

SELF ASSESSMENT EXERCISES

Emergency Medicine

PAF Hunt

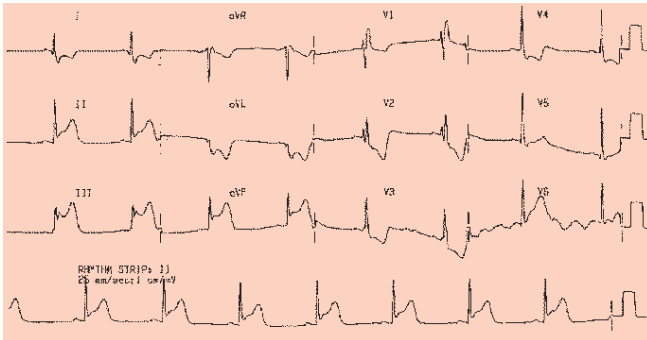
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You are a medical officer undertaking your Acute Care Common Stem training appointment in Emergency Medicine working in a large UK teaching hospital near Catterick. You have just started your afternoon shift when one of the nurses asks you to see a patient in the resuscitation room.

Question 1

A 55-year-old male officer presents with central "crushing" chest pain of around 1 hour duration. He is clammy, pale and nauseated. His ECG is shown below.

- What is your diagnosis?
- Which vessel(s) is/are most likely implicated in this case?
- List the risk factors for this condition.
- Describe your initial treatment of this condition including any drug names and dosages as appropriate.
- List the recommended secondary prevention drug names/classes.



Question 2

A 44-year-old SNCO presents to the department with severe central abdominal pain radiating to his back. He is pale, clammy and is vomiting. On examination he has central abdominal tenderness. Initial blood test results are shown below:

WCC	11.3	Glucose	10.0
Neut	10.0	Total Protein	73
Hb	15.9	Albumin	45
PLT	266	Globulin	28
PT	11	ALP	215
PTR	0.9	Ca ²⁺	2.52
APTT	19	Corrected Ca ²⁺	2.42
Fib	5.5	Bilirubin	119
Na ⁺	142	Phosphate	1.17
K ⁺	3.8	GGT	827
Ur	4.7	ALT	780
Cr	112	Amylase	2711
CRP	43	Cholesterol	7.26

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- What is the diagnosis?
- What are the two most likely causes of this in the UK?
- List the criteria for illness severity and describe how these relate to mortality.
- Describe the initial management of this condition.
- What are the complications of this condition?

Question 3

An 18-year-old soldier attends the emergency department. He has a respiratory rate of 38, is confused and pyrexial (38.5°C tympanic) with dry mucosa and complains of non-localising abdominal pain.

Arterial blood gases on 15L/min O₂:

pH	7.095	Bicarb	5.9
PaO ₂	27.1 kPa	BE	-28.1
PaCO ₂	1.86 kPa	Anion Gap	24mmol

- Briefly describe the significance of these blood gas results.
- Give the most likely diagnosis.
- What is the investigation most likely to help differentiate the diagnosis?
- List three key aspects of treatment.
- What electrolyte will require careful monitoring during treatment?

Question 4

A 23-year-old female civilian with known asthma presents to the emergency department acutely short of breath. The symptoms have worsened since the morning and she is now exhausted. She is too breathless to speak in full sentences.

- Briefly describe your initial approach to this patient and your immediate actions.
- List the features of life threatening asthma.
- What initial investigations are indicated in this patient?
- List those drugs used in the management of severe asthma in addition to oxygen and nebulisers.

Question 5

A 22-year-old soldier attends the department with his partner having returned from annual leave in Thailand two weeks previously. During the holiday he was trekking in the jungle regions bordering Cambodia. He received all advised immunisations before travel. He denies any new sexual contacts or intravenous drug abuse. He started feeling unwell three days ago with fatigue, aching joints and a periodic high fever followed by chills and shivering. His condition has worsened in the last 24 hours and he is now drowsy and lethargic with a constant headache. The full blood count results reveal anaemia and thrombocytopenia.

- List the three most likely diagnoses highlighting your provisional working diagnosis.
- What specific laboratory investigations would you request?

- c. What are the major complications that may occur with this disease?

The patient deteriorates rapidly, becoming increasingly drowsy, while you are waiting for further results to return.

- d. What is the likely cause of his reduced level of consciousness and what treatment should you initiate at this stage?

Answers to self-assessment exercises:

Question 1

- a. This ECG demonstrates ST elevation in the inferior leads II, III and aVF with reciprocal ST depression in the anterior leads, consistent with an acute inferior myocardial infarction. ECGs should also be checked for posterior (RV) extension as this is described as occurring in as many as 50% of inferior myocardial infarctions.
- b. The inferior region of the heart is supplied by both the left anterior descending (LAD) and left circumflex arteries, although mainly by the distal branches of the LAD.
- c. Reduction in coronary blood flow is related to progressive atherosclerosis with increasing occlusion of coronary arteries. Blood flow can be further decreased by superimposed events such as vasospasm, thrombosis, or circulatory changes leading to hypoperfusion. Risk factors for atherosclerosis may be modifiable or non-modifiable. The non-modifiable risk factors for atherosclerosis include:
- Increasing age
 - Male gender
 - Family history of premature coronary heart disease
 - Premature menopause
 - Ethnic Group - In the UK, the highest recorded rates of coronary artery disease mortality are in people born in India, Pakistan and Bangladesh (3)

