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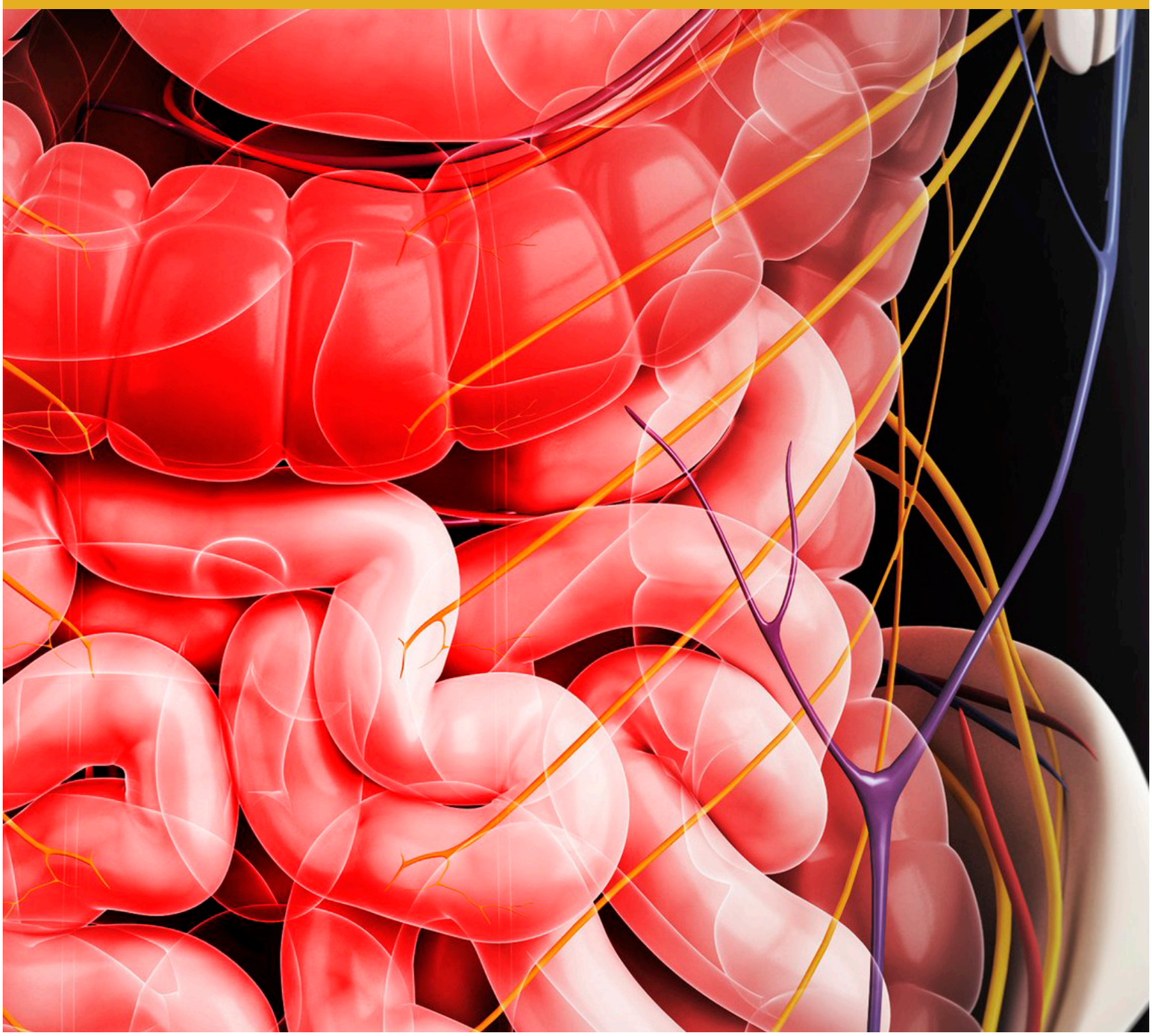

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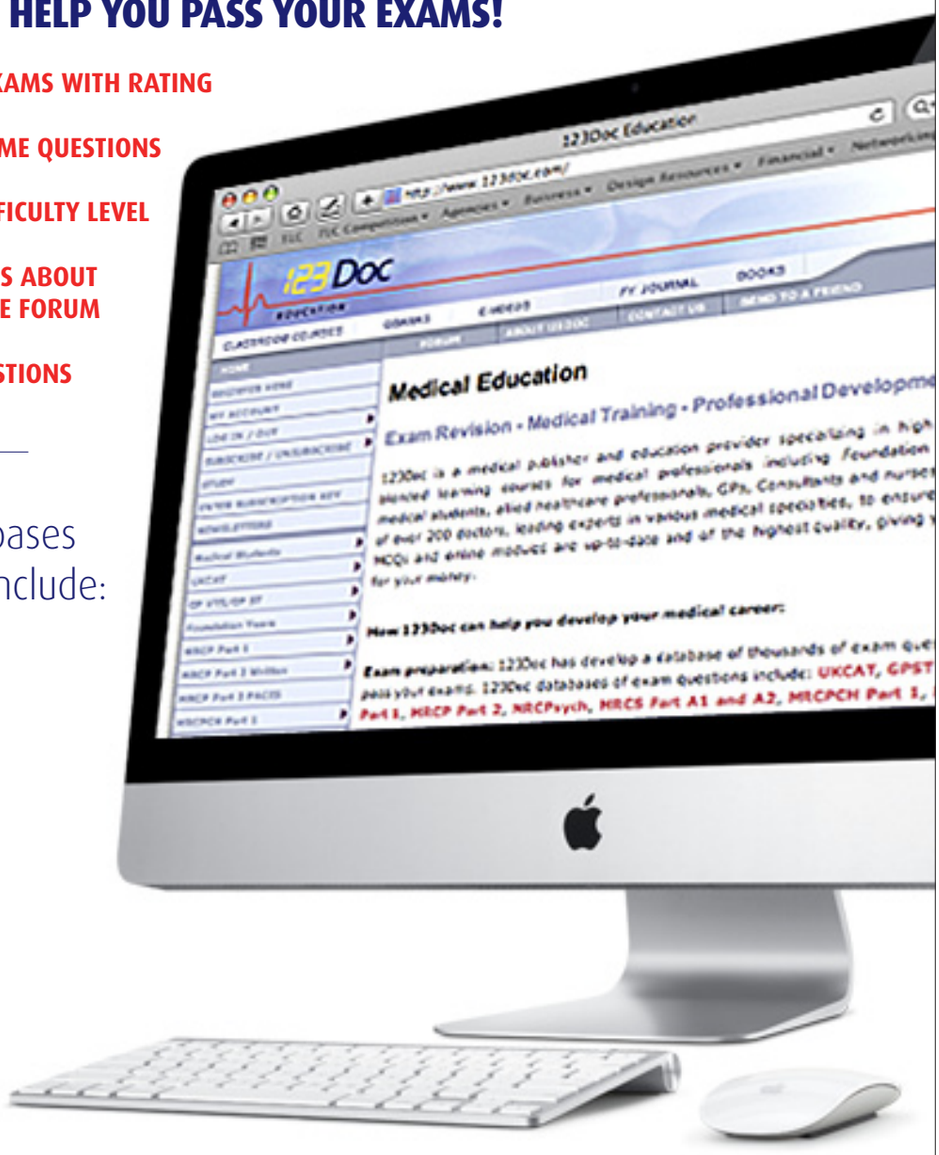

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Volume 10

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PRACTICALITIES OF MANAGING DKA: A GUIDE FOR THE FOUNDATION TRAINEE

M James, D Barnes, M Haq

Abstract

Diabetic ketoacidosis is a common medical emergency that can be associated with significant morbidity and mortality. Junior doctors often initiate treatment. Their lack of experience may contribute to management errors. The Joint British Diabetes Societies (JBDS) provide clear guidance on safe clinical management. This article uses a case study to illustrate optimal treatment; specifically, fluid therapy, insulin treatment and correction of electrolyte imbalance.

Case History

A previously well eighteen-year-old male (let's call him Mr Sweet) was referred to A&E with a two-week history of thirst and urinary frequency. He was seen by the medical team at 18.00 and appeared well. Clinical examination was normal, with pulse rate of 80 and blood pressure 123/73. Initial investigations were as follows:

- *Urine dipstix: ketonuria 3+ and glucose 3+, negative for nitrites and leucocytes.*

- *Venous blood gas (VBG): pH 7.20, K+ 4.9mmol/L, glucose >41.6mmol/L, HCO_3 20.0mmol/L.*

- *Lab bloods: glucose 46.2mmol/L, full blood count normal, enzymatic creatinine 64umol/L, Na+ 127mmol/L, K+ 5.0 mmol/L.*

Q1: As the junior doctor first assessing the patient, you suspect diabetic ketoacidosis?

How would you make this diagnosis?

Diabetic ketoacidosis (DKA) is a metabolic state induced by insulin deficiency resulting in hyperglycaemia, acidosis and ketonaemia (1). It is a common and potentially life-threatening complication in those with known diabetes but occasionally may be the initial presentation of undiagnosed type 1 diabetes. Diagnosis requires three specific findings:

1. Diabetes mellitus (known diagnosis) or blood glucose >11.0mmol/L

2. Ketosis: serum ketones >3.0mmol/L or urine ketones ++ or more

3. Acidosis: bicarbonate <15mmol/L or venous pH <7.3

Q2: What should be the first priority in the management of this patient with confirmed DKA?

Management should follow the Joint British Diabetes Societies' (JBDS) National guidelines (2). The following management should be initiated within the first 60 minutes from the time of diagnosis:

1. Check airway

Many patients are unable to protect their own airway due to drowsiness and vomiting. Seek senior advice and urgently contact critical care.

2. Urgent IV access and fluids

Prompt fluid replacement is required as patients are often significantly dehydrated. The fluid of choice is 0.9% Saline. Typical fluid replacement is illustrated in Figure 1 and is based on a 70kg adult. The degree of fluid replacement is dependent on a number of factors and should be guided by clinical parameters such as weight and urine output.

More cautious fluid replacement is required in young adults (18-25) (as there is a risk of cerebral oedema due to osmotic shifts), and the elderly, pregnancy and individuals affected by heart or renal failure due to potential fluid overload. If a patient remains hypotensive (systolic <90 mmHg) despite initial fluids, urgently seek senior advice and contact critical care.

3. Arrange investigations

Full blood count, electrolytes, and laboratory glucose. Consider serum amylase if abdominal pain is present as pancreatitis may present with similar symptoms to DKA. Also take blood cultures (if febrile), urine dipstix and culture and a chest X-ray.

These investigations, however, should not delay initial treatment. Continuous cardiac monitoring should follow a 12-lead ECG. Consider nasogastric tube insertion if drowsy or vomiting to avoid aspiration.

4. Fixed rate intravenous insulin infusion (FRIII)

All patients should be started on a FRIII based on 0.1 units per kg body weight per hour. Add 50 Units of soluble human insulin (eg., Actrapid) made up to 50ml with 0.9% Saline administered using a syringe driver.

PRACTICALITIES OF MANAGING DKA: A GUIDE FOR THE FOUNDATION TRAINEE

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5. Potassium replacement

Derangement is common in DKA and can be life-threatening. Serum potassium is often initially high but typically falls with insulin delivery. However, if initial potassium is low as a consequence of vomiting, then prompt correction is required. Following initial fluids, regular monitoring should guide further potassium replacement (Table 1).

Mr Sweet: *met the diagnostic criteria for DKA. His systolic BP (SBP) was greater than 90mmHg on admission, so he received 1L of 0.9% Saline over the first hour. The patient weighed 60kg, so the FRIII was started at 6 units per hour. Subsequent bags of 0.9% Saline were prescribed with potassium supplementation.*

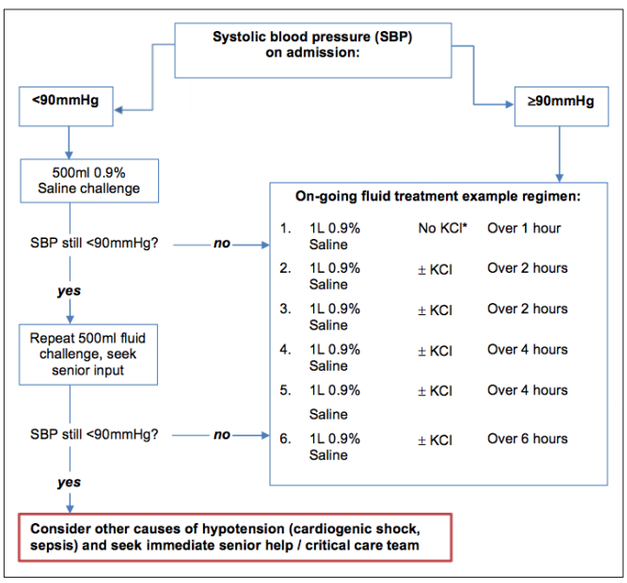

Figure 1: Fluid replacement in DKA.

Serum	K+ replacement
>5.5	Nil
3.5-5.5	40mmol/L
<3.5	Senior review*

**options include speeding up fluids or giving more concentrated potassium.*

Table 1: Potassium replacement.

Q3: How would you manage the patient between 60 minutes to 12hrs?

Further management should focus on clearing blood ketones, maintaining safe potassium levels and preventing hypoglycaemia. Run a VBG at 60 minutes, two hours and then every two hours until acidosis resolves.

1. Re-assess the patient regularly: *monitor fluid balance and maintain urine output above 0.5ml/kg/hour (consider catheterisation).*

2. Review metabolic parameters: *blood ketone testing is the recommended means of assessing ketonaemia but if this is not available check urine instead. Acidosis should be assessed using venous pH levels. If metabolic targets (Table 2) are not achieved, the FRIII will need to be increased with repeat VBG arranged subsequently. Once blood glucose is <14mmol/L, start IV 10% Dextrose to run concurrently alongside IV 0.9% Saline, as this needs to continue for fluid replacement.*

3. Identify and treat precipitating factors: *such as infection.*

4. Prescribe prophylactic low molecular weight heparin*: patients are at increased risk of venous thromboembolism.*

Mr Sweet: *was started on Levemir 10 units at night. VBGs were requested 2 hourly and the acidosis resolved two hours into his admission.*

Q4: What are the common pitfalls in the management of DKA?

• Over-zealous fluids, or insufficient fluid therapy.

• Use of a variable rate intravenous insulin infusion (VRIII) ('sliding scale'): FRIII clear ketonaemia and corrects acidosis more promptly.

• Use of arterial blood gases: repeated venous sampling is traumatic to the patient.

• Insufficient potassium monitoring and replacement: potassium can fall very quickly, therefore two-hourly VBGs are desirable during this stage.

• Switching 0.9% Saline to Dextrose once blood glucose falls: 10% Dextrose (run over 8 hrs) is required once blood glucose falls <14mmol/L in order to prevent hypoglycaemia; however 0.9% Saline should continue to run concurrently for fluid replacement.

• Relying on urinary ketones to look for DKA resolution: urinary ketones can be still be detected even though ketone body production by the liver has ceased.

PRACTICALITIES OF MANAGING DKA: A GUIDE FOR THE FOUNDATION TRAINEE

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Target	Action if not achieved
Fall in blood ketones by >0.5mmol/L per hour	Increase FRIII by 1.0 unit per hour, until ketones are falling sufficiently
Rise in venous bicarbonate by >3.0mmol/L per hour	Increase FRIII by 1.0 unit per hour, until venous bicarbonate is falling sufficiently
Fall in capillary glucose by >3.0mmol/L per hour	Increase FRIII by 1.0 unit per hour, until plasma glucose is falling sufficiently

Table 2: Metabolic targets.

Q5: What complications might you encounter in a patient with DKA?

• Fatality – although most patients with DKA recover, some patient will die. It is important to urgently contact critical care if the patient is unable to protect their own airway (due to drowsiness and vomiting) and for those with severe hypotension and other complications (see below).

• Cardiac arrest due to hypokalaemia induced arrhythmias and/or underlying ischaemic heart disease.

• Pulmonary oedema due to excessive fluid replacement.

• Cerebral oedema: a rare, unpredictable complication. most commonly seen in children and young adults.

• Multi-organ failure.

• Venous thromboembolism.

Q6: What should you do once the patient is improving?

Between 6-12 hours you should review biochemical parameters and look for resolution of DKA (Figure 2). If resolved and the patient can eat, they should be converted to subcutaneous insulin.

If the patient is not eating, then switch to VRIII. If DKA has not resolved, then continue to monitor 2 hourly and adjust FRIII as discussed previously. DKA usually resolves by 12-24 hours. It is unusual for DKA to have not resolved by 24 hours; seek senior advice if this is the case.

• *Serum ketones <0.6mmol/L (or trace or no urine ketones)*
AND
• Venous pH >7.3

Figure 2: Resolution of DKA.

Mr Sweet: *VBG after six hours showed glucose of 5.0mmol/L and a normal pH. Urine at this point was negative for ketones. Resolution of DKA was confirmed, so the FRIII was switched to a VRIII, with 10% Dextrose running (as blood glucose was <14mmol/L).*

Q7: How do I start subcutaneous insulin?

The diabetes specialist team should ideally do this but as a general rule, a subcutaneous bolus of rapid-acting insulin should be given with a meal with the insulin infusion stopped 30-60 minutes later. Basal insulin must be started in a patient with newly diagnosed diabetes before the FRIII or VRIII can be discontinued. See Figure 3 for guidance on starting insulin.

Mr Sweet: *received Levemir on the night of admission and then received 4 units of NovoRapid with lunch the next day, after which his VRIII was stopped an hour later.*

Q8. What are the common pitfalls surrounding recovery?

• Relying on venous bicarbonate (rather than venous pH) as a marker of resolution: administration of 0.9% Saline can lead to hyperchloraemic acidosis and a lower than expected bicarbonate, impairing recognition of DKA resolution.

• Unnecessarily keeping the patient on FRIII once biochemical recovery is achieved. Start subcutaneous insulin, or switch to VRIII, depending on whether the patient is eating or not.

• Stopping FRIII or VRIII without starting subcutaneous insulin: IV insulin has a short half-life (5 minutes) so meal-time insulin must be administered before stopping FRIII/VRIII 30 to 60 minutes later, to avoid re-bound hyperglycaemia.

• In a patient with pre-existing type 1 diabetes, it is essential to continue background (long-acting) insulin even if a patient is admitted with DKA and requires FRIII.

This helps to avoid the risk of rebound hyperglycaemia when a patient resumes their usual insulin regimen. In a newly diagnosed type 1, it is essential to start basal insulin before stopping either a FRIII or VRIII when converting to meal-time subcutaneous insulin.

PRACTICALITIES OF MANAGING DKA: A GUIDE FOR THE FOUNDATION TRAINEE

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Calculate the Total Daily Dose (TDD) required based on body weight

TDD = patient's weight in kg x 0.3 units

For a basal bolus regime: give 50% of the TDD as long acting insulin at bedtime and divide the remaining 50% equally into three as rapid acting insulin at each meal.

Worked example

Patients weight = 80kg. The TDD would be 80 x 0.3 = 24 Units.

- *Prescribe 12 units as long acting insulin (eg., Levemir) at bedtime.*

- *And 4 units rapid acting insulin (eg. NovoRapid) at breakfast, lunch and dinner.*

Figure 3: Insulin requirements in newly diagnosed type 1 diabetes.

Conclusion

DKA can be both a challenging and intimidating condition to manage as a junior doctor. National guidelines provide clear recommendations in ensuring safe clinical management, which will help reduce the morbidity and mortality associated with the condition. Cornerstones of treatment include fluid therapy, FRIII and electrolyte correction, in conjunction with regular review. Early referral to the diabetes specialist team is recommended.

MCQs

MCQ 1: Your patient has 3+ ketonuria and their VBG shows pH 7.02, HCO_3 16.7mmol/L, glucose 48mmol/L. How do you prioritise your treatment?

a) Subcutaneous bolus of rapid acting insulin bolus ➔ cannula and bloods ➔ start fluids ➔ tart fixed rate insulin infusion

b) Subcutaneous bolus of rapid acting insulin bolus ➔ cannula and bloods ➔ start variable rate insulin infusion ➔ start fluids

c) Cannula and bloods ➔ start fluids ➔ start fixed rate insulin infusion

d) Cannula and bloods ➔ start fixed rate insulin infusion ➔ start fluids

e) Cannula and bloods ➔ start fluids ➔ start variable rate insulin infusion

MCQ 2: You have been treating your patient with DKA for 18 hours. They are still acidotic (pH 7.21), with blood ketones of 1.3mmol/L (similar to two hours ago). Their FRIII is running at 7.5 units/hour. What action do you take?

a) Seek senior advice and make no changes to the FRIII

b) Seek senior advice, increase the FRIII to 8.5units/hour and repeat VBG in one hour

c) Seek senior advice, make no changes to the FRIII and repeat a VBG in one hour

d) Increase FRIII to 9 units/hour and repeat VBG in one hour

e) Give an additional 5 units of Actrapid subcutaneously and repeat VBG in one hour

MCQ 3: A 30-year old male presents to AE with DKA. After an initial 1L 0.9% Saline, he has a pH of 6.82, HCO_3 4.1 mmol/L and K+ 4.1 mmol/L on venous gas. They remain unwell with a blood pressure of 99/54. What is the next fluid of choice?

a) 1L of Hartmann's solution run over one hour

b) 500ml 1.26% sodium bicarbonate run over 15 minutes

c) 500ml 2.74% sodium bicarbonate run over 15 minutes

d) 1L of 0.9% Saline run over thirty minutes

e) 1L of 0.9% Saline with 40mmol/L KCl run over one hour

MCQ 4: Your patient with known type 1 diabetes and an episode of DKA has shown biochemical recovery at 9am. All of their normal insulin (Levemir 28 units at night, NovoRapid with meals) was stopped yesterday morning when they commenced a FRIII for DKA. They can now eat and drink. What action do you take?

a) Give them NovoRapid with lunch and stop the FRIII one hour later

b) Give 14 units of Levemir now, NovoRapid with lunch and stop the FRIII one hour later

c) Give 1.5 times the normal lunch NovoRapid dose and bring the FRIII down one hour later

d) Switch them to a VRIII, give NovoRapid with lunch and then bring the VRIII down one hour later

e) Give 28 units of Levemir now, keep nil by mouth and continue the FRIII

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Answers

Answer 1: C

IV access is always the first priority in management of DKA, as infusions are the mainstay of treatment. Fluid resuscitation takes priority above insulin as these patients are often profoundly dehydrated. FRIII is preferred over VRIII as more aggressive insulin treatment clears ketones and acidosis more promptly.

Answer 2: B

By the 12-24 hour window, DKA should be resolving. If it has not improved by this point, urgent senior help is required. Metabolic improvement targets in DKA are a reduction in blood ketones of at least 0.5mmol/L per hour, an increase in venous bicarbonate of at least 3mmol/L per hour and a fall in blood glucose of at least 3mmol/L per hour.

If these have not been achieved, then the FRIII should be increased by 1.0 unit/hour, with a repeat test after one hour to see if further adjustments are needed. In this case blood ketones have failed to fall over the last two hours. The FRIII rate should be increased whilst awaiting a senior review.

Answer 3: E

Bicarbonate is not indicated in the treatment of DKA as insulin treatment and fluids will ultimately correct acidosis (3). Giving bicarbonate can be counter-productive as acidosis helps maintain oxygen delivery to tissues by means of the Bohr effect.

As his systolic blood pressure is above 90mmHg, he no longer needs fluid challenges and can be commenced on the fluid regimen suggested by National guidelines, commencing with 1L 0.9% Saline over one hour. As he has already had 1L of 0.9% Saline, it is pertinent to consider potassium replacement with further administration of fluids.

Answer 4: B

As the patient has recovered from DKA they no longer need to be on a FRIII, so this should come down as soon as possible. As the patient can eat and drink, it is appropriate to switch them directly to subcutaneous insulin at lunchtime.

Unfortunately, their background insulin was incorrectly withheld the night before and it is therefore important to provide some background insulin prior to discontinuation of the FRIII. Half the standard bedtime dose of Levemir should be administered straight away. Their standard dose of Levemir can be reintroduced at bedtime.

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CASE STUDY: DIFFICULTY IN MANAGING ACUTE KIDNEY INJURY IN A POST-OPERATIVE PATIENT WITH DIABETES

H Wells, D Jenkins

Abstract

A 73-year old man was admitted with multiple type 2 diabetes-related complications that resulted in a prolonged hospital admission. Foot sepsis, acute kidney injury (AKI) and difficulties with fluid balance were chiefly responsible. These problems were compounded by side-effects of drug treatment. The case highlights the difficulties faced when managing patients with complex co-morbidities and polypharmacy, which despite being a common presentation, is often poorly managed.

Case History

This 73-year old man had been diagnosed with diabetes 30 years previously. Long-term glycaemic control had been suboptimal. He was using high doses of insulin to maintain glycaemic control, which consisted of 74 units of Novomix30 with breakfast and 12 units at lunch and dinner. He had previously undergone a triple coronary artery bypass graft operation, been diagnosed with peripheral neuropathy and a right sided Charcot foot, peripheral vascular disease, chronic kidney disease, and diabetic retinopathy. The Charcot foot had resulted in significant residual deformity.

He presented to hospital in September 2015 with increasing pain in his right foot. On examination, his blood pressure was 144/66 mm Hg, and both the 1st and 3rd toes of the right foot were dry and gangrenous. His foot pulses were weak but palpable, and his peripheries were cold (Ankle Brachial Pressure Index = 0.54). An X-ray of the right foot showed no obvious evidence of osteomyelitis. Both toes were amputated and, following a course of antibiotics, he was discharged home. His Creatinine was noted to be 150mcmol/l at discharge.

He was readmitted with wet gangrene of the right foot in October 2015, one week following his discharge from hospital. He was experiencing rest pain in his right leg, and his right sided lower limb pulses were not palpable. He had diffuse peripheral oedema, and bilateral effusions on chest radiograph. Duplex ultrasonography was performed which revealed posterior tibial artery occlusion and popliteal stenosis. He was diagnosed with critical limb ischaemia, sepsis, and fluid overload. Creatinine levels had risen to 200mcmol/l. Serum albumin was 38g/L, wound cultures revealed pseudomonas growth and CRP was noted to be CRP 110mg/L.

The patient underwent an arteriogram followed by an anterior tibial artery angioplasty. This was preceded by cautious pre-hydration to minimise the impact on his renal function. Despite this, creatinine levels rose from 194mcmol/l to 225mcmol/l. After the procedure he became acutely breathless. On examination, there were widespread fine end-expiratory crackles, and a chest radiograph confirmed acute pulmonary oedema. His arterial blood gases demonstrated a type 1 respiratory failure.

An intravenous infusion of furosemide and CPAP (via mask) was commenced. The indication for CPAP was the type 1 respiratory failure that was not responsive to oxygen therapy via facemask. Albumin and BNP were 33g/L, and 12937ng/L respectively. Maggots were applied to the gangrenous foot. Blood glucose control was optimized with an intravenous insulin infusion. Albumin fell to 27g/L and CRP rose to 374mg/L.

The Furosemide infusion was associated with worsening renal function. Furosemide boluses (80mg three times a day), were substituted. Despite therapy with furosemide, he remained grossly oedematous. Alternative diuretics (spironolactone and metolazone) were trialled, and his fluid intake was restricted to one litre daily. Other medicines included ramipril and opiate analgaesia. His creatinine rose to 240mcmol/l. The diagnosis was updated to gross oedema, probably attributable to a combination of congestive cardiac failure, acute kidney injury, and iatrogenic intravenous fluid therapy.

The patient became increasingly oedematous and resistant to diuretics. Renal replacement therapy (haemofiltration) was considered but it was felt that the patient's cardiovascular status was too unstable to tolerate this. He became delirious, increasingly drowsy and hypoxic despite increasing oxygen therapy.

Extensive multidisciplinary discussion concluded that in view of his multi-organ dysfunction, multiple co-morbidities, and poor physiological reserve, active treatment should be discontinued. The palliative care team was involved and all regular medications and CPAP were withdrawn. His extensive medication list can be viewed in Table 1. Creatinine levels were 282mcmol/l when the decision for palliation was made.

CASE STUDY: DIFFICULTY IN MANAGING ACUTE KIDNEY INJURY IN A POST-OPERATIVE PATIENT WITH DIABETES

H Wells, D Jenkins

Clopidogrel 75mg OD	Enoxaparin 20mg OD	Aspirin 75mg OD
Amlodipine 10mg OM	Ramipril 1.25mg OD	Isosorbide Mononitrate 40mg BD
Clindamycin 600mg QDS	Pipperacillin/ Tazobactam 4.5g BD	Novomix 30, 53 units AM, 12 units PM
Spironolactone 25mg OD	Furosemide 80mg BD	Metolazone 10mg OM
Levothyroxine 150mcg OD	Atorvastatin 80mg ON	Lansoprazole 15mg OD
Ferrous Sulphate 200mg TDS	1-Alfacalcidol 0.5mcg OD	Lactulose 15ml BD
Paracetamol 1g QDS	Codeine 60mg PRN	Morphine Sulphate 10mg PRN
Gabapentin 300mg TDS	Tramadol 100mg PRN	

Table 1: A medication list at the time of withdrawal of treatment.

24 hours later the patient became more alert. Over the next few days he slowly improved until he was fully awake and communicating verbally. In view of his improvement active treatment (insulin and judicious diuretics) was reinstated.

He continued to make progress and was eventually discharged home in early December 2015. Insulin therapy at discharge consisted of twice daily Novomix 30, with 40 units at breakfast and 10 units at dinner. Creatinine levels had improved to 189mcmol/l on discharge.

In late December 2015 he was readmitted with a sloughy wound and cellulitis tracking up his right leg. He had developed a new, dry, necrotic right-heel ulcer. This was initially managed conservatively with dressings, and antibiotics for suspected osteomyelitis. He was noted to have an elevated CRP (339mg/L), and a white cell count (22.1 x 10^9/L).

