysis affords control of fluid overload and uraemia, however cautious delay avoids potential risks (anticoagulation, lines, infections) and may reduce costs if the patient recovers.

5. Answer 1

Patients with low eGFR (< 40 ml/min/m2), with co-morbidity (e.g. diabetes, heart failure), aged over 75 years old, with single kidneys/renal transplant, receiving high doses of contrast or intra-arterial contrast e.g. vascular and cardiac procedures, are at highest risk of AKI following contrast. Nephrotoxic drugs such as ACE inhibitors should be discontinued the day before and the day of the procedure. Intravenous re-hydration with either normal saline or 1.26% sodium bicarbonate offers the best protection against contrast nephropathy.

The best regimen for administering this fluid is not currently known. Shorter regimens e.g. 1.26% sodium bicarbonate 3ml/kg one hour pre-procedure and 1ml/kg for 6 hours post-procedure, may be preferred in outpatients, and where fluid overload needs to be avoided e.g. cardiac failure. The addition of N-acetylcysteine to intravenous saline or 1.26% sodium bicarbonate increases costs, increases the risk of a reaction to N-acetylcysteine, with very little QALY benefit, and is therefore not recommended.

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ANAEMIA IN CHRONIC KIDNEY DISEASE: A PITFALL

A Shrestha & V Suresh

Anaemia in chronic kidney disease: a pitfall
Patient Management

Introduction

Anaemia is common in chronic kidney disease (CKD), and the prevalence increases as the glomerular filtration rate (GFR) progressively falls (1). Using the World Health Organisation criteria for anaemia of haemoglobin (Hb) less than 13 g/dl in men and less than 12 g/dl in women, 15.3% of patients with CKD 3 to 5 were anaemic in a UK population (2). Higher or normal Hb levels are associated with reduced hospitalisation, less severe left ventricular hypertrophy and improved quality of life, up until Hb of 13 g/dl is achieved (where anything above is associated with worse outcome (3)) which makes it important to recognise and treat.

The mechanism of anaemia in CKD is multifactorial, including impaired erythropoietin synthesis, haematinic deficiency and anaemia of chronic disease. Iron deficiency may occur due to reduced absorption from the gut, due to inflammation (4) which is common in CKD. This is thought to be associated with inflammatory cytokines inducing hepcidin transcription, which inhibits iron absorption (5). Functional iron deficiency can also occur due to the use of erythropoesis stimulating agents (ESAs) which deplete the iron pool by increasing erythropoeisis (5), often defined by a transferrin saturation (TSAT) of below 20% (6).

Guidelines such as the National Institute for Clinical Excellence (NICE) recommend the need for replenishing iron stores before commencing ESA therapy in those who are iron deficient (7). However, it is important to remember that iron deficiency is also an important manifestation of gastrointestinal (GI) malignancy and other GI bleeding lesions. Upper GI malignancy was reported as 5.5% and lower GI malignancy 10% in the presence of iron deficiency anaemia (IDA), in one study (8).

Case history

A 68 year old female, with a background of type 2 diabetes mellitus of four years, was referred to the renal clinic in February 2009 with deterioration of her renal function and anaemia. Four months previously, she was admitted under the Urology team with urosepsis and acute kidney injury. Computed tomography (CT) scan of her abdomen revealed a 9 mm left renal pelvic stone with moderate dilatation of the renal pelvis extending down into the upper ureter, and perinephric stranding.

A nephrostomy was inserted and then she went onto antegrade stenting of the left ureter. She was anaemic with haemoglobin (Hb) 7.3 g/l and MCV 81 fl. Iron studies were performed during this time which showed iron 35 µmol/l (reference 14-29), total iron binding (TIB) 9.1 µmol/l (reference 45-72) and ferritin 571 ng/ml (reference 13-150), whilst her C reactive protein (CRP) was 94 mg/l. She was discharged with a creatinine of 132 µmol/l; her baseline had been 87 previously. An outpatient dimercaptosuccinic acid (DMSA) scan of her kidneys showed the left kidney uptake 74% and the right only 26%.

Her creatinine remained in that range and was 136 (eGFR 35 ml/min/1.73m2) at the time of the clinic. Her full blood count showed an Hb of 8.4 g/l with MCV 84 fl, whilst being on oral ferrous sulphate therapy. Her iron studies at the time of clinic showed low iron (7.7 µmol/l) with normal total iron binding (66 µmol/l) and haematinics showed normal folate and vitamin B12 with ferritin level of 16 ng/ml. Myeloma screen was negative. Of note, she had undergone an oesophagogastroduodenoscopy (OGD) five months previously for melaena which showed moderate reflux oesophagitis, with superficial ulcer and severe duodenitis.

She was then escalated to intravenous iron in March 2009. However, her anaemia persisted and haemoglobin actually dropped to as low 7.3 g/l (MCV 75 fl) six weeks later. During this time her renal function was stable and her eGFR even improved, ranging from 41 to 49 ml/min/1.73m2. Ferritin was repeated which was 135 ng/ml, but iron studies were not performed. She was then commenced on weekly erythropoietin injections. Her haemoglobin improved to 9.3 g/l at its highest, but did fluctuate (figure 1).

ANAEMIA IN CHRONIC KIDNEY DISEASE: A PITFALL

A Shrestha & V Suresh

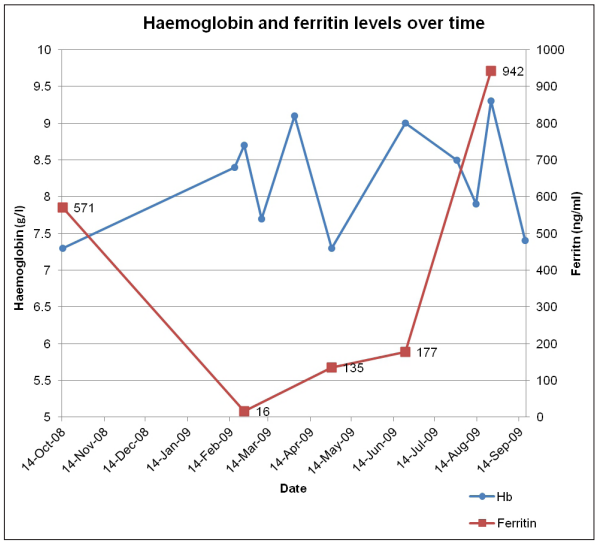


Figure 1: Haemoglobin and ferritin levels. IV, intravenous. EPO, erythropoietin.

Meanwhile, she was being followed up by urologists who organised laser lithotripsy for her renal calculi. She was then admitted for elective left stent removal and ureteroscopic removal of an upper ureteric stone, when her pre-op bloods revealed a haemoglobin of 7.3 g/l and MCV 72 fl. Her procedure was cancelled and she was transfused packed red blood cells.

Her stay was complicated by diarrhoea and fever, so a CT abdomen was performed which unfortunately revealed a caecal tumour (figure 2) with liver metastases. She did provide a retrospective history of erratic bowel habit and weight loss. She required a palliative right hemicolectomy due to subacute bowel obstruction.

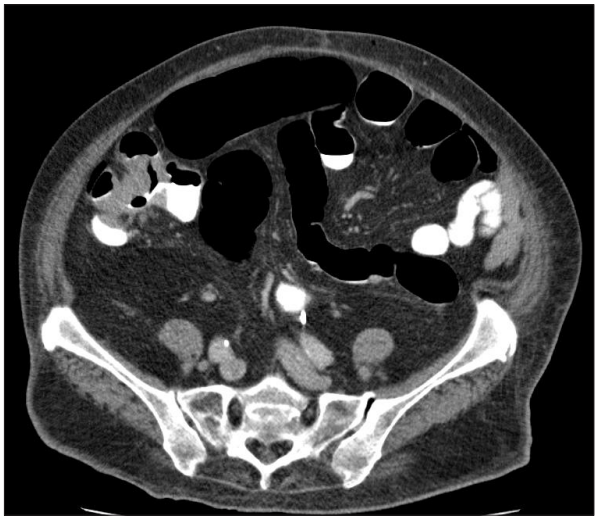


Figure 2: CT abdomen: caecal tumour.

Discussion

We have highlighted how important diagnoses, in this case GI malignancy, may be missed if anaemia, most importantly iron deficiency anaemia, is ascribed to CKD. At the time of presentation to clinic, the patient was likely to be iron deficient with a borderline low ferritin (16 ng/ml) whilst on oral iron replacement.

Whilst there may be a renal element to the anaemia, especially given her history of diabetes which is known to cause anaemia earlier in CKD (9), a thorough clinical assessment would have been necessary at this point and a low threshold for referral for endoscopy. Another opportunity may also have been missed during follow up when her Hb dropped further (7.3 g/l) despite intravenous iron. At this point her ferritin was 135 ng/ml which may have been a response to iron or partly inflammatory. There were no iron studies performed to support replete iron levels.

Establishing iron deficiency can be difficult in CKD, or where there is other inflammatory or chronic disease, due to ferritin rising as an acute inflammatory response. In these cases, the following may be helpful in pointing towards iron deficiency:

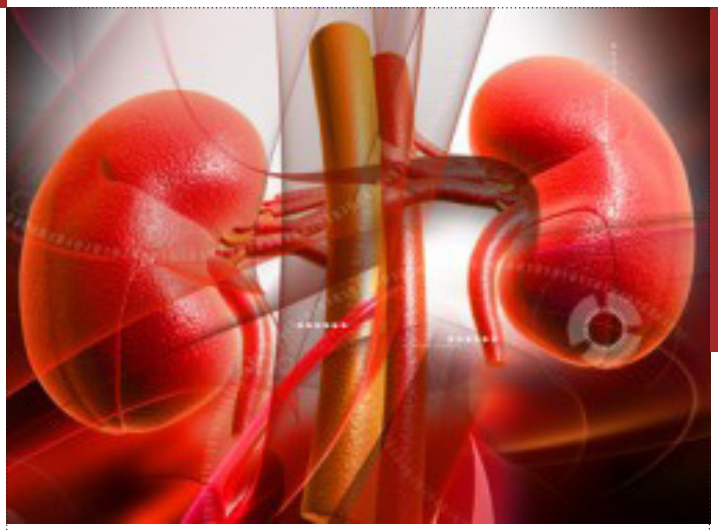
- *performing iron studies, may show low iron levels and raised binding capacity*
- *low transferrin saturation (TSAT) <20%*
- *declining MCV*
- *high percentage hypochromic red cells (PHRC)*
- *repeating a raised ferritin level if it was performed in the context of acute inflammation (eg infection), once the patient has overcome the acute illness*
- *increasing the cut off for ferritin to 50 ng/ml could be considered in inflammatory states, as this may still be consistent with IDA (10)*

The British Society of Gastroenterologists (BSG) recommends investigating iron deficiency with an OGD and colonoscopy, along with a coeliac screen (9). Specifically they recommend:

- *OGD to evaluate the upper GI tract*
- *If OGD is performed as the initial investigation, only the presence of gastric cancer or coeliac disease should deter lower GI investigation*
- *Colonoscopy or double contrast barium enema to evaluate the lower GI tract*
- *Urine dipstick to determine haematuria which may suggest renal tract malignancy*

ANAEMIA IN CHRONIC KIDNEY DISEASE: A PITFALL

A Shrestha & V Suresh



There is a high rate of malignancy even in asymptomatic patients with iron deficiency anaemia. 14 out of 48 (29%) patients, who were men aged 50 or older or post-menopausal women, and who had IDA without any GI symptoms were found to have a GI malignancy (11). Therefore lack of clinical findings in light of strong biochemical evidence of IDA should not deter further investigations.

Key points

1. Various laboratory features such as low TSAT, high PHRC and iron studies should be performed regularly in CKD to investigate anaemia, without solely relying on ferritin

2. The low end of normal reference for ferritin should be increased, for example to 50 ng/ml, in CKD

3. If the above features are present or the anaemia seems disproportionate to the level of renal impairment, referral for GI investigation should be considered

4. Only after GI investigations are performed should possible iron deficiency anaemia be ascribed to CKD.

Anaemia in chronic kidney disease: a pitfall
Patient Management

Best of 5 MCQs

1. Which 2 of the following are suggestive of anaemia of chronic disease?

a) Low iron, low transferrin saturations, high transferrin, low ferritin

b) Low iron, low transferrin saturations, normal transferrin, normal ferritin

c) Low iron, low transferrin saturations, normal transferrin, high ferritin

d) High iron, high transferrin saturations, low transferrin, high ferritin

e) Low iron, high transferrin saturations, low transferrin, low ferritin

2. A 64 year old diabetic with stable CKD 4 (eGFR 25 ml/min/1.73m2) presents with tiredness. The GP performs blood tests which shows Hb 7.8 g/l, MCV 80 fl, ferritin 12 ng/ml, iron saturation 6%. What is the next course of action?

a) He should be reassured (as no red flag symptoms), commenced on oral iron supplement and have his Hb monitored

b) He should be referred for intravenous iron to reach a target ferritin of >200 ng/ml or iron saturation of >20% as per NICE CKD anaemia guidelines

c) He should have erythropoietin as he as anaemia related CKD

d) He should be referred as a 2 week wait for urgent OGD and colonoscopy

e) He should be referred as a non-urgent outpatient to Gastroenterology for consideration of further treatment

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Answers

1. Answer: b) and c)

a) Is diagnostic of iron deficiency. A low ferritin is specific (but not sensitive) for iron deficiency. A low iron level is compensated by more production of transferrin (which binds to iron).

b) Low iron which does not produce high transferrin is consistent with anaemia of chronic disease. The ferritin may be normal or high in acute inflammation

c) As b), but here ferritin is high, suggesting anaemia of chronic disease and/or acute inflammation

d) This is suggestive of haemachromatosis (excess iron). The ferritin level is often in excess of 1000 ng/ml

e) Low ferritin suggests iron deficiency, which should induce higher transferrin level. This is thus an improbable scenario.

2. Answer: d)

a) Whilst he does not have red flag signs (change in bowel habit, per rectal bleeding, weight loss), he has iron deficiency anaemia (low ferritin). This alone produces a greater than 25% risk of GI malignancy regardless of symptoms.

b) The cause of his anaemia needs to be investigated first (eg to exclude blood loss), before his anaemia can be ascribed to CKD. If it is CKD related anaemia, then he will need iron supplementation (intravenous) to achieve sufficient iron stores (ferritin >200) before commencing erythropoietin

c) See b)

d) Correct. He has iron deficiency anaemia and needs urgent OGD and colonoscopy as the risk of malignancy is significant.

e) He needs investigations and should be referred as a 2 week wait

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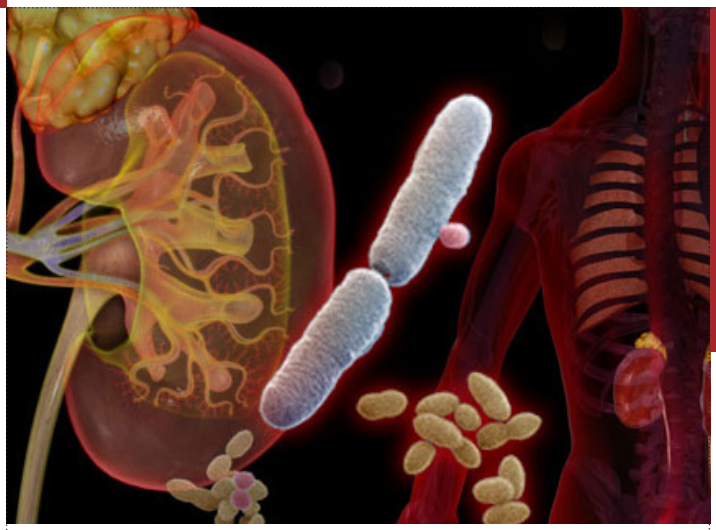
PATIENT MANAGEMENT - CLINICAL ASPECTS OF URINARY TRACT INFECTIONS

L Murray & M Hunter



Patient management - clinical aspects of urinary tract infections
Patient Management

Abstract

Suspected urinary tract infection (UTI) is the second most common indication for antibiotic use in primary and secondary care. Inappropriate antibiotic use is associated with toxicity, emergence of resistant bacteria, selection of pathogenic organisms (such as *C difficile*), and poor clinical outcome. This article reviews the spectrum of disease, diagnosis, and clinical management.

Introduction

UTI is a frequently considered diagnosis in all healthcare settings (1). In general practice, 1-3% of consultations are related to UTI, and one-third of women have had a UTI by the age of 24, (3). In hospitalised patients, UTIs account for 17% of nosocomial infections (4). In the context of high UTI incidence, escalating hospital acquired infection costs, and antibiotic stewardship programmes, National guidelines have been developed to improve diagnosis and treatment (2, 5, 6, 7).

The majority of UTIs are caused by bacteria ascending into the urinary tract via. the urethra. The female urethra is much shorter than the male urethra, and is therefore more likely to become colonised with bacteria (3). The causative organism is typically derived from the patient's bowel flora (Figure 1), but haematogenous or direct infection can occur. Diabetes mellitus, renal calculi, dehydration, sexual intercourse, GU instrumentation, and catheterisation are all established risk factors for UTI (2, 3, 8).

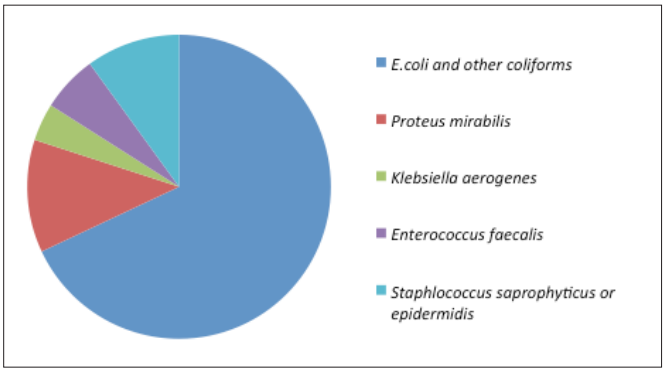


Figure 1: Frequency of bacteria isolated in patients with a UTI.

'Asymptomatic bacteriuria' may be a normal finding in patients with indwelling urinary catheters, diabetes, or elderly patients. Catheterised patients have bacteriuria at a rate of 3 to 10% per day (10). In the absence of symptoms or signs of infection this should not be treated with antibiotics. 'Uncomplicated UTI' is defined as Cystitis or Urethritis in the presence of a normal renal tract and normal renal function (2,5). 'Complicated UTI' is any UTI in a man, or a UTI in the presence a structural abnormality of the urinary tract, acute kidney injury, diabetes mellitus, immunosuppression, or symptoms lasting more than 7 days. 'Complicated UTI' also includes pyelonephritis or bacteraemia (2, 5, 8).

