

Long Cases In Clinical Medicine

For The Final MBBS

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Case 1

Mr SJ, a 54-year-old clerk, was admitted to hospital complaining of chest pain for 2 hours. He was well, attending to his usual work, when he suddenly developed left-sided tightening chest pain. The pain radiated down his left arm, and was associated with sweating and nausea, but was not made worse by movement or breathing. He felt dizzy, and felt that his heart was thumping. The pain had continued at the same intensity until admission to hospital. He had no difficulty in breathing or cough. He had no previous history of chest pain or shortness of breath on exertion, no pain in the calves when walking or climbing hillocks, and no abdominal pain after a heavy meal.

Three years ago he had had an episode of weakness involving the left side of the body, which had resolved after about an hour. During that admission he had been found to be hypertensive and hypercholesterolaemic, and was commenced on enalapril, hydrochlorothiazide, atorvastatin and aspirin. He had been followed up in the medical clinic, and was compliant with his medications. He does not have diabetes mellitus, or any other medical problem, and had no known allergies. He had not undergone any surgeries in the past.

His father had been diagnosed to have hypertension at the age of 53 years and had died of a heart attack at the age of 74 years. Mr SJ had smoked five cigarettes daily, totaling four pack-years, and consumed 1/4 bottle of spirits daily, which was about five units a day. He lived with his wife, who was a schoolteacher, and his 20-year-old daughter who was planning her wedding, which was in two weeks time.

On examination he was in pain, intensity of 8/10 on a pain scale of 0-10, (0 being no pain and 10 being excruciating pain), but was not dyspnoeic at rest. His body mass index was 29. There were no xanthomas palpebrae, and there was no pallor, or peripheral or central cyanosis. He had no ankle oedema. His pulse rate was regular, good volume, at 80/min, all peripheral pulse were felt, and blood pressure was 140/80mmHg, equal on both arms. The jugular venous pressure was not elevated. His heart was in dual rhythm, and there were no cardiac murmurs, added heart sounds, or carotid bruits. The respiratory rate was 18/min and oxygen saturation was 98% on room air. Examination of the lungs and abdomen were normal. Fundoscopy revealed changes of grade 1 hypertensive retinopathy.

Would you like to Summarize the Case?

A 54-year-old male with acute onset cardiac sounding chest pain brought on at rest, for 2 hours duration. He had a history of hypertension, hyperlipidemia and transient ischemic attack (TIA), and is currently on enalapril, HCT, atorvastatin and aspirin. He has smoked four pack years, and drinks alcohol above the recommended limit. On examination was in severe pain, but rest of the examination was normal except for grade 1 hypertensive retinopathy; he was normotensive and not in heart failure.

What Diagnosis Would you Consider?

The clinical history suggests that this is cardiac chest pain. This is supported by his risk factors (smoking, hypertension, hyperlipidemia, family history and overweight) and the history of a previous vascular event, i.e., TIA. Since this is of acute onset, and the patient has not had angina before, this would most likely be an acute coronary syndrome (ACS). ACS includes 3 conditions: unstable angina, NSTEMI and STEMI. Investigations help to differentiate these, as they cannot be clearly differentiated on clinical grounds.

be considered, since the risk factors are similar. Examination of all the peripheral pulses and checking blood pressure on both arms is a must. During a dissection of the ascending aorta, the dissection can cut through the origins of the coronary arteries, thus giving rise to concomitant MI.

Any other possibilities?

Mr SJ had pulses on both arms and the femoral pulses were felt, with good volume; blood pressure on both arms was 140/80mmHg. The pain in aortic dissection is often very severe and radiates to interscapular area, and the patient could be haemodynamically unstable, which is not the case here.

Other possibilities to be ruled out would include pulmonary embolism (PE) and pneumothorax, though one would expect the patient to be breathless in those conditions. In PE, the pain is often pleuritic in nature and the patient could have a unilateral swelling of a calf suggesting co-existing deep vein thrombosis (DVT). I would expect lung signs if it was a pneumothorax. Gastro-oesophageal reflux disease and musculoskeletal pain are also possible causes, lower down in the list.