A right-sided below knee amputation was performed to control sepsis. Limb salvage surgery to treat his heel-ulcer was considered futile due to poor wound healing. This surgery was complicated by a post-amputation haematoma which required surgical evacuation twice. His renal function deteriorated again following surgery. He is currently being assessed for a hospital haemodialysis programme.

Discussion

This gentleman presented with critical limb ischaemia and sepsis. This was accompanied by severe acute kidney injury, followed by pulmonary oedema and delirium. Factors that contributed to the AKI are listed in Table 2. Iatrogenic causes (contrast angiography and drugs) were significant contributors in this case.

Contributor to AKI	Non-iatrogenic	Iatrogenic
	Diabetic nephropathy	Radiological contrast
	Renovascular disease	Diuretics
	Sepsis	ACE inhibitors
	Hypoxia	

Table 2: Factors that contributed to the AKI.

It proved very difficult to balance this worsening renal function with increasing fluid overload, which progressed to pulmonary oedema and respiratory failure. Opiate toxicity due to reduced renal clearance compounded his deterioration. Withdrawal of therapy reduced the renal insult and opioid toxicity, leading to significant overall improvement. Figure 1 illustrates the change in serum creatinine with time.

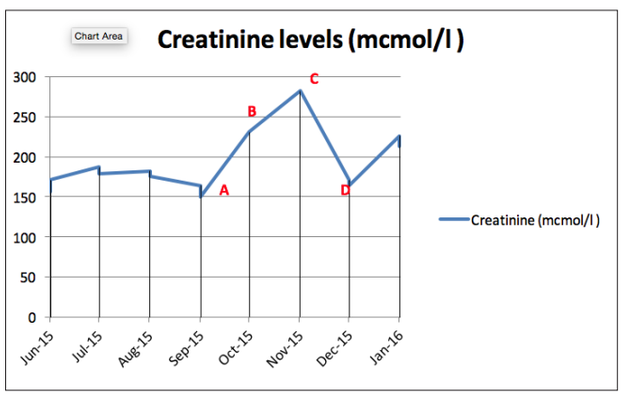

Figure 1: Creatinine levels of the patient discussed. Creatinine can be seen to sharply drop following the decision for palliation in late November. Point A demonstrates the patient's initial admission for toe amputations.

Point B represents when the patient was readmitted with critical limb ischaemia. Point C demonstrates when a decision for palliation was made. Point D shows creatinine levels at discharge.

CASE STUDY: DIFFICULTY IN MANAGING ACUTE KIDNEY INJURY IN A POST-OPERATIVE PATIENT WITH DIABETES

H Wells, D Jenkins

Diabetes and post-operative recovery

Diabetes impairs wound healing if poorly controlled. Local tissue ischaemia and neuropathy both delay the healing process. A combination of chronic hyperglycaemia and a pro-inflammatory environment increases the susceptibility of the wound to infection, by inhibiting cells essential to good wound repair (macrophages, neutrophils and fibroblasts).

Hyperglycaemia also causes decreased efficacy of cytokines and growth factors. For surgical patients, it is proven that poor glycaemic control in hospital results in increased morbidity and mortality. Animal studies have shown that the strength of wounds is impaired in diabetes. This patient was known to have poorly controlled diabetes with chronically elevated HbA1c levels, and this will have undoubtedly impacted on wound healing in his lower limbs.

Other factors that interfered with our patient's post-operative recovery were his ischaemic heart disease (predisposing him to left ventricular failure and pulmonary oedema) and chronic kidney disease (predisposing him further to pulmonary oedema and also opiate toxicity).

Diabetes and renal disease

Diabetic nephropathy presents with worsening renal function, hypertension and progressive albuminuria, resulting in glomerular sclerosis and fibrosis. The glomerular basement membrane becomes thickened due to mesangial cell proliferation, matrix expansion and vascular endothelial damage driven by hyperglycaemia. Kimmelstiel-Wilson lesions can be seen on microscopy in the late stages of this disease.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) advise annual screening of patients with type 2 diabetes for kidney disease, with a urinary albumin:creatinine ratio, and measurement of serum creatinine and eGFR. CKD can be diagnosed as attributable to diabetes if there is confirmed presence of macroalbuminuria (ACR >300 mg/l) on two first void specimens, or microalbuminaemia (30-300 mg/l) with diabetic retinopathy.

If there is isolated microalbuminaemia but no diabetic retinopathy, it is important to consider other causes of CKD. ACE inhibitors such as Ramipril are useful in slowing the rate of deterioration of renal function in diabetic nephropathy and other proteinuric renal diseases.

This patient was known to have a background of diabetic nephropathy. In addition he was known to have peripheral vascular disease, making renovascular disease a likely contributor to his CKD. His renal function deteriorated during his admission primarily as a result of iatrogenic causes, including contrast angiography and polypharmacy.

Contrast-induced renal failure is the third most common cause of hospital acquired renal failure. Patients with both diabetes and CKD are at extremely high risk of contrast-induced nephropathy. In addition this patient had foot sepsis. Sepsis is also known to cause AKI.

Of those with sepsis approximately 20% can be expected to develop an AKI. An acute kidney injury is believed to be due to ischaemic-reperfusion injury, direct inflammatory injury, coagulopathy and apoptosis during sepsis. On top of this, drugs are also likely to have contributed to the AKI.

Polypharmacy

Furosemide is a loop diuretic, which acts by inhibiting the sodium-potassium-chloride channel in the thick ascending limb of the nephron. Metolazone is a thiazide-like diuretic which inhibits the sodium-chloride transporter in the distal tubule of the nephron. Spironolactone is a potassium sparing diuretic that acts in the distal tubule. The combination of these three diuretics contributed to the worsening renal function in this patient.

The mechanisms for this are likely to include intravascular depletion, changes to intraglomerular haemodynamics and interstitial nephritis. In addition, ACE inhibitors (such as Ramipril) aggravate the decline in renal function in volume-depleted patients, particularly in the context of renovascular disease, because of their effect on reducing intra-glomerular pressure. Polypharmacy is known to have many negative effects.

The duration of polypharmacy has been directly linked to occurrence of AKI. Half of all commonly prescribed drugs are renally excreted, and therefore dosing must be appropriately adjusted for patients with renal failure. In this patient, the combination of AKI and morphine caused a downward spiral of opiate accumulation, contributing to his drowsiness and delirium. In retrospect, an opiate such as Alfentanil would have been preferable to morphine as it is predominantly excreted by the liver .

CASE STUDY: DIFFICULTY IN MANAGING ACUTE KIDNEY INJURY IN A POST-OPERATIVE PATIENT WITH DIABETES

H Wells, D Jenkins

Summary

Patients with multiple complications of diabetes are particularly susceptible to complications of medicines, especially during the post-operative period. Our case demonstrates that frequent review of all medicines is needed in such patients to balance the potential harms of drugs against their potential benefits.

MCQs

1) Which of the following medications will not exacerbate renal failure?

a) Naproxen

b) Gentamicin

c) Heparin

d) Cisplatin

e) Methotrexate.

2) Which of the following is not a risk factor for developing diabetic nephropathy?

a) Having chronically elevated HbA1c levels

b) Being of African-American ethnicity

c) Being overweight or obese

d) Having a diagnosis of diabetic neuropathy/retinopathy

e) Taking a regular ACE inhibitor

3) Which of the following is not a feature of opioid toxicity?

a) Tremor

b) Pupillary Mydriasis

c) Respiratory Depression

d) Nausea and vomiting

e) Conjunctival Injection

4) Which of the following diuretics acts upon the ascending loop of Henle on the Na+-K+-2Cl– symporter to inhibit sodium, potassium and chloride reabsorption?

a) Bendroflumethiazide

b) Mannitol

c) Spironolactone

d) Bumetanide

e) Metolazone

5) Which of the following is specific to diabetes?

a) Renovascular disease

b) Kimmelstiel-Wilson lesions

c) Retinal cotton wool spots

d) Peripheral neuropathy

e) Cataract

CASE STUDY: DIFFICULTY IN MANAGING ACUTE KIDNEY INJURY IN A POST-OPERATIVE PATIENT WITH DIABETES

H Wells, D Jenkins

Answers

1. Answer = c)

Heparin does not exacerbate renal failure, although its dose must be adjusted in renal failure as it is renally excreted. NSAIDs such as Naproxen reduce renal blood flow and are known to be nephrotoxic. Gentamicin is an aminoglycoside which is directly nephrotoxic. Cisplatin is a chemotherapy drug which is nephrotoxic. Methotrexate is an antimetabolite and antifolate drug which is also nephrotoxic.

2. Answer = e)

Taking an ACE inhibitor. An ACE inhibitor in diabetic nephropathy decreases levels of protein in the urine and slows the progression of the disease, whilst also lowering blood pressure. ACE inhibitors can, however, aggravate AKI in renovascular disease and volume depletion.

Having chronically elevated HbA1c levels implies poor glycaemic control and therefore increased risk of diabetic nephropathy. Certain ethnic groups are at an increased risk of developing diabetic nephropathy, including African-Americans, Mexicans and Pima-Indians. Obesity is a risk factor for developing diabetic nephropathy. The presence of other microvascular complications such as neuropathy and retinopathy indicate an increased risk of nephropathy.

3. Answer = b)

Pupillary Mydriasis. Typically pupillary miosis (constriction) is seen in opiate toxicity. The other features listed are all common in opiate overdose.

4. Answer = d)

Bumetanide. Bumetanide is a loop diuretic, and has the same mechanism of action as Furosemide. Mannitol is an osmotic diuretic. Spirinolactone is a potassium sparing diuretic, and Metolazone and bendroflumethiazide are both thiazide-like diuretics.

5. Answer = b)

Kimmelstiel-Wilson lesions are microscopic changes seen specifically in diabetic nephropathy. Renovascular disease is typically due to atheroma which is more commonly but, not exclusively, seen in diabetes. Retinal cotton wool spots are typically seen in retinal ischaemia of any cause. Peripheral neuropathy is most frequently caused by diabetes in the UK but has many other causes.

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APPROACH TO THE PITUITARY INCIDENTALOMA

D Barnes, S Arshad, M Haq

Abstract

A "pituitary incidentaloma" is defined as a previously unsuspected lesion that is detected on an imaging study performed for reasons other than pituitary symptoms. Due to the increased use of imaging studies, the frequency of pituitary incidentalomas has been reported to be between 4-20% by CT and 10-38% by MRI scans (1-3).

This article aims to highlight the evaluation and management of a pituitary incidentaloma by way of a case study. The clinical and biochemical implications in relation to structure and function are discussed.

Case study

A 71 year old gentleman was referred to the Endocrine Clinic as he was discovered to have a 2.5cm pituitary adenoma as an incidental finding when being investigated for hearing loss in the ENT clinic. His past medical history included type 2 diabetes, hypertension, a coronary artery bypass graft and peripheral neuropathy. His medications consisted of metformin, perindopril, indapamide and atorvastatin.

You are the doctor in the Endocrine Clinic. What additional questions are important to consider in the history?

In endocrinopathies, patients may present with problems relating to the structure or function of a gland or both. This patient has a macroadenoma as the tumour is >10 mm in size. It is important therefore to ask about any visual symptoms, as compression of the optic chiasm by the pituitary tumour may lead to visual field loss. Headache may also be present but there are no distinguishing features of this symptom in patients with a macroadenoma. Diplopia (due to oculomotor nerve compression by lateral extension of the tumour) is a less common feature.

The key diagnoses to consider for a "hyperfunctioning" pituitary adenoma are acromegaly (growth hormone, GH), Cushing's disease (ACTH) and a prolactinoma (prolactin). Acromegaly and Cushing's disease are usually associated with symptoms and typical clinical features. Symptoms of acromegaly include sweating, increased size of hands and feet, enlargement of the jaw, headache and visual disturbance. It can be associated with type 2 diabetes, sleep apnoea and carpal tunnel syndrome. Symptoms of Cushing's disease include central obesity with proximal muscle weakness, easy bruising, thin skin, and abdominal striae which are typically dark in colour.

A prolactinoma in a man may present with reduced libido, erectile dysfunction, infertility and gynaecomastia. Galactorrhoea may also occur but is a rare symptom compared to women with prolactinomas – oligomenorrhoea/amenorrhoea may also be a symptom in pre-menopausal women. Very rarely, a pituitary adenoma may secrete TSH inappropriately leading to a hyperthyroid clinical picture. Bleeding into a pituitary adenoma may occur (apoplexy) but this is invariably associated with acute symptoms, such as severe headache, visual disturbance and vomiting.

The majority of pituitary incidentalomas are clinically non-functioning or "silent" – 80-90% of these are gonadotroph adenomas (4). They may present with visual loss and/or headache, but hypopituitarism needs to be looked for due to compression of normal pituitary tissue by the adenoma. Thus low sex hormone levels, growth hormone, cortisol (due to secondary hypoadrenalism from a pituitary cause) and thyroid hormone (due to "central" hypothyroidism) may ensue.

Symptoms may be non-specific (eg tiredness or fatigue) but it is also important to enquire about sex hormone deficiency (eg reduced libido, erectile dysfunction in men, and menstrual disturbances in women), cortisol deficiency (eg unexplained weight loss, anorexia) and thyroid hormone deficiency (eg cold intolerance, unintentional weight gain, constipation and dry skin).

Our patient had no history of visual disturbance nor headache, but did describe fatigue, reduced libido and erectile dysfunction.

Examination Findings

The patient was alert and orientated, and had a peripheral neuropathy thought to be secondary to his diabetes.

What other specific areas should be examined in this patient?

The patient's general appearance should be assessed to look for clinical features of acromegaly or Cushing's syndrome. Acromegaly is associated with macroglossia, broad hands and feet, doughy skin and coarse facial features, with enlargement of the nose and frontal bones as well as the jaw (macrognathia). Excess cortisol production is associated with truncal obesity, dorsocervical fat pad, proximal myopathy and prominent purple striae.

Signs of hypopituitarism include gynaecomastia and loss of body hair in men (low testosterone), pallor and wasting (low cortisol) and sallow complexion, bradycardia and slow-relaxing reflexes (low thyroid hormone). Galactorrhoea may be present especially in women with hyperprolactinaemia.

It is important to specifically examine the eyes in the context of a pituitary macroadenoma. Visual fields should ideally be checked using a red pin to look for the possibility of a bitemporal hemianopia which is the classical defect in patients with compression of the optic chiasm. The use of finger movement to assess visual fields is less discriminatory. Eye movements should also be checked to look for ophthalmoplegia, and fundoscopy should be performed to exclude optic nerve pallor and papilloedema.

Our patient appeared clinically eupituitary apart from mild gynaecomastia. He had no evidence of visual field defect on confrontation.

Investigations

Figures 1 and 2 show MRI images of a normal pituitary gland. Figures 3 and 4 show images of our patient with a 2.5 cm pituitary adenoma extending into the suprasellar cistern, compressing the optic chiasm.

APPROACH TO THE PITUITARY INCIDENTALOMA

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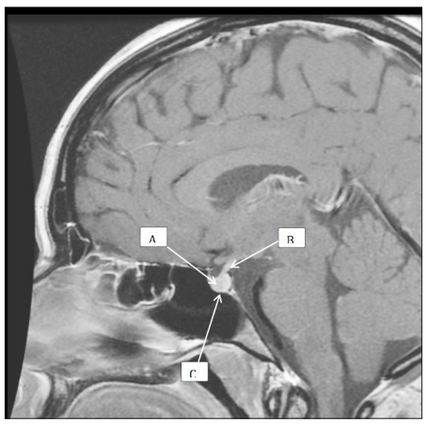

Figure 1: Sagittal section of normal pituitary gland on MRI scan.
A. Pituitary gland
B. Infundibular stalk
C. Sella turcica

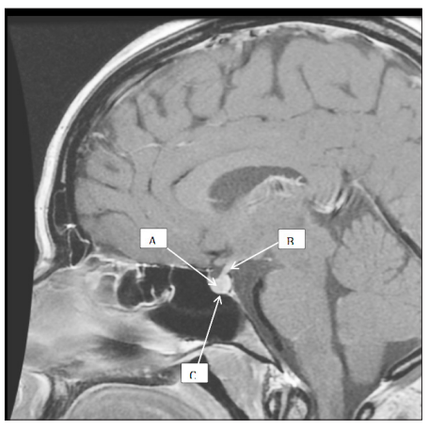

Figure 2: Coronal section of normal pituitary gland on MRI scan.
A. Pituitary gland
B. Infundibular stalk

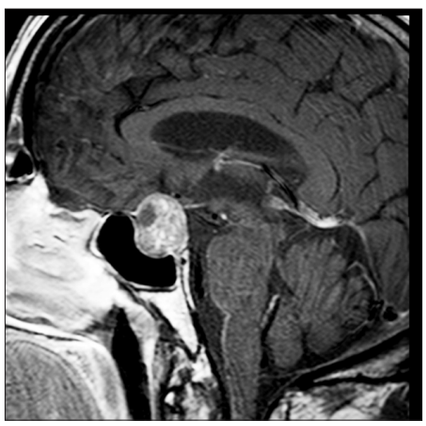

Figure 3: Sagittal section of pituitary incidentaloma on MRI scan.

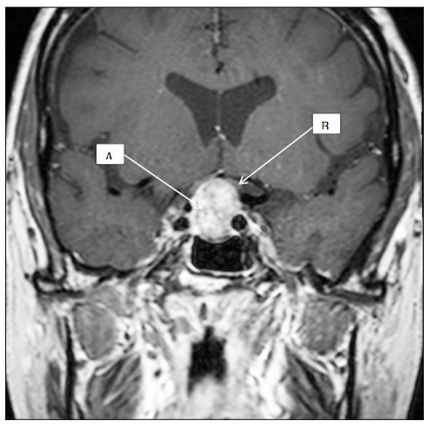

Figure 4: Coronal section of pituitary incidentaloma on MRI scan.
A. Suprasellar extension of pituitary tumour
B. Compression of optic chiasm

What baseline pituitary function tests would you order for this patient? Are any other tests required prior to treatment?

"Baseline" pituitary function tests are not simply a set of hormones produced by the anterior pituitary gland. This is because some of these hormones may appear to be within the normal reference range (eg TSH) but unless the effector hormone (eg free T4) is measured, one would miss the presence of hypopituitarism.

Furthermore, some hormones are released in a pulsatile fashion (eg ACTH and GH), and it is thus more helpful to measure the effector hormone (ie cortisol) or an integrated index of hormone levels (ie Insulin-like Growth Factor-1, IGF-1). Thus, baseline pituitary function tests consist of the following:

LH
FSH
Prolactin
9am testosterone (in men) or oestradiol (in women)
TSH
Free T4
9am cortisol (in view of Circadian rhythm)
Growth Hormone
IGF-1

If these results were suggestive of hypopituitarism, then further dynamic pituitary function tests would be considered. These include an insulin stress test (to assess ACTH and GH reserve), a Thyrotropin-Releasing Hormone (TRH) test (to assess TSH reserve), and a Gonadotropin Releasing Hormone (GnRH) test (to assess LH and FSH response).

APPROACH TO THE PITUITARY INCIDENTALOMA

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The other important investigation in this case would be to carry out formal perimetry (eg using the Goldmann method). This would identify any subtle abnormality that may have been missed on clinical examination and also serves as a useful baseline prior to instituting treatment.

Our patient had normal baseline pituitary function tests apart from an unequivocally low 9 am testosterone of 1.8 nmol/l (normal range is 10-28). Gonadotropins and prolactin were normal – FSH 3.3 U/l (normal 1.5-12.4), LH 1.8 U/l (normal 1.7-8.6) and prolactin 168 mU/l (normal 86-324). IGF-1 level was towards the lower end of the normal reference range at 15 nmol/l (normal 12.1-31.8). 9 am cortisol was 556 nmol/l (normal 150-620) and free T4 18.6 pmol/l (normal 12-22). His formal perimetry was normal.

Management

How would you manage this patient?

This patient is likely to have a non-functioning pituitary macroadenoma with partial hypopituitarism (low testosterone level and borderline low IGF-1 level) and no clinical evidence of optic chiasmal compression despite the MRI findings. He should be referred to a specialist neurosurgical unit for consideration of a hypophysectomy.

Transsphenoidal surgery is the approach of choice. Multidisciplinary team-working with the Endocrine team is important in order to reassess pituitary function post-operatively. Radiotherapy may be considered at a later date if insufficient tumour is removed at operation, or if there is significant tumour regrowth with the passage of time.

A special mention should be made if a pituitary macroadenoma is thought to be a prolactinoma (5). Under such circumstances, serum prolactin levels are extremely high. This particular tumour is highly responsive to medical therapy in the form of dopamine agonist treatment (eg cabergoline or bromocriptine) and often surgery can be avoided with prompt and effective medical therapy. However, such patients need to be monitored very carefully biochemically, radiologically and ophthalmologically as it is important to avoid irreversible visual loss due to optic chiasmal compression.

Our patient had a successful removal of his pituitary macroadenoma which was confirmed as a gonadotroph adenoma on histology. He was found to be cortisol- and GH-deficient post-operatively and has been treated with hydrocortisone, testosterone and GH replacement therapy. He will receive long term follow-up in the Endocrine Clinic.

Summary

A pituitary incidentaloma is a previously unsuspected lesion that is detected on an imaging study performed for reasons other than pituitary symptoms. The majority of incidentalomas are non-functioning, but it is important to consider "hyper-functioning" lesions such as prolactinomas, or GH-producing tumours causing acromegaly or ACTH-producing tumours causing Cushing's disease. Pituitary macroadenomas (> 10 mm in size) may cause visual disturbance or headache.

Non-functioning macroadenomas may be associated with hypopituitarism and it is important to understand which tests need to be carried out when assessing baseline pituitary function. Dynamic pituitary function tests may be necessary to confirm or refute the presence of hypopituitarism. The management of macroadenomas often requires a multi-disciplinary approach, with definitive therapy being surgical. The exception to this is prolactinomas which respond very well to dopamine agonist therapy.

MCQs

1. A 32 year old primary school teacher presents to the Neurology Department with intermittent paraesthesia. Demyelination is considered but an MRI brain scan is normal, apart from an incidental finding of a 1.8cm pituitary mass.

The patient is referred to the Endocrine Clinic for further investigation. She denies having any headache, visual disturbance, nor galactorrhoea. Her only medication is cetirizine for hayfever. Her hormonal profile taken early on in her menstrual cycle is shown below:

		Normal range
Prolactin	*1360 mIU/l*	*102 - 496 mIU/l*
LH	*2.1 IU/l*	*2 – 12.5 IU/l*
FSH	*3.1 IU/l*	*4.7 – 21.4 IU/l*
9am cortisol	*510 nmol/l*	*140 - 620 nmol/l*
TSH	*2.3 mU/l*	*0.3 – 4.2 mU/l*
Free T4	*16 pmol/l*	*12 – 22 pmol/l*
IGF-1	*18 nmol/l*	*12 – 32 nmol/L*

APPROACH TO THE PITUITARY INCIDENTALOMA

D Barnes, S Arshad, M Haq

What is the most likely cause of the hyperprolactinaemia?

A. Drug-induced
B. Prolactinoma
C. Compression of the infundibular stalk
D. Stress
E. Interference by macroprolactin

2. A 25 year old lady presents to the ENT Clinic with vertigo. An MRI brain scan is arranged and is reported as normal, apart from an incidental finding of a 6 mm pituitary adenoma. She is referred to the Endocrine Clinic for a further assessment. She does not take any medication. On examination, she looks entirely well and has no obvious features of an endocrinopathy. Which of the following is the most important question to ask in the clinical history and why?

A. Has there been a change in your shoe size in recent years?
B. Are your periods regular?
C. Do you have difficulty getting up from a chair?
D. Do you suffer from headaches?
E. Have you noticed a change in your eyesight?

Answers

1. C is the correct answer.

One would expect a much higher level of prolactin in a patient with an actively secreting macroprolactinoma. Compression of the infundibular stalk leads to a impairment of dopamine delivery to the pituitary gland, which in turn disinhibits the lactotropes.

Drugs which antagonise dopamine (eg anti-psychotic medications, anti-emetics etc) may lead to hyperprolactinaemia. Stress can increase prolactin levels but rarely to levels greater than 1000 mIU/l. Macroprolactin may falsely elevate the total prolactin level but most laboratories will report this separately if there is evidence of interference from this prolactin isomer.

2. B is the correct answer.

In a young woman with a pituitary microadenoma (ie < 10 mm), one would need to consider a prolactinoma. This may present with oligomenorrhoea / amenorrhoea, galactorrhoea or subfertility. Patients with acromegaly usually present with a macroadenoma and have symptoms and signs of the disease (including an increase in shoe size).

Patients with Cushing's disease may have proximal muscle weakness but usually look unwell and have other other features of the condition. A microadenoma is unlikely to be the cause of headache or visual disturbance.

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VISUAL IMPAIRMENT IN DIABETES: DIABETIC RETINOPATHY

E Ingram, K Shotliff

Abstract

Diabetic retinopathy is a leading cause of preventable blindness in the Western World. It is a common but treatable complication - affecting over 60% of diabetics within 20 years of diagnosis. Screening plays a fundamental role in reducing the risk of visual impairment and current UK guidelines advise annual retinal imaging for all patients with diabetes.

Although often detected on routine screening, patients may also present acutely with visual impairment. The mainstay of treatment is risk factor modification, in particular optimising glycaemic control, but surgical intervention also plays an important role in preventing visual impairment in severe disease. The pathophysiology, clinical features and management of diabetic retinopathy are discussed in this article.

Case Vignette

A forty-year-old gentleman with a background of Type 1 Diabetes Mellitus (T1DM) presented to the Urgent Care Centre (UCC) with recent onset painless, loss of vision in his left eye. He reported progressively more blurred vison in the left eye over the last 48 hours, and at presentation reported that he 'could not see anything out of his left eye'. He was aware of intermittent floaters and grey shadows in his left eye, predominantly in the upper outer quadrant. He was known to have longstanding poor glycaemic control and was not up to date with his annual diabetic retinal screening.

He is of South Asian ethnicity, smokes 20 cigarettes a day and had no relevant past medical or family history of note. On examination, both of his pupils were equal and reactive. There was no evidence of trauma or infection to the eyes, and eye movements were intact. Peripheral visual fields were intact in the right eye but markedly reduced in the left eye. Visual acuity for was 6/36 in the left eye, and 6/6 in the right. Fundoscopy of the left eye revealed a completely detached retina, and the patient was referred urgently to the local eye hospital.

Introduction

Given its increasing prevalence and associated complications, it is not surprising that diabetes has been labelled a 'pandemic' and a 'public health crisis' (1, 2). One of these complications, diabetic retinopathy, has historically been the leading cause of preventable blindness in the working population of the western world (3).

Diabetic retinopathy is a chronic but preventable and treatable condition. Indeed, for the first time in several decades it is no longer the leading cause of blindness among adults of working age in England and Wales, and this likely reflects the introduction of a national screening programme, advances in treatment of retinopathy when detected and improvement of glycaemic control (4). Nonetheless it carries a significant human and economic burden and so prevention, early detection and timely treatment remain paramount.

Who Gets Diabetic Retinopathy?

Diabetic retinopathy affects patients with both type one (T1DM) and type two diabetes mellitus (T2DM). Epidemiological studies suggest that within the first two decades of disease nearly all patients with T1DM and over 60% of patients with T2DM develop some degree of retinopathy (5). The Wisconsin Epidemiological Study of Diabetic Retinopathy found that approximately 25% of people with T1DM develop retinopathy within 5 years of diagnosis, with a 25-year cumulative rate of progression to proliferative diabetic retinopathy of 42% (5-7).

The following risk factors have been identified for the development and progression of diabetic retinopathy and their presence should prompt earlier consideration of retinal screening and/or ophthalmology referral (8-10):

- **Longer duration of diabetes**
- **Poor glycaemic control**
- **Type of diabetes:** *evidence suggests that people with T1DM are at greater risk of developing proliferative retinopathy whilst those with T2DM are at increased risk of maculopathy (11).*
- **Hypertension**
- **Diabetic nephropathy**
- **Dyslipidaemia**
- **Obesity**
- **Pregnancy**
- **Puberty**
- **Alcohol**
- **Smoking**
- **Ethnicity:** *South Asian, African, Latin American and Indigenous ethnicity (12).*

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How Does Diabetic Retinopathy Develop?

The pathogenesis of diabetic retinopathy is multifactorial but predominantly results from microvascular changes to the retina secondary to chronic hyperglycaemia (13, 14).

- *Hyperglycaemia results in capillary basement membrane thickening and pericyte death. Pericytes are found in the capillary endothelial layer and provide vascular stability and control endothelial proliferation.*

- *These changes lead to capillary leakage, endothelial proliferation and subsequent microaneurysm formation, and vessel occlusion.*

- *In turn, this results in a reduced oxygen supply to the retina.*

- *In an attempt to counteract this ischaemia, the retina – with the help of locally secreted growth factors, such as vascular endothelial growth factor (VEGF) - begins to produce new but friable blood vessels (neovascularisation).*

- *These new vessels are prone to leakage, leading to vitreous haemorrhage and the development of retinal scar tissue, both of which can affect vision.*

How Do We Detect Diabetic Retinopathy?

In the initial stages, diabetic retinopathy is asymptomatic and can progress silently and therefore may not be identified until it is too late for effective treatment (13). Given that it is both preventable and treatable, early detection therefore plays an important role in preventing longer term complications such as blindness.

In 2007, the National Service Framework for Diabetes (15) advised a national screening programme, recommending all people with diabetes aged 12 years or over should be screened annually for retinopathy, preferably by digital retinal photography (13, 15, 16). In retinal photography, the pupils are first dilated, images (two pictures in England and Wales – one image in Scotland) are then taken of each eye (e.g. one 45^0 image centred on the macula and one centred on the optic disc in the English scheme) and these images are graded using a nationally agreed grading criteria by a quality assured grader.

This process is fairly labour intensive and interestingly, recent evidence suggests that automated grading may be a safe and effective alternative (17). This could potentially reduce manual workload perhaps allowing for more frequent screening.