Modifiable risk factors for atherosclerosis include:

- Smoking
- Diabetes mellitus (and impaired glucose tolerance)
- Hypertension
- Raised LDL cholesterol and reduced HDL cholesterol
- Obesity, inactivity and poor physical fitness

Non-atherosclerotic causes may be implicated in younger patients such as coronary emboli from sources such as an infected cardiac valves, coronary occlusion secondary to vasculitis, coronary artery spasm, cocaine use, congenital coronary anomalies, coronary trauma and increased oxygen requirements (e.g. hyperthyroidism) or decreased oxygen delivery (e.g. severe anaemia).

- d. Initial treatment should focus on ensuring adequate oxygen delivery in order to prevent further ischaemia as well as pain relief and the prevention and treatment of any complications that may arise. Management should therefore include:
- High concentration oxygen.
 - Pain relief with diamorphine (2.5 - 5mg) or morphine (5 - 10mg) along with a suitable antiemetic.
 - GTN (usually by sublingual spray or buccal tablet).
 - Aspirin 300mg chewed or dispersible (or clopidogrel - see discussion).
 - Percutaneous coronary intervention (PCI) or thrombolysis depending on transport times, local guidelines and access to services.
 - Tight glucose control and secondary prevention therapies.
 - Intravenous access should be obtained and blood taken for full blood count, renal function and electrolytes, glucose, lipids, clotting screen, CRP and cardiac enzymes (Troponin I or T).
 - ECG and chest radiograph.

- e. The four main secondary prevention drugs are:

- Beta-blockers
- Aspirin
- Statins
- ACE inhibitors

Discussion

The ECG signs of ischaemia and non-ST segment elevation infarction may be identical although findings are more specific with respect to ST segment elevation infarction. ECG changes indicative of myocardial ischaemia that may progress to infarction include patients with new or presumed new ST segment elevation at the J point in two or more contiguous leads with the elevation equal to or more than 0.2 mV in leads V1, V2, or V3 and equal to or more than 0.1 mV in other leads. An established myocardial infarction is defined by an ECG pattern demonstrating a QR pattern in leads V1-V3 that is at least 30 ms in duration and/or an abnormal Q wave (1 mm in depth) in any two contiguous leads involving leads I, II, aVL, aVF, or V4-V6.

New criteria for diagnosing myocardial infarction are an increase in biochemical markers of myocardial necrosis, with at least one of the following:

- Ischaemic symptoms
- Development of pathological Q waves on the ECG
- ECG changes indicative of ischaemia
- Coronary artery intervention (e.g. angioplasty)

Myocardial infarction is now considered part of a spectrum referred to as acute coronary syndrome, with a range of causes of acute myocardial ischaemia including unstable angina and non-ST segment elevation myocardial infarction. The differential diagnosis of acute chest pain may include other cardiovascular causes such as aortic dissection or myocarditis, respiratory causes such as pneumonia and pneumothorax, gastrointestinal causes such as oesophageal spasm, oesophagitis, gastro-oesophageal reflux, acute gastritis, cholecystitis, pancreatitis or musculoskeletal pain.

The immediate medical care of myocardial infarction should include high concentration oxygen delivery and pain relief with 2.5 - 5mg diamorphine or 5 - 10mg morphine intravenously (along with a suitable anti-emetic). Nitrates have no apparent impact on mortality rate in patients with ischaemic syndromes and their utility is in symptomatic relief and preload reduction and should be administered to all patients with acute MI within the first 48 hours of presentation, unless contraindicated (i.e., in RV infarction). Aspirin 300 mg should be given orally (dispersible or chewed) although clopidogrel may be used as an alternative in cases of aspirin resistance or allergy. Recent data from the CLARITY trial (4) suggests that adding clopidogrel to the standard aspirin regimen is safe and effective. The clopidogrel dose used in that study was 300 mg.

Hospital management should also include close glucose control for all diabetics with an insulin-glucose infusion. Beta-blockers should be started within 12 hours of infarction in patients without evidence of heart failure as they are shown to reduce the rates of reinfarction and recurrent ischaemia, and possibly reduce the mortality rate. Unless contraindicated, the usual regime is to give beta-blockers intravenously on admission and then continue with oral administration afterwards. Angiotensin-converting enzyme (ACE) inhibitors are also shown to reduce mortality whether or not patients have clinical heart failure or left ventricular dysfunction and also reduce the risk of non-fatal heart failure. Angiotensin-receptor blockers may be used as an alternative in patients who develop adverse effects, such as a persistent cough, although initial trials need to be

confirmed. Heparin infusion should be used as an adjunctive agent in patients receiving rTPA and is also indicated in patients undergoing primary angioplasty. Prophylaxis against thromboembolism should be started if patients are not already receiving heparin by infusion. Little data exists with regard to efficacy in patients not receiving thrombolytic therapy in the setting of acute MI. Low-molecular-weight heparins (LMWHs) have been shown to be superior to unfractionated heparin in patients with unstable angina or non-ST elevation MI.