Diagnosis

Typical symptoms of an uncomplicated UTI include increased frequency of micturition, dysuria, suprapubic pain, haematuria or foul-smelling urine (3). However, UTI may present with non-specific symptoms, such as abdominal pain or malaise. In children, fever or failure to thrive may be the only clinical finding. In frail older adults, UTI commonly presents with incontinence or delirium (8, 11).

In a patient with suspected UTI, biochemical urinalysis (also known as a urine dipstick test) is the first-line investigation. Urinalysis can detect leucocyte esterase and nitrite. Leucocyte esterase, an enzyme released by white blood cells, is used to detect pyuria.

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Nitrite, the product of Enterobacteriaceae(such as E. *coli*)-mediated conversion of urinary nitrate, is used to detect significant quantities of these microorganisms. Suspected UTI and a positive dipstick tests (for nitrite and leucocyte esterase) is predictive of a UTI (sensitivity 75%; specificity 82%) (12). If either biochemical test is positive and the patient is symptomatic, antibiotic treatment should be commenced (2, 3, 13, 14).

Sexually transmitted infections, including Chlamydia and Gonorrhoea, can also cause lower urinary tract symptoms. Clinical assessment, diagnosis (including specific nucleic acid amplification testing (NAAT)), and treatment is different from other community acquired UTIs. Doctors should refer to specific guidelines or refer to a sexual health clinic (15).

Further investigation

Urine culture and antibiotic susceptibility testing should be performed in all patients with a suspected complicated UTI, or a relapse of symptoms. This sample must be a mid-stream sample (to minimise contamination from surrounding skin) and taken before commencing antibiotics. Urine culture is used to distinguish contamination (typically a lower number of bacteria) from a potentially significant concentration of pathogenic bacteria (reflecting true bacterial infection of the bladder or urethra). The classification of UTI by these colony forming unit (cfu) semi-quantitative thresholds are summarised in table 1.

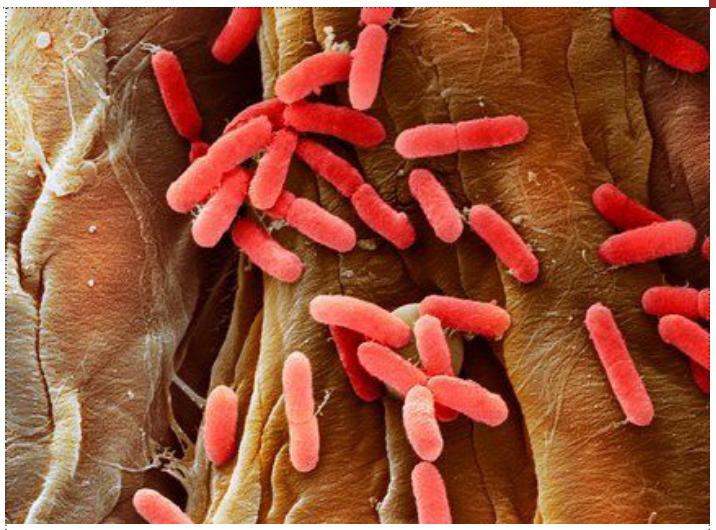
Asymptomatic bacteriuria	Symptomatic Women	Symptomatic men
$\geq 10^5$ colony forming units (cfu) of pathogenic bacteria /mL urine on two occasions	$\geq 10^2$ cfu/mL urine, plus pyuria (>10 WCC/mm^3), **or** $\geq 10^5$ cfu/mL urine	$\geq 10^3$ cfu/mL urine

Table 1 (2, 16)

If a patient presents with loin pain, fever or systemic upset, this suggests a more extensive infection, such as pyelonephritis (3). If the patient has a systemic inflammatory response syndrome (SIRS) or renal angle tenderness, blood should be drawn for full blood count, renal biochemistry, CRP, and culture. (2, 3).

Catheter associated UTI (CA-UTI) may be difficult to diagnose. In addition to urinary tract symptoms, non-specific clinical features include fever, rigors, delirium, pelvic discomfort, flank pain, and haematuria (7). CA-UTI is defined by clinical suspicion of UTI and 10 (3) cfu/mL of a single species of bacteria in a catheter specimen of urine (7).

Further investigations to consider for patients with a complicated UTI include renal tract ultrasound, CT scan kidneys, ureter and bladder (KUB), or flexible cystoscopy. Ultrasound is sufficiently sensitive to detect large calculi, renal abnormalities, or hydronephrosis. CT-KUB should be discussed with a radiologist. It is a more sensitive investigation for smaller calculi or other renal tract abnormalities. Flexible cystoscopy is performed by a Urology surgeon, and should be considered during the acute admission in a patient with uncontrolled sepsis (and known urinary tract abscess or infected calculi).



Treatment

The treatment of UTIs depends upon the classification. Guidelines for empiric therapy of an uncomplicated or a complicated UTI vary according to local antibiotic resistance patterns.

Asymptomatic bacteriuria should not normally be treated (2). However, if the patient is pregnant, they should receive 7 days of antibiotics, as up to 30% of mothers may develop pyelonephritis. This is associated low birth weight and premature birth (11).

Uncomplicated UTI can be treated in an outpatient setting with oral antibiotics. Trimethoprim or Nitrofurantoin for 3 to 5 days are associated with early clinical cure in 84 to 100% of patients in small comparative trials (5). Patients should notice symptomatic improvement within 36 hours. If urine culture demonstrates a resistant bacteria (e.g. ESBL producing E.coli), the suitability of other oral agents, such as Fosfomycin, should be discussed with a microbiologist. On occasion, the only effective treatment for multi-drug resistant bacteria be with IV antibiotics.

Complicated UTIs require investigation and treatment in hospital. Patients with a complicated UTI may have a sepsis syndrome, require investigation and need a longer course of bactericidal antibiotics. Empiric therapy is typically with Gentamicin, Ciprofloxacin or Piperacillin-Tazobactam and will need to be administered for between 5 days and >2 weeks. Indications for longer treatment include bacteraemia, renal tract abscesses, or infected calculi (2, 15, 17). If there is a catheter in situ, this foreign body should be removed or changed as soon as possible.

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Although there are a plethora of clinical guidelines regarding diagnosis and treatment of UTIs, this review summarises the best available evidence. On-going education of medical and nursing staff is important to ensure early diagnosis & treatment, and the judicious use of antibiotics.

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DIARRHOEA IN THE RETURNED TRAVELLER

A Rashid & MBJ Beadsworth

Diarrhoea in the returned traveller
Patient Management

Abstract

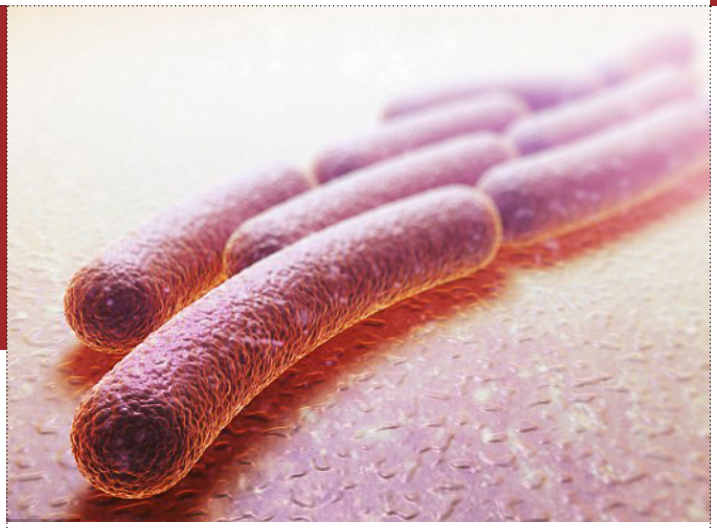
With increasing travel, worldwide from the UK, travel related pathologies increase in importance. Before a travel related diagnosis can be made, an appropriate history of travel is vital. We highlight, both reasons why and how to undertake an appropriate travel history. Furthermore, we discuss aetiology, and management of travel-related diarrhoea and in particular we focus on shigellosis, its pathophysiology, and recent changes in anti-microbial management.

Introduction

It is said that travel broadens the mind, but loosens the bowels. Geo-sentinel surveys echo the truth of this saying by revealing diarrhoea as one of the commonest clinical presentations in the returned traveller - significantly associated with visits to the Indian subcontinent (1). International tourist arrivals continue with virtually uninterrupted growth (2), with increasing rates of travel also holding true for the UK holiday-maker (3). Assessing and managing travel related diarrhoea becomes more important and complex.

Recognition is the first step and requires a detailed travel history, particularly since a traveller can return with any communicable disease. Unfortunately, a recent study in the North West of England revealed only 19.7% of travellers in acute medical units underwent a travel history (4). Knowing which of your patients are travellers is vital, currently highlighted with the on-going Ebola epidemic. In order to form a complete differential list, it is critical to ascertain environmental exposures according to where, when and why the patient travelled.

In this article we will review the diagnosis, investigations and management appropriate for diarrhoea in the returned traveller, with an exploration of the main causes. With travel to the Indian sub-continent being particularly associated with diarrhoea, we include a particular focus on shigellosis, which can be more complex to treat given increasing antimicrobial resistance.



Diagnosis

Traveller's diarrhoea is diagnosed by:

- *the passage of three or more loose-to-watery stools in a 24 hour period*
- *beginning during or shortly after a period of foreign travel (usually within the first week)*

Traveller's diarrhoea can be further sub-divided as acute if symptoms last less than four weeks, or chronic if longer.

Assessment

History

You won't know a patient has travelled unless you ask!
The essentials of the travel history are the five Ws:

- *Where? Log an itinerary of destinations if appropriate*
- *When? Dates are important for assessing incubation periods*
- *Why? Visiting friends/relatives, tourists (short or long haul), business, military, asylum*
- *What high-risk activities? Determine exposures - e.g. sexual, food, swimming*
- *Who else is sick? Ask after the health of any co-travellers*

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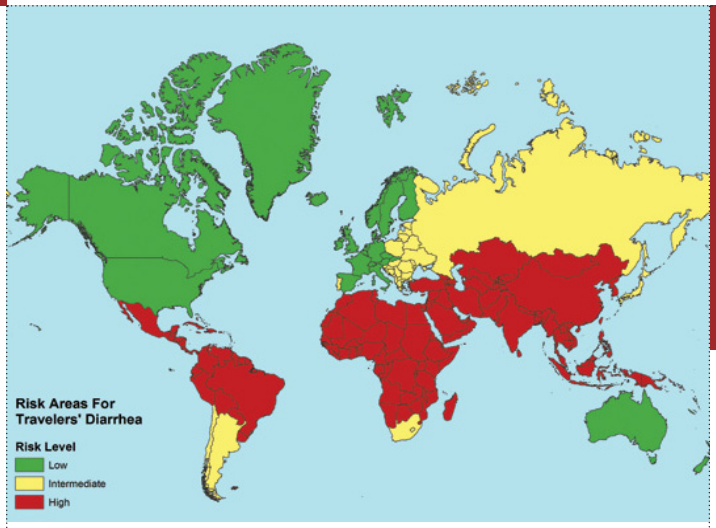

The destination of travel in particular is the main determinant of risk, particularly to sub-Saharan Africa, South America and South Asia. Lower income countries have been shown to be associated with greater risk (5).

Other risk factors include eating in restaurants (6), younger age, female sex (7), and being a traveller from a high income country (8), particularly British! (9)

In the history of the presenting complaint, it is important to ask about associated symptoms such as cramping, nausea or vomiting. The patient may be pyrexial. Blood in the stool is uncommon and can indicate invasive and more severe disease (10).

The pattern of stool passage is used to assess severity of the diarrhoea. It can be graded as mild if 1-2 loose stools per day, moderate if more than 2 stools or severe if more than 2 stools with blood, fever or incapacitating symptoms (11). The severity grade is useful in judging dehydration and guiding subsequent fluid replacement.

It is compulsory to review all systems in these patients as diarrhoea has non-infectious aetiologies. Malaria, common in returning travellers, can also present with diarrhoea.

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Examination

Key points to pick up on examination include:

- *Pyrexia - can indicate invasive disease*
- *Look for clinical signs of dehydration*
- *Severe abdominal tenderness/peritonitic picture can indicate severe colitis*
- *Digital rectal examination: rule out overflow diarrhoea secondary to constipation, rectal masses*

Bloods

- *FBC, U&Es with eGFR, CRP, coagulation screen*
- *Malaria films*

Stool sample

- *Send for microscopy, culture and sensitivity*
- *C. difficile toxin*
- *Norovirus PCR*
- *Ova, cysts and parasites if diarrhoea has been present for longer than 2 weeks*

Imaging

- *Plain abdominal radiograph can be considered to look for colitis (mucosal thickening or "thumb-printing") or toxic megacolon (dilated bowel). The latter warrants urgent surgical review.*

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Causes

Enteric Pathogen	High risk area	Incubation period	Symptoms	Adult treatment
BACTERIAL				
Enterotoxogenic *E. coli*	Latin America	1-2 days	watery diarrhoea, abdominal pain	ciprofloxacin azithromycin rifaximin
Campylobacter	South Asia, South East Asia	1-5 days	watery diarrhoea (sometimes bloody), fever	azithromycin
Salmonella (non-typhoidal)	South East Asia, Oceania	12-36 hours	watery diarrhoea	ciprofloxacin azithromycin
Shigella	North Africa, South and South East Asia	1-7 days	bloody diarrhoea, fever	ciprofloxacin
VIRAL				
Norovirus	Worldwide	1-2 days	acute vomiting and diarrhoea	supportive
Rotavirus	Worldwide	2-6 days	acute vomiting and diarrhoea	supportive
PARASITIC				
Giardia	South Asia, Middle East, South America	7-10 days	abdominal pain, nausea, chronic diarrhoea	metronidazole
Entamoeba histolytica	South and South East Asia, Middle East, South America	11-21 days	watery/bloody diarrhoea, abdominal pain, fever	metronidazole
Cryptosporidium	South Asia	1-12 days	watery diarrhoea	usually supportive

Table 1

Bacteria

Though a pathogen is not identified in over 50% of cases, bacteria are the commonest isolated cause. 30.4% of traveller's diarrhoea worldwide is attributed to enterotoxogenic E. coli (ETEC)12. Campylobacter causes up to 30%, with non-typhoidal Salmonellae and Shigellae responsible for around 15% each. Campylobacter and Shigellae can cause bloody diarrhoea – think of these as bacterial causes in travellers returning from South Asia, as this region is a high risk area for both.

Snapshot case

An eighteen-year-old girl presents with a five-day history of diarrhoea.

She returned from her gap year in Goa a week ago and initially experienced watery diarrhoea associated with fever and tiredness. She has presented today as she has developed blood in her stool and abdominal cramps. She is opening her bowels 8 times a day.

On examination she is pyrexic at 38.2°C, HR 105 and blood pressure 110/70 mmHg. There is no significant postural drop. Her mucous membranes are dry and she has reduced skin turgor.
A diagnosis of shigellosis is suspected.

Shigella close-up

Shigella species are a common cause of diarrhoea, requiring as few as 10-100 organisms to cause infection due to their increased resistance to stomach acid. Humans are the only natural reservoir and with such a low infectious dose, transmission occurs easily - via contaminated food/drink as well as direct person-to-person transmission. (13)

Four species of Shigella are known: S. dysenteriae, S. flexner i (predominant in developing countries), S. boydii, S. sonnei. They are Gram-negative rods, facultatively anaerobic and non-flagellated; however, this lack of motility is only temporary. Once Shigella senses it is at the colonic cell surface, it injects bacterial proteins to hijack the host cytoskeleton signalling pathways. This forces the cell to engulf the bacterium, and with entry, Shigella organises host cell actin filaments into a "tail" which it then uses for movement and further invasion into neighbouring cells. However, widespread bacteraemia due to Shigella is rare and infection does not usually extend beyond the intestinal mucosa. (14)

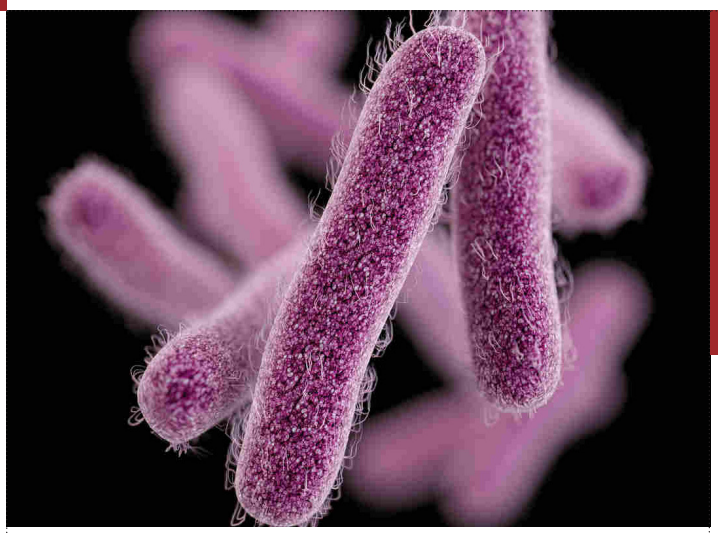
Their invasion of the colonic mucosa instigates an inflammatory response so intense that ulcerations and abscesses form. Shigella strains elaborate three types of enterotoxins, with S. dysenteriae producing Shiga toxin that is associated with haemolytic uraemic syndrome. These toxins contribute to intestinal secretion of solutes and water, but the major cause of symptoms is the acute inflammatory response that Shigella induces. (14)

Patients will typically present with high fever, abdominal cramps and diarrhoea which is initially watery but develops mucus and blood. The incubation period is between one to seven days; three on average. Generally S. dysenteriae and S. flexneri will cause dysenteric symptoms, whereas S. sonnei is associated with more mild disease. In all cases the infection is usually self-resolving within seven days. Care must be taken with immunocompromised or malnourished patients, as they are more susceptible to complications. (13)

Due to the self-limiting nature of the disease, oral rehydration therapy is usually sufficient. However, antibiotics reduce the duration of diarrhoea which also reduces the risk of spread. Unfortunately, rapidly spreading antimicrobial resistance of Shigella is a major concern, particularly in travellers from the Asian subcontinent or Africa; here, widespread resistance to ciprofloxacin, co-trimoxazole and azithromycin exists. Immunity develops following natural infection, but no effective vaccine is yet available. (15)

DIARRHOEA IN THE RETURNED TRAVELLER

A Rashid & MBJ Beadsworth



Viruses

Viruses are not as commonly isolated as causes for traveller's diarrhoea, with studies quoting figures up to 20% - mostly norovirus and rotavirus. Norovirus is implicated in cruise ship and resort outbreaks.

Protozoa

Parasites tend to cause chronic diarrhoea. Examples include Giardia lambia, and less commonly Cryptosporidium spp. and Entamoeba histolytica. Again, South Asia is a high risk area for these pathogens.