Let's discuss his acute management, if you were the house officer on call when this patient was admitted.

With a working diagnosis of ACS, Mr SJ would require prompt assessment, bed rest, and urgent treatment. I will insert a cannula, preferably a large bore one, take blood for basic investigations, give him oxygen by mask, and since he is in pain I will give him morphine 2.5mg-5.0mg intravenously, with a suitable anti-emetic such as IV metoclopramide 10mg. With the clinical diagnosis of ACS, I will give him loading doses of soluble aspirin 300mg and clopidogrel 300mg orally. I will arrange for an urgent ECG, and plan to do a troponin at 6 hours after the onset of chest pain. I will

also do random capillary blood glucose, arrange for a portable chest x-ray to rule out pneumothorax, and to look for complications like pulmonary oedema. My further plan would depend on the findings on his ECG.

Would you give him morphine intravenously or intramuscularly?

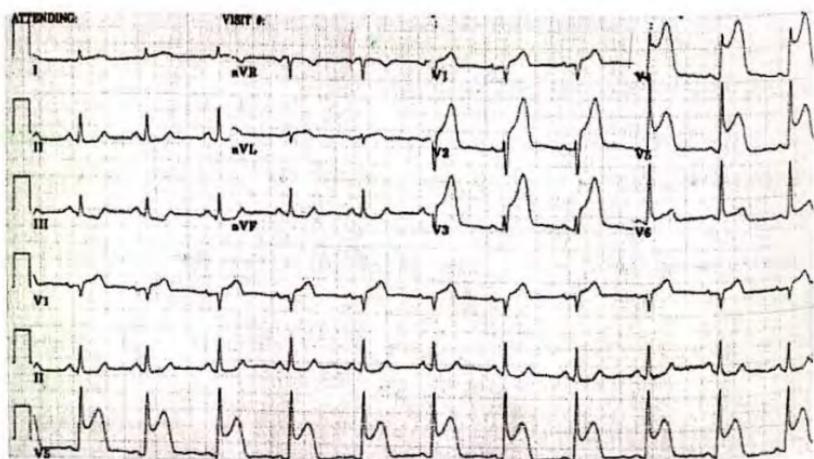
Wouldn't intramuscular morphine be adequate?

I would give morphine intravenously. I would avoid intramuscular injections, in case he requires thrombolysis, as this will result in a painful haematoma at the site of the injection.

How does morphine help in an acute MI?

First of all, it will alleviate the pain. Morphine is also an anxiolytic and will reduce the anxiety and restlessness of the patient, thus reducing the load on the heart. It also is a respiratory depressant, and thus would reduce the work of breathing. By these mechanisms it will reduce myocardial oxygen demand. If there is associated LV failure, morphine will help by causing pulmonary venodilatation and reducing venous return to the left heart, resulting in reduced preload, and thus reduced cardiac workload.

This is the patient's ECG. What are your comments?



The most striking abnormality is the presence of saddle shaped ST elevations in the anterior leads, i.e., leads V1-V6, with some reciprocal changes in the inferior leads. He is in sinus rhythm. This is compatible with an acute anterior STEMI.

What will you do next?

The likely diagnosis here is acute ST segment elevation myocardial infarction (STEMI). There are two options of treatment, i.e., thrombolysis, or primary percutaneous coronary intervention (primary PCI). Primary PCI is not always available, but I will discuss with the on-call cardiology team whether primary PCI could be arranged. If not, I will consider Mr SJ for intravenous thrombolysis.

What drugs are used for thrombolysis?

There are several thrombolytic agents. Streptokinase is the most commonly used agent in Sri Lanka. The ISIS-2 Trial was the first trial to show survival benefit with streptokinase in acute MI. This trial showed a 25% reduction in mortality with streptokinase. Other trials have shown similar benefits with thrombolytic agents. The sooner thrombolysis is administered, the greater the benefit. There are several other thrombolytic agents recommended following MI. These are fibrin specific thrombolytics such as tenecteplase or alteplase (rt-PA).