How Do We Grade Diabetic Retinopathy?

As retinopathy develops, changes relating to the underlying pathological process become evident on Fundoscopy and retinal photography (Table 1; Figure 1). Diabetic retinopathy is classically considered in two different subtypes, although these may co-exist (13).

- **Non-proliferative and proliferative diabetic retinopathy**

- Non-proliferative: microaneurysms, haemorrhages, hard and soft exudates, venous beading and capillary loss.
- Proliferative: new vessel growth.

- **Maculopathy**

- Retinopathy affecting the macula thus threatening central visual acuity.

Based upon current UK Guidelines (15, 16, 18, 19), Table 1 describes the staging of diabetic retinopathy, the underlying pathological process, what we might expect to see one fundoscopy/retinal photography and the clinical action that should then be taken. Figures 1a-h demonstrate the fundoscopy findings associated with each grade.

Stage of DR	Underlying pathological process	Clinical feature	Retinal appearance	Clinical action
Normal fundi (*Grade R0*)	None or there may be early BM thickening and pericyte death	None	Normal Fundus	Screen annually
Proliferative - Grade R3	Capillary wall disruption	Capillary microaneurysms 'Dot haemorrhages'	Tiny red dots, usually located far away from visible blood vessels	Screen annually
	Intra-retinal haemorrhage	Haemorrhages 'blot haemorrhages'	Small red dots, with indistinct margins	
	Lipid deposition	Hard exudates	Shiny yellow lesions with well-defined edges	
Pre-Proliferative (*Grade R2*)	Retinal nerve fibre layer infarction	Soft exudates 'cotton wool spots'	Pale lesions with fuzzy, undefined edges	Refer to Ophthalmologist
	Retinal ischaemia leading to development of dilated, tortuous vessels	Intra-retinal microvascular abnormalities (IRMAs)	Tortuous, dilated collections of capillaries located away from larger blood vessels.	
	Alternating venous dilatation and constriction secondary to local growth factor production.	Venous beading	Bulges and contractions in the walls of vessels	
Proliferative (*Grade 3*)	New blood vessel development secondary to local growth hormone release from ischaemic areas of the retina	NVD: New vessels on the optic disc or within on disc diameter of it. NVE: new vessels elsewhere	Collection of blood vessels, abnormal in appearance, in an area where they should not be	Urgent referral to ophthalmologist
No Maculopathy (*Grade M0*)	None seen, but may have underlying basement membrane thickening and loss of pericytes	None	Normal fundus	Annual rescreen
Maculopathy (*grade M1*)	Any underlying process seen in R1-R3.	Any of the above features seen in R1-R3	Any of above in the region of the macula or within one disc diameter of it	Refer to ophthalmologist (urgently if R3 equivalent)

Table 1: Stages of Diabetic Retinopathy (DR) and the Corresponding Underlying Pathological Processes, Clinical Features and Advised Clinical Action (Adapted from Shotliff et al. 2014 (20)).

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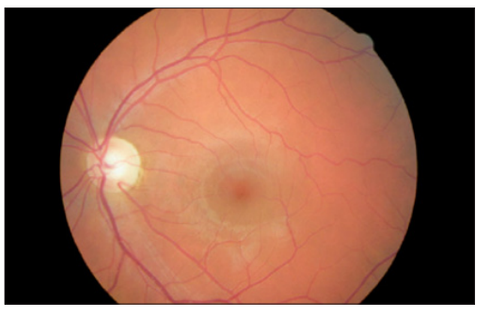
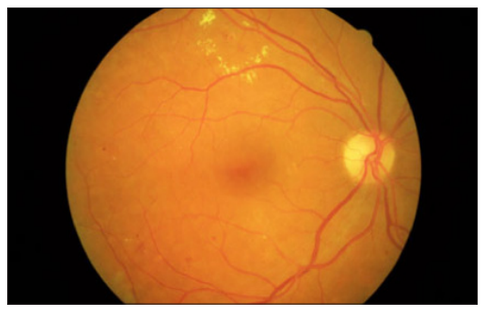
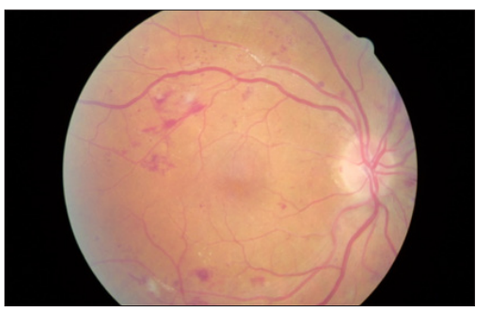
Figures 1a-h: Retinal Images demonstrating the Changes Seen with Different Grades of Diabetic Retinopathy (Adapted from Shotliff et al. 2014 (20)).



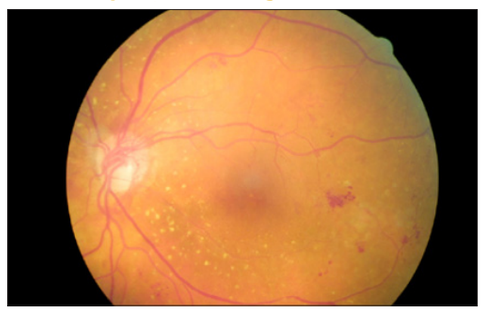
1a) Grade R0: Normal retina with no diabetic retinopathy



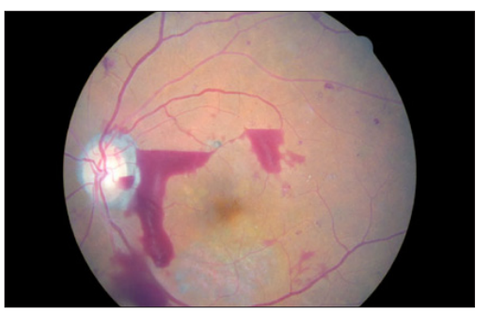
1b) Grade R1: Background diabetic retinopathy with microaneurysms, haemorrhages and exudates



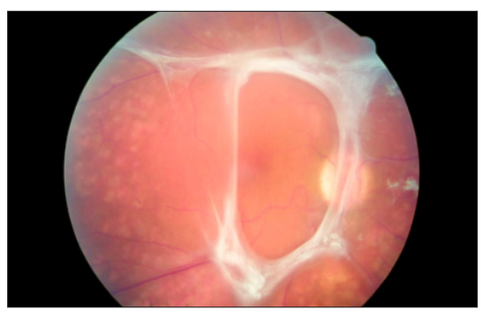
1c) Grade R2: Pre-proliferative diabetic retinopathy with CWS, IRMA and multiple blot haemorrhages



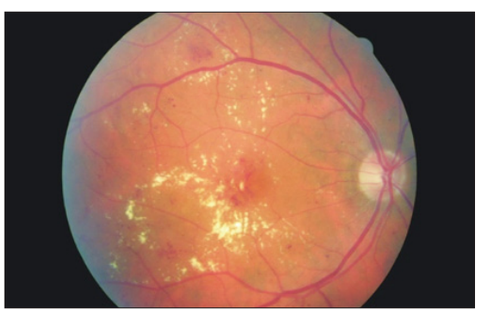
1d) Grade R3: Proliferative diabetic retinopathy with new vessels at the optic disc (NVD)



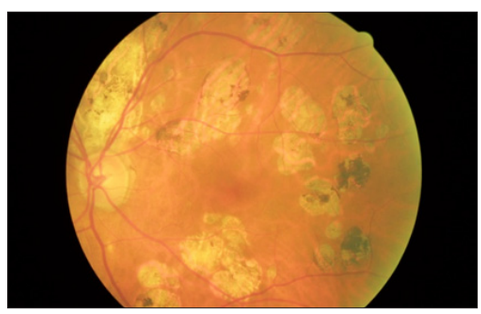
1e) Grade R3: Proliferative diabetic retinopathy with pre- retinal and vitreous haemorrhages



1f) Grade R3: Proliferative diabetic retinopathy with fibrous proliferation and scar tissue



1g) Grade M1: Diabetic maculopathy with haemorrhages and circinate exudates



1h) Grade P: Evidence of previous laser therapy

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When to Refer to Ophthalmology?

Whilst findings of diabetic retinopathy are often picked up in screening, patients may also present acutely, as evidenced in the case vignette. It is therefore important for doctors of all specialties to know when to refer to an ophthalmologist.

A diabetic patient presenting with any of the following clinical features warrants urgent referral to ophthalmology as these may indicate potentially sight-threating conditions such as pre-retinal or vitreous haemorrhage, retinal detachment or rubeosis iridis (20-22).

Indications for urgent referral

- *Sudden loss of vision*
- *Sudden change in visual acuity*
- *Irregular pupil*
- *Hazy cornea*
- *Painful eye*
- *Reddening of the iris – may indicate rubeosis iridis (neovascularisation of the iris)*
- *Evidence on examination/ fundoscopy of:*
  - *New vessel formation*
  - *Retinal detachment*
  - *Central retinal vein occlusion*
  - *Neovascular glaucoma – (neovascularisation in the anterior chamber angle)*

Indications for early referral (within 6 weeks)

- *Pre-proliferative changes (R1-R2)*
- *Maculopathy (M1)*

Indications for routine referral

- *Cataracts – a common cause of visual impairment in diabetics*
- *Pre-proliferative disease not involving the macula*

What is the Treatment of Diabetic Retinopathy?

Medical management

This focuses on risk factor modification and includes:

- Optimisation of glycaemic control: *Intensive glycaemic control has been shown to significantly reduce the risk of deterioration of diabetic retinopathy and these effects may even persist once intensive treatment has stopped (23-25).*

- Blood pressure control: *tight blood pressure control has also been shown to significantly reduce risk of retinopathy progression. Current best practice is to aim for a BP <140/80 and ACE inhibitors are first line treatment (25-27).*

- Lipid lowering agents: *Evidence suggests that aggressive lipid control may improve outcomes in diabetic retinopathy (28).*

- Antiplatelet therapy: *low dose aspirin may play a protective role in the deterioration of retinopathy but evidence is limited (29).*

- Smoking cessation: *smoking is associated with increased risk of development and progression of retinopathy and so advice regarding smoking cessation is important.*

Surgical treatment of established retinopathy:

Most patients will not need surgical intervention and are instead managed medically, as described above, alongside regular screening. For those with signs of maculopathy or severe retinopathy, surgical procedures can play an important role in preventing visual loss.

- Intra-vitreal injection of anti-VEGF: *VEGF concentrations are raised in diabetic retinopathy and contribute to neovascularisation. Evidence suggests that intra-vitreal injection of anti-VEGF agents such as ranibizumab (Lucentis) at 1-2 monthly intervals can significantly improve visual acuity (30). Treatment is expensive and so collection of long-term follow-up data is important.*

- Laser photocoagulation: for *the role of laser photocoagulation the prevention of visual impairment in pre-proliferative and proliferative diabetic retinopathy is well established in the literature (25). The administration of lasers to the retina results in thermal destruction of the pigment epithelial cells thus leading to reduced VEGF production and therefore reducing new vessel formation. Patients often require 3-4 treatment sessions in the outpatient setting. It can be uncomfortable and some patients may require general anaesthetic. Patients often report temporary blurring of their vision and photophobia after the treatment but this is usually self-limiting. Figure 1h demonstrates the appearance of a retina post-photocoagulation.*

- Vitrectomy: *The surgical removal of the vitreous (vitrectomy) has been shown to improve visual outcomes in patients with proliferative diabetic retinopathy, particularly those with retinal detachment or vitreous haemorrhage (25, 31). It aims to improve vision by removing any vitreal blood and by reattaching any detached areas of retina.*

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Case Vignette Continued: Retinal Detachment

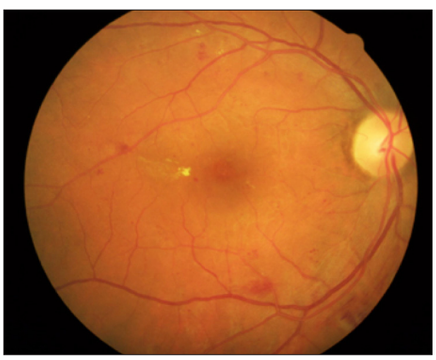
With regards to the opening case, retinal detachment is considered a severe complication of proliferative diabetic retinopathy. The retinal detachment seen in diabetes tends to be tractional (TRD) whereby scar tissue (see Figure 1f) resulting from the formation of new blood vessels, pulls on the retina, causing it to detach. It is a primary indication for surgery (vitrectomy) and warrants urgent referral (31, 32). It carries a poor prognosis, particularly when complete, involving the macular or if treatment is delayed.

Key points

• Diabetic retinopathy is a common but preventable and treatable cause of visual impairment.
• All patients with diabetes should be screened annually for diabetic retinopathy.
• Optimising glycaemic control is important in the prevention of development and progression of diabetic retinopathy.
• Surgical intervention can play a role in preventing visual impairment in maculopathy or severe retinopathy.
• Urgently refer any diabetic patient presenting with acute visual loss or change in acuity.

Test Yourself: MCQs

1) Which grade of retinopathy best describes the fundus below?



a. R0M0
b. R3M0
c. R1M1
d. R2M1
e.R2M0

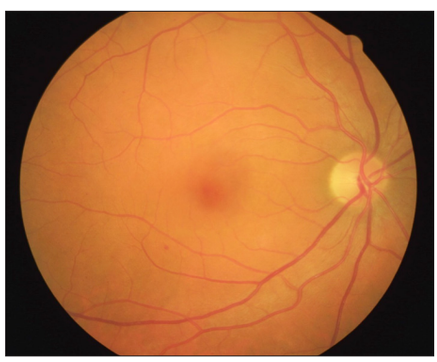
2) With regards to the pathogenesis of diabetic retinopathy which of the following is incorrect?

a. Microaneurysms represent sacular dilatation of retinal capillaries.
b. Hard exudates represent calcium deposits in the retina.
c. Grade R3 retinopathy is characterised by neovascularisation.
d. There may be basement membrane thickening in R0 retinopathy.
e. Cotton wool spots represent infarcts in the nerve fibre layer of the retina

3) You are a FY2 doctor working in general practice and are reviewing one of your patients with type 1 diabetes. You note that they are hypertensive at 152/98 and that this has also been confirmed previously on ambulatory blood pressure monitoring. They have no other comorbidities and are not currently on an antihypertensive. Which medication is most appropriate to start?

a. Amlodipine
b. Bendroflumethiazide
c. Doxazosin
d. Ramipril
e. Losartan

4) Which grade of retinopathy best describes the fundus below?



a) R0M0
b) R1M0
c) R3M1
d) R2M1
e) R1M1

5) One of your patient's annual retinal screening result comes through as grade R2M0. Their most recent HbA1c was 88mmol/L, what is the most appropriate next management step?

a. Urgent ophthalmology referral
b. Risk factor modification + early ophthalmology referral (within 6 weeks)
c. Risk factor modification + continue annual screening
d. Early ophthalmology referral
e. No further management required

MCQ Answers

1) Answer d
R2M1 - hard exudates and microaneurysms are seen in the macula with a possible cotton wool spot at 4 o'clock in the peripheral retina.

2) Answer b
Hard exudates represent lipid deposits in the retina.

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3) Answer d

Ramipril - ACE inhibitors are first line treatment for hypertension in diabetes and you should aim for a blood pressure <140/90.

4) Answer b

There is a microaneurysm seen in the periphery at 7 o'clock from the macula.

5) Answer b

This patient has signs of pre-proliferative diabetic retinopathy and so warrants referral to ophthalmology, ideally within 6 weeks. They also have suboptimal gylcaemic control as evidenced by their HbA1C and so efforts should be made to optimise their glycaemic control and address any other modifiable risk factors for retinopathy.

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ABDOMINAL TUBERCULOSIS

JDT Esland, AK Kapila, SHC Anderson

Abstract

A 26 year-old Ethiopian man presented with loose stools, vomiting, weight loss and fevers. Examination demonstrated generalised non-peritonitic abdominal tenderness and no palpable masses. Initial investigations were inconclusive and an opinion from other specialties was therefore warranted. CT-Abdomen & Pelvis revealed terminal-ileal thickening and ascites.

Colonic biopsies showed a single mycobacterium. Anti-tuberculosis medication was commenced but the abdominal pain did not improve. A subsequent ascitic fluid sample showed mixed bacterial organisms, likely due to a small-bowel perforation associated with intestinal tuberculosis (TB). This was treated successfully with antibiotics and he was discharged home on anti-tuberculosis medications with Infectious Diseases clinic follow up.

In this case report, the differential diagnoses, diagnostic work up and necessity for a detailed infectious diseases history in the diagnosis of abdominal TB are discussed.

Case History

A 26-year-old previously well Ethiopian man presented to our Emergency Department with an eight-day history of passing loose stool every 30-60 minutes, which had become bloody in the last 2 days. His attendance was prompted by the onset of bilious vomiting and cramping generalised abdominal pain. He reported a 12kg weight-loss over the preceding year. He had last been to Ethiopia 18 months ago and had no contact with any ill people.

Observations revealed a temperature of 37.6°C, blood pressure 117/79, pulse rate 110, respiratory rate of 18 and oxygen saturations of 99% on air. He was vomiting large volumes of bilious vomitus, had generalised abdominal tenderness with voluntary guarding and dullness to percussion in the flanks. Bowel sounds were present and active.

The blood results on presentation are included in Table 1 and showed a neutrophilia, normocytic anaemia and a raised CRP. An arterial blood gas was normal. Stool samples were sent for bacterial culture (Salmonella, Shigella, Campylobacter and E. coli), Norovirus and C. difficile, all of which were negative. A mid stream urine was unremarkable and a plain abdominal x-ray was essentially normal. He was treated conservatively with anti-emetics, anti-pyretics and IV fluids.

Test	Result	Reference range
WBC	12.0 ↑	4-11 x 10^9/L
HB	117 ↓	130-180g/L
MCV	81	76-96fL
PLT	361	150-400 x 10^9/L
Neutrophils	9.5 ↑	2-7.5 x 10^9/L
Lymphocytes	1.1 ↓	1.2-3.65 x 10^9/L
Monocytes	1.0	0.2-1.0 x 10^9/L
Eosinophils	0.4	0.0-0.4 x 10^9/L
Basophils	0.1	0.0-0.1 x 10^9/L
INR	1.3 ↑	0.8-1.1
APTT Ratio	1.2	0.8-1.2
Sodium	137	135-145mmol/L
Potassium	3.9	3.5-5.0mmol/L
Urea	3.5	2.5-6.7mmol/L
Creatinine	72	70-150µmol/L
Corrected Calcium	2.37	2.12-2.65mmol/L
Bilirubin	9	3-17µmol/L
ALT	9	3-35iu/L
ALP	87	30-150iu/L
Albumin	37	33-49g/L
Amylase	110	0-180iu/dL
CRP	111 ↑	<10mg/L
HIV antigen/antibody	Not detected	
Hepatitis B Surface Antigen	Not detected	

Table 1. Results of blood tests at presentation.

After two days he was referred to the Gastroenterology service who advised a stool parasite screen, a CT-Abdomen & Pelvis and a flexible sigmoidoscopy. The CT demonstrated 1) marked mural thickening in a long segment of terminal ileum and the caecal pole 2) moderate/large volume ascites 3) widespread mesenteric fat stranding 4) prominent (but not enlarged) para-aortic and pelvic lymph nodes. The flexible sigmoidoscopy was normal apart from a small ulcer in the distal transverse colon which was biopsied.

On day-five of admission an Infectious Diseases consultant reviewed this gentleman. The history revealed, in addition to what was already known, severe day- and night- time sweating for the past 2 months and a chronic cough with occasional yellow/black expectorations. A diagnosis of disseminated tuberculosis (TB) was therefore considered.

To confirm the diagnosis, an induced sputum, an ascitic fluid aspirate and a colonoscopy with biopsies from the terminal ileum were requested. Induced sputum was negative for acid-fast bacilli and the ascitic fluid had a light growth of S. aureus, which was thought to be contaminant.

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A colonoscopy was performed on day eight. There were two areas of deep ulceration in the transverse colon, a large inflammatory mass opposite the iliocaecal valve (Figure 1a) and scattered ulceration in the terminal ileum (Figure 1b). Biopsies from the inflammed tissue were reviewed the same day and showed crypt elongation, diffuse cryptitis, crypt abscesses, and moderate chronic inflammation. A Ziehl-Neelsen stain was negative. In the interim a Ziehl-Neelsen stain of the biopsy taken at the flexible sigmoidoscopy found a single acid-fast bacillus. A diagnosis of TB was confirmed and treatment was started with Rifampicin, Isoniazide, Pyrazinamide, Ethambutol and Pyridoxine.

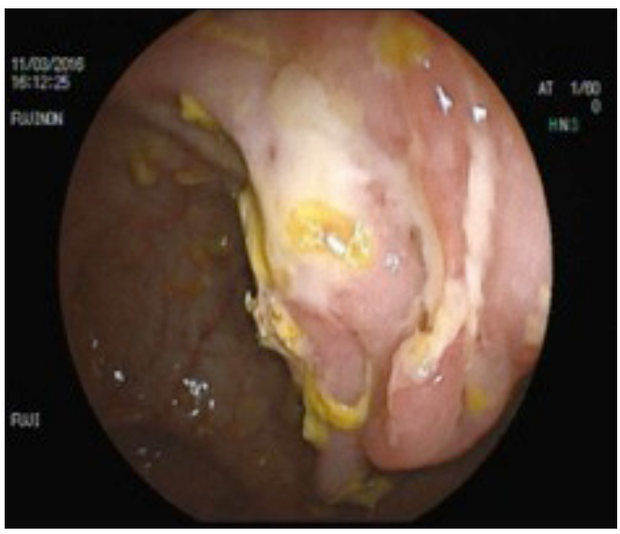

Figure 1A: A large inflammatory mass found opposite the iliocaecal valve.

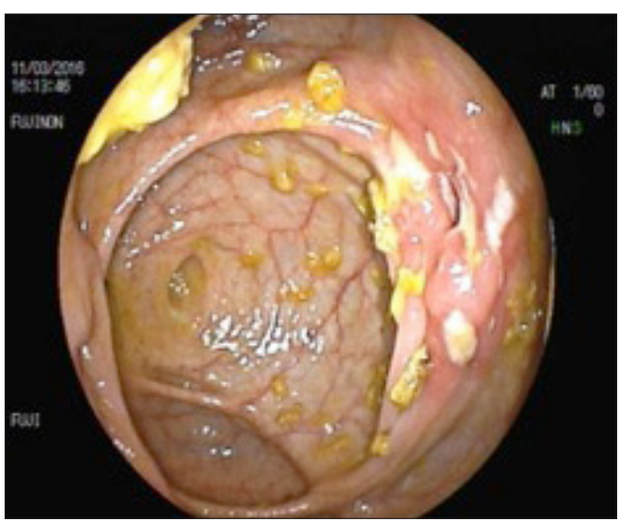

Figure 1B: Colonoscopic appearance again of an inflammatory mass, seen here on the right hand side of the image. The appendiceal orifice can be appreciated at the 9 o'clock position and a deep ulcer at 2 o'clock.

Although he initially improved, on day fourteen he developed worsening predominantly left-sided abdominal pain. His abdomen was tender, distended and tympanic. An abdominal x-ray excluded an obvious bowel obstruction. He was kept nil-by-mouth and received intravenous fluids.

Over the next three days the abdominal pain had worsened and ascites increased. A CT-Abdomen & Pelvis demonstrated increased abdominal fluid with gas loculation, thought to be either: a) bowel perforation, secondary to TB or iatrogenic injury following the ascitic tap, or b) air introduced during the ascitic tap. The fluid was drained by the interventional radiologists and cultures grew E. coli and two alpha-haemolytic streptococci, suggestive of a bowel perforation. The Infectious Disease consultant thought this was secondary to abdominal TB rather than iatrogenic following the earlier ascitic tap. Co-amoxiclav was commenced for a total of 2 weeks.

The abdominal pain and distention slowly improved. An abdominal ultrasound demonstrated a reduction in the size of the collections. He was discharged on anti-TB medications for 6 months and followed up in the Infectious Diseases and Respiratory clinics.

Discussion

Abdominal Tuberculosis and a condition with significant morbidity and mortality, is an increasingly common illness that poses multiple diagnostic difficulties due its non-specific presentation (1). As such, a high index of clinical suspicion is necessary along with a careful history and thorough examination.

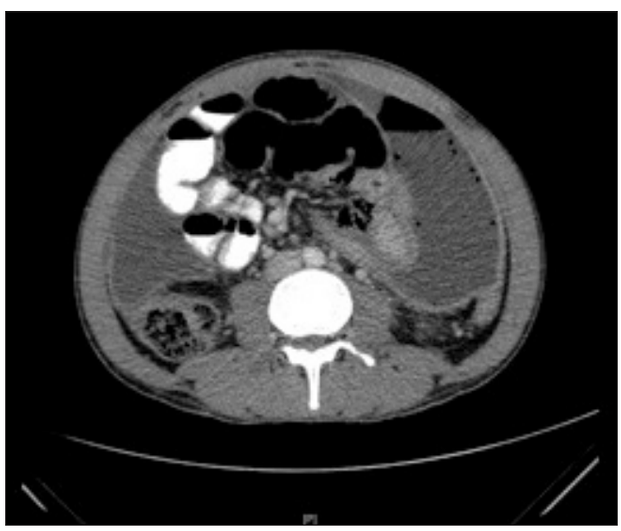

Figure 2: A CT-abdomen study demonstrating large volume ascites bilaterally in the flanks. Multiple small gas loculations can be seen in the ascitic collection on the patient's left hand side.

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Differential Diagnosis

The presentation of abdominal TB can vary greatly and depends on the gastrointestinal location that is involved. The ileocaecal region is affected most commonly, as in this patient, and symptoms include colicky abdominal pain, vomiting and borborygmi (2). The differentials that must be considered for this variant of abdominal TB should therefore include:

1) Bacterial gastroenteritis: *The common infective organisms include Salmonella, Shigella, Campylobacter and E. coli, but there are many others. A short history of acute diarrhoea and vomiting following ingestion of contaminated food or water, with or without a fever, is typical, but symptoms vary depending upon the infectious organism. A prolonged history with constitutional or respiratory symptoms should encourage the clinician to consider different causes (2).*

2) Crohn's disease: *Patients generally present for the first time aged 20-30 with a change in bowel habit (tending towards diarrhoea), abdominal pain in the lower quadrants and weight loss. Differentiating abdominal TB can be difficult, as was exemplified in this case study. The CT findings do however differ between these two conditions and are described in Table 2. In Crohn's disease, a colonoscopy often shows, skip lesions and involvement of the terminal ileum.*

Aphthoid or longditudinal ulceration, cobblestoning and fistulation are also often found (3) whereas, in intestinal TB, transversely placed ulcers, a nodular appearance and hypertrophic lesions (with the appearance of masses) are more characteristic (4). Histologically, a neutrophilic inflammation, cryptitis with crypt abscesses, transmural inflammation and granulomas may be seen. The characteristics of the granulomas may help differentiate Crohn's disease from TB, with those in the former being small (<200μm), infrequent (<5) and discrete, whereas those in TB are larger (>400μm), frequent (>5) and confluent (1). A final salient point is that initial empirical treatment with steroids may exacerbate abdominal TB; hence the need for an early diagnosis.

Intestinal Tuberculosis	Crohn's Disease
Mural Thickening without stratification	Mural thickening with stratification
Strictures concentric	Strictures eccentric
Rare fibrofatty proliferation of mesentery	Common fibrofatty proliferation of mesentery
Mesenteric inflammation without vascular engorgement	Hypervascular mesentery (comb sign)
Hypodense lymph nodes with peripheral enhancement	Mild lymphadenopathy
High density ascites	Abscesses

Table 2. Distinguishing features on Computed Tomography between Crohn's Disease and Intestinal Tuberculosis. Adapted with permission from Dr Anna Pulimood (4).

3) Yersinia enterocolitica: *A gram-negative bacilli which penetrates the terminal ileum mucosa through the Peyer's patches, resulting in ulceration and thickening of the ileal wall. Children are affected more often than adults and it is most commonly contracted from the ingestion of undercooked pork (5). Symptoms often include diarrhoea (which may be blood stained) lasting ≤3 weeks associated with vomiting, abdominal pain and a low-grade fever. Colonoscopic appearances of the terminal ileum and caecum include aphthous lesions, round or oval elevations of the mucosa and ulcers of uniform size or shape, differing from those seen in Crohn's disease and abdominal TB (6).*

4) Malignancy: *Abdominal malignancies often present with non-specific symptoms including changes in bowel habit, abdominal discomfort, weight loss and night sweats. Common examples include colorectal, ovarian and pancreatic cancer, and this differential should therefore always be borne in mind.*

5) Myobacterium avium: *This infection generally only occurs in patients with advanced stages of HIV and other immunosuppressed conditions. It generally presents as a systemic infection with diarrhoea, abdominal pain, weight loss, fever and malabsorption. This is diagnosed with mucosal biopsy and culture (1).*

6) Lymphoid hyperplasia: *This is proliferation of lymphoid tissue as a response to infection and most commonly affects the terminal ileum. It is generally asymptomatic, but may present with mild symptoms of abdominal pain, chronic diarrhoea, and occasionally intestinal obstruction. Appearances on CT scan include mild terminal ileal wall thickening which can resemble early abdominal TB or Crohn's disease (7).*

7) NSAID associated enterocolopathy: *NSAIDs not only cause ulceration in the upper gastrointestinal tract but also in the small bowel. Although generally asymptomatic it may present with anaemia, perforation and obstruction. The colonoscopic appearances are non-specific but may include inflammation, ulceration or structuring of the terminal ileum, similar to Crohn's disease and abdominal TB. Histological examination can help to distinguish these (8).*

Diagnostic Workup

Investigation of these patients should start with the least invasive investigations – initially stool, sputum and urine analysis. Routine blood tests may show signs of inflammation or infection and, if the patient is acutely unwell, a blood gas analysis will be of benefit.