Management

There are four aims in the treatment of traveller's diarrhoea:

1) Prevent dehydration

2) Alleviate severity of symptoms

3) Shorten duration of symptoms

4) Reduce complications of diarrhoeal illness

Although most patients will self-manage these symptoms at home with increased oral fluid intake/oral rehydration solutions, a proportion will present for further medical attention. Maintaining adequate hydration is the priority and if the patient is unable to keep down fluids or vomiting, intravenous fluids should be prescribed as per NICE guidelines.

Loperamide and other antimotility drugs should be prescribed with care. They may reduce stool frequency, but should not be used in dysentery as this may worsen outcome (16).

Antibiotics reduce the duration of diarrhoea, but the benefits must be weighed against the risks including development of resistant organisms and side-effects of the drugs themselves. As traveller's diarrhoea is usually a self-limiting illness it is not felt that antibiotics are commonly necessary; consider in moderate-severe disease, in particular if the diarrhoea is bloody, there are abdominal signs, fever or shock.

Ciprofloxacin is the antibiotic of choice in bacterial traveller's diarrhoea. However, due to increasing resistance of Campylobacter in the developing world, azithromycin should be offered instead to travellers from South and South East Asia. Quinolones are contraindicated in children, who should also be prescribed azithromycin.

In parasitic disease metronidazole is effective against giardiasis and amoebiasis (for the latter, a luminal agent such as paromomycin is also necessary). If a parasite is identified as the cause of traveller's diarrhoea, an Infectious Diseases referral should be made for further discussion.

Although traveller's diarrhoea is common and self-limiting, increasingly, a post-infectious complication of irritable bowel syndrome is being described. This affects 10-17% of patients and can last for years after the episode of tropical diarrhoea. Reactive arthritis has also been described in patients following traveller's diarrhoea17. Important to note is the association with Campylobacter spp. in up to 40% of patients with Guillan-Barre syndrome.

Summary

All patients presenting with diarrhoea should undergo a travel history – traveller's diarrhoea affects up to 60% of visitors to low-income areas. In most patients this is a benign condition where maintaining hydration is the key approach; improvement is typically seen by 48 hours, before an average resolution time of 4 days.

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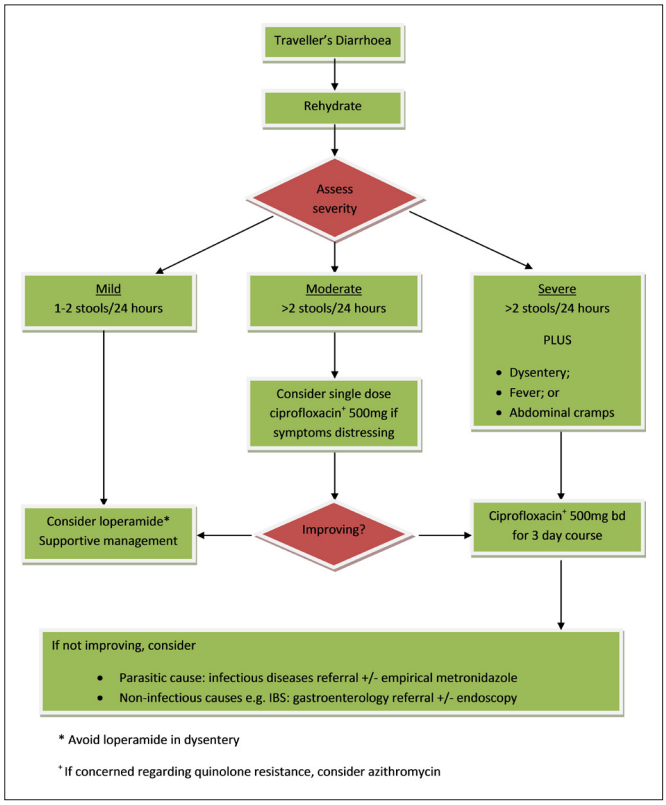
If there are signs of moderate or severe disease, antibiotics may be given, noting ciprofloxacin resistance in South and South East Asia. Care must be taken with the old, very young and immunocompromised who may not recover as quickly. Chronic diarrhoea should prompt investigations, as appropriate, for inflammatory bowel disease, protozoal infection, HIV, malignancy, endocrine or autoimmune causes.



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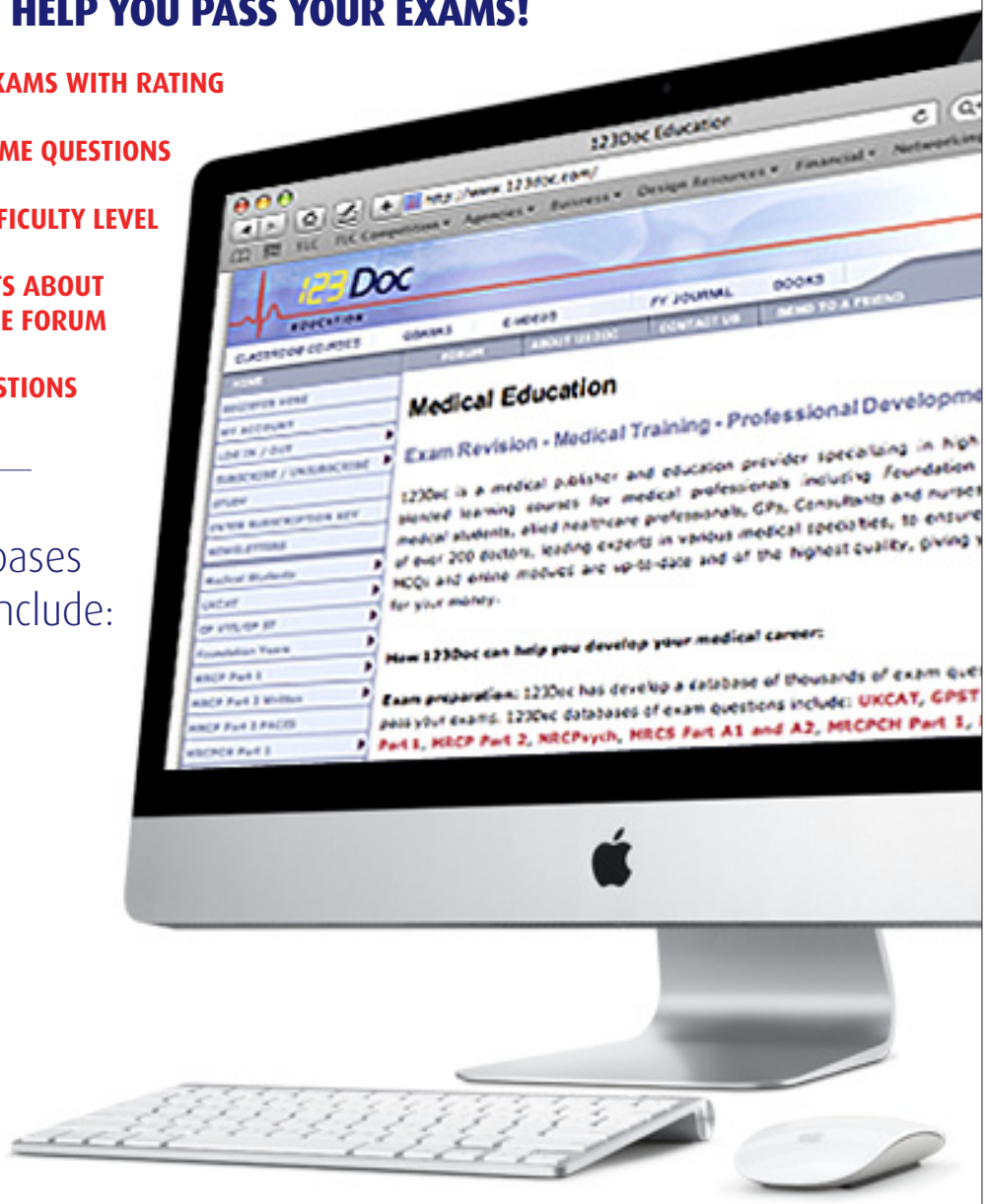

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DIFFERENTIAL DIAGNOSIS OF INFECTIOUS GENITAL LESIONS

VL Parker, WAE Parker & K Farag

Differential diagnosis of infectious genital lesions
Patient Management

Abstract

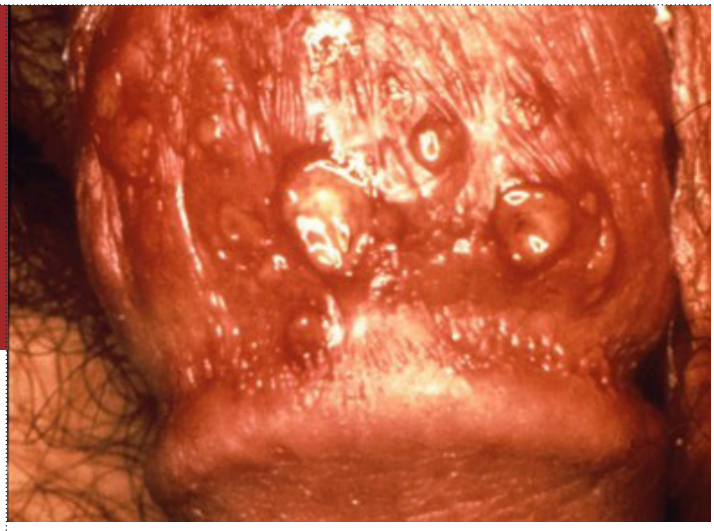
Genital lesions are a common condition (>20 million cases worldwide each year), (1) which may present to a variety of medical specialties including Accident and Emergency, Genito-urinary medicine, Obstetrics and Gynecology or Primary Care. Lesions may have an infectious or non-infectious aetiology, and it is crucial that doctors perform a structured history and examination to optimize management and prevent misdiagnosis. The most common infectious genital lesion is genital herpes or warts, although the prevalence of previously uncommon conditions (eg: syphilitic lesions) is gradually increasing. This article will discuss the salient points of medical review and clinical investigation to help physicians pinpoint the diagnosis and optimise patient management.

Case history

A 20-year-old university student attends Primary Care describing a 5 day history of a painful vulva and dysuria which is gradually worsening. She has palpated some lesions and is very concerned. She has never had anything similar before, but has recently been treated for a Chlamydia infection. She has been using her mother's steroid cream, which has worsened her symptoms. How would you proceed with history taking, examination, investigations and management?

INFECTIOUS	NON-INFECTIOUS
Herpes simplex	Beçhet's disease
Primary syphillis	Stevens-Johnson syndrome
Chancroid	Crohn's disease
Lymphogranuloma vereereum	Pemphigus and pemphigoid
Granuloma inguinale (donovanosis)	Cutaneous malignancy
Genital warts (condylomata acuminata)	

Table 1: Differential diagnosis of genital lesions with infective and non-infective causes.



Discussion

History

History taking should initially focus on open questions regarding the course of symptoms and progression of the condition, asking the patient to start from the beginning of the illness and take the clinician through the events prompting medical presentation. The incubation period may guide diagnosis:

- *Herpes simplex: 2-7 days for primary genital herpes*
- *Primary syphilis: 30-90 days*
- *Chancroid: 5-14 days*
- *Lymphogranuloma vereereum: 3-30 days*
- *Granuloma inguinale: 1-180 days*

One of the most important facts to establish early on in the consultation concerns whether the lesions are painful or painless: genital warts, primary syphilitic, granuloma inguinale and lymphogranuloma vererum lesions are characteristically painless, whereas chancroid and herpes simplex lesions are painful.

Furthermore, it must be clarified whether the lesions have always been painful (suggesting diagnosis such as herpes), or whether they recently became painful (eg: abscess formation/lesion with superimposed infection). The distribution of the lesions and order of appearance, in addition to discharge, redness and presence of groin pain and lesions should be established. Herpes and genital warts tend to present with multiple lesions, whereas primary syphilis and lymphogranuloma vererum often begin with a single, painless ulcer. Granuloma inguinale may present with single or multiple progressive ulcerative lesions. Pruritis may be a feature of herpes simplex infection and bleeding is suggestive of granuloma inguinale.

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The patient should be asked if they have previously experienced similar symptoms, as reactivation of the herpes simplex virus tends to produce less painful and severe attacks, often preceded by genital tingling. Differentiating between a primary and recurrent attack alters management, particularly if the patient is pregnant, determining mode of delivery. Primary herpes carries a 50% neonatal transmission rate during vaginal delivery, with high morbidity and mortality. Delivery by caesarean section is therefore recommended if labour occurs within 6 weeks of primary herpes infection. On the contrary, the risk of neonatal transmission is low with recurrent genital herpes (0-3%) and vaginal delivery should be recommended.

Questions concerning prodromal illness (eg: flu like symptoms, pharyngitis) or genital tingling sensations, shooting pains into back, legs and buttocks suggest primary herpes infection. Systemic symptoms such as fevers, rigors, vomiting may point to abscess formation eg. a chancroid bubo.

Urinary and bowel symptoms should be explored including urinary frequency, dysuria, hesitancy, retention, anal pruritis, dyschezia, PR bleeding or discharge, diarrhoea, constipation and tenesmus. Herpes simplex and lymphogranuloma verereum infections can be associated with urinary symptoms and proctitis, whilst other differential diagnoses include urinary tract infection, Crohns disease or infectious diarrhoea.

A comprehensive sexual history is essential to differentiate between an infectious and non-infectious cause. This should include: age of first sexual intercourse, total and current number of sexual partners, any partners from overseas, homosexual or heterosexual relationships, use of contraception (including barrier protection), vaginal or anal intercourse, commercial sex, previous sexually transmitted infections and treatment, HIV, hepatitis B and C risk assessment, last menstrual period and cervical smear history. Symptoms in the patients' partner should also be explored.

Place of birth and travel history is essential, including the duration and areas visited, as lymphogranuloma venereum and chancroid is mostly found in tropical countries. Herpes simplex type 2 is found in 20% of UK females and is the most common STIs causing genital ulcers. Syphilis used to be uncommon in the UK, however the prevalence has gradually increased over recent years.

Past medical and surgical history (especially of immunocompromise); medications; allergies; smoking; and occupation should also be included. Of course the patients' ideas, concerns and expectations must also be explored.

Specific risk factors increasing the likelihood of genital ulcers include lack of male circumcision, multiple sexual partners, failure to recognize ulcers during prodromal stage, unprotected sexual intercourse, unprotected skin to skin contact with ulcers, serodiscordant sexual partners (eg: one partner with herpes simplex and one without) and exposure to trauma or medications such as corticosteroids or perfumed lotions.

Examination

Examination should include an assessment of vital signs including pulse, blood pressure, temperature, respiration rate, oxygen saturations and peripheral perfusion. A full systemic examination of the neurological, cardiovascular, respiratory and abdominal system should be performed. This baseline examination is especially important in diagnoses of syphilis, to screen for signs of secondary or tertiary syphilis.

Groin examination should be performed, looking for inguinal lymphadenopathy or abscesses, which may be present in chancroid and herpes infections.

Herpes simplex virus exists as type 1 and type 2, with the latter accounting for >70% genital infections. The lesions are vesicular around the introitus and perianal region, becoming painful shallow ulcers. There may be signs of erythema, excoriation or superadded bacterial infection.

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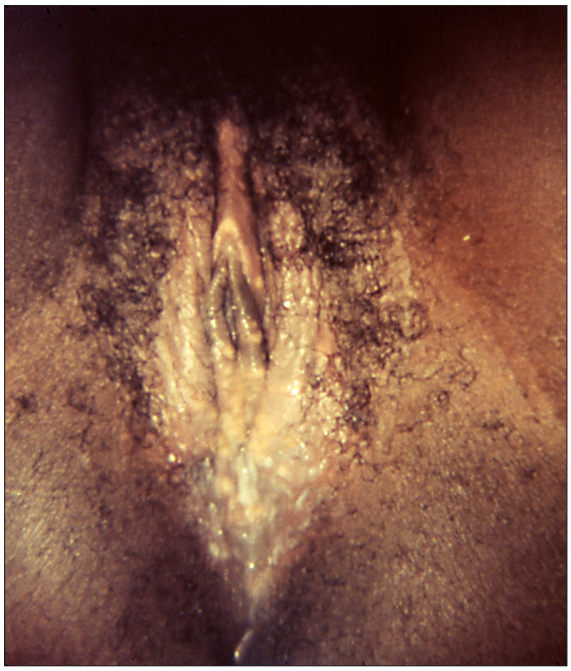

Figure 1: Blistering around the introitus caused by herpes simplex infection. Open source image via US Public Health Image Library (content provider:CDC/Susan Lindsley).

Primary syphilis initially appears as a dull red papule on the external genitalia and develops into a single, well demarcated, painless ulcer with an indurated border, associated with mildly tender bilateral lymphadenopathy. The lesion usually heals within 8 weeks.

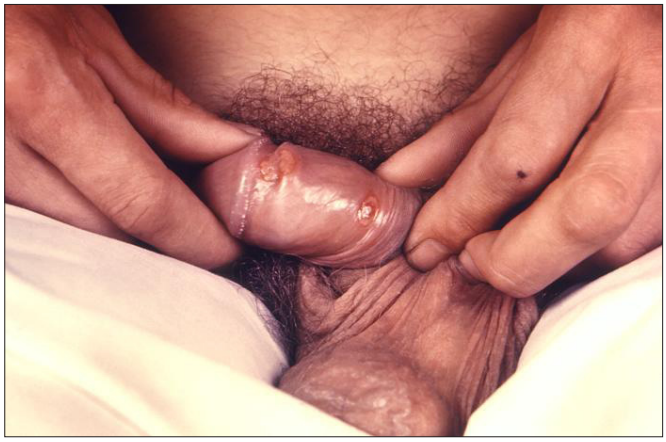

Figure 2: Ulcerated lesions typical of primary syphilis or chancroid. Open source image via US Public Health Image Library (content provider: CDC/Dr Pirozzi)

Chancroid primarily occurs as a small papule which eventually ulcerates to form single or multiple, painful, non-indurated lesions, with a serpiginous border and friable base. The lesions are often covered with a necrotic, purulent exudate. There is tender, suppurative, unilateral inguinal lymphadenopathy with potential abscess (bubo) formation.

Lymphogranuloma venereum initially appears as a small painless genital or rectal papule 3-21 days following infection, which ulcerates (without induration) and heals after a few days. Subsequent tender lymphadenopathy develops, which is unilateral in two-thirds of cases. Rectal bleeding, discharge or proctitis may additionally be identified.