PCI is the treatment of choice in most patients with STEMI, assuming a door to needle time of less than 90 minutes. PCI provides greater coronary patency, lower risk of bleeding and instant knowledge about the extent of the underlying disease. Studies have shown that primary PCI has a mortality benefit over thrombolytic therapy. If PCI capability is not available or will cause a delay greater than 90 minutes, then the optimal approach is to administer thrombolytics within 12 hours of onset of symptoms in patients. NICE recommendations state that pre-hospital thrombolysis is indicated if the time from the initial call to arrival at hospital is likely to be over 30 minutes and that using intravenous bolus therapy (e.g. reteplase or tenecteplase) should be used rather than an infusion.

All patients should be offered long term treatment with a beta-blocker and antiplatelet drug (aspirin), and then with a statin and an ACE inhibitor. NICE guidelines recommend measuring cholesterol at 12 weeks to exclude familial lipid disorders and identify those needing long-term statin therapy. The precise level of cholesterol that should be treated is unclear. Beta-blockers and ACE inhibitors can also be considered for the management of symptoms (e.g. in stable angina) or risk factors (e.g. hypertension). Calcium channel blockers, nitrates, and potassium channel activators have no effect on premature mortality making their role the management of symptoms and risk factors (principally hypertension). They should therefore only be used in those patients who are intolerant of beta-blockers and ACE inhibitors. Given their benefits in non-fatal myocardial infarction, verapamil or diltiazem should be considered initially. Subsequent necessary treatment with other calcium channel blockers, nitrates or potassium channel activators may then be appropriate. Long-term use of clopidogrel with aspirin increases the risk of bleeding and there is little evidence for the benefit of this combination in the long term.

Patients with heart failure should be offered long term treatment with an ACE inhibitor and then a beta-blocker (not all beta-blockers have a license for this indication). In addition they should be treated with an antiplatelet drug (such as aspirin). Patients who have moderate or severe heart failure (New York Heart Association grade 3 or 4) should be treated with spironolactone.

Question 2

- The significantly raised amylase level and clinical presentation suggests acute pancreatitis as the diagnosis. Other causes of a raised amylase level, although rarely beyond a level of 500 include mumps, pancreatic carcinoma, mesenteric ischaemia or infarction, hepatitis, post-ERCP, peritonitis, trauma, ectopic pregnancy, gastrointestinal obstruction or perforation, opiates, renal failure, ruptured aortic aneurysm and diabetic ketoacidosis.
- Alcohol and Gallstones are the two commonest causes of acute pancreatitis in the UK.
- The modified Glasgow (Imrie) criteria (see below) remains the most commonly used method of assessing severity of acute pancreatitis. It assesses 9 criteria on admission and over

the following 48 hours, 3 or more positive criteria define a severe attack. The level of serum amylase on admission or subsequently does not correlate with severity and offers no prognostic information. Other indicators of severity as suggested by the UK Working Party on Acute Pancreatitis are the clinical impression of severity, obesity, APACHE II score >8 in the first 24 hours of admission, the Ranson score greater than 3, a C reactive protein level >210 mg/l or persisting organ failure after 48 hours in hospital (5).

Imrie criteria:

- Age >55 years
- White blood count >15x10⁹/l
- Glucose >11.0 mmol/l
- LDH >600 IU/l
- AST or ALT >125 U/l
- Calcium <2 mmol/l
- Arterial PaO₂ ≤8.0kPa
- Urea >16mmol/L
- Albumin ≤ 32g/l

Mortality is related to the number of positive criteria as follows:

- 0-2 = <1% mortality
- 3-4 = 16% mortality
- ≥6 = 100% mortality

- Mild cases may be managed on a general ward. Treatment consists of pain relief, antiemesis and rehydration. Traditionally morphine has been relatively contraindicated due to the possible spastic effect on the sphincter of Oddi, in favour of pethidine but in practice this is rarely implemented. Until the diagnosis and severity scoring is confirmed the patient should remain nil-by-mouth but if a mild attack is confirmed then free fluids may be allowed, as well as intravenous rehydration. Urine output should be closely monitored but catheterisation is not required. Antibiotics should be given for specific infections only. As symptoms resolve and blood tests return to normal oral intake can increase and feeding begin. Underlying conditions, such as gallstones, will need appropriate management.

Urgent therapeutic ERCP should be performed in patients with acute pancreatitis of suspected or proven gall stone aetiology who satisfy the criteria for predicted or actual severe pancreatitis, or when there is cholangitis, jaundice or a dilated common bile duct. The procedure is best carried out within the first 72 hours after the onset of pain (5).

Severe cases should be managed in a critical care environment such as HDU or ITU. Treatment should follow the same course as with milder cases, with an extra focus on organ supportive care and close observation for possible complications. Antibiotics should be strongly considered in severe cases - in accordance with BSG guidelines, although the evidence for this is not convincing (6) - and where there is evidence of pancreatic necrosis antibiotics is mandatory, preferably with results of specific cultures and sensitivities from peritoneal fluid (5). Enteric feeding should be instituted as soon as possible by placement of a naso-enteric tube beyond the ligament of Treitz (the anatomical landmark of the duodenojejunal junction). The use of enteral feeding may be limited by ileus. If this persists for more than five days, parenteral nutrition will be required. Open surgical debridement is generally indicated only where there is evidence of infection and necrosis. Postoperative lavage or abdominal packing with partial or non-closure of abdomen may be required.