An initial plain abdominal x-ray can exclude an intestinal obstruction. A CT-abdomen & pelvis is the best initial investigation and will show masses, collections, lymphadenopathy or bowel wall thickening. When disease is located within the colon or terminal ileum, a colonoscopy may be needed to confirm the diagnosis. Histology showing granulomatous inflammation with caseous necrosis is the hallmark of abdominal TB (9).

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Biopsies should generally be taken even if the mucosa appears normal (10). Percutaneous sampling of abdominal fluid or collections should be performed; however, the detection of AFBs using this method is generally poor. Percutaneous biopsy of abdominal lymph nodes or inflammatory masses is not recommended due to the risk of chronic entero-cutenous fistula formation with abdominal TB. Should diagnostic uncertainty remain, a laparoscopy with biopsies can confirm the diagnosis. (11).

Despite these diagnostic tests, abdominal TB remains a difficult condition to diagnose due to its varied and non-specific presentation. No single diagnostic test is definite and high level of clinical suspicion, is needed (12). Table 3 summarises the possible findings in abdominal TB.

Blood Tests	• Hypoalbuminaemia • Raised Erythrocyte Sedimentation Rate (ESR) • Non-specific markers of infection/inflammation

Imaging	• Plain AXR
	  o Features of perforation
	  o Features of bowel obstruction
	• CT abdomen
	  o Ascites (55%)
	  o Peritoneal, mesenteric or omental thickening
	  o Lymphadenopathy (~45%)
	  o Bowel wall thickening (38%)
	  o Solid organ involvement (20%), such as liver, spleen and pancreas

Ascitic Fluid	• Raised protein >3g/L • Lymphocytosis • Positive Ziehl-Neelsen stain for acid fast bacilli (<3%) • Positive culture (~20%)
Endoscopy	• Multiple granulomas which are large (>400μm), frequent (>5) and confluent o Histologically, the granulomas are caseous

Table 3. Possible investigation findings in the workup of abdominal TB (9,13)

Infectious Disease History

In our case, the initial assessment focussed on the common conditions found in young men presenting with a recent history of loose stool and a fever. Although reference was briefly made to the ethnic origin, travel history and recent contacts, these facts were not fully explored. Indeed, it was only later that it was elicited that he had returned from Ethiopia 18 months ago and later still that he had a chronic cough.

This highlights the need for a thorough infectious diseases history. In addition to a systematic exploration of the presenting complaint, Table 4 outlines some pertinent questions the clinicians should elicit (adapted from (14)).

Systemic review	Explore symptoms attributable to the respiratory, cardiac, gastrointestinal, genito-urinary, neurological, dermatological (new rashes) and reticuloendothelial (enlarged/tender lymph nodes) systems
Past medical history	This should specifically include a history of immunosuppression, TB or HIV infection
Drug history	Are they fully immunised? Have they ever used intravenous drugs – did they needle share?
Family history	Recent unwell family members?
Social history	Travel – if so, where to and did they take prophylaxis if required? Occupation? Abode – do they live in close proximity to animals? Risk factors for hepatitis and HIV?

Table 4. Important aspects of the clinical history.

Overall, abdominal TB poses significant diagnostic difficulties due to its variable presentation and non-specific symptoms. A comprehensive infectious diseases history, as well as a high degree of clinical suspicion in the at-risk patients groups, is necessary for early diagnosis. The diagnostic process in this group involves stepwise escalation of investigations and many will require cross-sectional imaging and endoscopic examination.

Questions

1. What is the most common type of abdominal TB?

a. Tubercular lymphadenopathy

b. Peritoneal tuberculosis

c. Visceral tuberculosis

d. Tuberculosis of the rectus sheath

e. Gastrointestinal tuberculosis

2. The following endoscopic appearances are all consistent with a diagnosis of abdominal TB, except:

a. Mucosal granulomas

b. Confluent ulceration

c. Polypoid lesions

d. Transmural ulceration

e. Stricturing

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3. Staining for M. tuberculosis requires the use of the following stain:

a. Ziehl-Neelsen

b. Period acid-Schiff

c. Haematoxylin and eosin

d. Wright's

e. Methylene blue

4. The most common complication of iliocaecal TB is:

a. Intestinal perforation

b. Intussusception

c. Small bowel obstruction

d. Gastrointestinal haemorrhage

e. Malabsorption

5. Which of the following is supplemented during therapy with rifampicin, isoniazid, pyrazinamide and ethambutol (RIPE)?

a. Thiamine

b. Pyridoxine

c. Folate

d. Niacin

e. Hydroxycobalamin

Answers

1. Answer A: Abdominal TB can present as four types (2)

- Tubercular lymphadenopathy in the abdomen: t*his is the most common manifestation of abdominal TB. The commonest route of transmission is secondary to ingestion of infected bacilli along with intestinal TB. Further routes are haematogenous (via seeding from a primary TB infection) and directly from affected organs. The most common presentation is of multiple mildly enlarged nodes in clusters which have central areas of caseous necrosis and peripheral enhancement seen on CT assessment (15).*

- *Peritoneal tuberculosis is divided into wet ascitic, fixed fibrotic and dry plastic types. Classically, the wet ascitic type is more common and consists of large amounts of free- or loculated fluid. The fixed fibrotic type involves the omentum and mesentery and on imaging presents with matted bowel loops. The dry plastic type manifests itself with a fibrous peritoneal reaction, peritoneal nodules and adhesions. Usually a combination of features of different types are noted.*

- Visceral tuberculosis: *Isolated involvement of abdominal organs only occurs in 15-20 % of patients with abdominal TB, usually as the result of haematogenous spread. Common organs involved include the liver, spleen and pancreas.*

- Gastrointestinal TB: *the most common site is ileocaecal. The jejunum and colon are also often affected, with the oesophagus, stomach and duodenum rarely involved. These present with non-specific GI symptoms similar to bacterial gastroenteritis, such as colicky abdominal pain, vomiting and borborygmi.*

2. Answer D: Appearance on colonoscopy is an interesting feature of abdominal TB.

Tuberculous granulomas are initially formed in the mucosa or Peyer's patches and tend to be of varying size and confluent compared to discrete ones in Crohn's disease. They are caseating in approximately 60% of patients (16). Ulcers related to abdominal TB are predominantly superficial and do not penetrate beyond the muscularis. They may be single or multiple and tend to be shaped in a transverse direction rather than serpiginous or longitudinal, as in Crohn's disease (17). Importantly, as a result of the healing of circumferential ulcers, strictures may form.

3. Answer A: The Ziehl-Neelsen stain, also referred to as the 'acid-fast stain', is used to identify Mycobacterium.

The initial stain – carbol fuschin – penetrates the cell wall of every cell and colours them red. A decolourising agent is then added; however, due to the mycolic acid constituent of Mycobacterium cell wall, it is not affected and therefore remains red whilst other organisms are decolourised. As the decolourising agent contains an acid (typically hydrochloric), but it is unable to penetrate the Mycobacterium cell wall, this is where the term 'acid-fast' is derived. A methylene blue counterstain is then added, turning non-Mycobacterium organisms and debris blue and leaving the Mycobacterium red (18).

4. Answer C: The most common complication of iliocaecal TB is small bowel obstruction.

This is thought to be due to stricturing, adhesions, and adjacent lymph node involvement that may compress and subsequently narrow the bowel lumen. Perforation is also relatively common and there should therefore be a high degree of clinical suspicion. Interestingly, pneumoperitoneum is seen in only 50% of these cases. Malabsorption is frequently seen and, when this occurs in association with abdominal pain, abdominal TB should be considered in at-risk populations (17). Gastrointestinal haemorrhage and intussusception are uncommon, but instances have been described in case reports (19,20).

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5. Answer B: Pyridoxine (Vitamin B6) is required during treatment with RIPE to counteract the pyridoxine deficiency associated with isoniazid (21).

This is via two main mechanisms - 1) Directly binding and inactivating pyridoxine and 2) inhibiting pyridoxine phosphokinase – an enzyme required to activate pyridoxine (22). Without treatment, pyridoxine deficiency leads to a symmetrical peripheral neuropathy in a 'glove-and-stocking' distribution. Whilst predominantly sensory deficits are seen in the earlier stages, ataxia, weakness and paralysis may occur if left untreated.

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ACUTE ALCOHOLIC HEPATITIS

B Vijayan, Georgina KP Choi, SK Gangadharan, A Gandagule

Abstract

Alcohol-related health harm is a well recognised problem in the United Kingdom resulting in morbidity and mortality for the patients and economic burden for the country. Rates of alcohol-related hospital admissions have increased significantly for both men and women since 1980s, peaking in 2008. Since then they have fallen by 22% (1, 2).

Despite the fall in the number, we frequently admit patients with chronic alcohol consumption leading to liver disorders in day-to-day practice. Alcohol-induced liver damage consists of a spectrum ranging from benign fatty liver disease progressing to steatohepatitis and cirrhosis of the liver. Approximately 35% of heavy drinkers develop alcoholic hepatitis which has a mortality of up to 50 % in the severe forms (3).

Acute Alcoholic Hepatitis (AAH) is an inflammatory condition of the liver resulting from chronic excess alcohol ingestion. It can present as a mild asymptomatic elevation of liver enzymes to more severe devastating hepatitis with a very high mortality. Severe AAH presents with features of liver failure including jaundice, coagulopathy and encephalopathy (3).

There have been no proven treatment options available yet for severe AAH. Recent multicentre randomised controlled trial (STOPAH trial) identified a subset of patients with severe AAH who benefitted from steroid therapy (4). Various scoring systems have been devised for predicting the outcome of severe AAH like Maddrey's Discriminant Function (DF), Model for end-stage liver disease (MELD) score and Glasgow Alcoholic Hepatitis Score (GAHS).

As practicing clinicians, we are faced with this common condition on a day-to-day basis and it is extremely important to understand the pathophysiology, clinical features, prognosis and treatment options in AAH.This would help us to identify patients early, stratify the risk and provide the current evidence based treatment for this debilitating disorder.

Case

A 64-year-old lady was admitted to the gastroenterology ward with painless jaundice and increasing abdominal distension. She described noticing bruising with minor trauma. There was no significant past medical history of note. She admitted to drinking at least two glasses of wine every night (home measures) until admission, for many years. She was malnourished, jaundiced and had bilateral pitting pedal oedema. Abdominal examination revealed hepatomegaly and shifting dullness indicative of ascites.

On admission her GAHS score was 8 (Age 64, WBC 15.3, urea 2.5, INR 1.3, bilirubin 174). Chronic liver screen including HBsAg, HCVAb, Immunoglobulin profile, iron studies and autoimmune profile were normal. Abdominal ultrasound scan showed a grossly enlarged liver with coarse echotexture, reversal of flow in the portal vein and ascites. Gastroscopy revealed portal hypertensive gastropathy. She was treated with nutritional supplements Pabrinex, Thiamine, Diazepam for alcohol detox and diuretics.

Six days into her admission, the patient developed confusion and altered sensorium suggestive of hepatic encephalopathy. A septic screen including ascitic tap for spontaneous bacterial peritonitis was negative and she was commenced on lactulose for treatment of encephalopathy. Her GAHS score deteriorated to 9 (age – 64, WBC – 15.7, urea – 5.9, INR – 1.3, bilirubin – 247). She was diagnosed with severe alcoholic hepatitis and commenced on Prednisolone 40 mg daily. Initially there was a mild improvement in her confusion however, her liver function tests continued to deteriorate.

Despite all supportive treatments, her liver synthetic function (Bilirubin, Albumin, and Prothrombin Time/INR) continued to worsen and she became progressively breathless and developed Type 1Hepatorenal syndrome. (Urea-35.9 and Creatinine -357). She died 19 days after admission from complications of liver failure secondary to AAH. This case highlights the multiorgan involvement and high mortality in patients with severe AAH.

Introduction

Alcohol is now widely available, easily accessible and is cheap to obtain. Hence, we are faced with an increasing number of alcohol related hospital admissions and alcohol-related mortality (1, 2). Alcoholic hepatitis is a clinical syndrome secondary to progressive inflammatory liver damage, manifesting as recent onset of jaundice and /or ascites in a patient with ongoing alcohol misuse (5).

Intake of >80 g/day of alcohol in males and >40 gm/day in females are required to cause alcohol related liver disease (6). It can present as a mild asymptomatic elevation of liver enzymes to more severe hepatitis with very high mortality. Severe AAH presents with features of liver failure including jaundice, coagulopathy encephalopathy. The usual precipitant is intercurrent infection, vomiting or diarrhoea in a malnourished patient who has been drinking heavily.

The breakdown of alcohol in the liver leads to the production of acetaldehyde and reactive oxygen species which is toxic to the liver cells. Most heavy drinkers are malnourished and the lack of nutrients and vitamins in their diet contributes to impaired ability of liver to regenerate. Additionally, alcohol disturbs the intestinal mucosal lining permitting lipopolysaccharides from gram-negative bacteria to be transported to the liver via the portal vein, which in turn causes cytokines to promote hepatocyte inflammation, apoptosis and necrosis (7)

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Symptoms

Alcoholic hepatitis can range from mild form which can be asymptomatic or present with nonspecific symptoms like fatigue, anorexia, weight loss and low grade fever to a severe form with jaundice, encephalopathy and liver failure. Other signs and symptoms which may also be seen are fever, nausea, repeated vomiting, abdominal pain, malnourishment, tender hepatomegaly, ascites, encephalopathy and bleeding diathesis (3). Signs of chronic liver disease such as such as spider naevi, Dupuytren's contracture, gynaecomastia and testicular atrophy are also common.

Diagnosis

There is no gold standard laboratory test for the diagnosis of AAH. It is mainly dependent on typical clinical history, amount of alcohol consumed, clinical presentation and pattern of LFT derangement. An elevation of bilirubin >80mg/dL and transaminases <300 IU/ml are hallmarks of the disease and typically the AST/ALT ratio is ≥ 2. (5) Additional evidence in the form of a high MCV and raised gamma GT are also useful. The serum alkaline phosphatase and WBC counts can also be very high depending on the severity (3, 4, 7).

Liver biopsy can provide a confirmatory diagnosis of AAH but is rarely needed due to a high bleeding risk due to coagulopathy the presence of coagulopathy. It can be useful in excluding other causes of hepatitis and in assessing the prognosis in AAH (7).

Hepatitis B and C are more common in this group of patients than in the general population and coexistent infection alters the natural course AAH adversely. Hence, all patients should be tested for viral hepatitis and treat them accordingly (7).

Treatment and Prognosis

Patients presenting with mild alcoholic hepatitis have a good prognosis and majority improve with supportive management. Severe alcoholic hepatitis has a high short term mortality of up to 50% in 28 days (8). Recent evidence has shown a reduction in short term mortality in a select group of patients treated with steroids (4). Hence, it is important to recognize this subset of patients. Several scoring systems such as Maddrey's Discriminant Function (DF), ABIC score and MELD score are used to stratify the risk of mortality from AAH. In the United Kingdom, Glasgow Alcoholic Hepatitis Score (GAHS) is more commonly used.

GAHS – Prognostic score

Glasgow Alcoholic Hepatitis Score (GAHS) is used to identify patients with AAH who are at an increased risk of mortality (9). The GAHS is calculated using the following variables patient's age, serum bilirubin, blood urea, INR, and white cell count. GAHS score is calculated on a daily basis and the Day 1 and day 7 score has been used to predict the prognosis as given in Table 1. The 28-day survival for patients with GAHS <9 on day 1 is 87% whereas, if GAHS≥9 on day 1, the survival drops to 46% in the absence of treatment as shown in Table 2 (9).

		Score
Age (years)	<50	1
	>50	2
WCC (10^9/L)	<15	1
	>15	2
Urea (mmol/L)	<5	1
	>5	2
INR	<1.5	1
	1.5-2.0	2
	>2	3
Bilirubin (µmol/L)	<125	1
	125-250	2
	>250	3

Table 1: Glasgow Alcoholic Hepatitis Score

	GAHS	Day 28 survival (%)	Day 84 survival (%)
Day 1	GAHS<9	87	79
	GAHS≥9	46	40
Day 6-9	GAHS<9	93	86
	GAHS≥9	47	37

Table 2: GAHS and the survival at day 28 and day 84 (6)

Variables in Lille Model for AAH

Age	**Years**
Albumin	**g/L**
Bilirubin(Initial)	**µmol/L**
Bilirubin(Day 7)	**µmol/L**
Creatinine	**µmol/L**
Prothrombin time	**Sec**

The Lille Model calculator is available online and can be accessed easily.

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Evidence from the recently published STOPAH trial shows that a carefully selected subset of patients benefits from steroid therapy (4). A 25% reduction in the bilirubin from the pre-treatment level after 7 days is a simple bedside method to assess the response to treatment. .

AAH patients treated with Prednisolone who fail to show a reduction in bilirubin on day 7 are unlikely to respond and carry a worse prognosis. This can be assessed by the Lille scoring on Day 7 (age, albumin, initial bilirubin, bilirubin on day 7, creatinine and Prothrombin time) (10).

Management

The mainstay of treatment for alcoholic hepatitis is abstinence from alcohol. This can be achieved by a multidisciplinary team approach comprising of Physicians, Psychiatrists, Dieticians and other allied paramedical services. Patients should be started on alcohol withdrawal treatment including Benzodiazepines, Pabrinex and nutritional support.

Early involvement of an alcohol liaison service is paramount and continued after discharge from the hospital. Evidence has shown that corticosteroids can sometimes reduce the hepatocyte injury by suppressing inflammatory mediators (8). Refeeding syndrome is a major risk particularly in this group of patients. Therefore, regular monitoring of Potassium, Magnesium, Phosphate and Glucose is crucial during the acute phase and abnormalities should be identified and corrected promptly according to local guidelines.

Suggested Algorithm For The Severe Alcoholic Hepatitis

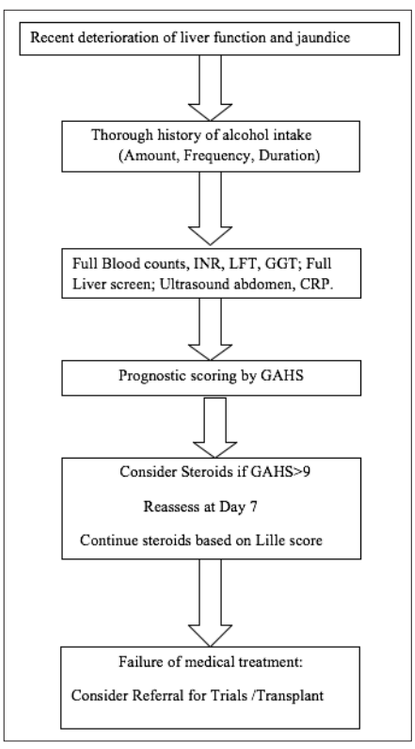

Figure 1: Algorithm for the severe alcoholic hepatitis.

Elicit a thorough history of alcohol intake and duration in patients admitted with recent deterioration of liver function and jaundice. Stratify the severity of hepatitis by prognostic scoring system (GAHS) and consider steroid therapy in suitable patients. Monitor the progress on a daily basis and reassess the response to steroid therapy in 7 days by Lille scoring. Patients who fail to respond to medical therapy should be counselled appropriately to participate in clinical trials and be referred to Regional Liver Units for consideration of Liver Transplantation.

Conclusion

Chronic excess alcohol consumption remains a major public health issue with significant morbidity and mortality. The symptoms of alcoholic hepatitis can be vague and non-specific. A detailed history and thorough examination allows prompt recognition and treatment of this life threatening illness.

Risk stratification can be done with serial GAHS measurement. Precipitating factors need to be identified early and treated promptly. A multidisciplinary team approach including alcohol liaison, dieticians, microbiologists, is crucial. Corticosteroids improve short term survival in a select subset of AAH as defined by the Lille score.

MCQ questions

1. What is the most common sign seen in alcoholic hepatitis patients?

- *Ascites*
- *Malnutrition*
- *Jaundice*
- *Encephalopathy*
- *Low grade fever*

2. Which of the following is not a component of the GAHS?

- *Bilirubin*
- *Urea*
- *INR*
- *Liver transaminase*
- *WCC*

3. Which trial has shown survival benefit in AAH?

- *Maddreys*
- *STOPAH*
- *GAHS*
- *EASL*
- *AASLD*

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4. At what GAHS does survival drop by 41% in the absence of treatment?

- *5*
- *6*
- *7*
- *8*
- *9*

5. Which of the following are complications of alcohol hepatitis?

- *Encephalopathy*
- *Malnutrition*
- *Hepatorenal syndrome*
- *Ascites*
- *All the above*

Answers

1 - Jaundice

2 - Liver transaminase

3 - STOPAH

4 - 9

5 - All of the above

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ACUTE SEVERE COLITIS: PLANNING & DECISION MAKING DURING THE ACUTE ADMISSION

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Abstract

Ulcerative colitis is a lifelong condition causing mucosal inflammation, extending proximally from the rectum around the colon to a varying extent in different individuals. The disease course is characterised by relapses and periods of remission. The worldwide prevalence of ulcerative colitis is increasing due to rising incidence and improved life expectancy with the condition(1). One of the most serious complications of the disease is acute severe colitis.

The management of this life threatening condition involves several timely investigation and management steps to alter the disease course and improve patient outcomes. Key assessments of the patient should be performed on admission, after initiation of corticosteroids and after initiation of salvage medical treatment. As with many acute, complex illnesses communication with patients, relatives and involvement of a multidisciplinary team are essential components of the management.

As a foundation doctor in training you may come across the presentation of acute severe colitis in primary care, A&E or the medical admissions unit. Here we present a typical case and outline the management steps during the acute admission, with reference to many aspects of the foundation programme curriculum.

Case

A 25 year old man presented via his GP to A&E with a 2 month history of worsening diarrhoea. He had been febrile and vomiting on the day of admission which prompted the GP referral. On further questioning he had 6kg of unintentional weight loss over the preceding 3 months, had fresh blood mixed in with every stool and was opening his bowels 10 times a day. He had no recent travel and had been well 6 months ago. Blood results from A&E showed a CRP of 124mg/L, Hb of 120 g/L, WCC of 12 10*9/L, and platelets of 456 10*9/L.

Introduction

Ulcerative colitis is a lifelong relapsing and remitting condition causing continuous inflammation from the rectum to varying extents of the colon(2). It is classified according to the maximal extent of the colon that is involved as this corresponds to the risk of future complications including toxic dilatation and colorectal cancer(2).

The clinical symptoms are bloody diarrhoea, nocturnal diarrhoea, abdominal pain, fever, weight loss and those from anaemia. Advances in the management of ulcerative colitis now mean that patients only have a slight increase in mortality in the 2 years after diagnosis and a similar life expectancy to the general population thereafter(3).

Acute severe colitis is a potentially life threatening complication of ulcerative colitis and following an admission to hospital 40% of patients will eventually require a colectomy, 20% during the first admission(4). Acute severe colitis is defined by clinical and laboratory parameters proposed by Truelove and Witts'(5). It is diagnosed by the presence of 6 or more bloody stools per day accompanied by one, or more of the following; tachycardia, pyrexia, anaemia or raised inflammatory markers (ESR or CRP).

Current British Society of Gastroenterology guidelines(6) advocate that patients with severe colitis, as defined by these criteria, should be admitted to hospital for further investigation and intravenous treatment. The number of positive criteria has also been validated for predicting need for colectomy after admission. Our patient was classified as severe colitis based on these criteria (bloody diarrhoea >6 per day, CRP >30mg/L & fevers).

Investigations and management steps

Initial assessment

The initial evaluation of acute severe colitis is extremely important to try and identify the patients who are most likely to fail initial treatment, require an escalation in their medical therapy and potentially require surgery. The admission assessment should document the number of Truelove and Witts' criteria(5) as these can be used to aid clinical judgement and predict which patients are at the greatest risk. A systematic review and meta-analysis in 2010 showed that the risk of colectomy was three times higher with two or more additional criteria on admission compared to when there is only one(7).

Following admission to hospital several important investigations need to be requested (table 1) which are essential for the diagnosis and as a guide to prognosis. Important differential diagnoses to consider on admission are infective colitis, ischaemic colitis, malignancy and drug induced colitis.

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Investigation	Reason
Full blood count	Patients are at risk of both macrocytic (malabsorption), and microcytic (blood loss) anaemia. A raised white cell count can indicate an inflammatory response, steroid response or super-added infection. Thrombocytosis is also seen as an acute phase response.
Urea and electrolytes	Patients are at risk of acute kidney injury due to pre-renal failure. Hypokalaemia is common due to excess gastrointestinal losses.
CRP	Is an important marker of inflammation and used to guide prognosis and management.
LFTs	Hypoalbuminemia can be an acute phase response and/or a marker of a catabolic state. It can also be caused by a protein losing enteropathy. Mild acute rises in liver injury and cholestatic tests can be seen with the acute illness. More persistently, or markedly abnormal tests should be fully investigated remembering the known association with primary sclerosing cholangitis.
Stool sample	Gut pathogens that can cause a similar presentation need to be excluded. The more common organisms are *salmonella, campylobacter, E.Coli, shigella and clostridium difficile* remembering that co-infection is increasingly seen with acute ulcerative colitis.
Blood cultures	If the temperature is above 38 degrees C.
Abdominal X-ray	To assess for toxic dilatation (transverse colon greater than 5.5cm) and give an indication of disease distribution.
Erect CXR	If suspicion of colonic perforation
Flexible sigmoidoscopy (unprepared with minimal air insufflation)	This is essential for endoscopic and histological diagnosis. A full colonoscopy should not be performed for the acute diagnosis due to the risk of pain and perforation.
CT abdomen	Can be useful to define the extent of inflammation and to assess for complications such as perforation, abscesses, fistulae or small bowel involvement that may indicate Crohn's disease.
Thiopurine S-methyltransferase (TPMT).	It is essential to assess for activity of this enzyme before commencing thiopurine medications which may be the next step in management. Low levels can lead to pancytopenia.
Pre-biological medication screen	Before initiating immunosuppressive medication in the form of anti-TNF therapy check hepatitis B & C serology, HIV serology, for latent TB, and positive previous varicella exposure.

Table 1. Investigations to request when suspecting acute severe colitis Initial management.

The goals of management of acute severe colitis are to quickly gain control of the colonic inflammation, achieve remission, identify those who may require surgery and improve quality of life. After admission to hospital several treatments should be commenced as shown in table 2. There should be a prompt referral to the Gastroenterology team and an early surgical review as essential parts of this initial management.

The patient's medication charts should be reviewed and potentially constipating medications, including opiate analgesia, should be withheld as these can provoke toxic dilatation of the colon, as should NSAIDs and iron tablets as these can exacerbate the colitis. Patients should be prescribed subcutaneous low molecular weight heparin as patients with active colitis are at increased risk of thromboembolic events(8). There should be a nutrition assessment and oral supplements should be prescribed as appropriate.

A key treatment is intravenous corticosteroids, typically hydrocortisone. The introduction of corticosteroids improved mortality from acute severe colitis from >50% to around 2%(9). As an important differential is infective colitis there is some justifiable concern with using immunosuppressive medications in patients where infection can be one of the important differential diagnoses.

If the clinical history is strongly suggestive of idiopathic inflammatory bowel disease i.e. progressive symptoms over a period of weeks or months then steroid medications should be commenced whilst waiting for stool culture results and histopathology samples from the flexible sigmoidoscopy. If an infective cause is suspected due to positive contacts or a shorter clinical course then it may be prudent to hold immunosuppressive treatment whilst confirmatory results are sought. These decisions should be made in conjunction with a senior clinician or specialist and the patients should be regularly reviewed and re-evaluated.

Management step	Reason
Intravenous fluids	Patients may be hypovolemic due to the diarrhoea and reduced oral intake and are at risk of acute kidney injury. Potassium supplementation is often required.
Intravenous steroids, typically hydrocortisone 100mg 6 hourly.	To control the colonic mucosal inflammation. They should be commenced early in the admission but usually after specialist review.
Calcium and vitamin D supplementation	As prophylaxis against osteoporosis whilst on steroid medications.
DVT prophylaxis with low molecular weight heparin. E.g. tinzaparin 4500 units if renal function permits.	Patients are in a pro-thrombotic state during the acute flare. This should be given despite the presence of bloody diarrhoea. If there is concern about uncontrolled GI haemorrhage consult with a specialist colleague.
Review medication chart for potentially constipating medications	Opiate analgesia, antidiarrhoeal agents and anticholinergic drugs can precipitate a toxic, dilated colon. If the patient requires strong analgesia consult with a specialist. Non-steroidal anti-inflammatory drugs should be discontinued.
Stool chart	Patients should be instructed how to complete their own record which should include frequency, volume and presence, or absence of blood.
Early surgical review	Patients should be reviewed early in their admission by the on-call surgical team.

Table 2. Initial management of acute severe colitis.

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After initiation of treatment patients should be closely monitored for the clinical and biological response. Medical review should document stool frequency, presence of blood, the urgency, nocturnal symptoms, abdominal pain, fevers and the patients should be asked for subjective improvement. Laboratory tests including full blood count, CRP, platelets and albumin should also be used to guide the response to treatment.

Clinical progress

The patient was admitted to hospital and the investigations were ordered as outlined. Flexible sigmoidoscopy on day 2 showed confluent inflammation and ulceration to the descending colon. The endoscopic diagnosis was ulcerative colitis but confirmatory biopsies were fast-tracked to histopathology.

Communication with the patient

Breaking bad news is an important part of clinical work. It is especially pertinent in such cases where it may be the patient's first serious illness, they are often at a young age and the diagnosis can have serious future implications. There are also considerations for women of reproductive age about medical and surgical treatments that may affect future fertility. It is essential that information on management and possible escalations in treatment are conveyed to the patient in a timely manner to avoid rushed decisions if the severity of the illness escalates.

Information should be clear, contain no jargon and be tailored to the individual patient and often their family. Patient's fears and expectations should be explored and the management plan and timelines should be explained. It is important that the key clinical decisions are described in detail as there may be some diagnostic uncertainty.