Granuloma inguinale (donovanosis) forms a flat-topped, beefy red (highly vascular) papule, which develops on the genitalia days to months following infection. The papule may be hypertrophic, necrotic or sclerotic and persists for some time before degenerating into a painless ulcer. The ulcer spreads along skin folds and heals with scarring. Subcutaneous granulomas may be present and there is no associated lymphadenopathy. (2)

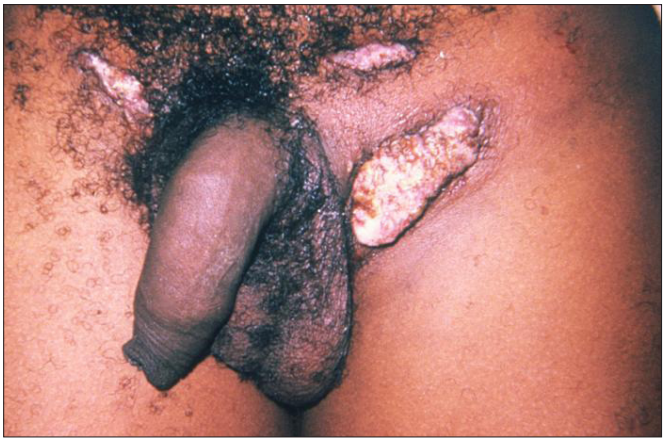

Figure 3: Granuloma inguinale, manifesting as inguinal lymph node granulomas. Open source image via US Public Health Image Library (content provider:CDC/Dr Perine).

Condylomata acuminate are very common and present with multiple lesions of variable appearances, ranging from flat tiny patches to small papilliform (cauliflower-like) swellings. Warts typically appear 3 months following infection, but may take up to 2 years to develop. Coalescence of large warts is described as condyloma acuminate. Genital warts increase in size during pregnancy and may be an indication for caesarean section.

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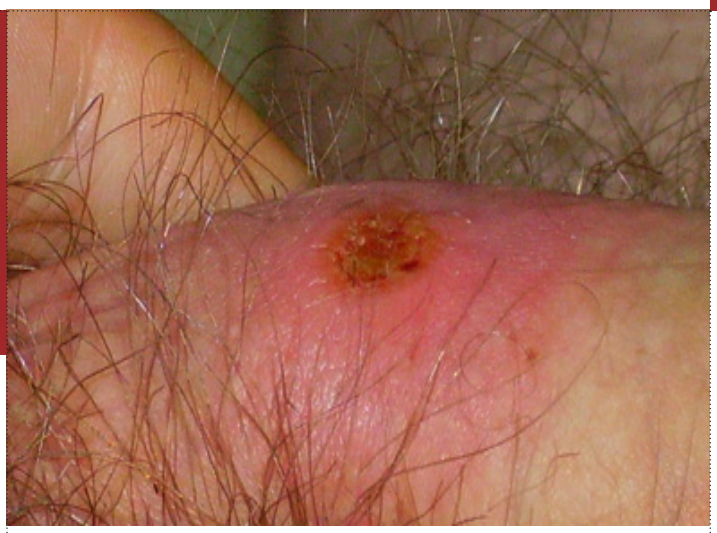

Investigations

Table 2 summarises the investigations for infectious genital lesions (typically performed by the Genito-urinary Medicine Department).

CONDITION	INVESTIGATION	REF
ALL	Offer Urinary pregnancy test (all females of childbearing age), HIV, Viral hepatitis screen, Urine dip	
HERPES SIMPLEX	Lesion swab/ulcer scraping for viral cell culture and PCR Serology (IgG)	3
SYPHILIS	Dark ground microscopy for Spirochaetes Treponemal enzyme immunoassay IgM/IgG VDRL or RPR (useful in staging and monitoring response to treatment) PCR	4
CHANCROID	Light microscopy (gram stain) for gram negative coccobacilli in short chains Culture on specialist media PCR/Serology in some laboratories	5
LYMPHOGRANULOMA VENEREUM	PCR (Chlamydia trachomatis serovars L1-3) Serology (IgM/IgG) Culture Lymph node biopsy and immunofluorecent microscopy	6
GRANULOMA INGUINALE (DONOVANOSIS)	Biopsy of lesion (Silver stain) - Donovan bodies Ulcer scraping (Giemsa stain) - Donovan bodies	7
GENITAL WARTS (CONDYLOMATA ACUMINATA)	Clinical Examination Meatoscopy, Urethroscopy, Proctoscopy Lesion biopsy and histology/electron microscopy	8

Abbreviations: HIV - Human Immunodeficiency virus, Ig - Immunoglobulin, VDRL - Venereal Disease Reference Laboratory, RPR - Rapid Plasm a Reagent, PCR - Polymerase Chain Reaction.

Management

The patient should be counselled regarding the likely diagnosis and referred to Genito-urinary medicine for diagnostic investigations, management, contact tracing follow-up. It should be explained that the service is strictly confidential. The use of steroid cream should be discontinued as this is likely to worsen all infectious genital ulcers. Table 3 summarises treatment options for each infectious genital lesion.

CONDITION	MANAGEMENT	REFERENCE
Herpes simplex - Primary infection or Episodic Treatment of Recurrence	Aciclovir 400mg PO TDS or 200mg 5x daily for at least 5 days. Can also use Valacyclovir or Famciclovir	3
Herpes simplex - Suppressive therapy	Aciclovir 400mg PO BD, or 200mg PO TDS long term. Can also use Valacyclovir or Famciclovir	3
Syphilis	Benzathine penicillin G 2.4 MU single dose IM or Procaine penicillin G 60 kU OD IM for 10 days. Doxycycline/Azithromycin if penicllin allergy.	4
Chancroid	Azithromycin 1g PO single dose, or Ceftriaxone 250mg IM single dose, or Erythromycin 500mg PO QDS for 7 days, or ciprofloxacin 500mg PO BD for 3 days	5
Lymphogranuloma venereum	Doxycycline 100mg BD PO for 21 days, or eryrthomycin 500mg QDS for 21 days (use latter in pregnancy or breastfeeding)	6
Granuloma inguinale	Doxycycline 100mg PO BD for 21 days (1st line) or Erythromycin 500mg PO QDS for 21 days (2nd line)	7
Genital warts	Topical agents for external warts including Podophyllotoxin, Trichloroacetic acid (specialist use only) and Imiquimod. Cryotherapy, electrocautery or excision for resistent lesions. Vaccine can be administered prior to first exposure. Condoms help even if both partners infected.	8

Table 3

Notably, aciclovir reduces the duration and severity of primary herpes simplex infections (and possibly reactivation attacks) if administered within 5 days of symptom onset.

Best of 5 MCQs

1. A 32-year-old man visiting from Africa has a one week history of painful ulcers on his penis with an associated phimosis. On examination there is inguinal node enlargement with an associated abscess and discharging sinus. What is the most likely diagnosis?

A: Syphilis

B: Chancroid

C: Herpes simplex

D: Genital warts

E: Gonorrhoea

2. A 24-year-old female with a recent change in sexual partner complained of a 5 day history of coryza, headache, myalgia and genital tingling. She presented on day 7 with urinary retention and multiple, generally painful lesions, with some ulcer formation inside the vagina and labia. What is the most likely diagnosis?

A: Secondary syphilis

B: Non specific urethritis

C: Lichen sclerosis

D: Herpes simplex infection

E: Trichomoniasis

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Answers

1. Answer: B Chancroid

Teaching notes: Chancroid is caused by the Gram negative bacillus Haemophilus ducreyi and is generally found in tropical countries. It causes genital ulcers which typically develop within a week following exposure. Chancroid lesions begin as a small papule, which ulcerates to form a single or multiple painful superficial ulcers.

The associated inflammation may lead to phimosis. Gradual enlargement and suppuration of the inguinal lymph nodes can subsequently occur, forming an abscess (bubo) that can rupture to produce a discharging sinus. Treatment is with antibiotics (eg. Azithromycin). Syphilis causes painless ulcers and Gonorrhea usually presents with discharge without ulceration. Herpes infection causes painful or painless lesions and inguinal lymphadenopathy but abscess formation is uncommon. Warts are typically painless and would not cause inguinal lymphadenopathy or phimosis.

2. Answer: D Herpes simplex infection

Genital Herpes simplex infection typically begins as multiple, painful (and occasionally painless) vesicular lesions around the introitus or rectum. Vesicles spontaneously rupture forming shallow, indurated ulcers. In 20% cases, patients may describe a prodromal flu-like illness. Other common symptoms include inguinal lymphadenopathy, vulvitis and severe pain leading to urinary retention.

Treatment is with aciclovir for at least 5 days. Non-specific urethritis would not cause lesions. Lichen sclerosis is not sexually transmitted nor associated with a prodromal illness. Patients with lichen sclerosis present with vulval or penile soreness and pruritis with small pearly white spots, which become confluent over time.

Trichomonas is a sexually transmitted protozoan infection that does not cause painful genital ulcers, instead presenting with offensive vaginal discharge, vulval irritation and superficial, dyspareunia. Secondary syphilis involves flu-like symptoms which develop 7-10 weeks after a primary infection, but does not typically occur in the presence of active lesions. Furthermore, primary syphilis lesions are characteristically painless.

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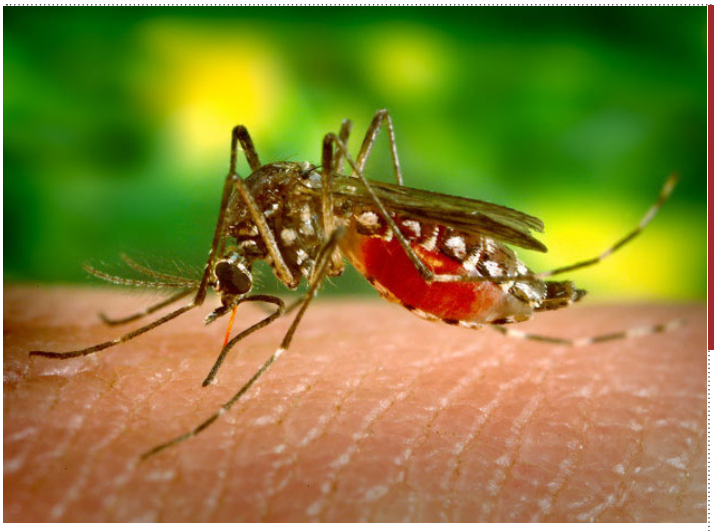
FEVER IN A RETURNING TRAVELLER FROM AFRICA

H Black & N Kennedy



Abstract

We describe a clinical case of a patient returning to the UK from Africa with fever in the context of a viral haemorrhagic fever (VHF) outbreak in 2014-15. A logical approach to the returning traveller is required, including a prompt VHF risk assessment in accordance with the UK Advisory Committee on Dangerous Pathogens (ACDP) guidance. Although important, cases of imported VHF are very rare in the UK with malaria being a much more common imported infection. Malaria can be severe and should be considered in every returning traveller with fever.

Introduction

International travel is increasing and many individuals present with fever during or following a trip abroad. Although the differential diagnosis is wide there are several common and important diseases that need to be considered early on in every patient returning from the tropics.

Clinical case

A 31 year old Nigerian man presented to his general practitioner with fever on return from Nigeria. He had lived in the UK for 4 years and travelled to visit family and friends. He was in Nigeria for 19 days, returning 15 days prior to presentation. He stayed in the city of Lagos and did not travel elsewhere. Specifically, there was no travel to viral haemorrhagic fever (VHF) endemic areas in Nigeria (see Public Health England (PHE) guidance (1) for details and maps of VHF distribution).

He did not have any vaccinations prior to travelling or take malarial prophylaxis. While in Nigeria he was diagnosed with malaria and treated with oral anti-malarials, the name of which he could not recall, for 2 days. He initially improved and felt well on return to the UK. However, his fever returned 12 days after his return (i.e. 3 days prior to presentation).

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The fever was associated with a mild sore throat, but he denied any other symptoms on systemic enquiry. Specifically, there was no history of vomiting, diarrhoea, bruising or haemorrhage, muscle aches or back pain

Prior to admission to hospital a VHF risk assessment was performed over the phone, agreed by the on-call Infectious Diseases consultant. Based on his history he was classified as 'low possibility of VHF', with Lassa fever (rather than Ebola) being the main concern for Nigeria (1).

Given his initial 'low possibility' VHF risk classification the patient was admitted to a single room and assessed by medical and nursing staff following standard infection control measures (hand hygiene, gloves and plastic aprons). High-level personal protective equipment (PPE) was not deemed necessary.

On initial assessment the history was confirmed. On examination he was pyrexial (38.5°C) and tachycardic. There was no rash, jaundice, haemorrhage, meningism or lympadenopathy. His throat was mildly erythematous. Cardiovascular, respiratory abdominal and neurological examinations were unremarkable.

The laboratories were informed of the 'low possibility of VHF' risk classification and therefore processed the malaria film and other blood samples as per normal, with initial results available within 40 minutes. These tests revealed thrombocytopenia (platelets 80 $x10^9$/L), mild transaminitis (ALT 68 IU/L) and elevated C-reactive protein (220 mg/L). A malaria antigen test was positive and blood film showed Plasmodium falciparum with 5% parasitaemia.

Once the malaria test result became available, the patient's VHF status was further downgraded to 'VHF unlikely'.

As his parasitaemia was high (>2%) he was regarded as having severe malaria and treated with intravenous (IV) quinine and oral doxycycline, in addition to penicillin to treat for tonsillitis. His parasite count gradually fell and his fever settled. He was discharged on day 4 to complete 7 days treatment in total (oral quinine, doxycycline and penicillin V).

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Discussion

Approach to fever in a returning traveler

The differential diagnosis in a returning traveller with fever is wide. Important and common imported infections to the UK should be considered promptly. These include malaria, enteric fever (typhoid and paratyphoid), HIV seroconversion, dengue fever and rickettsial infections (2). VHF is rare, but must also always be considered – particularly in a returning traveller from West Africa.

History taking is the key to formulating an accurate differential diagnosis. Given the need to perform a VHF assessment, the key elements of the history should be clarified prior to arranging hospital admission. Key history points include:

1. Countries visited

2. Dates of travel and illness onset

3. Malaria prophylaxis and vaccinations

4. Type of travel (e.g. leisure or healthcare worker)

5. Activities undertaken while abroad

6. Any relevant contacts

7. Symptoms and signs

A VHF risk assessment must be undertaken initially in all cases (see below). Unless the patient triggers as a possible case of VHF, in which case special precautions may be required, a careful physical examination should then be performed. Look specifically for rash, jaundice, lymphadenopathy, hepato-splenomegaly, meningism or haemorrhage. Initial investigations that should be considered in all returning travelers are included in Table 1. Other tests may be required – although this may require samples to be sent to specialist reference laboratories.

Full blood count, urea and electrolytes,
liver function tests, C-reactive protein
Blood cultures
Malaria antigen testing and films – 3 over 2 day period
HIV test
Urine and stool for culture and sensitivity
Chest X-ray
Ultrasound of liver and spleen

Table 1: Investigations in febrile returning traveller†
†Adapted from Bell DJ[2]

Viral haemorrhagic fever

The viral haemorrhagic fevers (VHFs) are a group of life-threatening viral infections characterised by their potential to cause a severe multi-system illness with a high case-fatality rate. Vascular damage is prominent and haemorrhage may occur. A number of viruses from several unrelated families (arenaviridae, bunyaviridae, flaviviridae and filoviridae), with a wide geographical distribution, can cause VHF (1). The 4 VHFs that are best known are:

1. Ebola Virus Disease (EVD)

2. Lassa Fever

3. Marburg Haemorrhagic Fever

4. Crimean Congo Haemorrhagic Fever (CCHF)

In addition to the severity of illness that these infections cause, their potential to be transmitted within healthcare settings is a major additional concern. Transmission is via direct or indirect contact with blood or body fluids; aerosol transmission does not occur. Management is largely supportive, although there are several emerging experimental treatments. Strict infection control measures are vital.

The possibility of VHF should be considered in all febrile returning travelers – prior to a decision to admit to hospital. The current Ebola virus outbreak in West Africa has increased the profile of the VHF group of illnesses significantly and education of both the public and healthcare professionals is part of the public health preparedness strategy in the UK.

The key element in a VHF assessment and management is a prompt and accurate risk assessment using the UK Advisory Committee on Dangerous Pathogens (ACDP) guidance (3) and associated algorithm. (4) The two key facts that you need to establish initially are:

1. Has the patient had a fever (temp > 37.5°C) in last 24 hours, or febrile symptoms?

2. Has the patient returned from a VHF endemic country (1) within the last 21 days?

If the answer to these questions is 'yes', then the patient should be regarded as a 'possible' case of VHF. You should urgently seek senior help at this point, before proceeding to examination or investigations, as the patient requires a detailed assessment - following the ACDP guidance and algorithm (3,4) - to determine if they should be classified as a 'low' or 'high' possibility of VHF case.

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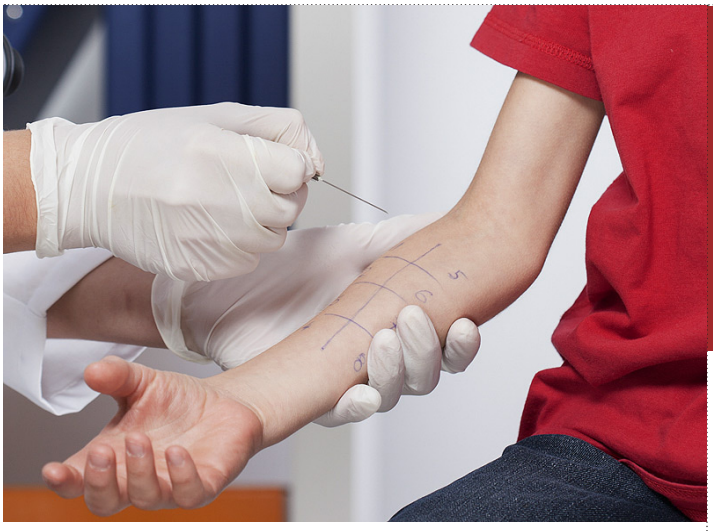

Details of the transport, investigation, infection control measures and public health actions required for 'possible' cases of VHF are beyond the scope of this article. In general terms, for 'low possibility of VHF' cases there are relatively few restrictions over and above standard infection control precautions (SICPs) - as was seen with our patient. However, for 'high possibility of VHF' cases a very rigorous infection control protocol, including the use of high-level PPE, needs to be implemented immediately. (3)

For both 'low' and 'high' possibility of VHF cases it is vital not to delay the diagnosis and treatment of commoner diseases, such as malaria.

Malaria

Malaria is caused by plasmodium parasites transmitted to humans by anopheles mosquito bites. There are four main types of plasmodium affecting humans – P.falciparum, P.ovale, P.vivax and P.malariae, P.falciparum is the most dangerous.