I will inform Mr SJ of ECG findings and the diagnosis, the treatment options, and after excluding any contraindications for thrombolysis, I will prescribe streptokinase 1.5 million units in 100ml normal saline over 1 hour, with verbal consent. The sooner it is administered, the greater the benefit to the patient. I would aim for a door-to-needle time (i.e., the time from arrival of the patient to the hospital till intravenous treatment is commenced) of 30 minutes. Intravenous thrombolysis can be used within 12 hours of the onset of STEMI (ideally 6 hours) and Mr SJ is well

What are the contraindications for intravenous thrombolysis?

The main side effect of streptokinase is bleeding, as it is a fibrinolytic agent. Previous haemorrhagic stroke, subarachnoid haemorrhage or ischemic stroke within the past 6 months, brain tumours, active internal bleeding within the past two weeks, and aortic dissection, are absolute contraindications. Severe uncontrolled hypertension, with blood pressure greater than 180/110mmHg, recent major trauma or surgery within the past 4 weeks, pregnancy, active peptic ulcer disease, oral anticoagulation, traumatic cardiopulmonary resuscitation, and allergy to streptokinase, are relative contraindications. If any contraindications are present, I will discuss again with the on-call cardiologist for primary PCI.

What side effects or complications would you look for while administering streptokinase?

Common side effects of thrombolytics are nausea, vomiting and bleeding. Reperfusion arrhythmias, recurrent ischaemia, pulmonary oedema and hypotension may occur. Hypotension could be due to anaphylaxis to streptokinase, though a minor degree of hypotension is not uncommon and responds to leg elevation and slowing down of the infusion. If hypotension is significant I will stop the infusion, administer hydrocortisone 200mg intravenously and an antihistamine, and consider restarting the infusion if the patient is stable. Reperfusion arrhythmias occur due to re-establishment of myocardial circulation by thrombolysis, predisposing the myocardium to arrhythmias, which could be atrial or ventricular, tachy or brady-arrhythmias. Therefore I would monitor the patient using a cardiac monitor, and treat arrhythmias if they should occur.

Mr SJ was treated with streptokinase and improved. His CK-MB level the next day was very high. What does this indicate?

It suggests that he had myocardial damage which caused cardiac biomarkers (CK-MB and Troponin) to be released into the circulation. The high value indicates reperfusion had been successful. Serial

cardiac biomarkers should decline rapidly, and I would also expect his ST segment elevations to return to baseline after thrombolysis.

What other medications would you start him on?

Antiplatelets should be commenced. Mr SJ was given loading doses of aspirin and clopidogrel on admission. Other drugs, such as glycoprotein IIb/IIIa inhibitors are given in patients undergoing primary PCI or in some patients with unstable angina or non-STEMI. Anticoagulants such as unfractionated heparin, low molecular weight heparin or fondaparinux may be indicated along with thrombolysis in STEMI, although these are not commonly used unless the patient does not respond to thrombolysis with streptokinase, and continues to have cardiac chest pain. Mr SJ was on aspirin 75mg daily on admission to the hospital. I will continue aspirin and add clopidogrel 75mg daily after the loading doses. If he continues to have chest pain I will consider this as post MI angina or poor response to thrombolytic therapy, and will start him on an anticoagulant like subcutaneous fondaparinux or low molecular weight heparin according to his body weight. Post MI angina is a form of unstable angina, and he will require further expert input if this occurs.

Beta blockers have been shown to prevent sudden cardiac death occurring within the first year after an MI by reducing cardiac tachyarrhythmias. Therefore I will start him on oral bisoprolol 2.5mg if there is no bradycardia, hypotension or evidence of acute heart failure. ACE-inhibitors have an effect on ventricular remodeling, and are cardioprotective, i.e., will prevent the development of heart failure later on. Mr SJ was already on enalapril, and if blood pressure and renal function are ok, I will increase the dose, but will at least maintain his regular dose. Mr SJ is already on atorvastatin, and I will increase it to 80mg daily as the

I will continue oxygen, bed rest and cardiac monitoring during the initial 24 hours. I will also prescribe GTN spray to use if he develops angina.