Possible medical and surgical treatments should be explained and written information should be provided. Discussions with specialist inflammatory bowel disease and stoma care nurses should be arranged. It is also useful to show patients how to access the Crohn's and Colitis UK website (https://www.crohnsandcolitis.org.uk) and register with the charity for further information.

Admission days 3-5

The clock is ticking from the time of admission. If there is no significant clinical improvement after 3 to 4 days of intravenous hydrocortisone treatment a different approach is required. A landmark study to guide management after day 3 of corticosteroids was performed by Travis et al(10) who developed criteria to predict the risk of colectomy (table 3). This study showed that patients with more than eight stools on that day, or a stool frequency greater than 2 with a CRP > 45 mg/l, are at high risk of requiring colectomy without an alternative therapy.

These criteria aid discussions with patients about the need for further treatment. In acute severe colitis intravenous corticosteroid treatment is effective in around 67% of patients(9). However, if a patient appears to be failing steroid therapy discussions should begin at an early point about alternative therapies including rescue medical therapy or surgery.

Day 3-5 assessment	Colectomy risk
Daily stool frequency >8	85% positive predictive value for requiring colectomy
Daily stool frequency >2 plus CRP > 45mg/litre	85% positive predictive value for requiring colectomy

Table 3. The Travis risk score for estimating risk of steroid failure and requirement for colectomy(10).

Medical rescue therapy

Approximately one third of patients will not respond adequately to corticosteroids. In this circumstance medical rescue therapy can be used to try to halt disease progression, reduce the need for emergency surgery and reduce long-term complications. There are two medications that are commonly used in acute severe colitis; the calcineurin inhibitor cyclosporine A and the anti-tumour necrosis factor alpha (anti-TNF) inhibitor Inflximab.

Cyclosporine A is most commonly prescribed at a dose of 2mg/kg/day intravenously until symptomatic improvement. This may then be converted to an oral regime which is discontinued after 3 months. Before commencing this medication serum magnesium and blood lipids should be checked and repeated after 1 month Oral regimes of Cyclosporine A are also sometimes used in the acute setting. This treatment was first used over 2 decades ago and has initial response rates of up to 80%(11). However, toxicity can be a problem in the short term and close monitoring of drug levels are required particularly during the intravenous phase Furthermore, colectomy may not be avoided in the long term in many patients.

More recently the anti-tumour necrosis factor alpha (anti-TNF) inhibitor infliximab (given as an intravenous dose of 5mg/Kg on weeks 0, 2 and 6) has been shown to have similar response rates to cyclosporine A (12,13) but with less side effects and without the need for monitoring of drug levels. Cyclosporine A and infliximab are the most established medications in the acute setting. Other anti-TNF inhibitors (e.g. adalimumab and golimuab) and other biological classes (e.g. vedolizumab) are available for the treatment of ulcerative colitis but are less commonly used in the setting of acute severe colitis.

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Rescue medical treatments such as infliximab and Cyclosporine A are usually used to bridge to long term disease control with immunomodulatory drugs such as azathioprine or 6-mercaptopurine, although anti-TNFs are now licenced for long term disease control with or without additional azathioprine.

These medications should usually be commenced between days 3-5 of an admission if a patient is not improving, as guided by the Travis criteria, and should only be commenced by specialists experienced in their use. The patient should be closely monitored after this medical salvage therapy has been commenced. Response times can vary but if no improvement has been seen after 4 or 5 days then treatment failure is likely and surgery may be indicated (12).

Surgery is still important

It is imperative that clear, documented plans are in place during days 3-5 of the admission. The acute surgical team should be made aware of the patients' progress in case an emergency operation is required. In the acute setting the preferred operation is a sub-total colectomy with an ileostomy and the rectum left in situ. This is a safe procedure, even in patients who are severely unwell with a mortality of <1%(14). It allows the patient to recover from the acute colitis after the inflamed bowel is removed. Most patients then go on to have restorative surgery with the formation of an ileoanal pouch in one or two further operations.

Absolute indications for surgical input are uncontrolled colonic bleeding or colonic perforation. Other relative indications include; toxic megacolon (defined by colonic dilatation >5.5cm) that fails to rapidly respond to medical therapy, failed medical therapy and patient preference. The purpose of timely surgery is to prevent complications such as perforation, which carries a high mortality risk. Surgery is indicated at any point where the patient is deteriorating and in any event should not be delayed for longer than 10-14 days after admission as the risks and complications from surgery increase the longer duration that the patient is in hospital and receiving intravenous corticosteroids. This again highlights the importance of timely investigations and intervention with medical treatments.

It is important that the long-term risks of surgery are discussed with the patient as following a colectomy with ileoanal pouch formation there is a risk of infections and inflammation of the pouch (pouchitis), female infertility, faecal incontinence and failure of the pouch necessitating ileostomy re-formation.

Clinical progress

After three days of intravenous steroids our patient had made little progress and was still opening his bowels 9 times a day with fresh red blood with every motion. His abdomen was soft and non-tender and repeat plain abdominal x-ray showed no sign of toxic dilatation. Blood tests showed some response but his CRP remained elevated at 55mg/litre. A surgical review was organised and possible operations were discussed. After discussions between the patient, the gastroenterologists and the surgical team a plan was put in place to start medical rescue therapy with the anti-TNF alpha medication infliximab on day 4.

Multidisciplinary team input

Timely management, patient communication and teamwork are imperative in this case. Acute inflammatory bowel disease is a multi-disciplinary disease and many key individuals are involved in the diagnosis and acute management. A list of allied health professionals that would typically be involved in the care is shown below with brief outlines of their roles (table 4).

Team member	Role
Gastroenterologist	Co-ordinating the admission. Performing the diagnostic flexible sigmoidoscopy.
Colorectal surgeon	Reviewing the patient early in the admission. Discussing possible acute surgical interventions.
Histopathologist	Reviewing the endoscopic specimens. Define the type of IBD - UC/Crohn's or infective with possible inclusion bodies, although primarily a concern if the patient is immunosuppressed before admission.
Radiologist	Reviewing plain films and any cross-sectional imaging. Extremely important to define the extent of inflammation and examine for any features which may suggest Crohn's disease or ischaemic colitis.
Inflammatory bowel disease specialist nurse	Providing extra information on treatments, prognosis and long-term management. Liaising with other allied health professionals - psychiatry, dieticians, stoma nurses, pharmacists. They are likely to be involved in the long term care for the patient. Leaflets and guidance from the Crohn's and Colitis UK. charity can be offered.
Pharmacist	Ensure that any infusion medications are prepared in a timely manner in case they are needed for rescue therapy.
Dietician & nutrition team	Optimise the nutritional state of the patient. Especially important before any surgical procedure where parenteral nutrition is sometimes indicated.
Nursing staff	Assist in filling in the stool chart which is essential to track response to treatment. Administered the requisite medications. Track patient's weight. Provide continuity of care and can highlight issues to the medical teams.

Table 4. List of allied health professionals involved in the management of acute severe colitis

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Long term management

Ulcerative colitis is a lifelong condition that is characterised by periods of remission and relapses and can have a significant burden on work-life and activities of daily living for those affected(15). Ongoing treatment should be co-ordinated in a dedicated inflammatory bowel disease clinic where the holistic care needs of the patients can be addressed. Even after achieving remission with medical salvage therapy such as infliximab, patients should be informed that colectomy may be the best alternative to treat their condition and that outcomes are good. Around half of patients will have frequent relapses during their disease course, and although rates have decreased up to 10-15% of patients will ultimately require a colectomy(15).

Clinical progress - Our patient was discharged on day 8 after receiving his first infliximab infusion. He had been commenced on oral azathioprine and a reducing course of oral prednisolone, he had achieved clinical remission as defined by <3 non-bloody stools per day(16) and his CRP was down to 13mg/litre. Calcium supplementation was continued for the duration of oral steroids as bone prophylaxis. He was followed up in a dedicated inflammatory bowel disease clinic 2 weeks after being discharged and continued to do well. He continues on maintenance medical management with infliximab and azathioprine but is aware that surgery may be required in the future.

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ACUTE UPPER GASTROINTESTINAL BLEEDING

RJR Peters, N Chandra, AD Silva

Abstract

Acute upper gastrointestinal bleeding (AUGIB) is one of the most common emergency presentations to UK hospitals. Whist endoscopy is the mainstay for achieving haemostasis timely and effective initial assessment with good post procedural care is critical to improving outcomes.

We focus on initial assessment and management of the acutely bleeding patient relevant to doctors working in Accident and Emergency departments and acute medical units. We discuss risk stratification using a validated risk scoring system and review the evidence behind the critical management decisions including rational transfusion and appropriate use of adjunctive medications. We also include advice on escalation of care in the deteriorating patient and discuss ongoing research into novel therapies for reducing bleeding.

Introduction

AUGIB is a common medical emergency. Presentation is typically with a history of haematemasis or melaena indicating a probable upper gastrointestinal source of blood loss. In the United Kingdom AUGIB accounts for greater than 50,000 hospital admissions per year with an incidence of between 100 and 200 per 100000 UK population (1). Mortality from AUGIB is strongly associated with the presence of co-morbid conditions (2), and, despite recent improvements, remains at 7% for new AUGIB presentations in the UK (3). Timely and appropriate intervention to optimise the condition of the acutely unwell patient is critical to good clinical outcomes.

Clinical case

06:20 am. A 57-year-old male is admitted to A&E with melaena. Suspecting an AUGIB the on-call doctor makes an assessment of the patient using the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. He notes that the patient has a slight tachycardia and a low blood pressure. The patient's hands and feet are cool with a prolonged capillary refill time indicating that the patient is in hypovolaemic shock. The patient's Glasgow Coma Score (GCS) is noted to be 15/15 and during the Exposure part of the examination the on-call doctor elicits no signs of chronic liver disease and no evidence of heart failure.

06:25 am. The on-call doctor inserts two 18G intravenous cannulas and commences a 1/L bag of crystalloid fluid bolus. At the same time he takes blood samples and requests Urea & Electrolytes (U&Es), Full Blood Count (FBC), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen, Blood Group and Save (G&S), Venous Blood Gas (VBG) and Liver Function Tests (LFT). The patient is connected to heart rate and blood pressure monitors to assess his response to the intravenous fluid bolus.

Initial approach to the bleeding patient

As demonstrated in the clinical case the immediate priority when faced with a patient presenting with AUGIB is to assess the degree of systemic compromise and make appropriate interventions to stabilise the patient. A rapid ABCDE assessment with a focus on circulation will provide the required information.

The second function of the initial assessment is to gather information to assist in formulating a diagnosis and assessing for evidence of co-morbidities particularly heart failure, renal disease or cirrhosis which have a bearing on management and prognosis.

Circulatory dysfunction in AUGIB is caused by hypovolaemic shock. The immediate goal is to restore adequate circulating volume without over correcting. This is best achieved by rapid infusion of fluid boluses followed by frequent re-assessment of the patient's circulatory status.

Following intervention to stabilise the patient's circulatory parameters a more formal history and examination can be performed. This should be targeted to identify the cause of the AUGIB (Table 1.). The most important distinction is to determine whether or not the patient has cirrhosis or suspected chronic liver disease as these raise the possibility of variceal bleeding. A rare cause of AUGIB includes aorto-enteric fistula, which usually occurs in patients who are known to have either a large abdominal aortic aneurysm, or, have a history of major surgery to organs supplied by the coeliac artery branch of the aorta. If there is high suspicion of aorto-enteric fistula, CT angiography should be performed in preference to upper gastrointestinal endoscopy as the initial investigation of choice.

Oesophagus	Oesophagitis
	Oesophageal Varicies
	Oesophageal tumour
	Mallory-Weiss Tear
Stomach	Gastritis
	Gastric Varicies
	Gastric Ulcer
	Gastric Antral Vascular Ectasia (GAVE)
	Dieulafoy Lesion
	Cameron's Ulcer
Duodenum	Duodenitis
	Duodenal Ulcer
	Duodenal Tumour
	Aorto-enteric Fistula

Table 1. Causes of Upper Gastrointestinal Bleeding

A thorough medication history is also important as a number of medications can cause AUGIB. Common culprit medications are Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). These have a direct action on the gastric epithelium causing ulceration and eventual bleeding. Anti-platelet (Aspirin and adenosine diphosphate (ADP) receptor antagonists) and anti-coagulant medication (coumarins and direct acting oral anti-coagulants (DOACs)) may exacerbate bleeding from other causes.

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Risk Stratification

All patients presenting with AUGIB should undergo risk stratification with a risk scoring tool. Whilst an appreciation of the potential mortality risk is helpful, scoring systems have pragmatic use in prioritisation of endoscopy and providing a quick and reproducible way of communicating risk within a multidisciplinary team. The two most commonly used risk-scoring tools are the Rockall score (4) and the Glasgow Blatchford score (GBS) (5).

We favour the Glasgow Blatchford as it relies on data that is routinely available at admission (Table 2.), unlike the Rockall score, which contains a domain for scoring endoscopic appearances. The Glasgow Blatchford score has been validated to be an effective predictor of outcomes, including mortality and need for surgery whilst also to identifying low risk patients (GBS of 0), who can safely be managed in an outpatient setting (6-8).

Risk Marker	Score
Blood Urea (mmol/L)	
≥6.5 <8.0	2
≥8.0 <10.0	3
≥10.0 <25.0	4
≥25.0	6
Haemaglobin g/L (Men)	
≥120 <130	1
≥100 <120	3
<100	6
Haemaglobin g/L (Women)	
≥100 <120	1
<100	6
Systolic Blood Pressure (mmHg)	
100 – 109	1
90 – 99	2
<90	3
Other	
Pulse ≥100 bpm	1
Presentation with Melaena	1
Presentation with Syncope	2
Hepatic Disease	2
Cardiac Failure	2
Adapted from Blatchford O., et al. 2000 (5)	

Table. 2 Glasgow Blatchford Score

Blood Transfusion and Blood Products

Established dogma is that red cell transfusion in AUGIB restores haemoglobin concentration and capacity for tissue oxygen delivery. Therefore historic practice has been to adopt a liberal approach to transfusion. A number of recent trials have called this assumption into question.

A large single centre RCT demonstrated that use of a transfusion threshold of 70 g L-1 was associated with a significant improvement in mortality and incidence of re-bleeding at 6 weeks when compared to the more liberal threshold of 90g L-1. The effect was most pronounced in patients with liver cirrhosis of a mild or moderate severity. This effect was attributed to higher portal venous pressures in the liberal transfusion group (9).

The TRIGGER study, a UK based multi-centre phase II feasibility trial, reported a non-significant trend towards improved mortality in the restrictive transfusion arm, however there was an excess of deaths in patients with ischaemic heart disease (10). Overall there is some evidence to suggest that a restrictive transfusion strategy is beneficial and future studies are likely to provide a more definitive answer. In current practice caution should be exercised in those patients with significant co-morbidities, particularly ischaemic heart disease.

National guidance is that those patients presenting with active bleeding and platelet counts below 50 x109l-1 should have platelet transfusions to correct the deficiency (11). In practice, aside from cirrhotic patients with variceal bleeding, it is uncommon to encounter patients with AUGIB and significant thrombocytopenia.

It has been reported in retrospective analysis that coagulopathy, INR >1.5, is associated with a 5 fold increase in risk-adjusted mortality. It remains unclear whether this increased mortality is directly related to coagulopathy or simply represents a cohort of patients who are more unwell at presentation (12). Current NICE guidelines do however recommend that coagulopathy, INR >1.5, is corrected with fresh frozen plasma (FFP) (11).

Patients taking Anticoagulant medication

Warfarin causes coagulopathy by depletion of vitamin K dependent clotting factors. In AUGIB presenting with active haemorrhage warfarin must be reversed. Administration of intravenous vitamin K will reverse the effect of warfarin within 8h (Table 3.) whilst more rapid reversal can be achieved using prothrombin complex concentrate (PCC) 25-50 U kg-1 (13).

When reversing warfarin always consider the indication for the medication. In cases where the patient has an absolute requirement for anticoagulation we would advise discussion with a haematologist about ongoing anticoagulation after reversal of warfarin.

Direct acting oral anticoagulants (DOACs) do not always cause abnormalities in the routinely measured coagulation parameters even when present at therapeutic levels. It is therefore essential to establish the timing of the patient's last dose as this, in combination with knowledge of the patient's renal function, will enable an estimation of the likely duration of therapeutic effect. Recent BSG/ESG anticoagulation guidelines provide some guidance on estimating the effect of different DOACs (14).

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Medication	Use in AUGIB
Proton Pump Inhibitor	No evidence for pre-endoscopy use. Reduces the incidence of re-bleeding in patients with peptic ulcer disease (post-endoscopy).
Vitamin K	Reversal of Warfarin (8h to peak effect).
Prothrombin Complex Concentrate	Used in combination with Vitamin K for rapid reversal of Warfarin.
Idarucizumab	Reversal agent for the thrombin inhibitor Dabigatran (UK licensed indication).
Andexanet Alfa	Reversal agent for factor Xa inhibitors Apixaban & Rivaroxaban (No current UK license).
Tranexamic Acid	Antifybrinolytic agent currently of unproven benefit in AUGIB.
Terlipressin	Vasopressin analogue used to reduce hepatic portal pressure in acute variceal bleeding. This drug should be give acutely (pre-endoscopy) to patients with suspected variceal bleeding.
Antibiotics	a. Broad-spectrum antibiotics should be given acutely to patients with suspected variceal bleeding. b. Given post-endoscopy in combination with a PPi as part of an H. Pylori eradication regimen for patients with H. Pylori positive peptic ulcer disease.

Table 3. Summary of Medication Use in AUGIB

Idarucizumab has been shown to be effective in reversing the effect of dabigatran (15) and is now available in some UK hospitals. Andexanet Alfa, a reversal agent for apixaban and rivaroxaban, has undergone phase III trials (16) and may be available for clinical use in the near future. We would therefore recommend early involvement of a haematologist in the management of all patients presenting with AUGIB whilst taking a DOAC medication.

Proton Pump Inhibitors and Antifibrinolytics

Gastric secretions are known to have a fibrinolytic effect that has been shown to be dependent upon a pH less than 4.0 (17). Proton pump inhibitors (PPi) increase the gastric pH by preventing hydrogen ion transport into the gastric lumen and are therefore thought to promote clot stability in acute bleeding as well as promoting longer term ulcer healing.

Khuroo et al (1997). Showed that Omeprazole in AUGIB was superior to placebo in rates of re-bleeding, need for surgery and mortality (18). The concept was refined in a landmark study from Hong Kong which recruited patients with either actively bleeding ulcers or ulcers containing a non-bleeding vessel.

All participants received dual endoscopic therapy in the form of adrenaline injection and thermocoagulation before being randomised to receive either an 80mg intravenous bolus of Omeprazole followed by an intravenous infusion of omeprazole at 8mg/h for 72 hours or placebo.

The study demonstrated a significant reduction in re-bleeding at 30 days, 6.7% in the Omeprazole group versus 22.5% in the placebo group (19). As such PPi treatment is now routine management post endoscopy for AUGIB, and, all patients who require endoscopic therapy to peptic ulcers should receive a post procedure PPi infusion as detailed in the Hong Kong paper protocol.

Early studies evaluating PPi in AUGIB preceded the widespread availability of emergency endoscopy. Therefore in the modern healthcare environment the case for acute PPi use pre-endoscopy, is less clear. A 2010 Cochrane meta-analysis did not find that pre-endoscopic use of PPi had any benefit to mortality, re-bleeding rates or the need for surgery. As such, despite forming the mainstay of post endoscopy peptic ulcer disease management, PPi use is not recommended as part of the initial pre-endoscopic management of AUGIB (20).

Tranexamic acid is an anti-fibrinolytic that has some evidence to suggest that it may be useful in AUGIB. It has been shown in vitro to prevent fibrinolysis by gastric acid (17) and has been shown to be clinically useful in reducing blood loss in other clinical situations, with a systematic review of its use in surgical patients demonstrating a reduction in blood transfusion requirements by a third (21).

The HALT-IT trial, a large multi-centre RCT designed to investigate whether or not Tranexamic Acid has a measurable clinical benefit in AUGIB, is currently underway (22). Currently, although potentially promising, the benefits of Tranexamic Acid in AUGIB are unproven and its use is not routinely recommended outside of a clinical trial.

Variceal AUGIB

Varicies are collateral vessels that allow blood to pass between the portal and systemic venous circulations bypassing the liver. Cirrhosis leads to portal hypertension causing these collaterals to become engorged with blood. This occurs when the portal pressure gradient exceeds 10mmHg (23). AUGIB from a variceal source carries a high mortality, up to 50% (24).

Vasoactive drugs are analogues of somatostatin or vasopressin and have been used to reduce the pressure in the portal circulation during AUGIB from a variceal source. Terlipressin has a longer duration of action than vasopressin and is the most commonly used vasoactive drug in the UK.

It should be administered intravenously at a dose of 2mg every 4-6 hours. A 2012 meta-analysis comparing vasoactive drugs to no vasoactive drugs demonstrated a significant reduction in mortality in the treatment arm. The same meta-analysis showed no difference in efficacy between vasopressin or somatostatin analogues (24).

Management of variceal AUGIB requires a holistic approach to the patient in who haemorrhage may be triggered by occult infection causing an elevation in portal pressure. Prophylactic antibiotics have been shown to reduce mortality in variceal AUGIB (25). All patients with variceal AUGIB should therefore receive antibiotics at presentation according to local protocol.

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Clinical Case

07:20 am. The patient becomes pale and vomits 700ml of fresh blood. Repeat ABCDE assessment identifies tachycardia, HR 147 and hypotension, BP 82/60 mmHg, with reduced G.C.S. 11/15. The on-call doctor identifies that the patient has an acute life threatening haemorrhage. He commences a further 1L stat intravenous fluid infusion and initiates the hospital's major haemorrhage protocol. Whilst transfusing the patient he contacts the on-call endoscopist and on-call anaesthetist to arrange an emergency endoscopy in the operating theatre.

08:00 am. Following adequate fluid resuscitation the patient is transferred to theatre where he undergoes an upper gastrointestinal endoscopy under general anaesthesia. He is found to have an actively bleeding duodenal ulcer and receives dual endoscopic therapy with adrenaline injection and endoscopic clipping of a bleeding vessel.

Major Haemorrhage

It remains critical to stabilise the patient with life-threatening haemorrhage before attempting to perform emergency endoscopy for AUGIB. This requires some additional considerations to be taken into account. Profuse bleeding can compromise the patient's airway both by reduced conscious level secondary to cerebral hypoperfusion and increased aspiration risk from large volumes of blood in the upper gastrointestinal tract. It is essential to involve an anaesthetist as under such circumstances endoscopy is only safe under general anaesthetic.

Major haemorrhage protocols were developed for use in battle trauma and have been adopted in civilian healthcare settings to ensure timely availability of blood and blood products to acutely bleeding patients (26). Local protocols vary but major haemorrhage packs usually consist of O rhesus negative blood with a set quantity of FFP and platelets. It is important to be aware that trials on restrictive transfusion strategies have excluded patients with life threatening AUGIB and therefore restrictive transfusion is not appropriate in major haemorrhage situations (13)

In the event of a failure to achieve endoscopic control of haemorrhage, radiological embolisation of a bleeding vessel or surgery, maybe required as rescue therapy. It is good practice to involve a surgeon and interventional radiologist at the earliest opportunity.

Post Endoscopy Care

Once endoscopic haemostasis has been achieved an endoscopist should provide a detailed report of the procedure. This will include details of the lesion and any therapy applied, but should also include instructions for post procedure care and a plan for further intervention in the event of repeated haemorrhage. Current European guidelines recommend repeat endoscopy as the first line intervention for repeated haemorrhage (27), but prompt radiological and surgical intervention should be considered if appropriate. If repeat endoscopy is not successful radiological embolisation or surgery will be required depending on the suitability of the patient.

Conclusion

AUGIB is a common presentation that remains associated with an appreciable mortality. Whilst endoscopic therapy may be required to achieve haemostasis in AUGIB, peri-procedural care is critical to survival. Timely assessment and resuscitation with judicious use of blood products, taking into account co-morbidities all contribute to improved outcomes.

Questions

1. The immediate priority in a patient with AUGIB is?

a. Call the endoscopist
b. Rapid 'ABCDE' assessment and intervention to stabilise vital signs
c. Calculate the Rockall score
d. Check the blood glucose
e. Review the patient's medication history for potential iatrogenic causes

2. Terlipressin should?

a. Be administered to all bleeding patients with Hb <60gL-1
b. Be administered to patients with AUGIB and peripheral vascular disease.
c. Only be used in patients with peptic ulcer bleeding
d. Not be given until endoscopy confirms variceal bleeding
e. Be administered to patients with AUGIB and suspicion of a variceal source of bleeding

3. A patient returns from endoscopy having had adrenaline injection and thermocoagulation with a heater probe applied to a large posterior duodenal ulcer. Appropriate post endoscopic management would include?

a. Empirical treatment for H.Pylori eradication
b. Intravenous Omeprazole 40mg twice daily
c. Oral Omeprazole 40mg twice daily
d. Intravenous Omeprazole 80mg loading dose followed by an intravenous infusion at 8mg/h for 72 hours
e. Tranexamic acid treatment for six weeks

4. Having assessed a patient presenting with an AUGIB, which of the following would indicate that the patient is appropriate for outpatient management?

a. The patient is alert and able to give a history
b. There was only a small volume of melaena
c. The patient's Glasgow Blatchford Score was 0
d. The patient stopped taking Ibuprofen when they had their first episode of melaena
e. The patient is normally 'fit and well'

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5. A patient taking warfarin presents with active AUGIB and haemodynamic instability. They have an INR of 10. Which of the following is medications should they receive?

a. Idarucizumab
b. Vitamin K alone
c. Vitamin K and Prothrombin Complex Concentrate
d. Tranexamic acid
e. Apixaban

Answers

1. b 2. e 3. d 4. c 5. c

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THE HIGH OUTPUT STOMA

R Das, A Mandal, D Leonard

Abstract

Control of a 'high output' stoma is often challenging, and a scenario many foundation trainees would encounter on the wards. By understanding the pathophysiology surrounding a high-output state, logical stepwise management can lead to better control of stoma output. This discussion presents an emergent scenario and further considers the stepwise management of a high output state.

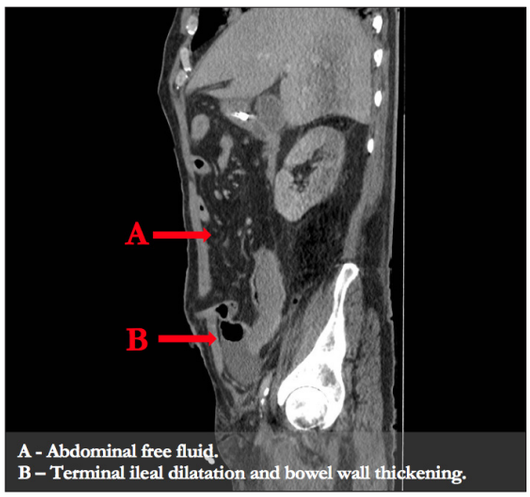
Case History - Abdominal Pain Post Total Knee Replacement

A 72-year-old inpatient began having intractable pain following an elective orthopaedic procedure. His medical history was only notable for paroxysmal atrial fibrillation (AF), treated with low dose aspirin. Examination revealed marked abdominal tenderness and central guarding. The patient was tachycardic, hypotensive and pyrexial (38.8^{0}C). Immediate blood tests were markedly deranged: WCC of 23.1 x10^9, CRP 224, and arterial blood lactate of 6.6 mmol/l. The concern was of a catastrophic intra-abdominal event such as ischaemic gut.

What would your initial management be?

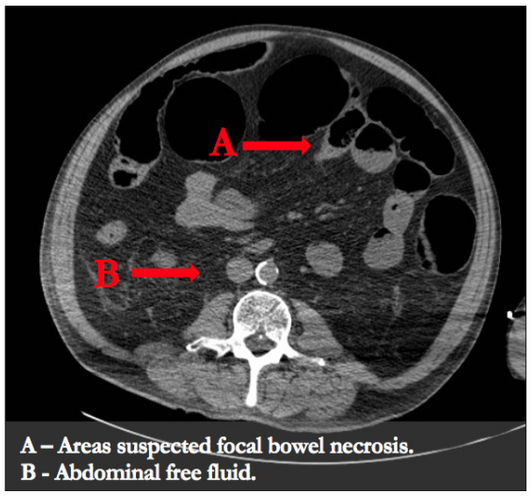
- Immediate Steps: ABCDE approach / IV access / Fluid resuscitation/ IV broad spectrum Antibiotics/O2
- Bloods: FBC / UE / CRP / Coagulation Screen / LFTs / Amylase
- Contact Radiology for an urgent CT abdomen
- Seek Senior input and urgent referral to Surgical Team & ITU

Urgent CT imaging revealed areas of small bowel wall thickening, terminal ileal dilatation, free abdominal fluid and areas of focal bowel wall mural necrosis. An emergency laparotomy noted necrotic small bowel, with blanched areas suggestive of compromised arterial supply. Extensive ileal resection was required - leaving the patient with a jejunostomy, and a proximal bowel of 110cm length.



A - Abdominal free fluid.
B – Terminal ileal dilatation and bowel wall thickening.

Image 1



A – Areas suspected focal bowel necrosis.
B - Abdominal free fluid.

Image 2

Once stabilised on ITU post bowel resection, the patient's jejunostomy began producing roughly 4-5L of output per day. Acute Kidney Injury resulted with the serum creatinine rising to > 600 umol/L within 48 hours. Oral intake was not restricted, with the patient consuming at minimum 1.5 L of fluid a day in an effort to rehydrate. Renal function fluctuated and any oral intake provoked torrential stoma output.