There are approximately 1,500 cases of imported malaria annually in the UK, the majority of these cases being P.falciparum infections. The prevention of malaria is therefore extremely important, with the key elements of prevention being awareness of risk, bite prevention, chemoprophylaxis and prompt diagnosis and treatment. (5)

Malaria usually presents as an acute febrile illness. Symptoms are often non-specific, including fever, rigors, headache and vomiting. In P.falciparum infection, without treatment, symptoms can progress rapidly to severe illness and death. Complications such as severe anaemia, respiratory distress syndrome and cerebral malaria are poor prognostic signs and seen more commonly in children (see Table 2). (6) In P.vivax and P.ovale relapse can occur weeks to months after primary infection due to dormant liver forms called hypnozoites. This does not occur with P.falciparum.

Impaired consciousness or seizures
Hypoglycaemia
Severe anaemia
Renal failure
Acidosis
Shock
Pulmonary oedema
Spontaneous bleeding/disseminated intravascular coagulation (DIC)
Haemoglobinuria (without G6PD deficiency)

Table 2: Major features of severe/complicated falciparum malaria in adults†

†Adapted from Lalloo et al[6]

Investigations

Routine blood tests may reveal anaemia, thrombocytopenia or elevated bilirubin. Diagnostic tests for malaria are blood antigen tests and blood films. Rapid diagnostic tests (RDT) detect parasite antigen or enzymes in whole blood. Advantages of RDTs include timely results and lack of necessity of highly trained operatives, but they should not be used as a substitute for blood films. (6) Two types of blood films are performed: Thick and thin. Thick films allow many red cells to be examined and used for calculating parasitaemia. Thin films are more useful in studying morphology and determining malarial species.

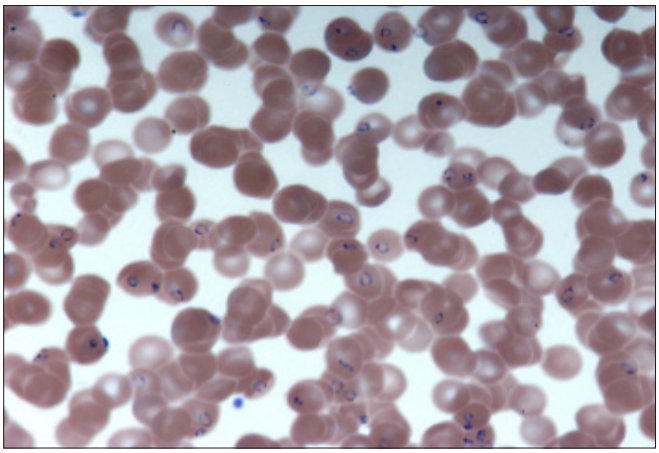

Figure 1: Thin film of Plasmodium falciparum. Notice the dark ring-forms (P. falciparum trophozoites) present within the red blood cells.

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Treatment

The ABCDE approach should be used for initial assessment and management, as with any acutely unwell patient. Malaria treatment is a specialist area and you should therefore always seek senior advice. Parenteral treatment should be given to all patients with P.falciparum infection and a high parasitaemia (> 2%), severe or complicated disease (see Table 2), vomiting, or inability to take oral anti-malarials. First-line therapy is intravenous quinine with a 20mg/kg loading dose then 10mg/kg 8 hourly, supplemented by oral doxycyline or clindamycin (6). Alternatively, you can use artesunate with a 2.4mg/kg dose at 0, 12 and 24 hours and daily thereafter. (6)

There are several oral treatment options for uncomplicated P.falciparum malaria (Table 3). For the benign malarias due to P.vivax and P.ovale, a 3-day course of oral chloroquine is usually adequate - but should be supplemented by a course of oral primaquine (check for G6DP deficiency first) to prevent relapse from hypnozoites.

1. Combination of oral quinine and doxycycline
2. Co-artem (artemether-lumefantrine - Riamet®)
3. Atovaquone-proguanil (Malarone®)

Table 3: Options for the treatment of uncomplicated falciparum malaria in adults†
†Adapted from Lalloo et al[5]

Summary

As international travel increases our approach to the returning traveler in a healthcare setting becomes increasingly important. A logical step-wise assessment, including consideration of VHF risk, is crucial. Malaria is one of the most common imported infections in the UK and we need to identify patients with severe malaria early to ensure effective treatment.

Learning points

1. A logical stepwise approach to returning travelers is key.

2. A brief VHF risk assessment should be performed on all febrile returning travellers.

3. Patients developing fever – or a history of fever - within 21 days of returning from a VHF endemic county require urgent further detailed assessment for possible VHF.

4. Malaria should be considered in all patients returning from affected areas with fever.

5. In the evaluation of a patient with P. falciparum malaria assess for severity criteria, as parenteral therapy may be required.

Test yourself

1. A 31 year old man presents with fever, headache, mild abdominal discomfort and malaise 2 weeks after returning from Nigeria. He was visiting family who live in a rural village. He took malaria prophylaxis throughout his time there and for 4 weeks on return.

Which of the following statements are TRUE:

a. Typhoid is unlikely as the patient is not complaining of diarrhoea.
b. He does not require risk assessment for viral haemorrhagic fever (VHF) as he is outside the incubation period for these infections.
c. You do not need to send blood for malaria films as he took malarial prophylaxis.
d. If he grew up in Nigeria he may have some immunity to malaria, but this diagnosis can still not be discounted.
e. If his symptoms are due to VHF, Ebola Virus Disease (EVD) is the most likely diagnosis.

2. With regards to malaria, which of the following statements are TRUE:

a. Infection is transmitted by male mosquitoes of the Culex genus.
b. Patients with P. falciparum infection and a parasitaemia of greater than 2% are at risk of severe illness and complications.
c. Benign malaria due to P.vivax or P.ovale is frequently fatal due to late relapses.
d. Primaquine is the treatment of choice for non-severe cases of P. falciparum infection.
e. Malaria can easily be distinguished from VHF due to differences in symptoms at presentation.

Answers

1a. FALSE: *Typhoid typically presents with a systemic febrile illness, similar to malaria. Abdominal discomfort is common, while diarrhea may not be a prominent symptom.*

1b. FALSE: *He does need to be assessed for VHF as he developed symptoms within 21 days of return. He is potentially at risk of Lassa fever, having been to rural areas within Nigeria.*

1c. FALSE: *You do need to test for malaria as prophylaxis is not 100% effective and compliance is often an issue. Avoidance of mosquito bites is an important additional component of malaria prevention.*

1d. CORRECT: *Immunity to malaria does develop during childhood in endemic areas. However, this immunity is incomplete and also wanes with time in individuals who subsequently leave malaria endemic areas.*

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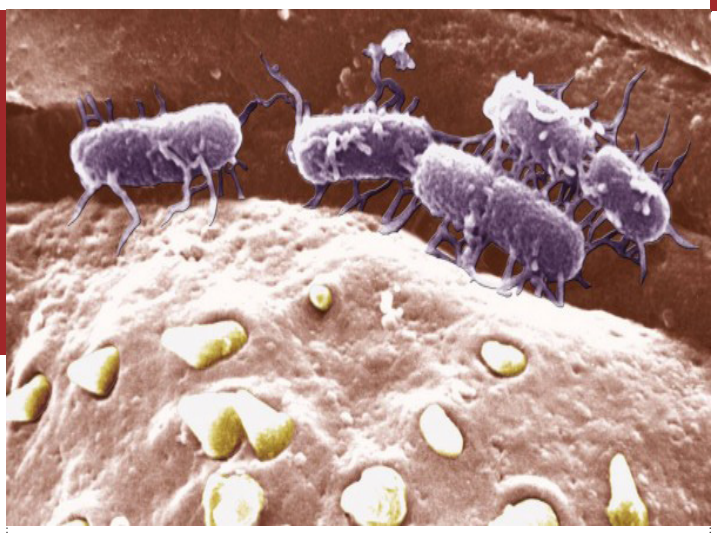

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1e. FALSE: *The 2014-15 Ebola outbreak has principally affected Sierra Leone, Liberia and Guinea in West Africa. Imported cases did occur in Nigeria, with secondary cases in healthcare workers, but with no widespread transmission. Lassa fever is the principle VHF of concern for travellers returning from rural Nigeria.*

2a. FALSE: *Malaria is transmitted by female mosquitoes of the Anopheles genus. Culex genus mosquitoes, by contrast, are vectors for various human arbovirus infections*

2b. TRUE: *Patients with a parasitaemia of > 2% are at risk of severe/ complicated falciparum malaria and should receive intravenous quinine, along with oral doxycycline or clindamycin*

2c. FALSE: *P.vivax and P.ovale benign malarias are rarely fatal, although they are associated with late relapses due to hypnozoites.*

2d. FALSE: *Primaquine is used to prevent relapses due to hypnozoites in benign malarias, but is not used for treating falciparum malaria.*

2e. FALSE: *Malaria and the early stages of VHF infection cannot be easily distinguished clinically.*

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PNEUMOTHORAX CAUSED BY CLOSTRIDIUM RAMOSUM BACTERAEMIA

I Tonna & K Cave

Pneumothorax caused by Clostridium ramosum bacteraemia
Patient Management

Abstract

Here we will present and discuss the case of a 33 year old injecting drug user presenting with sepsis and left-sided pneumothorax. He had recently been investigated and treated for a proximal right leg deep venous thrombosis (DVT). He was subsequently found to have Clostridium ramosum bacteraemia secondary to the infected DVT with subsequent development of multiple large septic pulmonary emboli (PE) and left-sided pneumothorax.

Case history

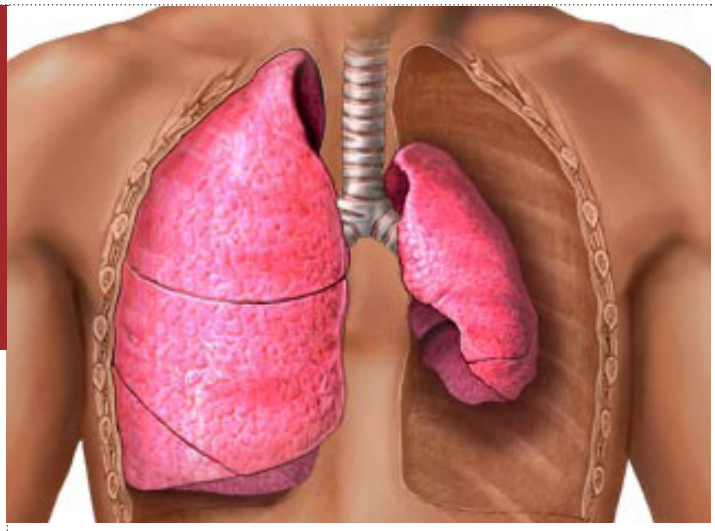
A 33 year old man with a history of injecting drug use presents to Accident & Emergency department with pleuritic chest pain, progressive dyspnoea and brown-coloured purulent sputum. He was at that time a current smoker of 12 grams of tobacco per day.

He had presented to secondary care on two earlier occasions within the previous three weeks and was confirmed using Doppler ultrasound as having a DVT. He described using his right groin as the primary site for regularly injecting heroin. Treatment with Rivaroxaban was commenced but he discharged himself against medical advice before further investigation or treatment could be undertaken.

On this occasion, he was unwell with oxygen saturations of 90% on air, tachycardia of 124 beats per minute, respiratory rate of 26 and temperature of 37.2 degrees Celsius. Physical examination revealed a discharging sinus in the right groin and auscultation of the thorax revealed bilateral crepitations, more prominent on the right side, along with reduced breath sounds at the left base. Heart sounds were pure and there were no stigmata of infective endocarditis.

Investigations

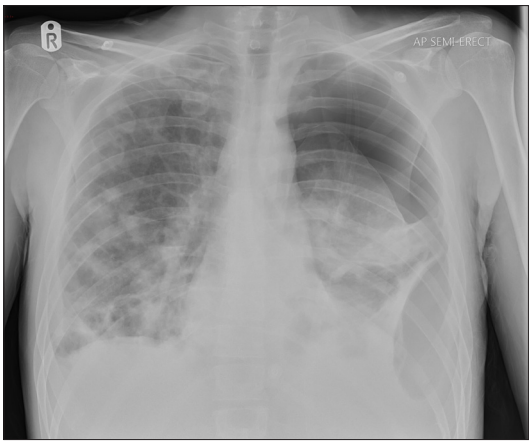
Admission blood investigations showed white cells of 20.2 x 10^9 with C-reactive protein of 301 mg/l. Clotting was deranged with prothrombin time of 21 seconds (control 11 seconds) and activated partial thromboplastin time of 55 seconds (control 26 seconds), with an acute drop in haemoglobin from 122 to 91 g/l over the previous 18 days.



What are the possible differential diagnoses at this stage?

Empirical antimicrobial therapy was commenced using Piperacillin/Tazobactam. Anticoagulation with unfractionated heparin infusion was used in place of Rivaroxaban. This was so as to treat the known DVT and to allow rapid reversal in the event of haemorrhage. Plain film x-ray of the chest was undertaken.

What does Figure 1 demonstrate?



This showed a large left-sided pneumothorax and numerous mixed-density nodular opacities within the right lung field suspicious of septic PE. An 18 gauge intercostal drain was inserted into the left hemithorax and this drained a small volume of purulent, blood-stained and malodorous fluid. Chest x-ray was repeated post-insertion of intercostal drain.

PNEUMOTHORAX CAUSED BY CLOSTRIDIUM RAMOSUM BACTERAEMIA

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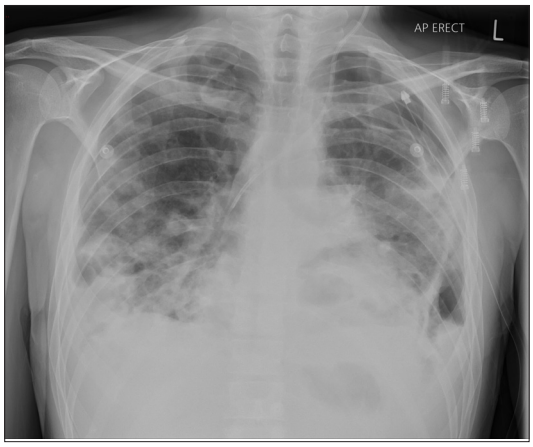
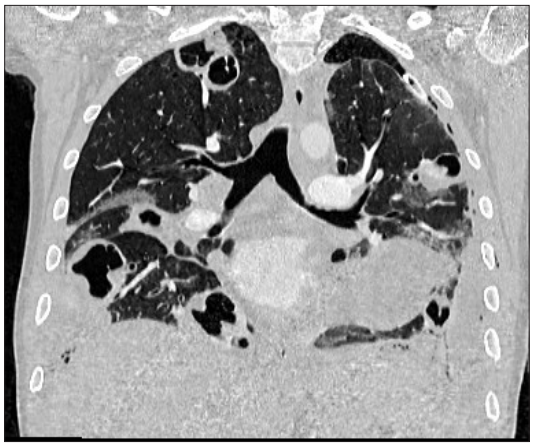
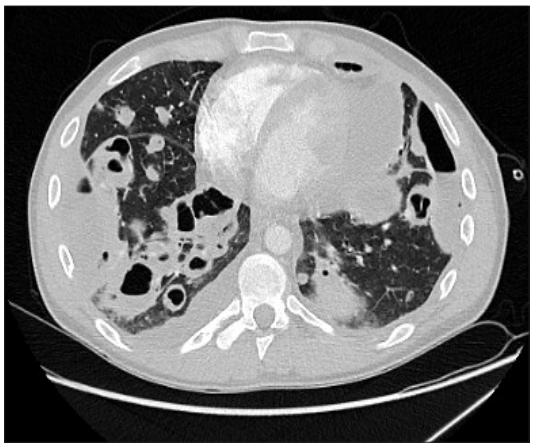
Has the pneumothorax completely resolved?



Despite the drain working well, this only partially improved the extent of the pneumothorax. Computer tomography (CT) thorax was undertaken three days into admission in order to further investigate the cause of persistent left-sided pneumothorax and the multiple lung lesions.

What abnormalities can you see here?



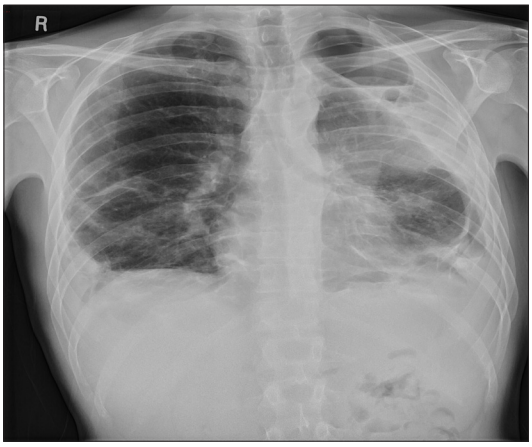


This revealed a large left-sided hydropneumothorax associated with a large number of vascular microemboli and diffuse cavitating lesions bilaterally, in keeping with septic PE. Transthoracic and transoesophageal echocardiograms did not show any evidence of infective endocarditis.

48 hours into admission, anaerobic Gram positive bacilli were isolated on blood culture. This was identified as Clostridium ramosum. The same organism was isolated from culture of the pleural fluid, along with a Streptococcus mitis species. Antibacterial therapy was rationalised to Co-amoxiclav in combination with Metronidazole for enhanced anaerobic activity.

HIV screening was negative and culture of pleural fluid for Mycobacteria was negative. The intercostal drain was removed and further x-ray of the thorax was undertaken.

How does this compare to the admission x-ray (Figure 1)?



There was a persisting left-sided pneumothorax, although more of the left lung had re-expanded. The cavitating lesions had significantly improved. Oxygenation was unaffected and since the patient had improved significantly since admission, he was therefore discharged with oral Co-amoxiclav monotherapy. He was reviewed four weeks later at the Respiratory clinic, and the pneumothorax remains unchanged. Antibiotics were stopped at this time after a total duration of twelve weeks, with further planned review in three months for consideration of repeat CT imaging.

Discussion

Septic PE is a relatively rare disease entity, constituting only 2.2% of all PEs found at post-mortem in a series of 11 367 cases (1). Pneumothorax as a consequence of septic PE is a rare phenomenon with only a few reported cases. Injection drug use has been causally linked to the development of septic pulmonary PE for a large number of years (2).

PNEUMOTHORAX CAUSED BY CLOSTRIDIUM RAMOSUM BACTERAEMIA

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This arises as a result of either right-sided infective endocarditis or septic thrombophlebitis (such as in this case) and subsequent distal embolism of infective material. The sequelae of septic PE are often severe as a result of simultaneous ischaemic and infective consequences (3).

Clostridium is a genus of Gram positive, obligate anaerobic bacilli. There have been no previous cases reported of Clostridium ramosum bacteraemia associated with pneumothorax.

There were a number of factors in this case which proved to be challenging:

Disease factors

Due to the rare nature of this condition, there is little data to support an evidence-based approach to treatment. This makes deciding treatment length very difficult, balancing adequate therapy duration versus potential side effects of broad-spectrum antibiotics, e.g. Clostridium difficile colitis.