- e. Early complications include the systemic manifestations of critical illness such as pulmonary oedema, ARDS, hypovolaemia and shock, disseminated intravascular coagulopathy (DIC), renal dysfunction, hypocalcaemia, hypomagnesaemia, hyperglycaemia and GI haemorrhage or ileus. Later complications include ascites, pancreatic necrosis (+/- infection), abscess, pancreatic pseudocyst and splenic vein thrombosis.

Discussion

Acute pancreatitis is an acute inflammatory process of the pancreas gland that can involve either peripancreatic tissues or remote organ systems, or both. It affects between 150 and 420 per million population and accounts for around 3% of all cases of abdominal pain admitted to hospital in the UK. Biliary disease and alcohol abuse together account for 70–80% of cases, 10% patients have both and 25% of cases are idiopathic. The incidence of acute pancreatitis in the UK appears to be rising (5). Overall mortality is around 5–10%, rising to 35% if severe.

There are numerous other causative factors including many drugs (see below), tumours obstructing the pancreatic duct which may be of the pancreatic head or cholangiocarcinomas of the biliary tree, trauma (including ERCP), anatomical variations such as pancreas divisum, hypercalcaemia and hyperlipidaemia, vasculitis, pregnancy, end stage renal failure, mycoplasma or viral (mumps) infection, venoms (scorpion bite, certain spider bites) and idiopathic causes.

Drugs with a definite association with acute pancreatitis include Azathioprine, 6-Mercaptopurine, Asparaginase, Pentamidine and Didanosine. Those with a probable association include valproic acid, furosemide, sulphonamides, tetracyclines, oestrogens and sulphasalazine (7).

Clinical features of continuous epigastric pain (radiating to the back in about 50% of cases) and vomiting, together with elevation of plasma concentrations of pancreatic enzymes are suggestive of the diagnosis. Pancreatic enzymes are released into the circulation during an acute attack with levels peaking early, and then declining over the following 3–4 days. Both lipase and amylase levels are suitable as biochemical markers of pancreatitis. A serum amylase greater than 5 times the upper limit of normal for that laboratory is diagnostic. Urinary amylase remains elevated for about 10 days and can be used to diagnose pancreatitis after the decline of the serum enzymes. Signs of peritoneal irritation such as rebound tenderness are typically absent on initial presentation, consistent with the retroperitoneal location of the pancreas. Acute ischaemia of the bowel should be considered as a differential diagnosis although the elevation of serum amylase is rarely of this degree.

Gastrointestinal ileus is common and a plain abdominal x-ray may show a sentinel loop of dilated small bowel. Patients are usually significantly dehydrated due to sequestration of fluid in the gut (third space losses) and will require close monitoring of urine output with IV fluid administration initially, then orally when able. Evidence of retroperitoneal haemorrhage, specifically periumbilical bruising (Cullen's sign) and flank bruising (Grey-Turner's sign) is rare. Ultrasound scanning may show pancreatic swelling although it is most useful in demonstrating gallstones and dilatation of the common bile duct. Contrast enhanced CT is occasionally indicated for confirming the diagnosis in the case of inconclusive clinical or biochemical findings, but should be performed between days 3–10 in cases of acute severe pancreatitis to exclude parenchymal ischaemia or necrosis.

Early systemic features in severe cases are frequent with respiratory failure, hypotensive shock and renal failure being the most common. Critical care with organ support is often

required for more severe cases. Requirement of organ support 48 hours after presentation is a poor prognostic factor. The important late complications of acute pancreatitis include chronicity, pancreatic necrosis, pseudocyst formation and fistulas. Necrosis represents a disruption of pancreatic microcirculation with hypoperfusion and subsequent tissue death. A pseudocyst is a localised collection of pancreatic secretions that lacks an epithelial lining and persists for more than 4 weeks. Drainage may be indicated if a pseudocyst enlarges and is at risk of perforation, or is causing pain or gastric outlet obstruction. Infection or haemorrhage involving a pseudocyst also requires intervention. Fistulas may communicate with the colon, small bowel or biliary system, or they may track to the skin. Surgery may be required to treat persistent pancreatic fistulas.