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Discussion

The creation of a stoma following emergent bowel resection is not uncommon. Bowel resection may be necessary in cases of perforation, inflammation, ischemia or obstruction. In the index case, the development of acute abdominal pain with high serum lactate on the background of AF suggested thromboembolic mesenteric infarction. Patients with AF with sub-optimal anti-coagulation remain at significant risk of developing embolic complications.(1) High index of clinical suspicion and early diagnosis led to the urgent resection of ischaemic gut segment.

The creation of a colostomy, ileostomy or jejunostomy represents a seismic physiological shift from normal function of the GI tract. Without the full water absorptive surface area of the colon, stoma output remains high volume. If a significant length of small bowel is absent, resorption of bile acids via the enterohepatic circulation is compromised.

Bile acids in the colon stimulate electrolyte and water secretion, increasing motility, decreasing transit time and thus worsening exit volume.(2) The 'high output stoma' is defined by an output greater than 1500ml per day. Formation of a jejunostomy (defined as having less than 200 cm of remaining small bowel) results in a high output state in at least 15-20% of patients.(3) The index patient retained only 110cm of jejunum.

In essence the high stoma output and patient can be managed by:

a. Decreasing the production of gastrointestinal secretions

b. Slowing intestinal motility

c. Increasing absorption of water and sodium

d. Close monitoring of the fluid balance, renal function, serum electrolytes

Salivary gland production is roughly 500-750 ml/day. The pancreas produces at least 1L/day of bicarbonate and enzymes, while the gastric secretions total roughly 4-5L/day. With the addition of bile the GI secretion volume totals roughly 6-8L/day. The majority of this is reabsorbed by the jejunum and ileum.

Drugs are effective in reducing net secretion and stoma output. Gastric acid secretion is demonstrably reduced by up to 95% with PPI use(4). Octreotide decreases gastric acid, bile and pancreatic juice release and slows small bowel transit(5,6). Initiating loperamide and codeine, both of which act upon the opioid 'Mu' receptor, reduces small bowel motility - enabling further water and electrolyte absorption, thereby reducing the stoma output.(7)

Absorption is perhaps best improved by decreasing the intake of oral water or clear fluids to a maximum of 500ml to 750ml a day. Increasing the sodium concentration of any oral fluid to 90 - 120 mmol/L with the addition of salt mixtures (such as WHO rehydration formula or St. Mark's Solution) enables the function of intestinal 'Sodium Glucose Transporters'(SGLT) which act as water channels.

A lack of appropriate sodium concentration within the small intestinal luminal fluid therefore results in suboptimal SGLT function, unabsorbed content and increased stoma transit volume. Finally minimizing dietary roughage and fibre increases bowel transit time.

Jejunal fluid contains high sodium (~100mmol/l) and magnesium but is low in potassium. High output of jejunal effluent therefore leads to profound loss of magnesium and sodium. Potassium balance is usually not an issue unless the patient develop secondary hyperaldosteronism as a result of chronic hyponatremia or has persistent hypomagnesemia (both states result in urinary potassium wasting). Urgent nutritional considerations (i.e. under-nutrition and refeeding syndrome) mandate the regular monitoring of magnesium, potassium, phosphate, and sodium.

Hypokalaemia and hypomagnesaemia can result in cardiac dysrhythmias. Hypophosphatemia disrupts intrinsic cellular processes, and at critical levels can cause seizures, cardiac arrest and an altered mental state. Magnesium is a multi-enzyme co-factor and influences potassium wasting via the renal 'ROMK' channel. In persistent hypomagnesaemia vitamin D levels should be assessed as hypovitaminosis prevents magnesium absorption.(8) The need for intravenous electrolyte replacement should be considered with critical levels or persistent imbalance.

Maintaining fluid balance is essential as volume loss depletes body free water. This begins with the accurate measurement of hourly urine output, stoma output, fistula drainage (if present), and an estimation of insensible losses. Of note insensible losses may be greater than 1-2 litres per day with hyperventilation states, sepsis, or extended pyrexia(9). Enteral intake will be unable to keep pace with losses, making intravenous fluids fundamental to establishing euvolaemia and a net positive balance.

Clinical signs such as hypotension, postural hypotension, loss of skin turgor, rapid loss of body weight, thirst, and parched mucous membranes may flag inadequate volume replacement. In the acute phase twice-daily electrolyte and renal function assessments may be required. A urinary sodium concentration of greater than 20 millimoles would reflect adequate renal perfusion.(10)

THE HIGH OUTPUT STOMA

R Das, A Mandal, D Leonard

Considering these essential management steps, several early measures could have been taken for our patient. Anticipation of the high output state, given a remaining bowel length of 110cm, would have prompted the need for strict fluid balance. The lack of oral sodium supplementation with unrestricted water intake clearly worsened stoma output.

Finally it should be noted that multiple drugs have the effect of increasing bowel motility. Metoclopramide and domperidone, both anti-dopaminergic pro-motility agents, are best avoided as anti-emetics. Macrolide antibiotics such as erythromycin and clarithryomycin are partial motilin receptor agonists and directly increase output volume.

Stepwise control of the high output stoma

1. If hypovolaemic – Volume replacement with IV normal saline

2. Exclude Infection & Address potential 'high output' triggers

3. Limit Oral fluid intake to 500-750 mls a day

4. Give St. Mark's Solution - 'Double dosage' use is common (i.e. Double solute content for 1L water)

5. Limit non-soluble dietary fibre

6. Omeprazole (40 mg PO – BD)

7. Loperamide (4 - 12mg po qds)

8. Codeine (30 - 60mg QDS)

9. Octreotide (Only with Senior input)

Additional Considerations:

- Exclude gut infection - Multiple stool cultures (including CDT)

- Stop Pro-motility Drugs (e.g. Metoclopramide, Domperidone)

- Add Sodium chloride salt/tablet to free fluid

- Diet - Specialist Dietician (Small meals, low fibre, higher salt content)

Once the patient was started on limited volume oral St. Mark's solution, Omeprazole, Codeine, Loperamide and intake restricted a stepwise decrease in stoma output was noted. Octreotide, the use of which varies with local practice, was not utilised or required. In our patient, as 5L/day of stoma output became 620ml/day and appropriate IV fluid replacement was given, Stage 3 Acute Kidney Injury rapidly resolved.

With persistent high volume stoma output other contributory factors must be considered. Intermittent obstruction may be a function of intra-abdominal adhesions. Active bowel inflammation, as in Crohn's disease, may increase stoma output. Sepsis and an exaggerated systemic inflammatory response may decrease bowel transit time and absorption.

The prolonged presence of inflammation or collections may result in internal fistulae.(10) The withdrawal of opiates and steroids, and the administration of oral magnesium supplements may be prokinetic.

Troubleshooting persistent high output states

Following 1st Line Measures - Think about:

- Intermittent Obstruction

- Active gut inflammation in Inflammatory Bowel Disease

- Intra-abdominal sepsis & other sources

- Internal fistula & connections

- Sudden withdrawal of medications - Steroids, Opiates

- Administrations of medications – Oral Magnesium, Prokinetics, Lasxatives

When all these measures fail, often in patients with less than 1m of remnant small bowel, extended intravenous fluid and parenteral nutrition (PN, intravenous nutrition delivery) can be considered. PN can then be a durable sustaining therapy, with dependent patients remaining on it for months to years.

In particular cases small bowel transplantation can be considered. Following a 174-day hospital and rehabilitation stay, our patient was discharged to his own home with restricted oral fluid (750 mls/day) and salt/glucose solution supplementation only. Now under surgical follow up, further re-anastomosis and bowel continuity restoration is being planned.

THE HIGH OUTPUT STOMA

R Das, A Mandal, D Leonard

St. Mark's electrolyte mix

The patient can produce fresh solution daily with the following recipe:

- 1L Tap water

- 20g (six level 5ml spoonfuls) of glucose

- 2.5g (one heaped 2.5ml spoonful) of sodium bicarbonate

- 5.5g (one level 5ml spoonful) of sodium chloride (salt)

- Mix until solution is clear

Multiple Choice Questions

1. What length of jejunum, in short bowel syndrome, is sufficient for a patient to remain without parenteral nutrition or IV fluid support?

a. Less than 100 cm
b. 100-150 cm
c. 150-200 cm
d. 300 cm
e. It is not possible

2. What is the most important intervention to decrease stoma output?

a. High dose PPI
b. Opiates
c. Octreotide
d. High sodium oral intake
e. Limiting oral fluid intake to 500ml

3. A patient with an ileostomy has had stable output for 2 years. Non-bloody watery output begins slowly over a course of weeks. What is the most probable diagnosis?

a. Coeliac disease
b. Pseudomembranous colitis
c. Infectious 'diarrhoea'
d. Small bowel bacterial overgrowth
e. Bile salt malabsorption

4. What electrolytes must be monitored if refeeding syndrome risk is high?

a. Potassium, Magnesium, Selenium
b. Thiamine, Pyridoxine
c. Zinc, Selenium, Iron
d. Phosphate, Potassium, Magnesium
e. Nitrogen, Calcium

5. Which area of the gastrointestinal tract is least prone to ischemia?

a. Oesophagus
b. Stomach
c. Small bowel
d. Large Bowel
e. Rectum

Answers

1. What length of jejunum, in short bowel syndrome, is sufficient for a patient to remain without parenteral nutrition or IV fluid support?

100-150cm of Jejunum. A patient with this length of remaining pre-stoma jejunum would be able to maintain nutritional requirement with oral nutrition and oral glucose/saline supplements only. Below 100cm of jejunal length there is a high likelihood of requiring both parenteral nutrition and intravenous fluid support. The requirements change significantly if the remaining enteral circuit is 'Jejunum-colon'.

2. What is the most important intervention to decrease stoma output?

Limiting oral intake. While all the listed interventions are key to improving stoma output the essential first step is to limit oral fluid intake. If an unlimited amount of oral fluid is allowed, achieving a sodium concentration of at least 90mmol/L in enteral fluid is highly unlikely and malabsorption with high losses will continue.

3. A patient with an ileostomy has had stable output for 2 years. Non-bloody watery output begins slowly over a course of weeks. What is the most probable diagnosis?

Small bowel bacterial overgrowth. The slow onset of diarrhoea without any acute-severe features such as abdominal pain, bloody diarrhea or associated vomiting is against an infectious cause. While C.Difficile infection and pseudomembranous colitis is a possibility the patient has not had any recent antibiotics to suggest this etiology.

The underlying anatomical abnormality significantly increases the risk of bacterial overgrowth and is the likely diagnosis. While a 'hydrogen breath test' is the appropriate diagnostic test, initial empirical antibiotic therapy and re-assessment is acceptable.

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4. What electrolytes must be monitored if refeeding syndrome risk is high?

Phosphate, Potassium, Magnesium - Phosphate is essential to all life processes as part of Adenosine Triphosphate and Diphosphate. Hypophosphatemia may result in seizures, cardiac arrhythmias and numerous subjective sensory disturbances. Potassium is essential to producing cardiac myocyte membrane potentials, while magnesium is a multi-enzyme co-factor and prevents potassium wasting via the nephron ROMK channel.

Selenium deficiency is the cause of Kashin-Beck disease (osteochrondropathy) prevalent in rural Indo-China. Zinc deficiency may be seen in patients on long term Parenteral Nutrition, and may manifest as functional immunosuppression, skin changes and cognitive impairment.

5. Which area of the gastrointestinal tract is least prone to ischemia?

Rectum. The rectum is the last part of the large intestine and has a rich and direct blood supply from the superior rectal artery (branch of the inferior mesenteric artery), middle rectal artery (branch of the internal iliac), and inferior rectal artery (branch of the internal pudendal artery). Ischaemia of the rectum is therefore is extremely unlikely and uncommon.

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HOW TO MANAGE HOSPITAL ALCOHOL DETOX - NICE GUIDANCE SIMPLIFIED

C Durrans, H Thompson, A Ososanya, L Mupfumira, D Ghosh

Abstract

Alcohol accounts for 10% of the UK burden of disease and death and alcohol related diseases are rapidly increasing the work load of gastroenterologists. During 2013/14 there were an estimated 1, 059, 210 (1) admissions related to alcohol consumption where alcohol related disease or injury was the primary reason for hospital admission.

During admission some patients may require alcohol detoxification. Symptoms may vary from mild tremors and anxiety to life-threating conditions such as alcohol withdrawal seizures and delirium tremens. Despite clear guidance from NICE regarding the importance of universal screening for alcohol misuse and prescribing appropriate detox regimens, junior doctors are not well aware of this important guideline resulting in ad-hoc detox prescriptions.

Case History

The following case study emphasizes the importance of a customised regimen for each individual. Mr AB was admitted via the Emergency Department (ED) with vomiting. Although a diagnosis of alcohol withdrawal was made on admission, neither a full alcohol history was recorded nor was he was monitored for alcohol withdrawal symptoms using the CIWA- Ar.

He was commenced on a standard chlordiazepoxide reducing regime without reference to his average daily intake or identification of time of last drink. Whilst on the ward he became increasingly difficult to manage, aggressive, agitated and had some features of paranoia.

The patient later absconded from the ward and went home where he made physical threats to his partner. He was returned to the ward by police and was abusive to staff. When he was reviewed by the Alcohol Liaison Nurse, it became evident that his alcohol intake was far greater than anticipated and therefore had received a much lower dose of chlordiazepoxide than required.

He was initiated on the symptom-triggered dose regime, made a steady detoxification and was later safely discharged. This case highlights the need for an accurate alcohol history for every patient regardless of initial presenting complaint. The history should include the frequency, type and quantity of alcohol consumption, and date of last alcoholic drink.

Discussion

Assessment of acute alcohol withdrawal is by history, examination and subjectively the 'Clinical Institute Withdrawal Assessment - Alcohol, revised' (CIWA-Ar) scale is used in hospitals. The CIWA-Ar scale is used to assess whether a patient requires inpatient detox and enables monitoring.

Alcohol detox usually uses benzodiazepines and can be administered by two regimes. NICE guidelines (2) recommend prescribing a symptom-triggered detox regime, however a fixed dose regime is often prescribed due to ease and lack of resources needed to frequently re-assess patients. Additional considerations are required for those patients with liver disease, or those with withdrawal seizures or delirium tremens.

Overview of NICE guidelines

NICE guidelines updated in March 2016 show a clear pathway for assesing patients in the ED who have consumed alcohol recently and for these patients alcohol detox regime may be appropriate, see figure 1.

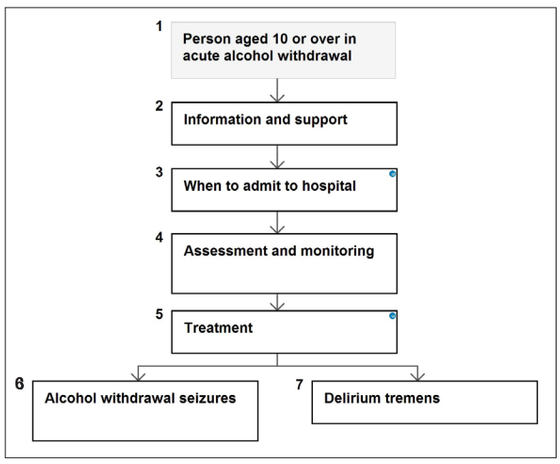

Figure 1: Acute alcohol withdrawal NICE guidelines. Taken from Nice guidelines March 2016.

Alcohol withdrawal symptoms and assessment

There is a spectrum of presentation of alcohol withdrawal ranging from minor symptoms such as tremors and insomnia to severe and potentially life-threatening complications such as withdrawal seizures and delirium tremens, see table 1.

In general the symptoms are proportional to the quantity of alcohol consumed during the patient's recent drinking cycle. Minor symptoms of alcohol withdrawal include insomnia, anxiety and tremors and can occur even when the patient has a measurable blood alcohol level.

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Withdrawal seizures are more common in patients who have presented to hospital with numerous previous episodes of detoxification and patients are at highest risk around 24hours after their last alcohol drink. Delirium tremens is the most severe form of alcohol withdrawal, patients can present 48-72 hours after the last alcoholic drink with symptoms including rapid onset of confusion and tachycardia, sweating and high body temperature related to a sympathetic overdrive (3).

Thiamine (Vitamin B1) deficiency due to chronic alcoholism and malnutrition can cause a spectrum of disorders including Wernike's encephalopathy, Korsakoff's syndrome and Beri Beri. Wernike's encephalopathy is characterised by a triad of opthalmoplegia, ataxia and confusion. Korsakoff's syndrome is a chronic memory disorder comprising a decreased ability to acquire new memories.

Due to the risk of thiamine deficiency in acute withdrawal Pabrinex, an intravenous preparation containing Vitamin C and B, is given prior to glucose. If glucose is given first this may increase thiamine metabolism hence exacerbating thiamine deficiency further and worsening symptoms of Wernike's encephalopathy.

Minor Withdrawal	Withdrawal seizures	Delerium tremens
• Anxiety • Insomnia • Tremours • Nausea • Onset usually within 12 hours of last drink	• Seizures • Can occur at any time but most commonly within 24hours of last drink	• Confusion • Severe anxiety • (visual) hallucinations • Profuse sweating • Seizures • Hypertension • Severe tremors • Low-grade fever • Highest risk around 5 days after final drink

Table 1: Table showing the range of symptoms in acute alcohol withdrawal.

Patients presenting to the ED who have a history of alcohol consumption should be assessed immediately on admission by a skilled healthcare professional. Often the history, examination and basic observations are sufficient to establish whether the patient requires admission for alcohol detoxification.

National recommendations set a maximum weekly intake of alcohol as 14 units per person where one unit is defined as 8g of pure alcohol. History should include quantity of alcohol consumption (in units), time since last drink, details of previous alcohol withdrawal attempts, medical history including psychiatric history, drug history including recreational drug use and details of the support network of the patient.

In addition to history and examination there is a subjective scoring method which aids diagnosis, monitoring and prescription of a suitable regime. The CIWA-Ar scale (4) is recommended for assessing and monitoring patients, see figure 2. The scale addresses 10 domains; nausea/ vomiting, tremors, anxiety, agitation, paroxysmal sweats, orientation, clouding of sensorium, tactile disturbances, auditory disturbances, visual disturbances and headache symptoms. Each domain is scaled from 0 to 7 (except for orientation and clouding which is rated from 0 to 4). If the CIWA-Ar score is 8 or greater withdrawal medication should be started.

Decision to admit patients should be guided by history, examination and CIWA-Ar scale. In addition, clinicians should have a lower threshold for vulnerable patients. NICE guidelines defines theses subset of patients as those who are frail, have cognitive impairment, lack social support, have learning difficulties or are aged 16-17 years.

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Patient:_____ **Date:** _____ **Time:** _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute:_____ **Blood pressure:**_____

NAUSEA AND VOMITING -- Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES -- Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

TREMOR -- Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

AUDITORY DISTURBANCES -- Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

PAROXYSMAL SWEATS -- Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

VISUAL DISTURBANCES -- Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

ANXIETY -- Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mild anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

HEADACHE, FULLNESS IN HEAD -- Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

AGITATION -- Observation.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM -- Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place/or person

Total **CIWA-Ar** Score _____
Rater's Initials _____
Maximum Possible Score 67

*The **CIWA-Ar** is not* copyrighted and may be reproduced freely. This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal.

Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (**CIWA-Ar**). *British Journal of Addiction* 84:1353–1357, 1989.

Figure 2: CIWA-Ar scale. Taken from Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale, 1989.

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Management of alcohol withdrawal

Medical management of alcohol withdrawal is used to prevent complications such as seizures and delirium tremens as well as providing additional support to maintain abstinence and asses any liver complications.

Benzodiazepine or carbamazepine are the drugs of choice. Second line therapy is clomethiazole however this should be used with caution and in an inpatient environment. Two regimes can be used; either symptom-trigger regime, or a fixed reducing regime.

Symptom-triggered regime

NICE guidelines recommend the symptom-triggered regime according to the CIWA-Ar score. If score is 0-8 and vital signs are stable there may be no need for inpatient hospital detox. Where CIWA-Ar score is >8 dosing regimes will depend on local hospital guidelines. The vital signs and CIWA-Ar score will then need to be repeated as per guidelines and then dose prescribed accordingly. This cycle of rechecking CIWA-Ar score and vital signs is repeated until benzodiazepines are no longer required.

There are concerns with the symptom-triggered regime including uncertainty about over or under dosing patients, though perhaps the major barrier is the time constraint on nurses and doctors who are unable to repeatedly assess the patients' CIWA-Ar score and vital signs.

Advantages of the symptom-triggered regime include lower doses of benzodiazepines administrated, a shorter admission time and no difference in symptoms experienced by the patient (5).

Fixed reducing regime

Fixed dose regimes should be used in the community but can also be an appropriate option for inpatient detox. The starting dose of chlordiazepoxide should be titrated according to the patient's usual daily alcohol consumption, see figure 3 (6), with higher daily alcohol intake requiring higher starting dose of benzodiazepine. See table 2 for example regime, as per NICE guidelines (7). The regimes continue by reducing the dose usually by 5mg per day. Once the dose has been weaned down to 5mg daily it can be stopped completely.

Figure 3: Diagram illustrating a unit of alcohol for different strengths of alcoholic drinks. Taken from Drink Aware.

Daily alcohol consumption	15–25 units		30–49 units		50–60 units
Severity of alcohol dependence	Moderate SADQ score 15–25		Severe SADQ score 30–40		Very severe SADQ score 40–60
Day 1 (starting dose)	15 mg four times a day	25 mg four times a day	30 mg four times a day	40 mg four times a day[a]	50 mg four times a day[b]
Day 2	10 mg four times a day	20 mg four times a day	25 mg four times a day	35 mg four times a day [a]	45 mg four times a day [b]
Day 3	10 mg three times a day	15 mg four times a day	20 mg four times a day	30 mg four times a day	40 mg four times a day [a]
Day 4	5 mg three times a day	10 mg four times a day	15 mg four times a day	25 mg four times a day	35 mg four times a day [a]
Day 5	5 mg twice a day	10 mg three times a day	10 mg four times a day	20 mg four times a day	30 mg four times a day
Day 6	5 mg at night	5 mg three times a day	10 mg three times a day	15 mg four times a day	25 mg four times a day

Table 2: Table showing an example of a fixed dose regime. Taken from Nice guidelines: Alcohol use disorders: sample chlordiazepoxide dosing regimes for use in managing alcohol withdrawal, 2010.

Adjuncts

In addition to the alcohol withdrawal regime thiamine should prescribed to treat or avoid Wernicke's encephalopathy. There are additional considerations for patients with known liver disease, such as using shorter acting benzodiazepines and appropriate medical assessment as well as treatment specifically relating to the liver disease.

Management of seizures and delirium tremens

Identification of these patients is most important so that additional support other than alcohol withdrawal regime can be offered. Patients who have experienced seizures or delirium tremens during the admission should receive lorazepam as first line treatment and second line with parenteral lorazepam, haloperidol or olanzapine.

Additional support after alcohol detox

Alongside the medical management of alcohol withdrawal patients should be seen by their alcohol liaison teams in hospital to provide information and help with abstinence.

Treatment of alcohol withdrawal should be seen as the beginning of a longer term rehabilitation programme which may include motivational interviewing and appropriate psychological and pharmacological support. Alcohol team should provide information about services such as Alcoholics Anonymous.

HOW TO MANAGE HOSPITAL ALCOHOL DETOX - NICE GUIDANCE SIMPLIFIED

C Durrans, H Thompson, A Ososanya, L Mupfumira, D Ghosh

Conclusion

By successfully identifying alcohol withdrawal in patients, prompt and appropriate detox regimes can be commenced. Patients may present with varied symptoms resulting from withdrawal, which depend on the magnitude of regular alcohol intake and the time since last drink. Although a symptom-triggered regime is the gold standard detox treatment, it is time and labour intensive which means that a fixed dose regime is generally more commonly prescribed, especially in the acute medical-take scenario.

A fixed dose regime is acceptable and appropriate if properly planned and dosed according to alcohol intake. This overview of alcohol detox simplifies some of the options available and gives a brief reference point for the management of these complex patients in whom there is a high risk of further complications.

MCQS

1) Which deficiency is the hallmark for the development of Wernicke's encephalopathy?

a. Folate

b. Thiamine

c. Vitamin A

d. Intrinsic factor

2) Which symptoms characterise Wernicke's Encephalopathy?

a. Opthalmoplegia, ataxia, confusion

b. Opthalmoplegia, tachycardia, pyrexia

c. Tachycardia, Pyrexia, Hypertension

d. Hallucination, weight loss, confusion

3) Which is the best regime for alcohol withdrawal?

a. PRN or as needed dose

b. Symptom-triggered regime

c. Fixed dose regime (weaning)- randomly prescribed with different doses by different doctors

d. Fixed dose regime (weaning)- customised according to alcohol amount consumed

4) What is the definition of one unit of alcohol

a. Two shots of spirit

b. 2 glasses of wine

c. 250ml of standard 4% beer

d. 8g of pure alcohol

5) What is the weekly recommendation for alcohol consumption?

a. 14 units per week for both genders

b. 14 units per week for woman and 21 units per week for man

c. 21 units per week for both genders

d. 6 units per week for woman and 8 units per week for man

Answers

1) b

Wernicke's encephalopathy is when neurological symptoms are present as a result of exhaustion of vitamin B reserves, in particular thiamine (vitamin b1). Treatment of Wernicke's is with thiamine replacement which can lead to improvement and even resolution of symptoms.

2) a

This is the typical triad for Wernicke's encephalopathy, however only 10% of patients show all three symptoms.

HOW TO MANAGE HOSPITAL ALCOHOL DETOX - NICE GUIDANCE SIMPLIFIED

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3) b

Symptom-triggered regime is recommended by NICE guidelines as best practice followed by option d

4) d

Depending on the type and strength of the alcoholic drink the volume of drink representing one unit will vary however the official measurement is weight of pure alcohol

5) a

Recently it has been changed from option b to option a – same amount for both gender rather than allowing higher amount for man

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IRON DEFICIENCY ANAEMIA: DIAGNOSIS & MANAGEMENT ILLUSTRATED BY AN INTERESTING CASE

J Morgan, T Wardle, J Elder

Abstract

The World Health Organization (WHO) define anaemia as a haemoglobin level of less than 130 g/L in men and less than 120 g/L in women. Iron deficiency is thought to account for 50% of cases of anaemia (1), occurring in 2-5% of the adult male and post-menopausal female population in the developed world (2). It is a common presentation and patients may be asymptomatic. Iron deficiency anaemia is a symptom of an underlying disease rather than a diagnosis. We will discuss a case which highlights a cause of iron deficiency anaemia and describe a diagnostic approach.

Causes of iron deficiency anaemia as a percentage

Aspirin/Non-steroidal anti-inflammatory drugs	10-15%	Coeliac disease	4-6%
Colonic cancer	5-10%	Gastrectomy	<5%
Gastric cancer	5%	Bariatric surgery including bowel resection	
Benign gastric ulceration	5%	Helicobacter pylori colonisation	<5%
Angiodysplasia	5%	Bacterial overgrowth	<1%
Inflammatory bowel disease		Menstruation	20-30%
Oesophagitis	2-4%	Blood donation	5%
Oesophageal cancer	1-2%	Haematuria	1%
Gastric antral vascular ectasia	1-2%	Epistaxis	<1%
Small bowel tumours	1-2%		
Cameron ulcer in a hiatus hernia	<1%		
Ampullary cancer	<1%		

Figure 1: Causes of Iron deficiency anaemia in the UK as a percentage, adapted from (2).

Although Inflammatory bowel disease and bariatric surgery are known causes of iron deficiency anaemia, there are no data regarding how common.

Case Report

A 59 year old diabetic gentleman presented with an incidental finding of iron deficiency anaemia; as a fast track referral. His Haemoglobin was 122 g/L (normal range 130- 170 g/L) with an MCV of 71 fL (normal range 82- 100 fL). There was no history of overt blood loss, weight loss, non-steroidal anti-inflammatory drug use and no family history of gastrointestinal or coeliac disease. His diet was sufficient, had no history of surgery and he was not a blood donor. He had a gastroscopy which showed a hiatus hernia, a 2cm segment of circumferential Barrett's oesophagus and a polyp in the gastric antrum.

Biopsy of the polyp showed a fundic gland polyp with associated inflammation, hence a benign lesion. He had negative coeliac serology. Urease testing for Helicobacter Pylori was negative. His colonoscopy showed a hyperplastic polyp and a tubular adenoma which did not require follow up. This is because the adenoma was less than 1cm in size and showed no high grade dysplasia. The current British Society of Gastroenterologists (BSG Guidance) is that such polyps do not require follow up. He was reassured, given lifestyle advice and discharged without iron replacement.

What are the Important Differential Diagnoses?

Age is important in the approach to iron deficiency anaemia. Women of child-bearing age are most likely to develop iron deficiency anaemia through menstrual losses. It is important therefore to check a full gynaecological history including previous hysterectomy. In the male and post-menopausal female population it is important to exclude malignancy and coeliac disease.

Eighteen months later he was admitted with breathlessness due to symptomatic anaemia and weight loss. His haemoglobin was 65 g/L with an MCV of 59 fL, ferritin of 5.5ug/L (normal range 20- 300 ug/L) and a normal CRP. He had attributed the weight loss down to his healthier lifestyle. He was given a 4 unit red cell transfusion and due to the severity of his anaemia he was listed for an urgent repeat gastroscopy, colonoscopy and CT thorax, abdomen and pelvis.

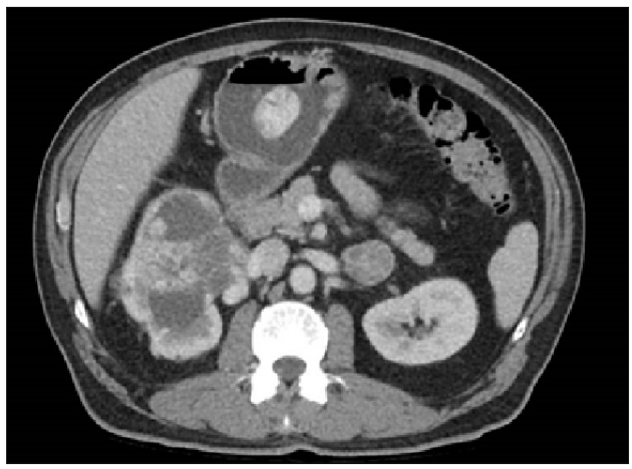

Figure 2: Cross sectional image from the patient's CT thorax, abdomen and pelvis.