The pneumothorax was refractory and persisted despite intercostal drainage with a suitably large-bore drain. The above factors necessitated a multidisciplinary approach involving the Respiratory Physicians, Infectious Diseases, Medical Microbiology and Cardiothoracic teams.

The balance between risk and benefit of anticoagulation and risk of bleeding had to be considered carefully. Therapeutic anticoagulation was required for treatment of the known DVT but there was a real risk of haemorrhage into the thoracic cavity with the intercostal drain in situ. The pleural fluid was also heavily bloodstained indicative of recent haemorrhage. Unfractionated heparin infusion was used; to allow rapid and full reversal if needed.

Patient factors

The patient in question had been reluctant to engage with healthcare services and had discharged himself twice in the three weeks leading up to this admission. On the second of these occasions he had presented with pleuritic chest pain and it is highly likely that this was due to the septic PE. These were of course unknown at that time and so no antibiotic treatment was given. When he presented on this occasion he was critically unwell and at a much more advanced stage of the disease. Such extreme illness could have been avoided with earlier intervention.

Substance dependence also needed to be addressed, including management of opiate withdrawal symptoms. Methadone was used in order to achieve this whilst an inpatient, with onward referral as an outpatient to the Substance Misuse Service.

Self assessment questions

1. Which ONE of the following statements regarding pneumothorax is TRUE?

a) Size of pneumothorax is the interpleural distance in centimetres at the hilum
b) Small spontaneous pneumothoraces (less than 2cm) are never suitable for outpatient management
c) All patients should be advised not to fly for at least six weeks after spontaneous pneumothorax
d) Bilateral pneumothoraces can be safely managed conservatively; without intercostal drainage
e) Patients with a spontaneous pneumothorax should receive antibiotic treatment due to the high risk of developing empyema without treatment

2. Which of the following conditions are caused by an organism other than a Clostridium species?

a) Gas gangrene
b) Pseudomembranous colitis
c) Botulism
d) Tetanus
e) Diphtheria

3. Which of the following conditions is a recognised complication of injecting drugs?

a) Rheumatoid arthritis
b) Infection with Borrelia burgdorferi
c) Arterial pseudoaneurysm
d) Crohn's disease
e) Hepatitis E infection

Answers

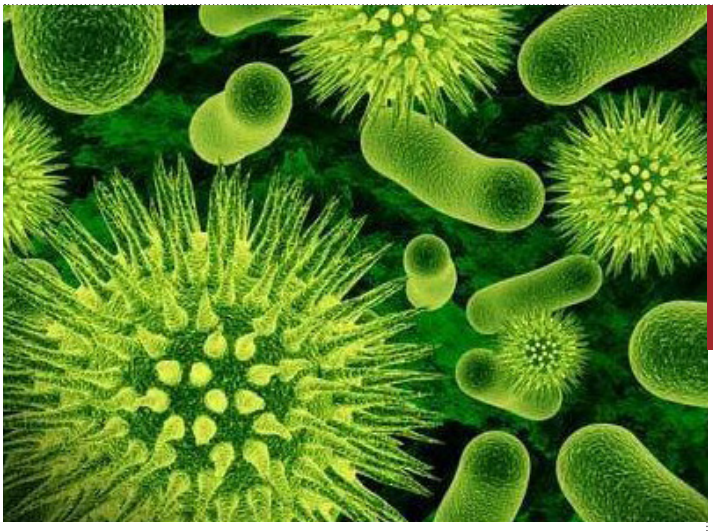
1. Answer: A

The patient in this case had a provoked pneumothorax as a result of his septic PEs and so the scenario in this question does not directly apply to him. Spontaneous pneumothorax is defined as either primary or secondary depending on the presence of underlying lung disease (or age over 50 years with a significant smoking history). They are measured in centimetres as the interpleural distance at the level of the hilum.

A British Thoracic Society guideline exists (4) which contains a very straightforward algorithm to aid decision regarding pneumothorax management. This is determined by primary versus secondary, size in centimetres and presence or absence of breathlessness. Haemodynamic instability or bilateral pneumothoraces always necessitate intercostal drain insertion.

PNEUMOTHORAX CAUSED BY CLOSTRIDIUM RAMOSUM BACTERAEMIA

I Tonna & K Cave



Pneumothorax caused by Clostridium ramosum bacteraemia
Patient Management

Limitations on flying following pneumothorax is a common question patients will ask doctors and the British Thoracic Society also have a guideline on this topic (5). A chest x-ray must be seen which confirms complete resolution of the pneumothorax, and patients must be advised not to fly for a further seven days thereafter (evidence level C).

2. Answer: E

Clostridia are a diverse genus of exotoxin producing bacteria and are responsible for a number of heterogeneous conditions associated with significant morbidity and mortality. C. perfringens, C. difficile, C. botulinum and C. tetani are responsible for the above conditions respectively. Early clinical suspicion is paramount to allow early diagnosis and therefore treatment. Diphtheria is an upper respiratory tract infection, often severe, caused by Corynebacterium diphtheriae.

3. Answer: C

Injecting drug use is associated with a number of complications(6), one of which is listed above. Inoculation of infective material, e.g. viruses from needle sharing or bacteria from preparation of the drug under less than sterile conditions can lead to blood borne virus infection and bacterial infections respectively, often with Staphylococcus aureus. Direct tissue trauma as a result of injecting can lead to problems such as arterial pseudoaneurysms, necrotising soft tissue ulcers and skin scarring. Lyme disease is a tick-borne infection caused by Borrelia burgdorferi, and Hepatitis E virus is transmitted through the faecal-oral, both diseases have no relation to drug use.

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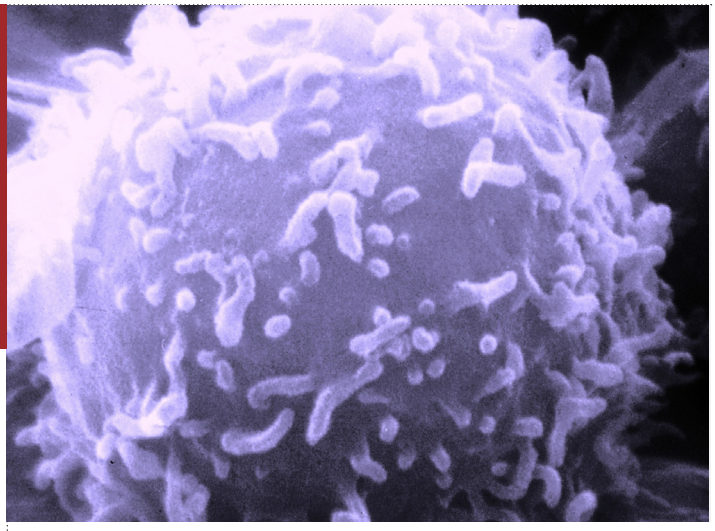
POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

I Oozeerally & J Barratt



Post-transplant lymphoproliferative disease
Patient Management

Abstract

Organ transplantation is one of the pillars of modern medicine. The increasing success of organ transplantation means the chances of Foundation doctors encountering a patient with a transplant on the acute medical or surgical take have never been higher. The immunosuppression used in transplantation increases the risk of developing a wide range of infectious complications. Post-transplant lymphoproliferative disorder (PTLD) is an important post-transplant complication that Foundation doctors should be aware of. In the vast majority of cases PTLD is caused by the Epstein-Barr Virus (EBV). We present a case of EBV-driven PTLD complicating renal transplantation followed by a brief overview of PTLD.

Case

A 51-year old lady presented in December 2010 with a tender submandibular lump. She was a renal transplant recipient having been transplanted in 1990. Prior to that, she had undergone two previous renal transplants; both of which had been surgically removed after allograft failure in 1985 and 1986 respectively. She had developed end-stage renal disease at the age of 25 secondary to chronic pyelonephritis. Her past medical history included hyperlipidaemia, hypertension and a cholecystectomy. At presentation her immunosuppression regimen was ciclosporin 75mg twice daily and azathioprine 50mg once daily.

On presentation there was obvious tender neck swelling and a provisional diagnosis of sialadenitis was made and antibiotics were initiated. Over the next three weeks the lump increased in size and she developed widespread cervical lymphadenopathy. She was admitted for investigations, which included a CT scan performed without contrast. This showed cervical lymphadenopathy with no significant intra-abdominal lymphadenopathy (See figure 1).

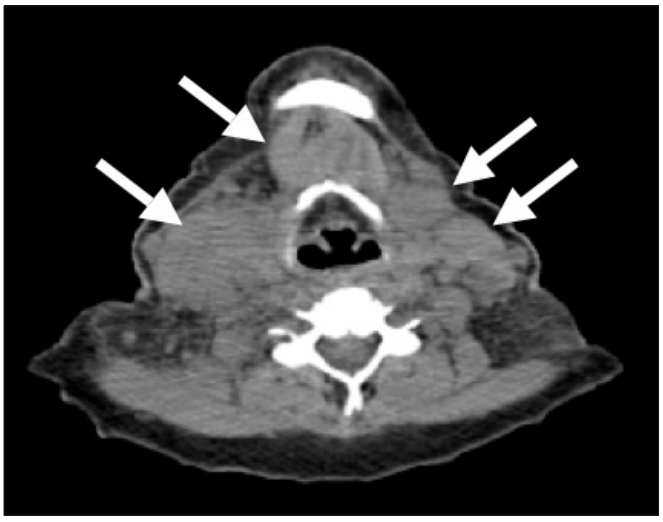


Figure 1: Non-contrast CT scan showing cervical lymphadenopathy at presentation (see arrows).

She was referred to the otorhinolaryngology service and underwent an excision biopsy of a left sided cervical lymph node. Histopathological examination of the biopsy demonstrated a diffuse large B cell lymphoma. Epstein-Barr virus in situ hybridization identified the presence of EBV within the lymphoma and EBV DNA PCR was 200 copies per ml. This confirmed a diagnosis of EBV driven post-transplant lymphoproliferative disorder (PTLD).

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

I Oozeerally & J Barratt

In parallel with a reduction in the level maintenance immunosuppression the patient was commenced on R-CHOP (Rituximab-Cyclophosphamide, Hydroxydaunorubicin (also called doxorubicin or adriamycin), Oncovin (vincristine) and Prednisolone. The patient completed 6 cycles of R-CHOP over four months. Three months into the treatment, EBV DNA PCR was repeated and was negative. Follow-up CT scans demonstrated complete remission had been achieved five months after starting R-CHOP (see figure 2).

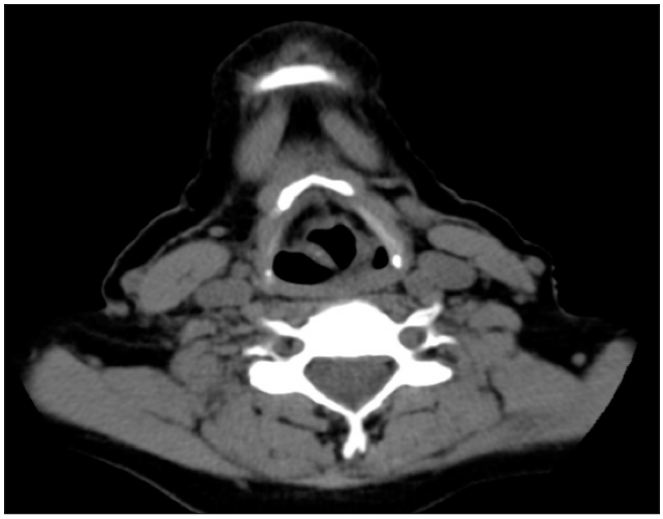


Figure 2: Non-contrast CT scan showing resolution of cervical lymphadenopathy post R-CHOP therapy.

She remains in complete remission 4 years later. Her current eGFR is 36 ml/min and she is maintained on ciclosporin 50mg twice daily and azathioprine 50mg once daily.

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease (PTLD) is a well recognised complication of solid organ or bone marrow transplantation (1). It is the second most common malignancy after skin cancers in solid organ transplant recipients (2-4). PTLD is a lymphoid proliferation arising in transplant recipients and may present in different organs including the allograft (2, 5, 6).

The spectrum of this neoplastic disease ranges from a polyclonal lymphoid proliferation resembling infectious mononucleosis to a highly aggressive monoclonal process such as diffuse large B-cell lymphoma (as in this case) (7). Mortality associated with PTLD can be as high as 60% (2, 8). Approximately 85% of PTLD is of B-cell origin and 80% of these cases are associated with the Epstein-Barr Virus (EBV) (3, 9). In addition, 30% of PTLD of T-cell origin have also been associated with EBV. PTLD arising from other cell lineages such as NK cells is rare (3).

The Epstein-Barr virus (EBV)

EBV is a double stranded DNA herpes virus (10-12) that was discovered by Michael Epstein and Yvonne Barr in 1964 during their research on Burkitt's lymphoma. It was the first virus to be implicated in oncogenesis (9, 13). EBV infection is extremely common with at least 90% of adults having been infected (11, 12, 14). EBV infects B-lymphocytes, T-lymphocytes, follicular dendritic cells, smooth muscle cells, squamous epithelium of the thyroid, stomach and salivary glands (14).

Memory B-cells act as the main reservoir for the virus (10, 11, 14, 15). In normal circumstances, there is a specific T cell response towards infected B-cells preventing over replication of latently infected memory B cells (14). Immunosuppression, as part of organ transplantation, upsets this balance between latently infected B cells and T-cells (11).

Clinical presentation of PTLD

PTLD typically presents within the first year of transplantation, on average 6 months after solid organ transplantation (5-7, 10). Typical presenting features include constitutional symptoms such as fever, weight loss and fatigue. Lymphadenopathy may be present but is not ubiquitous. Dependant on the site of the PTLD there may also be symptoms and signs of hepatitis, pneumonia, colitis and nephritis due to extra nodal involvement (3, 5, 14, 16).

Risk factors for developing PTLD

The risk of developing PTLD varies depending on the organ transplanted. Renal and liver transplants carry the lowest risk with published incidences of between 1-5% of transplanted organs. Lung and heart transplants carry a risk of 2-10%. The risk of PTLD is highest in intestinal and multi visceral transplants and is reported anywhere between 5-20% (9). The major risk factors for development of PTLD are:

- *Primary infection with EBV peri/post-transplant. This carries the greatest risk of developing PTLD (5, 8) (EBV seronegative transplant recipients have a 76 fold increased risk of developing PTLD compared to EBV seropositive recipients) (2).*

- *Active EBV infection at the time of transplantation (10)*

- *Co-existing CMV infection (2, 15)*

- *Use of T cell depleting therapies (monoclonal anti-CD3 antibody, OKT3 or polyclonal anti-lymphocyte antibody either for induction or treatment of acute rejection) (2, 5)*

- *Younger age (5)*

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

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Diagnosing PTLD

The diagnosis of PTLD should always be considered when a transplant recipient presents non-specifically unwell early after transplantation, and necessitates a thorough history and clinical examination. Routine haematological and biochemical analyses may be unremarkable although one should always consider PTLD if the lactate dehydrogenase (LDH) is elevated in the absence of an obvious cause.

Measurement of EBV DNA load by polymerase chain reaction (PCR) is useful for the diagnosis of PTLD (14) and measuring response to treatment (17). It has been reported that the EBV load can be positive up to 16 weeks prior to the presence of clinically detectable PTLD (18).

Radiological investigations will be directed by examination findings. Ultrasonography is often the first choice modality, particularly for kidney and liver transplants. Computed tomography (CT) is used for identifying the extent of disease and formal staging. Magnetic resonance is useful for CNS imaging and for bone; where it is superior to CT (3). Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) is gaining increasing importance in evaluation of tumour burden throughout oncological practice however is not yet routinely used for the evaluation of patients with PTLD in the UK.(3). Excision node biopsy is the preferred diagnostic test (3, 5). For CNS disease, a lumbar puncture should also be performed with cytology and immunophenotyping of the CSF (3).

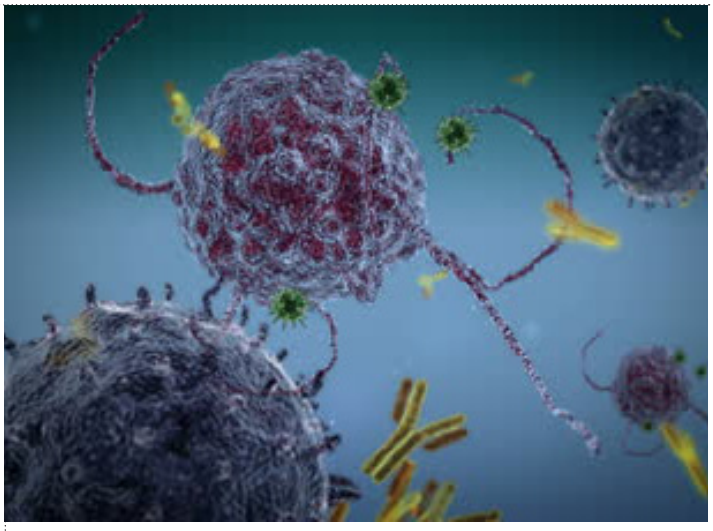
Classification of PTLD

The WHO histopathological classification of PTLD defines 4 subtypes: early lesions, polymorphic PTLD, monomorphic PTLD and classical Hodgkin Lymphoma-type PTLD (3, 11, 14). In practice, it can be difficult to subclassify PTLDs (3). In a single centre renal transplant cohort from Manchester, monomorphic PTLD was the commonest PTLD subtype responsible for 70% of reported cases (4).

Treatment of PTLD

The mainstay of treatment is a reduction in immunosuppression (2-5, 8, 10-12, 14-18). The rationale for this is to allow the recipient's natural immune surveillance, in the form of T cells, to recover (8, 10, 15). For kidney transplant recipients, European guidelines suggest a gradual reduction in the immunosuppression to 50% of the initial dose of calcineurin inhibitor (cyclosporine, tacrolimus) if tolerated and cessation of the anti-metabolite (azathioprine, mycophenolate mofetil) (2).

A step-wise reduction of a fifth of the dose every fortnight is preferred by some centres (15). Reported tumour regression rates vary widely with minimisation of immunosuppression alone (23-86%) (5, 12 16, 17). Perhaps not surprisingly, EBV-negative PTLD responds poorly to a reduction in immunosuppression alone (14).



If a reduction in immunosuppression fails, then the anti-B cell specific immunotherapy, rituximab, is advocated (4, 8, 12, 14). Remission rates with rituximab are reported to be 20-42% (4). Rituximab therapy results in a reduction in the total number B cells and hence a reduction in the number of EBV-infected cells and the viral load (17).

Failure of immunosuppression reduction and rituximab warrants the addition of alternative chemotherapy agents. The commonest chemotherapy regimen used to treat PTLD is the R-CHOP regimen (11). Remission rates with R-CHOP have been reported to be as high as 68% (4). This combination is also used in cases with a high tumour burden, EBV negative PTLD and PTLD occurring late after transplantation (as in this case) (17).