Question 3

- a. The blood gas results demonstrate a metabolic acidosis. The pH of 7.095 signifies acidosis while the low PaCO₂, significant base excess and lowered bicarbonate suggest a metabolic cause. The low PaCO₂ suggests respiratory compensation (Kussmaul breathing). The raised anion gap is likely to be secondary to ketone anion accumulation, or from lactate. It is also worth noting that the PaO₂ is relatively low despite the delivery of 100% oxygen. This may reflect a primary respiratory disease process such as pneumonia or pulmonary embolus.
- b. The most likely diagnosis is diabetic ketoacidosis (DKA). Alternatives in this case may include severe sepsis or poisoning with an acidic compound, such as salicylates.
- c. Either a raised blood glucose level or urinary dipstick test (to detect glycosuria or ketosis) will confirm the diagnosis.
- d. The key aspects of immediate treatment are fluid resuscitation, 'low dose' (see discussion) insulin administration, potassium replacement therapy and treatment of the underlying cause. Intravenous solutions replace extravascular and intravascular fluids as well as electrolyte losses. They also dilute both the glucose level and the levels of circulating counter regulatory hormones. Insulin is needed to help switch from a catabolic to an anabolic state, with uptake of glucose in tissues and the reduction of gluconeogenesis as well as free fatty acid and ketone production (8).
- e. DKA produces a total body potassium deficit, as well as total body water deficit. This may initially be masked by acidosis, which sustains an increased serum potassium level. The potassium level can drop precipitously once rehydration and insulin treatment start so level will need to be checked at least every 1 to 2 hours during initial management.
- f. The most common scenarios leading to DKA are an underlying or concomitant infection (30%), treatment non-compliance (20%), newly diagnosed or previously unknown diabetes (25%) or unknown cause (25%) (9). Urinary tract infections are the single most common infection associated with DKA, but many other associated illnesses need to be considered as well. Other precipitating factors include MI, CVA, complicated pregnancy, trauma, stress, surgery or the heavy intake of concentrated carbohydrate beverages such as sodas and sports drinks (8).

Discussion

Diabetic metabolic decompensation results from an absolute or

relative lack of insulin. This insulin deficiency is usually aggravated by the ensuing hyperglycaemia, dehydration, and acidosis-producing metabolic derangements. A precipitating factor such as infection or stress may be present causing an excess of stress hormones which antagonise the actions of insulin. DKA is typically characterized by hyperglycaemia, low bicarbonate, and acidosis (pH <7.30) with ketonaemia and ketonuria. DKA is seen primarily in patients with insulin dependent diabetes (type 1) although it may occur in patients with non-insulin dependent diabetes (type 2) as well.

Metabolism in DKA shifts from the normal 'fed state', characterized by carbohydrate metabolism, to a fasting state characterized by fat metabolism. Metabolic acidosis ensues as the ketone bodies produced by beta-oxidation of free fatty acids deplete extracellular and cellular acid buffers. The hyperglycaemia-induced osmotic diuresis depletes sodium, potassium, phosphates and water. Other acid-base disorders that may be present including lactic acidosis due to hypoperfusion and anaerobic muscle metabolism, metabolic alkalosis secondary to excessive vomiting, respiratory acidosis due to pneumonia or mental obtundation or respiratory alkalosis from sepsis.

Initial arterial blood gases are required in order to accurately assess the acid-base balance and measure arterial oxygenation. Venous pH may be appropriate for subsequent pH monitoring (10). Blood should be taken for urea and electrolytes and full blood count. Cultures will be necessary in order to identify sensitivities and guide antibiotic treatment for specific infections.

Airway protection with a cuffed endotracheal tube may be required for patients with significant obtundation or for ventilation in the case of respiratory failure. If intubated and ventilated, ventilatory parameters (tidal volume and rate) need to be set to continue with a high minute volume. If this is not done and PaCO₂ is inappropriately high, a severe acidemia and consequent severe cardiovascular collapse may occur (9).

Initial fluid resuscitation should be with standard solutions such as 0.9% saline or Hartmann's in order to restore intravascular volume and improve tissue perfusion. Further fluid replacement should be administered at a rate appropriate to maintain adequate blood pressure and pulse, urinary output, and mental status. Care should be taken as the use of large quantities of 0.9% saline may result in development of a hyperchloraemic acidosis. Subsequent fluids will need to be adjusted in order to provide 'free water' to replenish intracellular fluid and to provide glucose. Potassium replacement can be commenced when the level falls below 5 mmols/l, usually beginning at 10 mmols/hour.

A 'low dose' insulin replacement regime is associated with lower mortality than high dose treatment. A typical regime would be to give a stat dose initially (10-20U IV) and commence the patient on a continuous insulin infusion at 5 to 10 U/hr decreasing to 1-3 U/hr to maintain blood glucose at 5 to 10 mmols/l (9).

Bicarbonate is often the slowest biochemical parameter to recover, especially when substantial amounts of ketones have been lost in the urine. New bicarbonate is generated when the condition is reversed and ketones are being metabolised. Studies have not shown any benefit from bicarbonate treatment, although some physicians do administer bicarbonate when the pH is less than 7.0 (8). Problems with bicarbonate administration include sodium overload, CSF acidosis, intracellular acidosis, exacerbation of hypokalaemia, rebound alkalosis and impaired tissue oxygen delivery (from shift of the oxyhaemoglobin dissociation curve). It is also associated with cerebral oedema in children.

Patient with DKA are usually admitted to hospital for

treatment and may require critical care intervention. Since the discovery of insulin in 1922, the mortality from DKA has dropped dramatically from 100% to around 2 to 5% in Western countries today (11).

Complications of DKA include those associated with concurrent illnesses, such as sepsis or organ ischaemia. Acute pulmonary oedema may occur due to aggressive or excessive fluid therapy and hypokalaemia or hypoglycaemia may occur inadvertently due to inadequate monitoring and correction. Cerebral oedema is known to occur in 1% of children with DKA, with a mortality rate of 21% and neurological sequelae in another 21% of patients (12). The recommended treatment for cerebral oedema is immediate IV mannitol in a dose of 0.5 - 2.0 g/kg body weight (9).