There are 2 abnormalities on this cross sectional image.

1) The previously discussed stomach polyp
2) Right renal mass

The repeat gastroscopy showed a persistent polyp from which biopsies were non-diagnostic as only necrotic tissue was present. Due to the CT finding (figure 2), his colonoscopy was cancelled. The gentleman was referred to Urology and underwent radical nephrectomy.

Despite this operation he remained iron deficient with haemoglobin of 87 g/L and MCV 68 fL. He was seen in the gastroenterology outpatients' clinic where it was noted the antral polyp had increased significantly in size on his CT scan relative to his previous endoscopy.

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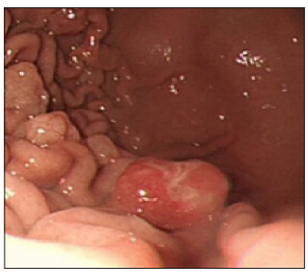
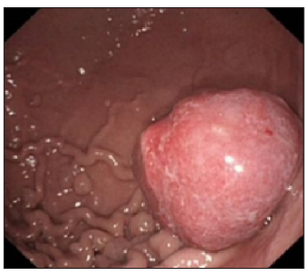
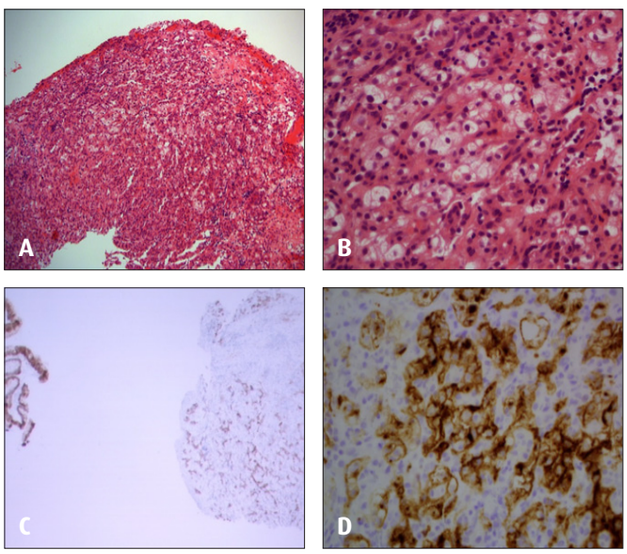




The above pictures are of the same polyp 18 months apart. When compared with the surrounding rugal folds it can be seen how significant the changes have been.

Polyp biopsies from his third gastroscopy revealed abnormal tissue with evidence of pleomorphic nuclei and clear cells. Staining with AE1/3 (which demonstrates the presence of epithelial cells) showed the presence of abnormal epithelium which was confirmed as metastatic Renal Cell Carcinoma using CD10 staining (Gastric mucosa is not stained but renal cells are). He was subsequently referred to Oncology for further management.



Histology from third endoscopy showing: A. Abnormal mucosa with some surface ulceration. B. Higher magnification of A showing clear cells with pleomorphic nuclei. C. AE1/3 staining contrasting normal epithelium (left) and distorted epithelium suggesting malignancy (right) D. CD10 staining confirming likely renal cell carcinoma (brown) contrasting with the unstained gastric mucosa (blue).

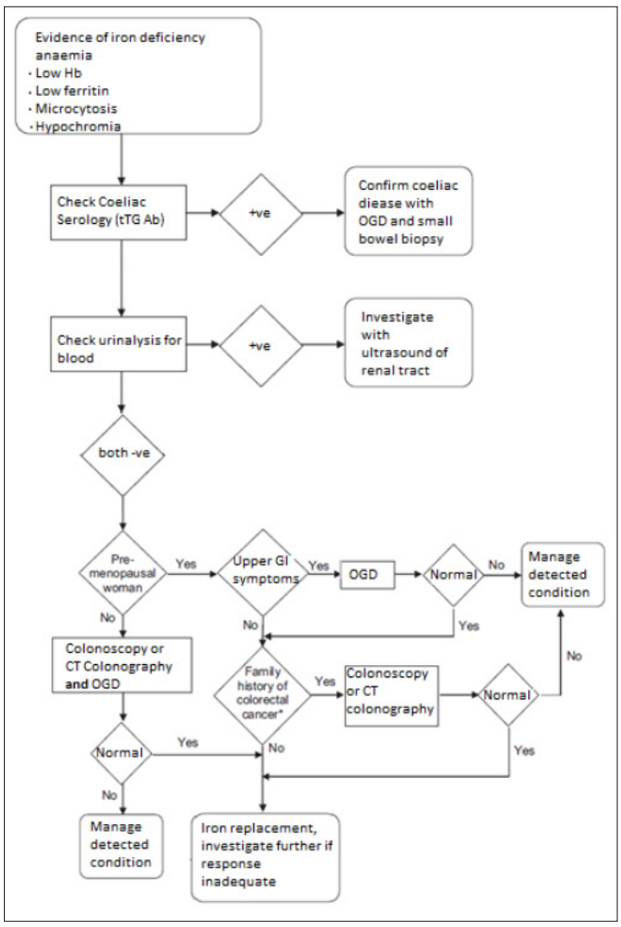
Discussion

How is Iron Deficiency Anaemia Diagnosed?

- Haemoglobin <130 g/L (men) or <120 g/L (women)
- Low Mean Cell Volume
- Ferritin <15ug/L or <50ug/L if co-existent inflammatory process
- High Total Iron Binding Capacity

The case above, although interesting, is not common. 1% of patients who have iron deficiency anaemia have renal tract malignancy (2). In the case of an incidental finding of iron deficiency anaemia, the most likely causes are either occult blood loss into the gastrointestinal lumen or malabsorption. The history is a salient part of the approach to the anaemic patient.

A history of diarrhoea, weight loss and an association with food may increase the possibility of malabsorption as well as either malignancy or inflammation of the gastrointestinal tract. Any patient with both iron deficiency anaemia and gastrointestinal symptoms should be investigated, regardless of age.



Algorithm for an approach to investigating iron deficiency anaemia, modified from (2).

IRON DEFICIENCY ANAEMIA: DIAGNOSIS & MANAGEMENT ILLUSTRATED BY AN INTERESTING CASE

J Morgan, T Wardle, J Elder

Any patient who presents with iron deficiency anaemia over the age of 50 years, or with a "red flag" symptom such as weight loss, change of bowel habit or dysphagia, requires investigation. The initial investigations are full blood count, ferritin, iron studies, B12, folate, serum tissue transglutaminase and urinalysis. The most sensitive investigation for the diagnosis of iron deficiency is the ferritin (2). If there is blood present on the urinalysis then an ultrasound of the renal tract is warranted. A positive tissue transglutaminase should be followed by gastroscopy and duodenal biopsies to confirm coeliac disease. Patients will require investigation of the gastrointestinal tract, usually with gastroscopy and colonoscopy.

Both investigations are required; the finding of oesophagitis or peptic ulceration does not preclude the need for a colonoscopy. An alternative to colonoscopy is CT colonography, with a sensitivity of 89% in detecting polyps of 6mm or larger (4). However the advantage of colonoscopy is that biopsies can be taken and flat lesions can be seen and treated. Two such lesions are polyps -which are treated with excision - and angiodysplasia, which can be treated using argon photocoagulation.

Colonoscopy is an invasive investigation which requires adequate bowel preparation using laxatives to improve diagnostic yield. As such the risks of perforation and failure of the procedure are greater than found in CT colonography. The sigmoid colon and the transverse colon lie within the peritoneal cavity and as such are not fixed, this can cause technical difficulties with a colonoscopy and can require the patient to change position multiple times during the procedure. This does limit its use in a select group of patients, particularly the elderly and those with limited mobility.

What about patients who have negative investigations?

A good approach is to give ferrous sulphate and then check haemoglobin again. The National Institute of Clinical Excellence recommends ferrous sulphate two or three times daily. If this has improved then continue for a period of 2-4 months and then check the full blood count. If the haemoglobin returns to normal then stop the iron and check a full blood count 3 monthly for a year. Should the patient become iron deficient again then further investigations should be organised. (5)

Once the patient's history and examination have been re-visited, the usual first step is to repeat the urinalysis, gastroscopy and colonoscopy to look for angiodysplasia. If these tests are still normal then investigation of the small bowel, with MRI studies or capsule enteroscopy, would be the next step.

There are cases whereby a patient does not respond to iron replacement. The first step is to establish compliance with therapy, given side effects such as constipation can prevent patients adhering to prescribed courses. Once this has been clarified then the endoscopic investigations should be repeated. Not all cases of iron deficiency are related to gastrointestinal causes and other diagnoses, such as malignancy of another site, should be considered.

Multiple Choice Questions

1. What is the most sensitive test for iron deficiency anaemia?

a. Mean cell volume
b. Ferritin
c. Total iron binding capacity
d. Haemoglobin
e. Serum Iron

2. What are the first investigations to do after confirming iron deficiency anaemia?

a. Tissue transglutaminase and ultrasound renal tract
b. Urinalysis and CT Thorax abdomen and Pelvis
c. Gastroscopy and colonoscopy
d. Repeat bloods in 3 months
e. Urinalysis and tissue transglutaminase

3. Which diagnosis may be missed if CT colonography is used instead of colonoscopy?

a. 9mm tubular adenoma
b. 12mm pedunculated polyp
c. 7mm hyperplastic polyp
d. Angiodyplasia
e. 25mm caecal tumour

4. Which statement best describes the management of iron deficiency with normal investigations?

a. 200mg ferrous sulphate twice daily for 4 weeks and recheck haemoglobin
b. 200mg ferrous sulphate once daily
c. 200mg ferrous sulphate twice daily. Recheck haemoglobin if symptoms recur
d. 200mg ferrous sulphate, increasing dose until side effects
e. Dietary changes

5. If iron deficiency anaemia recurs, what is the next appropriate step?

a. Long term iron replacement
b. CT Thorax abdomen and pelvis
c. Repeat gastroscopy and colonoscopy
d. Small bowel imaging
e. Repeat coeliac screen

IRON DEFICIENCY ANAEMIA: DIAGNOSIS & MANAGEMENT ILLUSTRATED BY AN INTERESTING CASE

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Answers

1. b

Ferritin is the most sensitive test available for the diagnosis of iron deficiency.

2. e

Although gastroscopy and colonoscopy would be required, the initial investigations to organise are urinalysis and coeliac screen. Only a third of renal tract malignancies present with anaemia but the presence of microscopic haematuria would warrant renal tract images. The coeliac screen would also give guidance for biopsies during the gastroscopy if positive.

3. d

CT Colonography is a very good test, especially in patients who are not suitable for a colonoscopy. Its main limitation is in seeing flat lesions, meaning angiodysplasia is the pathology which is likely to be missed with CT scanning.

4. a

NICE guidelines recommend the treatment of iron deficiency anaemia to return the haemoglobin and mean cell volume to normal. This requires iron supplementation and repeat blood tests at 3-4 weeks and continuing treatment until they have normalised.

5. c

Most angiodysplasia are accessible with conventional endoscopy so the first step would be to repeat the gastroscopy and colonoscopy.

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MANAGING A CASE OF REFRACTORY ULCERATIVE COLITIS WITH ASSOCIATED LIVER DISEASE

R Cooney, M Senbanjo

Abstract

Ulcerative Colitis is a form of inflammatory bowel disease which predominately affects the Colon. Patients with this condition frequently encounter junior doctors when they present to primary and secondary care with exacerbations of their symptoms.

Ulcerative Colitis can be challenging to manage and escalation to potent biological agents may be required. Many extra intestinal manifestations may be seen with this disease, which is thought to be due to an abnormal immunological response to the gut microbiome in a genetically predisposed patient.

Here, we describe a young man with refractory ulcerative colitis and associated liver disease and discuss his acute management.

Case History

A 22-year-old man, with a history of ulcerative colitis, presented to Accident & Emergency (A&E) with increased frequency of loose bloody stools and associated abdominal pain. He had lost 3 kg in weight (BMI 18). This was his seventh A&E presentations for similar symptoms (his attendance at clinic appointments was poor and he did not engage with IBD nurse specialists helpline). He had been referred to colorectal surgeons for consideration of colectomy but failed to attend appointment.

Background

This student previously fit and well, was diagnosed with pan-ulcerative colitis eighteen months prior to this admission. At diagnosis he was noted to have a raised CRP of 90mg/L (<5) , Hb of 9g/L (135-180) and normal liver bloods including transaminases (ALT/AST) but low albumin of 30 g/L (34-51). INR was not checked at that stage.

He is a non-smoker and drinks at most 4 units of alcohol a week. At diagnosis he was initially treated with oral steroids (prednisolone 40mg daily decreasing by 5 mg weekly to zero with concomitant Vitamin D supplementation) and oral Mesalazine. He initially responded quickly to this regimen.

He had full haematinics performed and it was determined that he had iron deficiency anaemia (low MCV, low transferrin saturations and high Total iron binding capacity). We did not rely on his ferritin as it can be falsely elevated in patients with a raised CRP. He could not tolerate oral iron so he was given intravenous Iron. Multiple attempts to wean him off prednisalone failed indicating refractory disease, he was therefore commenced on azathioprine.

Standard dosing was given (1.5mg-2mg/kg) as he had normal thiopurine methyl transferase (TPMT) levels and would be able to fully metabolise this drug.

Shortly after initiation of treatment he became leucopenic (WBC 2.8 x 10^9/L (4-11.0)). He was seen by haematology and his Azathioprine was stopped.His Mesalazine was also stopped as this can also cause leucopenia, although less commonly. The leucopenia persisted despite termination of these medications. He then also became thrombocytopenic (90 x 109/L (150-450)). A bone marrow, aspirate and trephine biopsy revealed a mild T-lymphocytosis only. The haematologists concluded that he had a form of mild autoimmune pancytopenia.

Seven months after initial presentation he was noted to have deranged liver function tests (LFTs) - ALT 53 U/L (5-41), BIL 27 umol/L (<22), INR 1.3 (0.8-1.2). Ultrasound abdomen revealed diffusely coarse and abnormal hepatic parenchyma with irregular edges and splenomegaly measuring 18cm.

The initial liver screen which included Hepatitis B and C serology, ferritin, caeruloplasmin level and alpha 1 antitrypsin level was negative/ normal. Autoimmune liver disease screen (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-smooth muscle antibody (SMA), anti-mitochondrial antibodies and immunoglobulins (including IgG)) was unremarkable other than a weakly positive SMA (1:100).

Magnetic resonance cholangiopancreatography (MRCP) findings were not consistent with Primary Sclerosing Cholangitis (PSC) and a subsequent liver biopsy showed cirrhotic changes and non-specific chronic hepatitis features. His investigations were indeterminative. After MDT discussion the consensus of the liver team was that, after taking his clinical, biochemical and histological features into account, he had a form of antibody negative autoimmune hepatitis leading to cirrhosis.

In view of his cirrhotic changes he had a screening endoscopy to check for varices. He did not have oesophageal varices but had features of portal hypertensive gastropathy.

After discussion with haematology his Mesalazine was restarted. As his colitis was difficult to control he was cautiously started Mercaptopurine (a metabolite of azathioprine). His white cell count unfortunately also dipped on Mercaptopurine so it was stopped. To avoid long term steroid side effects, he was escalated to biological treatment ie Infliximab (anti-tumour necrosis factor medication). Unfortunately he had an anaphylactoid reaction during his 2nd dose of Infliximab. Anaphylactic reactions occur in up to 8% of patients (7) and is more common in younger patients and those not receiving concomitant immunosupressants eg thiopurine (8).

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Therefore he was switched to another Anti-TNF agent, Adalumimab 10 weeks prior to the admission in question. Adalimumab is a fully humanised unlike infliximab which is a chimeric Anti TNF molecule with murine components. Patients who have an anaphylactic response to infliximab can therefore be switched to adalimumab.

Examination

On examination he had a low grade fever, oxygen saturations 100%, heart rate 114 bpm, respiratory rate 16/min. His abdomen was generally tender with no signs of peritonism. His chest was clear and heart sounds were normal. On per rectum examination, there was fresh blood on the finger but no melena.

Differential Diagnosis

This presentation is most in keeping with an acute flare of Ulcerative Colitis; however the presence of an infection must be excluded. Bacteria such as C.Difficile, Shigella and Campylobacter can cause a gastroenteritis which presents in a similar manner. Careful drug history should be taken to exclude NSAID use.

Initial Investigations

Admission bloods: *Haemoglobin (Hb) 82 g/L, White blood count (WBC) 10.2 10^9/L, Platelets 105, C-reactive protein (CRP) 22 mg/L and lactate of 2.6 mmol/L.*

Imaging: *Abdominal X-ray and an erect Chest X-ray ruled out a pneumoperitoneum and toxic megacolon.*

Stool: *Four negative stool samples for microscopy, culture and Clostridium Difficile.*

On the 2nd day of admission, the patient became pancytopenic – Hb 54 g/L, WBC 2.4 10^9/L, Neutrophils 1.3 10^9/L, Platelets 70 10^9/L, CRP 5mg/L. This was treated with 1 unit of Red Blood Cells and a dose of intravenous iron.

Inpatient management

He was managed initially with intravenous hydrocortisone to which he normally had a good response alongside Mesalazine (foam aerosol enema and oral preparations). We were concerned that he may need a colectomy and he was seen by the colorectal surgeons. He was given nutritional supplements as well Vitamin D and calcium supplements. He was commenced on DVT prophylaxis. His electrolytes were closely monitored (especially potassium levels which often fall with hydrocortisone) and replaced as appropriate.

A limited sigmoidoscopy was performed to take a biopsy to look for concomitant CMV colitis (which can complicate UC particularly in immunosuppressed patients) and also to look for any evidence of mucosal healing since commencing adalimumab. The endoscopist did a limited procedure only to decrease the risk of perforation at endoscopy. This showed severe colitis (Mayo grade 4) to the point of insertion (45cm) - see example of this in figure 1 (deep ulcerations, friable muscosa). He was thus felt to be a primary non responder to Adalumimab.

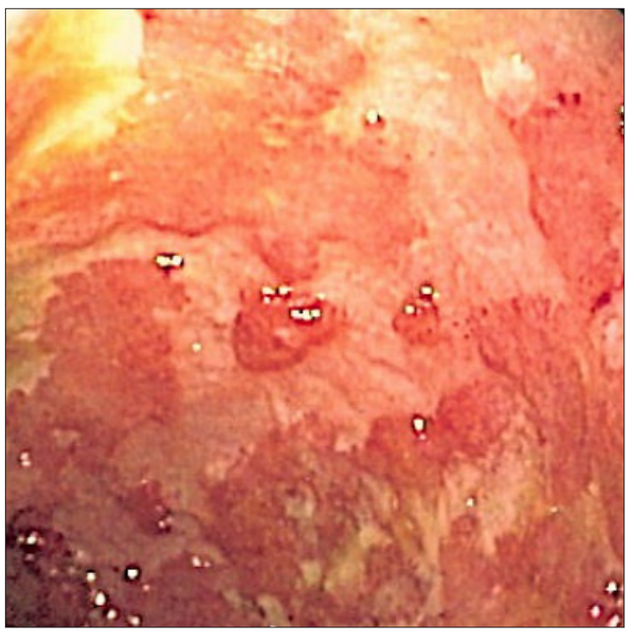

Figure 1: Endoscopic view of severely ulcerated colonic mucosa (1).

His symptoms had improved on intravenous hydrocortisone within 72 hours. He was converted to Prednisolone after 7 days.He was converted to Prednisolone after 7 days. Within hours he began passing frequent bloody loose stools and was recommenced on intravenous hydrocortisone for another week and reviewed again by the surgeons.

He was discussed at the local Inflammatory Bowel Disease Multidisciplinary Team Meeting (MDT) with the surgeons. His latest Computerised Axial Tomography (CT) scan showed a cirrhotic liver, increased splenomegaly, moderate amounts of free fluid (ascites), thick walled and oedematous bowel and moderate varices in the splenic hilum, mesentery and distal oesophagus. The surgeons were concerned about the risks of bleeding at surgery and requested a Transjugular Intrahepatic Portosystemic Shunt (TIPSS) to be performed prior to any abdominal surgery.

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His medical management was discussed. We had now used two anti- TNG agents, one resulted in an allergic reaction and the other had no benefit. An alternative biologic agent approved for ulcerative colitis is vedolizumab which has a different mode of action (see discussion below). It was agreed he should start this with the understanding that he should be optimised for surgery at the same time, in case he deteriorated despite this medication.

Response to Vedoluzimab can take 2-6 weeks so it is not a standard treatment for acute severe colitis. He received vedolizumab and his symptoms improved over the next few days (early response likely due to the intravenous hydrocortisone that he remained on) (9). He was switched to oral steroids and was well enough to be discharged five days later, with further vedolizumab infusions booked as an outpatient. As we were concerned that he could still relapse once his steroids were reduced and require surgery, he had a TIPSS procedure successfully performed prior to discharge.

Outpatient Management

Eight months after discharge he has remained very well on maintenance Vedoluzimab (which he has every 8 weeks) with his colitis in remission and weight improved (BMI 20). He is regularly reviewed by Haematology team. His blood counts are stable and apart from intravenous iron he hasn't required any other treatment. He is seen regularly by the hepatologists and his LFTs are stable.

Discussion

Assessing Severity of Ulcerative Colitis

• General Examination

Are there any signs of sepsis, shock or peritonism? BP/HR/Temp

• Consider differential diagnosis.

Travel history, Use of NSAID, Recent antibiotic use

• *Check bloods as below (table 1)*

CRP, FBC

• Ask patient / nurses to keep stool chart

An accurate stool chart will allow assessment of response to treatment. If patient is not responding after 72 hours to intravenous hydrocortisone they are at high risk of colectomy and escalation to anti TNF therapy should be considered. See Travis criteria – patients with stool frequency > 8 or CRP> 45 mg/dl are likely to require colectomy (6)

Truelove and Witt Criteria	Mild	Moderate	Severe
Bowel movements (no. per day)	Fewer than 4	4-6	6 or more plus at least one of the features of systemic upset (marked with * below)
Blood in stools	No more than small amounts of blood	Between mild and severe	Visible blood
Pyrexia (temperature greater than 37.8°C) *	no	no	yes
Pulse rate greater than 90 bpm *	no	no	yes
Anaemia (< 10g/100mL)*	no	no	yes
Erythrocyte sedimentation rate (mm/hour) *	30 or below	30 or below	above 30

Table 1: Truelove and Witts' Severity Index (3)

Acute Medical Management of Ulcerative Colitis

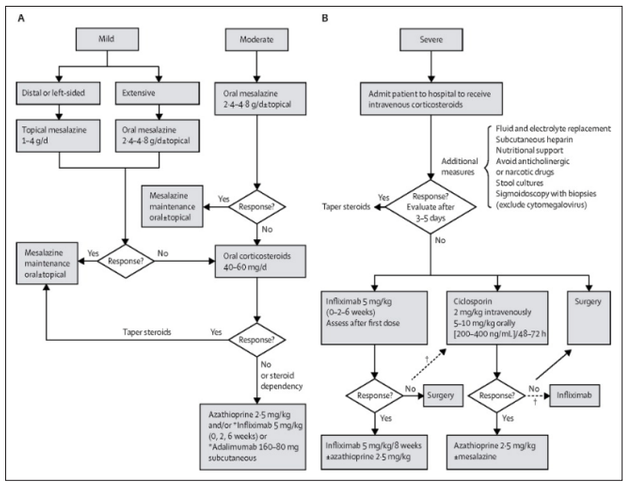

Figure 2: Treatment algorithm for Ulcerative Colitis (4)

(A) Mild to moderate ulcerative colitis. (B) Severe ulcerative colitis. †Carefully selected patients at specialist centres. *Dependent on the severity of symptoms and how quickly remission needs to be induced.

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Side effects of Mediations used to treat Ulcerative Colitis

Medication	Side effects	Serious Adverse Events	Monitoring and Precautions
Steroids	Mood changes Sleep disturbances Hypertension Cushingoid features Adrenal suppression	Osteoporosis Diabetes Cardiovascular disease	Co-prescribe with Vitamin D Blood Pressure Blood Sugar
Aminosalicylate (Mesalazine)	Diarrhoea Headache Nausea Rash	Myelosupression Pancreatitis Hepatitis	Avoid in salicylate hypersensitivity Renal Function
Thiopurines (Azathioprine and 6-Mercaptopurine)	Fever Arthralgia Rash Nausea Diarrhoea	Liver Dysfunction Pancreatitis Myelotoxicity Lymphoma Skin Cancer	FBC LFTs TPMT level pre drug commencement. Patients with low levels should be given a low dose of drug to reduce risk of myelosuppression. 6MMPN drug metabolite levels can be used to predict likelihood of Hepatoxticity High SPF sun cream use recommened
Ciclosporin	Tremor Paraesthesia Headache Gingival hyperplasia Hirsuitism	Renal impairment Opportunistic infections Teratogenicity	Blood Pressure FBC Renal Function Cholesterol Magnesium
Methotrexate	Nausea Diarrhoea Stomatitis	Hepatotoxicity Pnuemonitis Opportunistic infections Teratogenicity	FBC LTFs Co-prescribe with folate

Table 2: Side effects of medications used to treat Ulcerative Colitis

What is a Pre-biologics screen?

A Pre-biologics screen is performed prior to the administration of a biological agent to confirm that the patient in question is a suitable candidate.

It consists of:

- *Baseline bloods including FBC, U&E, LFTs, albumin, CRP, ESR, varicella antibodies, hepatitis screen, all biologics have the potential to reactivate Hepatitis B*

- *Chest Xray to rule out any infection and TB (NB Anti TNF agents have the potential to reactivate TB)*

- *Quantiferon testing to rule out latent TB or if unavailable Tuberculin skin test*

In addition, sepsis needs to be ruled out as all biologics have been associated with infections which can be very severe. It is not recommended in patients who have had a previous malignancy or a demyelinating disorder. Women should be advised to continue to have routine smear tests.

What is Vedoluzimab?

- *Vedoluzimab is a humanized IgG1 monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract by preventing the alpha4beta7 integrin subunit from binding to the gut specific mucosal addressin cell adhesion molecule-1 (MAdCAM-1)).*

- *It is NICE recommended in the treatment of moderate to severely active ulcerative colitis and has been available for use since Mid 2015 (5).It is also approved for use in Crohn's disease in patients who have failed to respond to Anti TNF medications.*

- *Common side effects include common cold symptoms, headache, joint pain, nausea, fever, rash and itching.*

Liver Conditions linked to Ulcerative Colitis

- *Primary Sclerosing Cholangitis*

- *Fatty Liver disease*

- *Autoimmune Hepatitis*

What is Portal Hypertensive Gastropathy?

Portal Hypertensive Gastropathy (PHG) is an engorgement of the veins in the wall of the stomach, which can cause severe bleeding. It is commonly seen on endoscopy in patients with portal hypertension.

What are the indications for TIPSS?

TIPSS stands for Transjugular Intrahepatic Portosystemic Shunt. This is an interventional radiological procedure that decompressed the portal vein to the hepatic vein via a shunt.

Common indications include:

- *Bleeding from oesophageal or gastric varices that cannot be managed endoscopically*

- *Budd-Chiari syndrome*

- *Any cause of Portal Hypertension that is refractory to medical management*

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5 MCQs

1. Which investigation is not routinely part of a biologics screen:

a. CXR

b. HIV

c. Hepatitis B & C

d. Varicella

e. Colonoscopy

2. Which blood test could be used to check if Azathioprine may cause hepatotoxicity?

a. Azathioprine metabolite levels (6MMPN)

b. LFT's

c. TPMT

d. INR

e. Infliximab Abs

3. Which of the following is a common cause of splenomegaly?

a. Trauma

b. Penicillin V

c. Cirrhosis with portal hypertension

d. Typhoid fever

e. Coeliac disease

4. A 30-year-old patient with known UC presents to A&E with increased frequency of bloody diarrhoea. Her bowels are opening 8-10x daily. Her HR is 110, BP 110/55, RR 19, 02 Sats 88% Temp 37.9. What is the next appropriate management step?

a. Start empirical Antibiotics

b. Give a fluid bolus

c. Call the gastroenterology SpR

d. Oxygen

e. Arrange for an urgent AXR/erect CXR

5. On endoscopy, a patient with cirrhosis of the liver was found to have large dilated sub-mucosal veins in the lower third of the oesophagus obscuring the lumen with evidence of recent bleeding. Which of the following would be the most appropriate way to manage this condition?

a. TIPSS

b. Furosemide

c. beta blocker

d. Banding

e. Spironolactone

Answers

1. E

Biologic screen refers to testing to be done to ensure that it is safe for patient to have these immunosuppressive medication. Colonoscopy may be done to assess disease activity but is not a necessary part of the screening procedure. All the other options should be performed before starting Anti-TNF medications.

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2. A

TPMT refers to thiopurine methyl transferase. There is genetic variation in the activity of this enzyme and if low, standard 1.5-2mg/kg dose can induce profound myelosuppression. Patients with reduced TPMT should receive lower doses of azathioprine. If there is an absence of activity thiopurines should be avoided.

3. C

All the others can cause a palpable or enlarged spleen but are uncommon.

4. D

As part of the 'ABC' of resuscitation. The other options are all appropriate but should not be done until the patient is resuscitated.

5. D

Banding is standard treatment of large oesophageal varices if there is evidence of recent bleeding clinically or endoscopically. Varices that have not bled (primary prevention) can be treated with beta blockade (eg carvedilol or propanol to decrease portal pressure).

If the varices are very large or if there is concern re compliance to beta blockers prophylactic banding can be performed.