Ganciclovir has been used for refractory lymphoma (4) but generally anti-viral therapies have little effect on tumour burden (12, 15). Therapy with programmed cytotoxic T cells has also been proposed as a potential therapy but this is at an early stage of clinical development at present (19).

Prognosis

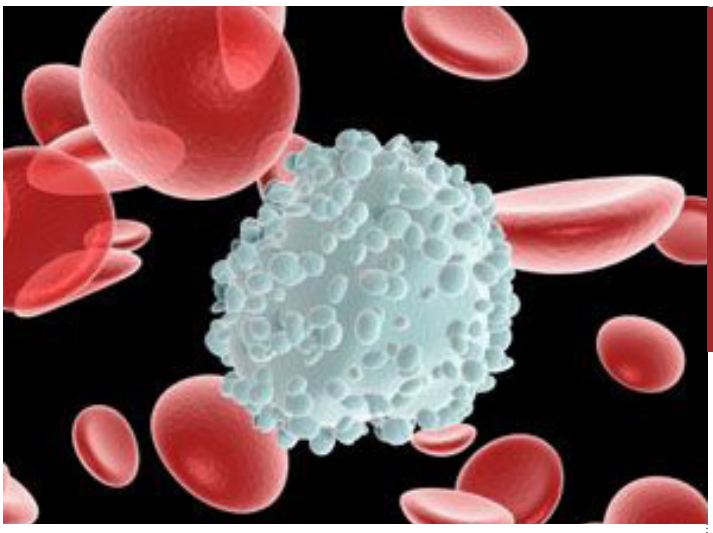
Mortality from PTLD can be as high as 60% (2, 8). The prognosis is poor if multiple sites are affected by PTLD (7, 20). Other poor prognostic factors include PTLD within the transplant and CNS disease (7).

Using the EBV viral load to prevent PTLD

In an effort to reduce the risk of PTLD and guide immunosuppression levels the KDIGO Transplant Working group (18) have proposed testing of all renal transplant recipients for EBV DNA in the first week of renal transplantation followed by monthly for the next 3-6 months followed by 3 monthly for the first year. More frequent testing is advised after episodes of acute rejection treated with high doses of immunosuppression (18). If there is a rising EBV load then reduction in immunosuppression is advised (10, 18). The hope is that with early intervention the risk of PTLD will be reduced in the future (4, 18).

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

I Oozeerally & J Barratt



Post-transplant lymphoproliferative disease
Patient Management

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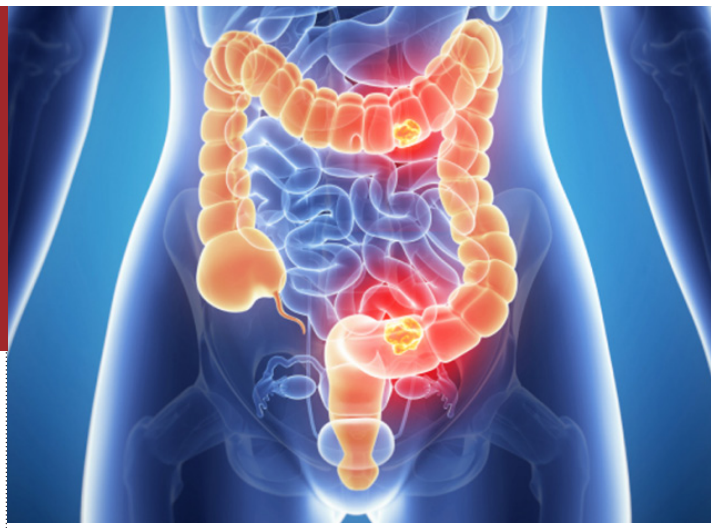
RELAPSING CLOSTRIDIUM DIFFICILE INFECTION & THE CURATIVE ROLE OF FAECAL TRANSPLANT

C Ilozue



Relapsing clostridium difficile infection & the curative role of faecal transplant
Patient Management

Abstract

This case-based discussion focuses on an elderly patient with multiple comorbidities who had over seven months of relapsing Clostridium difficile infection with diarrhoea. Treatment with all available pharmacological options including intravenous immunoglobulin therapy was unsuccessful. He received a faecal transplant via nasogastric tube to achieve cure after failure of all previous interventions. The case demonstrates the refractory nature of C. difficile infection in high risk populations and presents the important and perhaps underutilised role of faecal transplantation as a relatively low-cost curative intervention. The case highlights the importance of appropriate and targeted antibiotic use in clinical practice considering the high morbidity and mortality associated with severe C. difficile infection.

Case history

A 72 year old man underwent an elective laparoscopic cholecystectomy in 2013. He was discharged home after a stable post-operative period with a course of oral Co-amoxiclav to treat post-operative infection (of which the source and course length were incompletely documented). One month later he was re-admitted under the surgical team with generalised abdominal pain, pyrexia of 39.8°C and diarrhoea.

What are the infectious and non-infectious differential diagnoses in a patient presenting in this way?

In this situation you would initially be thinking of infectious versus non-infectious bowel conditions. Most commonly gastroenteritis (viral or bacterial) and inflammatory bowel disease with colitis. It is important to exclude infection even if there is a known diagnosis of inflammatory bowel disease (IBD) as acute gastrointestinal infection can commonly precipitate a flare in IBD.

What are the main aspects of the history that are important in narrowing down the aetiology?

You will want to know about timing of onset, stool frequency, travel history and systemic symptoms to help to distinguish the cause of his fever and diarrhoea.

The history of presenting complaint is of paramount importance:

- Onset: Acute/chronic
- Abdominal pain: Constant/intermittent/radiation/precipitating & relieving factors
- Severity of diarrhoea: Frequency, consistency, blood, mucus
- Any alteration in bowel habit, any symptom of tenesmus
- Associated vomiting
- Fever
- Weight loss
- Travel history and infectious contact history
- Recent antibiotic use or surgical history

This patient had developed diarrhoea 3 days prior to his re-admission. He described watery stool, several times per day with no blood or mucus. The abdominal pain was constant, worse in the left lower quadrant. There was no relationship between abdominal pain and defaecation. There was no associated vomiting. He reported no relevant travel or infectious contact history.

Aspects to elicit in the past medical history, drug history, family history & social history:

- Comorbidities (particularly a history of infection, immunocompromise or inflammatory conditions)
- Allergies
- Recent antibiotic, proton-pump inhibitor or laxative use
- Immunosuppressant therapy / chemotherapy (remember long-term steroid use)
- Family history of inflammatory bowel disease or bowel cancer
- Smoking and alcohol intake
- Occupation (e.g. food preparation)
- Performance status

RELAPSING CLOSTRIDIUM DIFFICILE INFECTION & THE CURATIVE ROLE OF FAECAL TRANSPLANT

C Ilozue

The patient had a history of ischaemic heart disease, previous myocardial infarction (1998), previous stroke (2012), right-sided deep vein thrombosis (2010), hyperlipidaemia & osteoporosis. He was a retired builder and lived with his wife, normally independent with unlimited exercise tolerance.

Clinical examination may focus on:

- Hydration status
- Haemodynamics and oxygenation
- Cardiorespiratory examination
- Abdominal palpation +/- per rectum examination as appropriate
- Lymphadenopathy and skin rashes
- Examine for any other source of infection
(ENT, neurological, soft tissue and skin)

His abdomen was soft with generalised lower abdominal tenderness on palpation. Blood pressure was 107/67, his heart rate 80 beats per minute, respiratory rate 30 per minute, oxygen saturations were normal.

What would you do next?

Think about your initial investigations, appropriate isolation measures and enteric precautions. Commence appropriate initial management such as intravenous fluids as appropriate.

Investigations

- Blood tests: FBC, U&Es, LFTs, CRP, Calcium, Magnesium
- Microbiology: Blood cultures; Stool microscopy and culture (MC&S); Urine dipstick MC&S
- Imaging: Chest xray, abdominal xray, consider CT
- Other (endoscopy, histology, arterial blood gases if acutely unwell)

Admission bloods showed most notably a raised white cell count (WCC 19.1 $x10^9$/l,) with neutrophilia (16.4 $x10^9$/l) and an elevated C-reactive protein (CRP) of 318mg/l.

CT abdomen on the day of admission showed an abnormally thickened colon. Appearances in keeping with acute colitis, likely to be pseudomembranous colitis. The report stated that less likely differentials include other infective colitis, and autoimmune causes such as inflammatory bowel disease.

What is your diagnosis based on the above results?

Pseudomembranous colitis is an inflammatory disease affecting the colon. It is a condition most commonly caused by antibiotic use causing changes in the colon microbiome (the micro-organisms constituting normal gut flora), leading to overgrowth of C. difficile and the development of pseudomembranes that line the mucosa of the colon. (1) Other organisms have less commonly been implicated in the aetiology of pseudomembranous colitis.

Stool culture was positive for Clostridium difficile toxin (ribotype 005) and negative for Salmonella, Shigella, Campylobacter, Escherichia Coli & oocysts of Cryptosporidium. Flexible sigmoidoscopy showed typical pseudomemebranous colitis, almost confluent. The underlying mucosa was deemed viable.

What is appropriate specific initial management for C.difficile infection (CDI)?

The first-line treatment for CDI is Metronidazole (oral or intravenous) or Vancomycin (oral). Consult the local antimicrobial formulary and local C. difficile pathway and liaise early with the Microbiology or Infectious Diseases team.

Piperacillin/Tazobactam was initiated at admission, (for sepsis of unknown source, presumed intra-abdominal) with Metronidazole added once the admission CT scan demonstrated colitis. Infection parameters deteriorated with a rise in WCC to 38.8 $x10^9$/L and a persistently raised CRP of 313mg/L.

Once the stool culture returned positive for C. difficile toxin, Piperacillin/Tazobactam was discontinued and oral Vancomycin 125mg QDS was added on microbiology advice (48 hours after admission). Intravenous (IV) Metronidazole 500mg TDS was continued. After a further 24 hours therapy, stool frequency remained high with 4-10 bowel movements at type 7 on the Bristol stool chart. (2) Therapy was thus escalated to Vancomycin 500mg qds plus Metronidazole 500mg tds IV. Plain abdominal x-ray showed no evidence of toxic dilatation, obstruction or perforation.

Stool frequency gradually improved over the next 5 days on maximal medical therapy. He remained haemodynamically stable and was discharged home after 8 days of admission to complete a total of 10 days of Vancomycin and Metronidazole.

RELAPSING CLOSTRIDIUM DIFFICILE INFECTION & THE CURATIVE ROLE OF FAECAL TRANSPLANT

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Management of CDI (2)

General

Supportive care, address fluid status and correct electrolyte abnormalities. Consider stopping the precipitating antibiotic only if not clinically required to treat significant concurrent infection.

Specific

Initially Metronidazole +/- Vancomycin, regular abdominal examination and consider plain x-ray or other imaging to exclude toxic megacolon. Liaise with Microbiology or Infectious Diseases team. Dietitian input and dietary supplementation as appropriate. The use of oral Fidaxomicin has been demonstrated to be non-inferior to Vancomycin and approved for use, however the cost involved is significant. Colectomy may be considered in the context of megacolon or septic shock.

Infection control and public health considerations

Isolation and careful enteric precautions using apron and gloves and handwashing with soap and water. If there has been antibiotic use in the month preceding the CDI, this should be reported using the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system. (3) CDIs are reported to Public Health England (PHE) for official surveillance statistics. Monthly data on CDI per NHS trust are published by PHE.

First relapse

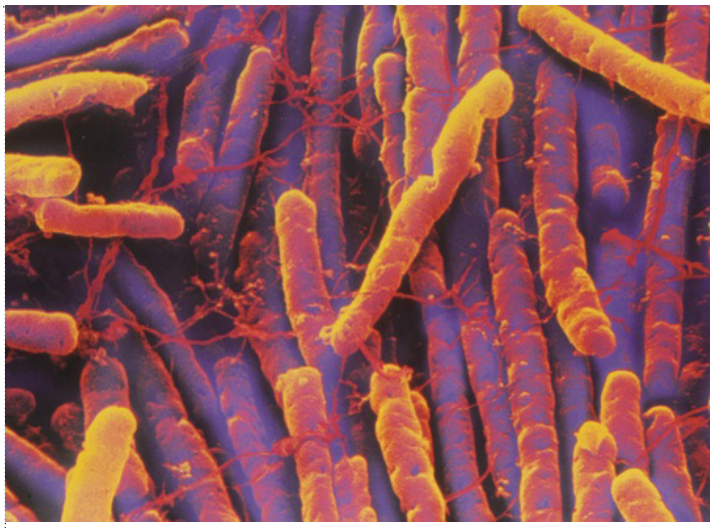
The patient was re-admitted under the medical team 2 months later with abdominal pain, relieved by defaecation. He was apyrexial with 1 episode of loose stool. His abdomen was tender in the left lower quadrant. Oral Vancomycin 125mg qds was recommenced. He was discharged home after a 6 day admission on a tapering Vancomycin dose, reducing from QDS to TDS to BD to OD each week. The patient and his wife were advised to deep clean at home to prevent re-infection. He was improving when seen in clinic 2 weeks later.

Second relapse

Ten days later (having completed the tapering Vancomycin course) he had a recurrence of diarrhoea and repeat stool culture remained C. difficile toxin positive.

Third relapse

He was seen one month later in clinic with persistent symptoms. Repeat stool MC&S remained C. difficile toxin positive and he received 2 doses of intravenous immunoglobulin (IVIG). He commenced a longer tapering and pulsed Vancomycin course: QDS for 2 weeks, then reducing weekly to TDS, then BD, then OD, then alternate days, then every 3rd day for 3 weeks (9 weeks in total).



Fourth relapse

2 ½ months later he presented to clinic with ongoing abdominal pain, his GP had recently commenced further oral Vancomycin in the community. He commenced Fidaxomicin 200mg BD for 10 days. It was thus discussed and decided to proceed with faecal transplant.

Seven months after his initial presentation, after 5 prolonged episodes of C. difficile toxin positive diarrhoea, he attended for faecal transplant using stool donated by his wife. Thirty milligrams of fresh stool was blended with 130ml of normal saline and filtered. Fifty millilitres of the infiltrate was introduced into a nasogastric tube. He remained well and was able to eat and drink normally immediately following procedure.

His symptoms had settled when seen in clinic after 2 weeks and again at 6 weeks. Two further stool specimens were C. difficile toxin negative. He was deemed cured of his refractory CDI. Twelve months after his faecal transplant he remains asymptomatic with no further recurrences of CDI.

Discussion

This case highlights the difficulty in treating recurrent CDI and the significant morbidity (and mortality) associated with this condition. Severe disease may result in toxic megacolon, bowel perforation and death. In this case, after 7 months of recurrent symptoms and failure of multiple interventions (Metronidazole, extended, tapered and pulsed Vancomycin, Fidaxomicin and IVIG) the patient achieved symptomatic and microbiological cure with faecal transplant.

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This highlights the important role of faecal transplant in routine clinical practice for such difficult to treat patients. The case also reiterates the utmost importance of antibiotic stewardship as only one course of broad spectrum antibiotics (as in this case) may trigger a long illness with recurrent CDI with its associated high morbidity and mortality and public health implications.

Faecal transplantation in the curative treatment of recurrent CDI

The national institute for health and care excellence (NICE) considers faecal transplant in recurrent CDI to be of sufficient efficacy and safety for use in clinical practice. (4) The goal of faecal transplant is to modify the abnormal gut flora (with overgrowth of C. difficile) caused by broad-spectrum antibiotic use and restore it to a healthier microbiome.

This is done by introducing bacteria from healthy donor faeces into the gut of the patient. There has been one significant randomised controlled trial (RCT) demonstrating efficacy in which 81% of patients with recurrent, difficult to treat CDI achieved cure with 1 infusion of donor faeces (94% overall cure after 2 infusions). (5) A seminal systematic review demonstrated 92% cure among 317 patients. (6)

Although the quanitity, preparation and route of administration have not been standardised and the method not yet officially regulated, (7) faecal transplant has been proven to be cost-effective, even taking into account the cost of donor screening and other routes of administration (e.g nasojejunal tube, colonoscopy or enema). After faecal transplant, the recipient gut flora alters to resemble that of the healthy donor. (5, 6)

Relapsing clostridium difficile infection & the curative role of faecal transplant
Patient Management

Questions

1. Which of the following is a risk factor for severe Clostridium difficile infection?

A WCC >15 x10^9/L
B. Evidence of severe colitis (on abdominal examination or radiology)
C. Acute rise in serum creatinine (e.g. >50% increase above baseline)
D. Pyrexia >38.5°C
E. All of the above

2. What is a key element of appropriate antibiotic prescribing in clinical practice?

A. Prescribing the longest recommended course length to avoid developing resistance.
B. Prescribing prophylactic antibiotics where possible.
C. Intravenous route is preferable.
D. Switch to narrow spectrum as soon as possible guided by available microbiology.
E. Prescribe antibiotics if any evidence of systemic inflammatory response syndrome (SIRS).

Answers

1. E

Recognised risk factors for severe C. difficile infection include age (although non-specific) and peak white cell count (≥15x10^9/L). This level of leucocytosis was chosen to include older or immunocompromised patients who may mount a less marked white cell response. Other known risk factors are serum Creatinine and other indicators such as ileus, colitis and high fever.

Further prospective studies are needed to establish a validated severity score for risk stratification in CDI. As with all risk indicators, each case must be evaluated within the individual clinical context. PHE recommend Vancomycin (or Fidaxomicin) first line if one indicator of severe CDI is present. Also consider stool frequency and serum Albumin. (2)

RELAPSING CLOSTRIDIUM DIFFICILE INFECTION & THE CURATIVE ROLE OF FAECAL TRANSPLANT

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2. D

Antimicrobial stewardship is critically important in this era and is the responsibility of every prescriber. The rise of resistant and multi-resistant organisms and the relative shortage of new antibiotics means that we must use the antibiotics we have at our disposal responsibly in order to minimise the development of further resistance.

The increasing prominence of the Carbapenemase producing organisms (resistant to Carbapenems such as Meropenem and Ertapenem) is of particular concern. The morbidity and mortality associated with healthcare associated infections, notably Methicillin-resistant Staphylococcus aureus (MRSA), and Clostridium difficile infection are significant. Antibiotic stewardship is part of a duty of care for all patients.

The "Start smart then focus" campaign from the Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection have produced national guidance for antimicrobial stewardship. Using the right drug at the right dose at the right time for the right duration for every patient. (8)

Start smart

Antibiotics should only be prescribed having confirmed infection in the clinical context (SIRS alone may be caused by other pathologies such as pancreatitis or burn injuries). The initial prescription should take into account relevant allergies, comply with local guidelines (based on regional resistance patterns) and be fully documented in the drug chart and notes. Review dates and/or duration should be documented clearly at initial prescription. Ensure that relevant samples (blood cultures, urine, sputum) are taken prior to initiation of broad spectrum antibiotics.