Special attention should be given to pregnant patients, as foetal mortality rates associated with DKA can be as high as 30%. This rate is as high as 60% in DKA with coma (8).

Question 4

- Patients with acute asthma are hypoxaemic and this will require immediate correction with a high concentration of inspired oxygen aiming to achieve an oxygen saturation of at least 92%. Nebulised β_2 agonist bronchodilators should also be commenced as soon as possible and ipratropium bromide added for patients with acute severe or life threatening asthma or those with a poor initial response to β_2 agonist therapy (13). Features of life-threatening asthma should alert the treating physician to the early requirement for senior help and critical care support.
 - Features of life threatening asthma include any of the following:
 - PEF <33% of best or predicted, SpO₂ < 92%.
 - PaO₂ < 8kPa, Normal PaCO₂ (4.6 - 6.0kPa).
 - Silent chest, Cyanosis, Feeble respiratory effort.
 - Bradycardia, Dysrhythmia, Hypotension.
 - Exhaustion, Confusion or Coma.
 - All patients with signs of acute asthma should have pulse oximetry. Measurement of arterial blood gases are indicated in all patients with SpO₂ <92% or with features of life threatening asthma. This should be repeated within two hours of starting treatment. Peak expiratory flow rate measurement improves recognition of the degree of asthma severity and will aid in the decision-making process for hospital management. A chest radiograph is indicated if there is clinical evidence of a pneumothorax or consolidation, if there are life-threatening signs, the need for ventilation or failure to respond satisfactorily to treatment. Serum potassium and blood glucose measurements should also be taken (13).
 - Corticosteroids should be administered in all cases of severe asthma. Either oral prednisolone 40-50mg or IV hydrocortisone 100mg can be given (or both in severely ill patients). In addition, the following drugs should also be considered in the management of severe asthma with life threatening features:
 - Continuous nebulised β_2 agonists.
 - IV magnesium.
 - IV β_2 agonists.
 - IV aminophylline.

Discussion

Bronchial asthma affects approximately 3.4 million people in the UK. The prevalence of asthma in young adults in the UK is the highest in Europe. On average 1,400 people die from

	Severe	Life-threatening	Near-fatal
Appearance	Worsening symptoms despite normal therapy	Cyanosis Feeble respiratory effort Exhaustion Confusion Coma	Any of the features of life-threatening asthma plus:
Speech	Inability to complete sentences in one breath		
PEF % *	33 – 50%	< 33%	Raised PaCO ₂ (>6.0 kPa)
Resp rate	≥ 25/min	≥25/min	
Heart rate	≥ 110/min	Bradycardia	<i>and/or</i>
SpO₂	> 92%	< 92%	
PaO₂	> 8 kPa	< 8 kPa	
PaCO₂	Lowered (< 4.6 kPa)	Normal (4.6 – 6.0 kPa)	Requiring mechanical ventilation and increased inflation pressures
Other	No features of life-threatening asthma	Silent chest Hypotension Dysrhythmias	

Table 1. Levels of acute asthma severity in adults (from 13). * % of best or predicted PEF

asthma each year in the UK and about a third of deaths are in people under 65. An estimated 75% of admissions for asthma are avoidable and as many as 90% of the deaths from asthma are preventable (14).

Most patients who die from asthma have chronically severe asthma and most deaths occur before admission to hospital. Patients with severe asthma and one or more adverse psychosocial factors (such as psychiatric illness, alcohol or drug abuse, illness denial or unemployment) are at greater risk of death. Most attacks of asthma severe enough to require hospital admission develop relatively slowly over a period of six hours or more. Peaks of asthma deaths occur in younger people (up to age of 44 years) in July and August, and in older patients in December and January (13).

The severity of an acute asthma attack can be graded by clinical appearance and physiological measurements as set out in the table 1. Predicted PEF values should only be used if the recent best PEF within the last 2 years is unknown.

All patients with acute severe asthma require urgent correction of hypoxaemia with high concentrations of inspired oxygen (BTS guidelines state 40-60% FiO₂). Unlike COPD, there is little chance of precipitating carbon dioxide retention in acute asthma. The aim is to achieve an SpO₂ of at least 92%. Inhaled high dose β₂ agonists act quickly, have few side effects and are at least as efficacious by this route as by intravenous administration in adult acute asthma in the majority of cases (15). The bolus dose regime is 2.5 – 5mg repeated at 15 - 30 minute intervals. Oxygen-driven nebulisers are the preferred method of delivery although the absence of this should not prevent β₂ agonist therapy from being administered where appropriate. Continuous nebulisation (5 - 10mg/hour) should be considered in patients with severe asthma that is poorly responsive to bolus therapy. In the pre-hospital environment, β₂ agonists may be delivered from measured dose inhalers via large volume spacers (4 - 6 puffs per dose, repeated at 10 - 20minute intervals). Nebulised ipratropium bromide 0.5mg 4 - 6 hourly should be given to patients with severe or life-threatening asthma or those with a poor initial response to 2 agonists.