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MANAGING THE PATIENT WITH ABDOMINAL PAIN & A RAISED AMYLASE

El Menabawey, C Franklin, K Heaney, S Mann

Abstract

Abdominal pain is one of the most common emergency presentations and pancreatitis is high on the list of differentials for the admitting physician. An elevated serum amylase is frequently considered diagnostic of pancreatitis prompting a subsequent referral to the surgeons. However, there are a number of other conditions that mimic the presentation of pancreatitis associated with hyperamylasaemia. This case highlights these other causes and what investigations to consider in cases of unexplained hyperamylasaemia.

Case History

We present the case of a 51-year old female who presented via accident and emergency with severe epigastric pain. The pain was associated with nausea and anorexia. Her past medical history included endometriosis, ovarian cystectomy, salpingoopherectomy, laparoscopies with adhesiolysis, appendicectomy, rectopexy for rectal prolapse and recurrent deep vein thromboses.

This was her fifth presentation over the past 10 years with the same symptoms, previously diagnosed as recurrent acute idiopathic pancreatitis. She had undergone several ultrasounds, a gastroscopy, 4 CT scans, 2 MRCPs and an ERCP with no aetiology for pancreatitis identified. Her alcohol intake had been minimal over the past 10 years.

On examination she was markedly tender in the epigastrium with no features of peritonism. There was no evidence of a systemic inflammatory response. Her investigations (Table 1) were unremarkable except for a significantly elevated amylase. The patient was referred to the surgical team with a diagnosis of suspected recurrent pancreatitis.

Hb	120 g/L
WCC	4.4x10^9/L
Neuts	2.2x10^9/L
Plt	301x10^9
Na	142 mmol/L
K	4.1 mmol/L
Ur	3.2 mmol/L
Cr	71 umol/L
Ca	2.23 mmol/L
Bil	10 umol/L
ALP	39 iu/L
ALT	13iu/L
Alb	40 iu/L
CRP	<1 mg/L
Triglycerides	0.69 mmol/L
Amylase	***618*** iu/L (25-125)

Table 1: Initial Investigations.

The American College of Gastroenterology, diagnosis likely if 2 out of 3 of:

i. Abdominal pain consistent with acute pancreatitis.

ii. Elevated serum amylase/lipase >3 times the upper limit of normal (ULN).

iii. Characteristic abnormal imaging then a diagnosis of pancreatitis is likely.

The British Society of Gastroenterology

Recommends the diagnosis is made based on the clinical features of abdominal pain and vomiting with elevation of pancreatic enzymes. They do not recommend relying on an arbitrary cut-off of >3 times ULN of enzymes but that interpretation should be made in the context of the presentation.

Box 1: The Diagnosis of Pancreatitis (1,2).

Gallstones are the most common cause of pancreatitis in the UK followed by alcohol (2). When a diagnosis of pancreatitis is suspected a search for the underlying aetiology must be sought. Other common causes important to consider include trauma, post-ERCP, autoimmune, viral (coxsackie, mumps, HSV), drug induced (commonly steroids), hypercalcaemia and hypertriglyceridaemia.

In 20% of cases no cause is found for acute pancreatitis. Many patients labelled as "recurrent idiopathic pancreatitis" actually have gallstone disease that has been missed or microlithiasis. The BSG recommends that no more than 20% of a centre's cases should be "idiopathic" and an extensive search for gallstones and other causes should be made. The following investigations are recommended (2):

- Fasting lipids and plasma calcium
- Viral antibody titres
- Repeat biliary ultrasound
- MRCP
- Endoscopic US (to look for microlithiasis)
- ERCP* (+/- bile acid sampling) – to look for anatomical variations such as pancreas divisum and sampling to assess for microlithiasis

**N.B This is a recommendation from the BSG guidelines last updated in 2005. More recent guidelines for example from the AGA (2013) (1) no longer recommend the routine use of ERCP diagnostically given the potential risks to the patient.*

Box 2: Idiopathic Pancreatitis.

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Pancreatitis is probably the commonest cause of abdominal pain and a raised amylase. However, there are several other conditions that could mimic this presentation, classically a perforated peptic ulcer. Table 2 lists other common causes of hyperamylasaemia that could be associated with abdominal pain.

Pancreatic
Pancreatitis and its complications[$]
Trauma/Surgery[$]
Ductal Obstruction[$]
Chronic pancreatitis[$]
GI diseases
Perforated peptic ulcer/bowel[$]
Obstruction[$]
Mesenteric infarction[$]
Appendicitis
Gynaecological
Ruptured ectopic pregnancy
Ovarian/Fallopian Cysts
Pelvic Inflammatory disease

[$]Those in *italics* could mimic pancreatitis with epigastric pain and hyperamylasaemia.

Table 2: Other Causes of Abdominal Pain and Hyperamylasaemia.

The patient underwent an ultrasound abdomen. The pancreas was not visualised due to overlying bowel gas. There were no biliary calculi and no dilatation of the intrahepatic or common bile ducts. A CT abdomen was performed, which demonstrated no radiological features of pancreatitis, bowel obstruction or ischaemia.

Amylase exists in two isoforms – "P" (pancreas) and "S" (salivary) – relating to the site of excretion. It is not limited to these two sites and there are other conditions associated with amylase release (Table 3). These should be considered in a patient presenting with atypical abdominal pain. There are multiple case reports of suspected pancreatitis and hyperamylasaemia actually being due to salivary pathology, malignancy or macroamylasaemia (3-5).

Amylase is partially renally excreted so in the patient with acute or chronic renal dysfunction the amylase may be elevated due to reduced clearance. A review of the patient's previous investigations revealed that their serum amylase had been persistently elevated >3x ULN between hospital admissions when she was asymptomatic.

Salivary
Infection
Trauma/Surgery
Ductal Obstruction
Radiation
Neoplasms
Solid tumours – ovary/prostate/lung/oesophagus/breast
Myeloma
Other
Renal failure
Alcoholism
Burns
Macroamylasaemia
Coeliac disease
Anorexia
Liver disease
Drug induced

Table 3: Extraintestinal Causes of Hyperamylasaemia.

Assessment of the patient by the gastroenterologists indicated that the symptoms were more in keeping with functional dyspepsia and that the patient may in fact have a benign cause of hyperamylasaemia. Macroamylasaemia was considered and the investigations listed below were undertaken to ascertain if the elevated amylase was genuine or due to the presence of macroamylase.

Serum amylase	618 IU/L
Urinary amylase (random)	50 IU/L
Timed urinary amylase excretion	5 IU/L (1-17 IU/L)
vol urine (ml) x urine amylase (IU/L) = IU/hour *---------- time (collection period in hours) x 1000*	
Amylase:Creatinine clearance ratio	0.15% (2-5%)
urine amylase x serum creatinine ---------- x100 (%) serum amylase x urine creatinine	
Lipase	28 IU/L (5-65)

Table 4: Investigations for Macroamylasaemia.

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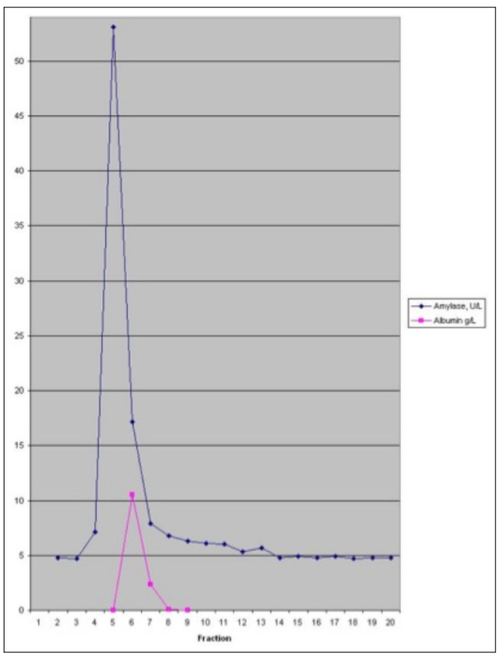

Figure 1: Confirmation of Macroamylase by gel filtration chromatography. Note the peak at the lower end of the spectrum indicating the increased molecular size of macromolecule. Normal amylase would be expected to peak around fraction (12-13) indicating its lower molecular weight.

The other pancreatic enzyme, lipase, which is also elevated in acute pancreatitis, was within the normal range, suggesting no active pancreatic inflammation. The amylase-creatinine clearance ratio was reduced, which is supportive of a diagnosis of macroamylasaemia so samples were sent to an external laboratory confirming the presence of macroamylase using gel filtration chromatography.

Macroamylase is formed when amylase complexes with larger macromolecules (typically immunoglobulins A and G) increasing the molecular size from 50kD to 160kD.

These large complexes are not readily renally excreted, resulting in high serum levels of inactive amylase.

It is a benign finding and not an indicator for any specific disease. It has been found to be both transient in some patients and persistent for many years in others.

The association of amylase with gamma-globulins postulated that the complex was more likely to form in patients with disorders with immunity, and although cases demonstrate its presence in some of these patients, it is in no way a consistent finding.

Patients most likely to benefit from identification of macroamylase are those with persistent, isolated raised amylase in which no obvious source can be found and whereby identification leads to the prevention of unnecessary exploratory surgery or repetitive imaging.

The normal excretion ratio is 2-5%.

An amylase:creatinine clearance ratio < 2% is suggestive of macroamylasaemia.

In contrast a ratio >8% is usually seen in pancreatitis.

Macroamylasaemia is relatively common; the prevalence in a study looking at 454 randomly selected patients with hyperamylasaemia was found to be as high as 5.5%.

Box 3: Macroamylasaemia – Key Facts.

Follow Up

Following discharge the patient was reviewed in outpatients. Her recurrent abdominal pain is thought to be functional. The hyperamylasaemia has been confirmed as macroamylasaemia and non-contributory to her abdominal symptoms.

Discussion

Pancreatitis is common and remains top of the differential in the patient presenting with abdominal pain and hyperamylasaemia. A small study looking at patients with non-diagnostic hyperamylasaemia (<3xULN) and abdominal pain retrospectively found 88% had aetiology relating to gallstones, microlithiasis, drug induced pancreatitis or chronic pancreatitis, indicating that even in the presence of a small increase in amylase in the context of abdominal pain then pancreatitis or biliary pathology remains the most likely diagnosis (7).

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Clinical assessment should include a thorough history regarding gallstones, alcohol intake and medications. The amylase should also be interpreted in the context of the onset of abdominal pain. Typically it begins to elevate 2-12 hours after onset and peaks at 48 hours (8). The half life of lipase is shorter than amylase and therefore returns to normal sooner after elevation making it a more sensitive and specific test to identify suspected pancreatitis (2).

Urinary amylase is high in acute pancreatitis but high serum amylase with low urinary amylase indicates macroamylasaemia i.e. a macromolecule too large to be filtered by the kidneys. Calculation of urinary amylase:creatinine clearance is an underutilised biochemical adjunct to the diagnosis of both macroamylasaemia and pancreatitis. In cases where doubt exists over the diagnosis then liaison with your local biochemistry laboratory may be beneficial to provide this.

In the atypical presentation of abdominal pain and hyperamylasaemia the clinician must remember there is a broad differential. Cross sectional imaging may elucidate alternative diagnoses in many cases such as intra-abdominal malignancy or perforated viscera. However there may be a need for more lateral thinking to make a diagnosis and avoid unnecessary irradiation.

Test Yourself – best of 5 MCQs

1. What is the most common cause of pancreatitis in the UK?

A. Gallstones
B. Ethanol
C. Autoimmune
D. Post-ERCP
E. Drug induced

2. Which of the following are not known to be associated with hyperamylasaemia?

A. Ruptured ovarian cyst
B. Perforated duodenal ulcer
C. Reflux oesophagitis
D. Mesenteric ischaemia
E. Ulcerative colitis

3. A 42 year old male presents with epigastric pain and nausea. Bloods reveal an elevated amylase and white cell count. What is the next most appropriate investigation?

A. CT abdomen
B. MRCP
C. US abdomen
D. Gastroscopy
E. Urine amylase:creatinine clearance ratio

4. What 2 investigations are the most useful for excluding acute pancreatitis when the diagnosis is in doubt?

A. Serum amylase
B. Faecal elastase
C. Urine amylase: creatinine clearance ratio
D. Serum lipase
E. US abdomen

5. Which of the following conditions have not been associated with macroamylasaemia?

A. Coeliac disease
B. Lymphoma
C. Parkinson's disease
D. Rheumatoid arthritis
E. Ulcerative colitis

Answer

1. Answer: A. Gallstones.

A history of biliary colic symptoms predating the presentation and obstructive LFTs will point towards the diagnosis. A thorough history and medication review is important to look for precipitants.

2. Answer: C. Reflux oesophagitis.

All of the other options are important presentations that may mimic pancreatitis by presenting with abdominal pain and hyperamylasaemia.

3. Answer: A.

US examination may not visualise the pancreas in up to 25% of cases and a contrast enhanced CT pancreas is the most reliable tool to aid diagnosis.

4. Answer: C and D.

Serum lipase is more sensitive and specific for pancreatitis than serum amylase. The amylase:creatinine clearance ratio would certainly be suggestive if >8% whereas <2% may suggest macroamylasaemia. Faecal elastase is a good screening tool for chronic pancreatitis.

5. Answer: C.

Macroamylasaemia is often associated with autoimmune conditions that are antibody producing thus providing the macromolecules with which to complex (although this is by no means a consistent finding). In patients with coeliac disease and macroamylasaemia a strict adherence to a gluten free diet and elimination of the immunoglobulins has resulted in normalisation of serum amylase in case reports.

MANAGING THE PATIENT WITH ABDOMINAL PAIN & A RAISED AMYLASE

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THE RECOGNITION, PREVENTION & TREATMENT OF REFEEDING SYNDROME

VM Barrow, L Gemmell, NP Thompson

Abstract

As demonstrated by David Blaine's uncomplicated recovery following a 44 day starvation whilst suspended above the Thames in a Perspex box, refeeding syndrome is largely preventable (1,2). However, failure to recognise it can be fatal (3). This article aims to reconcile the role of the doctor as both scientist and clinician by explaining the pathophysiology of refeeding syndrome and linking its clinical manifestations to underlying biochemical processes. Subsequently, we will discuss who is at risk and how to approach prevention and treatment.

Clinical Scenario

A 48 year old man with a background of alcohol excess was admitted with a productive cough, breathlessness and two stone weight loss over one year. His inflammatory markers were raised and a chest X ray showed left lower lobe consolidation.

He was prescribed intravenous (IV) antibiotics for community acquired pneumonia; symptom triggered chlordiazepoxide and five days of IV vitamin B replacement. Due to his weight loss he was prescribed an oral nutritional supplement in addition to his normal diet. Serum phosphate (PO4) was 0.55mmol/L (ref. range: 0.8-1.5mmol/L) but no further action was taken.

On day two, serum PO4 was 0.16mmol/L for which he was prescribed an IV phosphate infusion of 9mmol over 12 hours. Magnesium and potassium levels remained within normal range (0.87mmol/L and 3.8mmol/L respectively). The following day, he developed profound muscular weakness and fasciculations.

Repeat bloods highlighted a serum PO4 <0.1mmol/L. Magnesium level was 0.6mmol/L (ref. range 0.7-1.0mmol/L) with a potassium level of 3.2mmo/L (ref. range 3.5-5.3mmol/L). He was diagnosed with symptomatic hypophosphataemia secondary to refeeding syndrome and so was commenced on 30mmol IV phosphate over six hours. He was transferred to HDU for central access, electrolyte replacement and telemetry. After two days, he returned to the ward with stable electrolytes.

Introduction

The Minnesota Starvation Project of 1945, a clinical trial which explored the effects of prolonged reduced nutrition, provided an invaluable insight into both the metabolic and behavioural changes associated with starvation(4). Unfortunately, however, this came too late to prevent the overzealous feeding of survivors from Belsen Concentration Camp.

Clinical reports from Belsen make no reference to phosphate, magnesium and potassium deficiency(5), which are now known to underlie this condition(1), and which are responsible for a clinical syndrome that includes fatal diarrhoea, heart failure and neurological complications, such as coma and convulsions(6).

Metabolism In Starvation

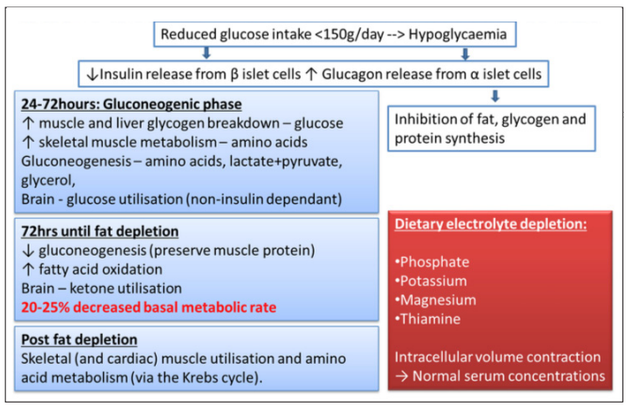

Figure 1: The body's response to glucose intake <150g/day (recommended daily carbohydrate intake = 300g) occurs in a number of stages. These are mediated by glucagon, the hormone of starvation. A 20-25%, reduction in basal metabolic rate reduces adenylyl triphosphate (ATP) requirements and utilisation of other metabolic intermediates which are dependent on dietary electrolytes(9). Despite electrolyte depletion, intracellular and serum levels remain stable due to intracellular volume contraction and no manifestations of depletion occur.

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Metabolism Changes During Refeeding

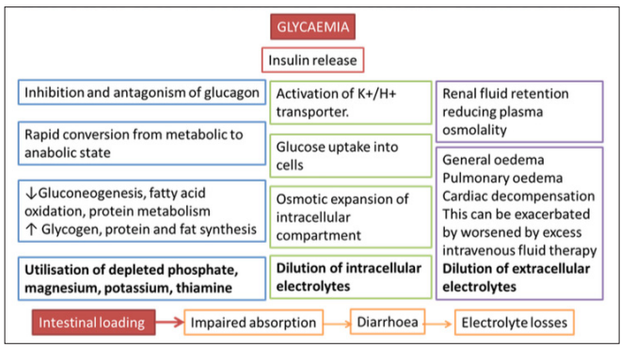
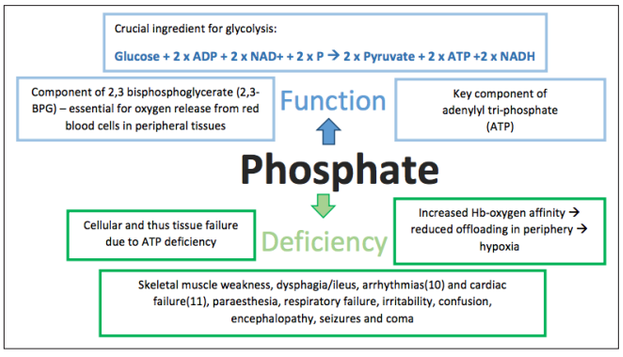


Figure 2: Insulin is the hormone of the fed state. It is released in response to glycaemia and antagonises glucagon, promoting glucose metabolism (to produce ATP) and glucose conversion to glycogen and lipids. These processes require a variety of electrolytes, both as co-factors to metabolic pathways and for incorporation into products of anabolism. In contrast to the fed state, when these are replete and homeostatic mechanisms ensure that serum concentrations remain stable, refeeding syndrome occurs when electrolyte utilisation exceeds supply, leading to significant depletion, failure of essential intracellular processes and changes in membrane potential. Insulin promotes cellular uptake of glucose with potassium, via the K+/Na+ transporter, leading to further potassium depletion. Intravenous fluids and fluid retention, via renal mechanisms, further dilutes serum electrolytes, exacerbating the effects of their depletion. Processes within the renal nephrons further increase water retention.(9)

Phosphate, magnesium, potassium and the B vitamin depletion is primarily responsible for the refeeding syndrome.

Phosphate

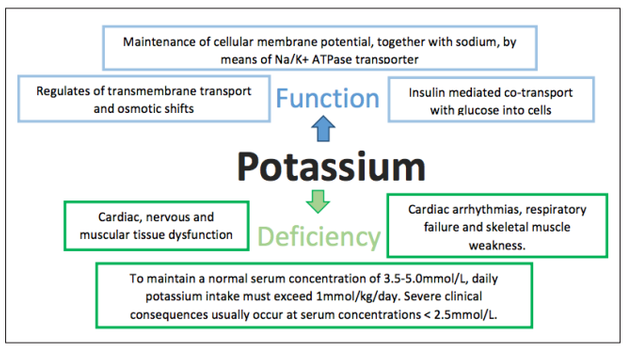


The mode of replacement depends on serum concentration and the presence/absence of symptoms. Oral replacement, however, can exacerbate diarrhoea and therefore IV phosphate may be more appropriate.

Definition	Serum PO4 (mmol/l)	Management
Normal	0.80–1.50	n/a
Mild	0.60-0.79	ORAL – Phosphate adjusted according to response (16mmol/tablets) – up to 6 tablets a day for 2-3 days or IV - Phosphate infusion (50mmol/500ml) 9mmol over 12 hours Daily phosphate level until in normal range
Moderate	0.30-0.59	
Severe	<0.30 (or if symptomatic)	IV - Phosphate Polyfusor (50mmol/500ml) 0.2-0.5 mmol/kg (max. 50 mmol per Day(13)) over 6-12 hours ECG telemetry, RR and BP monitoring 6 hourly phosphate level Calcium, potassium and magnesium monitoring

Figure 3: A suggested algorithm for phosphate replacement(12)

Potassium



On a ward, IV potassium replacement is safely limited to 40mmol potassium chloride in 1L base solution (either N.Saline/ 5% dextrose or 4% dextrose-saline) over a minimum two hours(14). Rates above 20mmol/hr require ECG monitoring. The concentration infused by central replacement on HDU/ITU may be higher depending on local guidelines.

In non-urgent replacement, oral potassium chloride of 2 x 12mmol tablets may be given up to three times a day for three days, with additional replacement if serum levels remain low(14).

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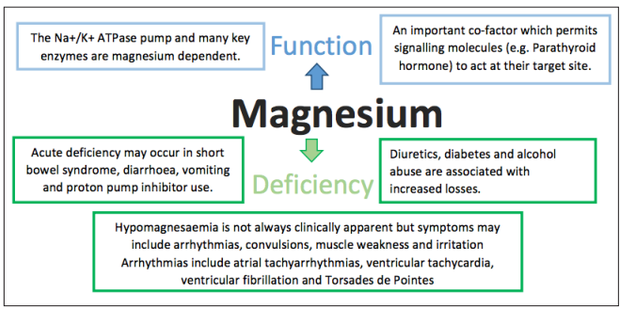
Magnesium

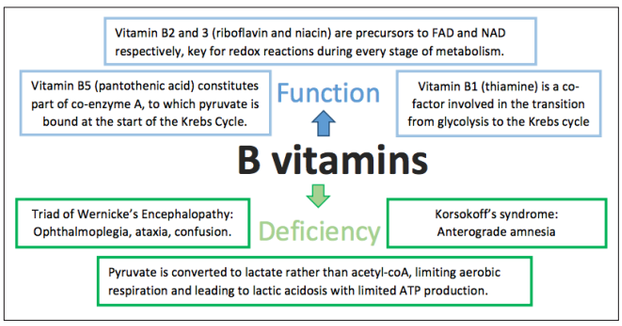


The recommended daily magnesium intake is 0.2mmol/kg(15). <1% body magnesium is contained within the extracellular compartment therefore serum levels should be interpreted and replaced according to the clinical context(16). Oral replacement may exacerbate diarrhoea and therefore IV replacement may be most appropriate

Definition	Serum Mg (mmol/l)	Management
Mild	0.51-0.69	ORAL – Magnesium Aspartate 10mmol BD for 5-7 days Note – there are alternative preparations available.
Moderate	0.31 – 0.5	IV - 50% MgSO4 0.25mmol/kg in 100ml 5% Dextrose over 2 hours
Severe OR Symptomatic	<0.3	IV – 50% MgSO4 0.5mmol/kg in 250ml 5% Dextrose over 2 hours. ECG monitoring

Figure 4: Suggested algorithm for Magnesium replacement(17)

The B vitamins



Enteral vitamin B transporter proteins become rapidly saturated: in order to achieve sufficient and timely repletion, IV, not oral, replacement is essential.

Who is at risk of refeeding syndrome?

Patients are at high risk if they have either(15)

One of:

- BMI less than 16 kg/m^2
- Unintentional weight loss greater than 15% within the last 3–6 months
- Little or no nutritional intake for more than 5-10 days
- Low levels of phosphate or magnesium prior to feeding

Or two of:

- BMI less than 18.5 kg/m^2
- Unintentional weight loss greater than 10% within the last 3–6 months
- Little or no nutritional intake for more than 3-5 days
- Drugs including insulin, chemotherapy, antacids or diuretics or a history of alcohol abuse

Although some patients are admitted due to their poor nutrition (e.g. parenteral nutrition commencement/ refeeding in anorexia), many high risk patients may be admitted with unrelated issues, meaning that refeeding might be overlooked. For example in cases of:

- *Cognitive impairment where poor oral intake cannot be reported*
- *Alcohol abuse with poor diet*
- *Unsafe swallow, when SALT assessment or NG insertion is delayed*
- *Prolonged emesis*
- *Peri-operative period*

The incidence of hypophosphataemia amongst such patients can be as high as 50%. IV dextrose above 5% increases the risk of refeeding syndrome in those at risk by stimulating insulin production. This includes the use of 10% glucose in GKI infusions. Where this is necessary, close monitoring is essential.

THE RECOGNITION, PREVENTION & TREATMENT OF REFEEDING SYNDROME

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Prevention strategies and safe feeding(18).

1. A nutrition screening tool, such as the MUST score, should be calculated, acknowledged and acted upon, on admission. This should be reviewed if the patient's condition changes such that it places the patient at increased risk.

2. Daily electrolyte monitoring (including phosphate, magnesium and potassium) and replacement, where appropriate, is essential in all 'at-risk' patients.

3. Twice-weekly monitoring is appropriate once electrolytes remain in range for 48 hours.

4. Five days of IV B vitamins is essential for all 'at-risk' patients

5. TPN should only be commenced with a suitable work up and appropriate electrolyte monitoring/ replacement.

6. Refeeding should be undertaken slowly, with dietitian guidance and daily electrolyte monitoring and replacement.

7. Food and weight charts should be accurately recorded. Intake should be limited to that prescribed by the dietitian.

MCQs

1. A 55 year old obese woman with a history of alcohol excess attends A+E with a three day history of right upper quadrant pain, jaundice, vomiting and rigors. She is treated with analgaesia, IVT and co-amoxiclav for ascending cholangitis. Of the following, which statement is true?

a) This lady has a high BMI and therefore risk of refeeding is very low
b) Alcohol excess and vomiting mean that she is at risk of developing refeeding syndrome
c) Normal electrolytes on admission rule out refeeding syndrome
d) She is likely to be nil by mouth so dietitian review is not appropriate at this stage

2. She is listed for an MRCP for ?CBD stones but owing to a number of priority cases, this takes two days to occur. Each day she remains NBM in case she obtains a slot and subsequently requires ERCP. On evenings she skips dinner due to ongoing nausea and poor appetite. Of the following, which statement is true?

a) Electrolytes may appear normal even if the patient has tissue depletion due to poor oral intake and/or increased losses
b) 10% dextrose is a good choice of IVT in this patient as it will prevent refeeding syndrome
c) Potassium depletion is unlikely to occur during this acute illness unless dietary intake has been chronically low for some time prior to admission
d) Remaining NBM for a couple of days is common in hospitals and won't lead to refeeding syndrome in this case

3. On the third day, MRCP shows no stones and she is improving clinically. The decision is made to watch and wait. The nurse is advised that she no longer needs to remain NBM. Which of the following is true?

a) This lady is now deemed high risk for refeeding syndrome and is at risk of severe hyperphosphataemia which could potentially lead to respiratory depression
b) High dose oral thiamine TDS is indicated now she is no longer nil by mouth
c) Mg, K and PO4 must all be deplete for refeeding syndrome to be diagnosed
d) IV potassium supplementation can be given at a maximum rate of 20mmol/hr on a ward but this requires ECG monitoring.

4. Muscle weakness is associated with severe hypophosphataemia because of impaired glucose metabolism but what is the role of phosphate in this process?

a) It is a co-enzyme involved in conversion of pyruvate to acetyl co-A
b) It is essential for the co-transport of glucose into cells in the presence of insulin
c) It is an essential ingredient for glycolysis
d) It is essential for maintaining membrane potential and nerve conduction

5. Which of the following blood tests is not routinely used?

a) Phosphate assay
b) Potassium assay
c) Thiamine assay
d) Magnesium assay

Answers

1 – B

This patient has a history of alcohol excess and her vomiting is likely to have limited her oral intake for three days. According to the guidance, she has two factors which make her at risk of refeeding. Refeeding syndrome occurs regardless of BMI as it relates to electrolyte depletion. Early dietician review is essential to identify patients at risk and to make a plan for safe refeeding.

2 – A

Serum electrolyte concentrations may remain normal until refeeding causes the release of insulin which triggers large electrolyte and fluid shifts. Normal baseline bloods do not mean a patient will not develop refeeding syndrome. 10% dextrose is sufficient to trigger insulin release so is not a good maintenance fluid in a patient who is already at risk. Daily potassium requirements are 50-90mmol and patients who do not obtain this can become rapidly hypokalaemic.

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3 – D

High rate IV potassium repletion requires ECG monitoring. This woman has not been eating for six days and is high risk for refeeding but this would cause hypo- not hyper-phosphataemia. Thiamine replacement is essential but this should be delivered IV not orally to maximise uptake. Refeeding syndrome may only initially manifest as a deficiency of one electrolyte, as in the case study.

4 – C

Phosphorylation is a key process in glycolysis. Thiamine is a co-enzyme in the conversion of pyruvate to acetyl co-A; potassium is transported into cells alongside glucose and is also essential for nerve conduction potentials.

5 – C

Potassium is routinely measured as part of U+Es. Phosphate is part of the Bone Profile. Thiamine is not routinely measured. Magnesium may need ordering separately.

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