Then focus

Clinical review should occur within 48 hours, including reviewing microbiology results and deciding on further management (Stopping, route switch, narrowing the spectrum, continuing, or outpatient parenteral therapy). The decision must be fully documented.

These measures should be routinely audited to ensure that standards are maintained in each centre. Infection is a significant proportion of hospital and community medicine and must be managed at the highest standard with consideration of both the individual and the wider public health implications.

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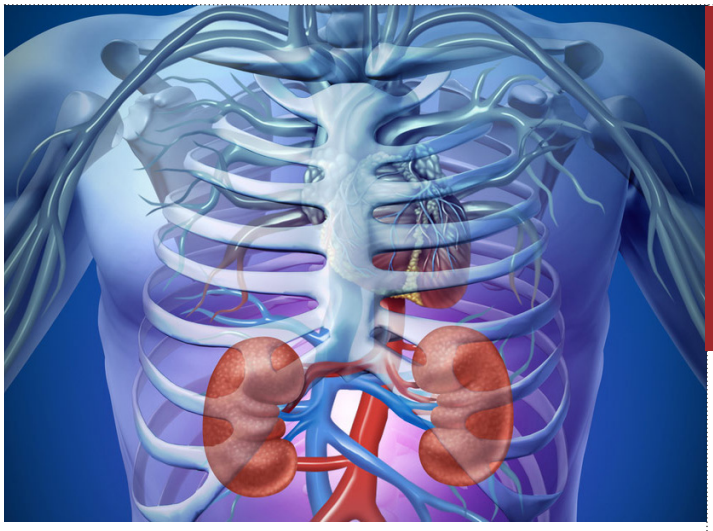
THE KIDNEY & HIV

A Shrestha & F Albaaj



The kidney & HIV
Patient Management

Case history

A 45 year old female, was referred to the Renal outpatient clinic with renal impairment (eGFR 57 ml/minute/1.73m^2) and proteinuria, with urine albumin:creatinine ratio (ACR) of 163 mg/mmol.

She was asymptomatic, with no systemic symptoms of joint pain, fever, rash or weight loss. Examination was unremarkable, normal jugular venous pressure, normal heart sounds, clear chest and no peripheral oedema.

Her past medical history consisted only of hypothyroidism and she had no family history of kidney disease. She had been pregnant twice, both times resulting in miscarriage. She was a non-smoker and did not drink alcohol.

Her blood pressure was raised at 150/100 mmHg in the clinic. Urinalysis showed blood 2+ and protein 2+.

Her bloods showed creatinine 130 µmol/l (reference 44-133), eGFR 39 ml/minute/1.73m2, albumin 31g/l (35-50), bicarbonate 28 mmol/l (22-29), CRP <5 mg/l (<5), potassium 5.0 mmol/l (3.5-5.3), haemoglobin (Hb) 12.0 g/dl (11.5-16), neutrophils 1.21 (1.7-7.5), platelets 180*10^9/l (150-450)

Working diagnosis & investigations

This patient has renal impairment which may be acute or chronic. Later, an ultrasound of the kidneys showed normal kidney size but with loss of cortico-medullary differentiation, suggesting chronic disease. Assuming this is chronic, she would have chronic kidney disease (CKD) stage 3.

The Kidney Disease Improving Global Outcomes (KDIGO) categorises CKD (Table 1) and albuminuria (table 2) as shown below.

Stage	eGFR (ml/minute/1.73m^2)	
1	>90	Normal kidney function but with abnormal urinalysis
2	60-89	
3a	45-59	
3b	30-44	
4	15-29	
5	<15 or on dialysis	Also called end stage renal failure

Table 1: Stages of chronic kidney disease.

Her urinalysis shows both microscopic haematuria and proteinuria. Whilst haematuria on its own can have either a urological or renal cause, proteinuria almost always has a renal cause. Proteinuria can be quantified by urine albumin:creatinine ratio or urine protein:creatinine ratio (both of which are now more commonly used than the cumbersome 24 hour urine collection).

Category	Urine ACR (mg/mmol)	Urine ACR (mg/g)	Terms
A1	<3	<30	Normal to mildly increased
A2	3-30	30-300	Moderately increased
A3	>30	>300	Severely increased

Table 2: Stages of albuminuria.

Urine ACR of above 220 mg/mmol is considered to be nephrotic range. Given the severe albuminuria, haematuria and renal impairment, the likeliest cause would be glomerular disease, including glomerulonephritis.

A glomerulonephritis and renal screen, which consisted of ANCA, ANA, ENA, dsDNA, complement, anti-GBM antibodies and immunoglobulins, was sent to look for a potential secondary cause of glomerulonephritis and chronic kidney disease; all the tests were negative.

A renal biopsy was performed as an outpatient and she was commenced on Amlodipine and Ramipril to control her hypertension. The histology showed glomeruli that were globally sclerosed, and one glomerulus that had focal sclerosis, suggesting a diagnosis of focal segmental glomerulosclerosis (FSGS). The GP was then asked to perform a blood borne virus screen (HIV and hepatitis) to look for a possible cause of FSGS, however the patient presented a month later to hospital (4 months following first outpatient visit) before this was achieved.

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She presented with shortness of breath, was found to be hypoxic with bilateral hilar infiltrates on chest x-ray (figure 1). Her CRP was 33 mg/l, with neutrophilia of $8.01*10^9$/l. An HIV test was performed when she was admitted, and it positive. A CT scan of the chest was performed and it showed widespread patchy ground-glass opacities bilaterally (figure 2), suggestive of Pneumocystis jirovecii pneumonia ("PJP"). Her kidney function had deteriorated; the creatinine was 225 µmol/l. She was successfully treated with IV Co-trimoxazole and highly active anti-retroviral treatment (HAART) was commenced by the Genito-urinary medicine (GUM) physician, consisting of Lamivudine, Zidovudine and Raltegravir.

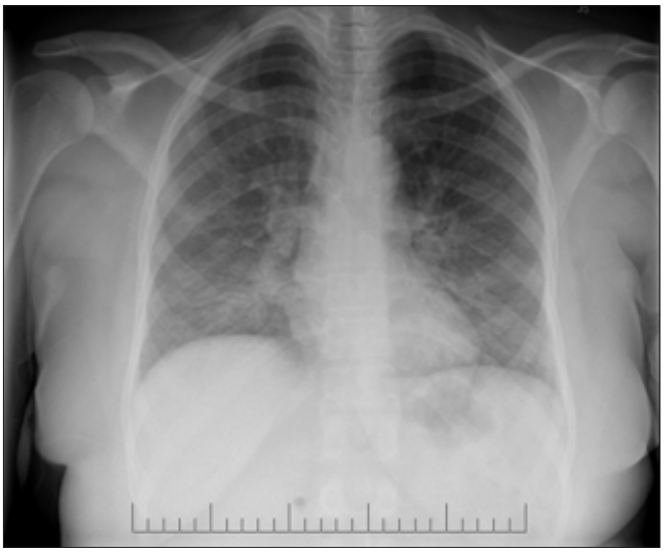


Figure 1

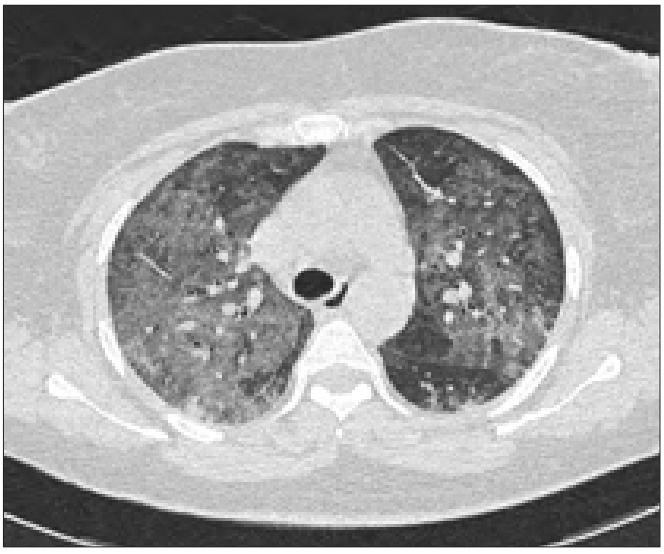
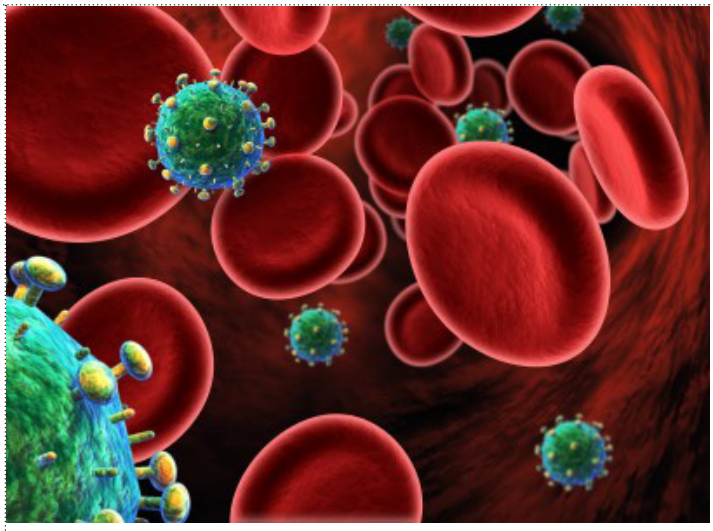


Figure 2



With HAART, her creatinine improved to 139 µmol/l (eGFR 43) by month 18. However, proteinuria remained a problem, with the urine ACR 169 mg/mmol in the same month.

Case discussion

An estimated 107,800 people were living with HIV in the UK in 2013. About 24% with HIV were unaware of their infection and at risk of transmitting it if they had unprotected sex. A late HIV diagnosis is defined as a CD4 count less than 350 cells/mm^3 within three months of an HIV diagnosis; the threshold at which anti-retroviral therapy (ART) should begin.

Although late diagnosis has improved from 57% in 2004, it remains high, with 42% (2,500) of adults (aged 15 years or above) having a late diagnosis in 2013. (2) This group presenting or being diagnosed late have the highest mortality rate despite effective treatment; a ten-fold increase in the risk of death within a year of diagnosis compared to those diagnosed with a CD4 count greater than 350 cells/mm^3 (25 vs. 2 per 1,000 population) .

The focus is now on early diagnosis, with a low threshold to screen patients. It can be argued that in our case, an HIV screen could have been offered when she had an unexplained mild neutropenia on presentation to the renal clinic, as per British HIV Association guidelines. Table 3 shows the British HIV association recommendations for HIV testing.

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System	AIDS-defining conditions	Other conditions where HIV testing should be offered
Respiratory	Tuberculosis	Bacterial pneumonia
	Pneumocystis	Aspergillosis
Neurology	Cerebral toxoplasmosis	Aseptic meningitis/encephalitis
	Primary cerebral lymphoma	Cerebral abscess
	Cryptococcal meningitis	Space occupying lesion of unknown cause
	Progressive multifocal leucoencephalopathy	Guillain Barre syndrome
		Transverse myelitis
		Peripheral neuropathy
		Dementia
		Leucoencephalopathy
Dermatology	Kaposi's sarcoma	Severe seborrhoeic dermatitis
		Severe psoriasis
		Multidermatomal or recurrent herpes zoster
Gastroenterology	Persistent cryptosporidiosis	Oral candidiasis
		Oral hairy leukoplakia
		Chronic diarrhoea
		Weight loss unkown cause
		Salmonella, shigella, campylobacter
		Hepatitis B infection
		Hepatitis C infection
Oncology	Non-Hodgkin's lymphoma	Anal cancer
		Lung cancer
		Seminoma
		Head and neck cancer
		Hodgkin's lymphoma
		Castleman's disease
Gynaecology	Cervical cancer	Vaginal intraepithelial neoplasia
		Cervical intraepithelial neoplasia grade 2 or above
Haematology		Any unexplained blood dyscrasia including thrombocytopenia, neutropenia, lymphopenia
Ophthalmology	Cytomegalovirus retinitis	Infective retinal diseases including herpesvirus and toxoplasma
		Unexplained retinopathy
ENT		Lymphadenopathy unknown cause
		Chronic parotitis
		Lymphoepithelial parotid cysts
Other		Mononucleosis-like syndrome (primary HIV infection)
		Pyrexia of unkown origin
		Any lymphadenopathy of unknown cause
		Any sexually transmitted infection

Table 3: British HIV Association guidelines on HIV testing.

HIV screening was considered following the diagnosis of FSGS during a follow-up clinic; however it was advised for the GP to perform. This was another missed opportunity, and the test was more appropriate to be performed there and then, due to the risk of delay in GP receiving the instruction, the possibility of non-attendance by the patient, the ongoing risk of being immunocompromised and risk of transmission whilst waiting for the test. Whilst the patient did end up with an opportunistic, potentially life threatening, PCP infection, she fortunately survived. She sustained a renal insult, with worsening renal function that did not return to baseline until sometime.

It is thought that 15% of those with HIV have CKD. (4) The kidneys may be involved in HIV for a variety of reasons, including: HIV associated nephropathy (HIVAN), acute kidney injury (AKI) in sepsis and nephrotoxicity from antiretroviral therapy.

HIVAN

HIVAN typically manifests as a severe form of FSGS, also known as collapsing FSGS, in which the renal biopsy shows collapse of the entire glomerulus. However, the differential diagnosis still includes primary FSGS (without an underlying cause). Black HIV-infected patients are at higher risk of HIVAN which is more likely to present with the nephrotic syndrome. This can progress rapidly to end stage renal failure without treatment of the underlying HIV infection. HIVAN is considered an AIDS-defining illness and therefore treatment is therefore commenced regardless of CD4 count.

Nephrotoxicity of antiviral drugs

Whilst it is recognised that generally HAART has a positive effect on renal function, some treatment regimens may have toxic effects on the kidney. Indinavir is the commonest protease inhibitor found to adversely affect the kidney; it causes renal stones, intratubular drug deposition, cyrstalluria, haematuria, papillary necrosis and acute interstitial nephritis. (4)

Tenofivir, a nucleoside reverse transcriptase inhbitor (NRTI) is the anti-retroviral that has received the most focus regarding nephrotoxicity. Its adverse effects include declining GFR and proximal tubular dysfunction by causing the Fanconi's syndrome.

Management

There is strong evidence to support treatment of HIVAN with antiretroviral therapy to reduce risk of progression to ESRD. Tenofovir and other nephrotoxic drugs (including NSAIDs) should be avoided. In patients receiving Tenofovir whose kidney function declines (25% from baseline, or to eGFR <60ml/minute/1.73m^2), Tenofovir should be switched to an alternative agent. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are recommended in HIVAN for albuminuria. Statins are also recommended in HIV patients with CKD in high-risk group (>7.5% 10-year risk).

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Previously, kidney transplantation was contraindicated in HIV. However, recent guidelines from UK transplant do not consider HIV a contraindication. The indications for kidney transplant remain the same as the CKD population. The outcomes show good graft and patient survival (88% survival at 3 years (7)), which lies between that of other transplanted patients and those aged >65 years (ie high risk group). Acute graft rejection rates have however been higher than population average.

Best of 5 MCQs

1. In which of the following should HIV testing be offered?

a. Proteinuria
b. Recurrent UTI
c. Chronic kidney disease
d. Pneumococcal pneumonia
e. Recurrent cellulitis

2: A 68 year old man who has been treated for HIV for 12 years has progressive chronic kidney disease. Which of the following precludes kidney transplantation as a form of renal replacement therapy?

a. Presence of HIV
b. CD4 count of 170 cells/mm^3 due to variable compliance
c. Age greater than 65
d. Previous bowel cancer resected and in remission for 11 years
e. History of percutaneous coronary intervention for coronary artery disease

Answers

1. Answer: d

According to the British HIV association, patients with bacterial pneumonia should be offered an HIV test. It should be noted that the guidelines also suggest testing in anyone where HIV enters the differential (3). Chronic kidney disease on its own does not warrant routine HIV testing, but once it is progressive (CKD 3 and above) and dialysis or transplantation is being considered, it should be performed.

2. Answer: b

Presence of HIV is no longer a contraindication to kidney transplantation, provided it is well controlled (including CD4 count >200). Both poorly controlled HIV infection (CD4 count <200 cells/mm^3) and poor compliance with treatment are contraindications. Age is not a contraindication, although greater age increases the risk of mortality. Active malignancy is a contraindication, however patients with previously cured cancer with a disease-free period (usually greater than 5 years) can be considered. Ischaemic heart disease is not a contraindication, but it should be treated and optimised.

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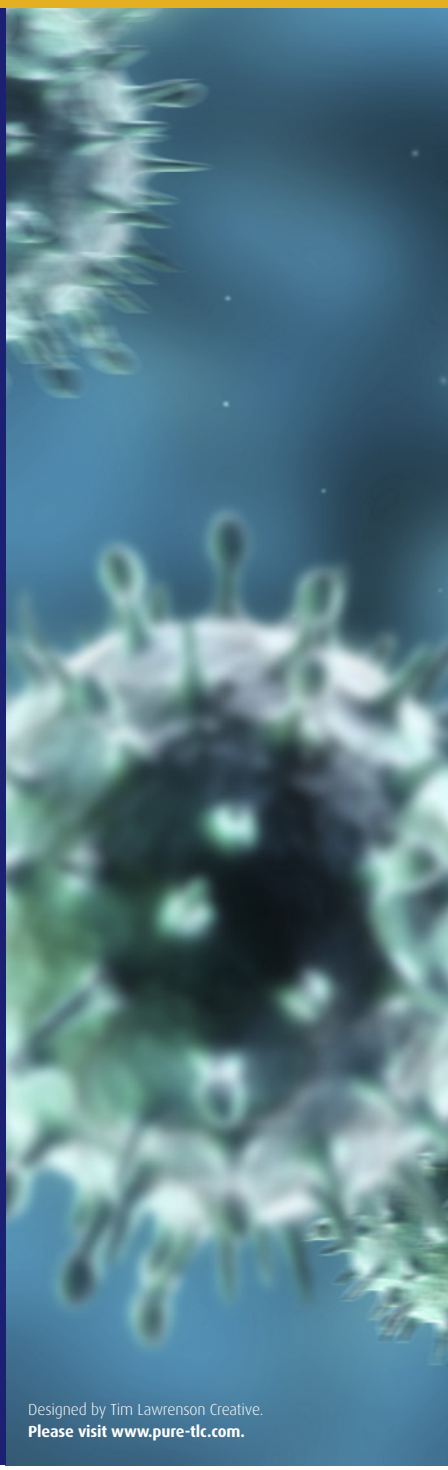

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