Oral prednisolone is as effective as injected steroids provided they can be swallowed and retained. The dose of corticosteroids should be 40-50mg prednisolone daily (or IV hydrocortisone 100mg every 6 hours) and should be continued for at least 5 days or until recovery. Following recovery from the acute exacerbation the oral prednisolone may be stopped abruptly; a tapering dose regime is unnecessary if the patient is receiving inhaled steroids (unless the patient is on a regular maintenance

dose) (13). A single dose of 1.2 – 2.0g IV magnesium sulphate over 20 minutes should be considered in patients with acute severe asthma with a poor initial response to conventional therapy and all those with life-threatening or near-fatal asthma.

Aminophylline is associated with significant side effects and has a narrow therapeutic range. Some individuals may gain additional benefit although it should only be used after consultation with senior medical staff. If used the loading dose is 5mg/kg over 20 minutes (unless the patient is on oral maintenance therapy) then an infusion of 0.5 - 0.7mg/kg/hour. Blood levels for patients taking oral therapy should be checked on admission and subsequent levels checked daily if treatment is continued. Side effects include palpitations, arrhythmias and vomiting, and are increased when using intravenous aminophylline. Intravenous fluids for rehydration and correction of electrolyte disturbances may be indicated for some patients. Hypokalaemia may be exacerbated or caused by 2 agonist or steroid therapy, and may require an intravenous infusion to correct it.

Indications for admission include any feature of a life threatening or near fatal attack, or those with severe asthma with persisting features after initial treatment. Admission for patients who are improving (PEF >75% best or predicted after 1 hour) is also appropriate in presentation at night, pregnancy, if there are concerns regarding compliance, a previous history of 'brittle asthma' or significant attacks requiring hospital admission or other psychosocial issues such as social isolation (13).

Critical care involvement is indicated in cases of respiratory arrest or where patients require ventilatory support and those with severe or life-threatening features who are failing to respond adequately to treatment. Such features include deteriorating PEF, persisting or worsening hypoxia or hypercapnia, exhaustion, confusion, drowsiness or coma. Not all such patients require intubation and ventilation. Non-invasive ventilation is now well established as a safe and effective alternative in some patients. All patients who require transfer to a critical care unit should be accompanied by a doctor suitably equipped and skilled to intubate if necessary (13).

Question 5

a. The three most likely diagnoses based on the information provided would be:

- Malaria.
- Dengue fever.
- Meningitis/encephalitis.

The history and illness timing most support a diagnosis of malaria.

Dengue virus is transmitted by the bite of an Aedes mosquito and symptoms appear in 3-14 days (average 4-7 days) after the

infective bite. Dengue fever is a severe, flu-like illness that mainly affects infants, young children and adults. There is no specific treatment for dengue fever. This case may also represent sepsis unrelated to foreign travel with primarily neurological features consistent with meningitis or encephalitis.

Other causes may be suggested including HIV where sexual contact with a high-risk partner was involved or typical tropical illnesses with diarrhoeal symptoms, such as cholera.

- b. Initial laboratory investigations that should be carried out include:
- Thin and thick peripheral blood smears to examine for parasites.
 - Rapid diagnostic tests: such as ParaSight F, ICT-Malaria Pf, OptiMALr, and Kat-Quick (for the detection of *P falciparum* only).
 - Urea and electrolytes.
 - Urine and blood cultures.
 - Pregnancy test in females.
- c. Most complications from malaria are the result of *P falciparum* infection and include cerebral malaria, seizures, renal failure, haemoglobinuria, non-cardiogenic pulmonary oedema, lactate acidosis from microvascular blockages, severe anaemia and coagulopathies.
- d. Cerebral malaria requires urgent treatment. In severe cases of *P. falciparum* malaria intravenous therapy should be given and in all such cases it is safer to presume drug resistance and start on drugs other than chloroquine, as waiting for a response to chloroquine may increase the risks for the patient. Quinine remains an effective first choice of antimalarial against *P. falciparum*, although in parts of SE Asia there is a decline in its sensitivity. Available evidence shows that quinine concentration profiles are similar with both intravenous and intramuscular administration, although sample sizes might have been insufficient to rule out clinically important differences. No clinically important difference on mortality is noted between high initial loading dose and no loading dose regimes and, although high initial dose quinine may clear parasites more rapidly, it increases the risk of adverse effects, compared with lower dose quinine (16). The World Health Organisation (WHO) currently advise a loading dose of quinine 20mg (salt)/kg followed by a total daily maintenance dose of 30mg (salt)/kg (usually divided into three equal administrations at 8 hour intervals). If an intravenous infusion cannot be safely administered then the intramuscular route is a satisfactory alternative. Quinine therapy may exacerbate hypoglycaemia. The use of artemisinin derivatives for severe malaria in adults is also recommended outside malaria endemic areas – see discussion below (17).

Discussion

Malaria is considered the most deadly vector borne disease in the world and remains an enormous international medical issue, with 300-500 million cases annually reported. It is most prevalent in rural tropical areas below elevations of 1000 m (3282 ft) but is not limited to these climates (18). Severe malaria is a medical emergency and mainly affects children under 5 years, non-immune travellers and migrants to endemic areas who have not developed partial immunity. Although the situation is improving, malaria is a significant public health problem in Thailand, especially in the forest regions bordering Cambodia and Myanmar. In 2005 there were 29,782 cases of malaria overall, around 50% of which were *P falciparum*. 6,212 cases were severe and there were 71 deaths (19).

Four parasitic protozoa of the genus *Plasmodium* cause human malaria: *P ovale*, *P vivax*, *P malariae* and *P falciparum*. Of these, *P falciparum* causes the most severe morbidity and mortality. *P falciparum* is found mostly in the tropics and, along with *P vivax*, accounts for 95% of malarial infections diagnosed worldwide. *P vivax* is distributed more widely than *P falciparum*, but it causes less morbidity and mortality. All four species are transmitted through the bite of an infected female *Anopheles* species of mosquito. Malaria also can be transmitted via a blood transfusion or congenitally between mother and foetus, although these forms of infection are rare. Replication of the protozoa induces haemolysis and causes the release of toxic metabolites into the bloodstream resulting in cyclical flu-like symptoms in the host, as well as jaundice and anaemia.

Energy for the malaria parasites is derived solely from glucose and is metabolised 70 times faster than the red cells they inhabit, resulting in hypoglycaemia and lactic acidosis. They also metabolise haemoglobin and other red cell proteins to create a toxic pigment termed hemozoin. *P falciparum* causes adhesion of infected red blood cells to the endothelial walls of small vessels in the brain, gut and other organs. This process is known as sequestration and can lead to life-threatening features of severe malaria, such as coma and acidosis.

The patient usually remains asymptomatic for a week or more after the infecting mosquito bite. Initial symptoms include cough, fatigue and malaise, shaking chills, arthralgia and myalgia. Classic paroxysms begin with a period of shivering and chills lasting for around 1 - 2 hours followed by a high fever. The patient then experiences excessive sweating, and the body temperature of the patient drops to normal or below normal. Physical signs that may be noted with malaria include tachycardia, fever, hypotension, anaemia, splenomegaly and jaundice (18). Fundoscopy may also reveal signs of malarial retinopathy including papilloedema, vessel changes, retinal haemorrhages and retinal whitening which may be used to confirm the disease (20).

Severe malaria may be defined by the presence of clinical or laboratory features including impaired consciousness, respiratory distress, jaundice, haemoglobinuria, severe anaemia, hypoglycaemia, acidosis, renal impairment or hyperparasitaemia (17).

Initial investigations should include a full blood count, electrolytes and renal function tests, pregnancy test, urinalysis, free serum haptoglobin and urine and blood cultures. Polymerase chain reaction (PCR) is very specific and sensitive if available. Several rapid diagnostic tests (RDT) are also available although these tests are useful in detecting only *P falciparum* infections. RDTs are based on antibody recognition of the HRP-2 antigen of *P falciparum* and, in most cases, it has been found to be as specific as microscopy studies (18). However, thick and thin peripheral blood smears are the principle investigation for malaria detection and should be sent to the laboratory immediately. One negative smear does not exclude malaria as a diagnosis and several more smears should be examined over the initial period. A chest x-ray may also be helpful if respiratory symptoms are present and a CT scan of the head should be considered in cases of neurological involvement in order to detect evidence of cerebral oedema or haemorrhage.

Initial treatment is supportive, with resuscitative airway, breathing or circulatory interventions as necessary. Life threatening anaemia may require urgent blood transfusion. Hypoglycaemia often occurs in young children and pregnant women and will require rapid detection, treatment and monitoring. Antipyretics, such as paracetamol or NSAIDs, are indicated to reduce pain and fever. However, NSAIDs should be used with caution if bleeding disorder or significant

haemolysis is suspected. If a patient is diagnosed with *P falciparum* malaria with a parasitaemia greater than 10% or if the patient is experiencing life-threatening complications (coma, respiratory failure, coagulopathy or fulminant kidney failure), then investigate exchange transfusion as a treatment option (18).

Quinine is still the initial drug of choice for severe malaria although a recent multicentre study from SE Asia demonstrated a significant reduction in mortality from severe malaria using IV artesunate (one of the artemisinin class of drugs) compared to IV quinine (21). With a growing body of evidence demonstrating reduced mortality, the WHO now advises the use of artesunate in low malaria transmission areas, or outside malaria endemic areas, to treat severe malaria in adults. The recommended dose of artesunate is 2.4mg/kg IV or IM at admission, then at 12 hours and 24 hours, then once a day. It is also associated with less risk of hypoglycaemia compared to quinine, especially in pregnant women (17). Specific advice should always be sought from a specialist in infectious or tropical diseases.

The mortality of untreated severe malaria is thought to approach 100%. With antimalarial treatment mortality falls to 15-20% overall (17). As many as 30% of non-immune adults infected with *P falciparum* suffer acute renal failure. Non-cardiogenic pulmonary oedema may also occur, most commonly in pregnant women, with a mortality of 80% (18). Severe malarial anaemia has a mortality rate of over 13%.

Cerebral malaria, causing encephalopathy and coma, is fatal in around 20% of children and adults, and neurological sequelae occur in over 2% of survivors (18). None of the ancillary treatments for cerebral malaria have sufficient supporting evidence to be used and the use of mannitol in paediatric or adult cerebral malaria cannot be recommended (22,23).

Pregnant women are up to 10 times more likely to contract malaria than non-pregnant women and also have a greater tendency to develop severe malaria. Children are more likely to present with hypoglycaemia, seizures, severe anaemia, and sudden death, but they are much less likely to develop renal failure, pulmonary oedema, or jaundice (17).

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