Could you mention some side effects and precautions with these drugs?

These drugs are relatively safe in this context and evidence based. Asthma would be a contraindication for using a beta-blocker. I would check his renal function prior to increasing his ACE-inhibitor enalapril. Statins can cause elevated liver enzymes, and also cause rhabdomyolysis in a small number of individuals. I will ask Mr SJ whether he had muscle pains and cramps with atorvastatin, and monitor his CPK and ALT levels. ACE-inhibitors can cause cough in up to 15% of individuals; if he has a tickly cough I will switch over to an angiotensin receptor blocker (ARB), such as losartan.

Tell me about the non-pharmacological management of this patient.

He requires lifestyle modification. I will advise him to stop smoking, as smoking will increase his risk of future MI as well as stroke and peripheral vascular disease. He should lose weight, and I will advise him on a low salt, low fat diet tailored to lose weight. I will advise him to exercise regularly – ideally aerobic or cardiovascular exercise for 30 minutes per day on 5 days of the week. He will have to start this gradually, depending on the level he tolerates. He also appears to be drinking above the recommended limit, and I would advise him to cut down his drinking to less than 21 units of alcohol per week.

Are there any further investigations you would do at this stage? If they have not been already requested, I would do his renal function, urine for proteinuria and red cells, liver function, ESR, fasting glucose and fasting lipid profile. Ideally the fasting lipid profile should be done within 24 hours of his admission.

or else the values could be falsely low. I will also arrange for an echocardiogram, to establish the degree of myocardial damage, identify valvular dysfunctions and to rule the rare complication of pericardial effusion.

What target blood pressure would you aim for?

Mr SJ was diagnosed with hypertension 3 years ago when he was admitted with a TIA. He has no diabetes and no evidence of proteinuria, so the standard target for hypertension control would be 130/80mmHg. If he did not have the history of TIA the target would be 140/90. I would titrate the anti-hypertensives to achieve target blood pressure level.

Would you prescribe him sublingual nitrates to take if he gets angina?

After an MI, there is usually no post-infarction angina, as the ischaemic area is infarcted. If the patient gets post-infarction angina, this would be considered unstable angina. Rather than using symptomatic relief with GTN spray, he would require urgent investigation, usually a coronary angiogram, to determine whether he needs revascularisation. Since he had a TIA 3 years ago with a history of hypertension, high cholesterol and a history of 4 pack years of smoking there is likely to be atherosclerosis in other coronary arteries. Therefore, I will prescribe sublingual nitrates to use if needed but would investigate if it occurs.

This gentleman has had a good recovery. However, could you tell us about the other complications after an acute MI?

In the acute stage, arrhythmias are common, usually ventricular tachycardia including ventricular fibrillation. If these occur within the first 24 hours they usually do not indicate a poor prognosis. Heart block can also occur – complete heart block is common after inferior MI as the ischaemia could have involved the AV node, and these usually revert to normal with time, and symptomatic

management with atropine is usually adequate. However in the case of anterior MI, if complete heart block occurs, it usually requires insertion of a pacemaker as it often means the bundle of His is infarcted, and this is unlikely to recover.

Acute LVF is another complication after MI. This is usually due to myocardial stunning or damage, but is sometimes due to papillary muscle dysfunction or rupture of a chorda. The patient will develop sudden difficulty in breathing, difficulty in lying flat in bed or orthopnoea, and non-productive cough. There will not be ankle swelling or increase in jugular venous pressure usually, but he will have bilateral fine crepitations of pulmonary oedema. I would treat this with bed rest, oxygen and loop diuretics given intravenously. If he is on intravenous fluid I will stop them. Other drugs which can be used include nitrate infusions and IV morphine.

The most serious complication in the acute stage is **cardiogenic shock**. This usually indicates severe damage to the myocardium. It is treated with **inotropic agents** and may need **immediate angiogram and revascularisation**. The prognosis is poor. Mortality rates approach 70%.

Late complications after MI include **Dressler's syndrome**, acquired **valvular lesions** due to ruptured chordae or papillary muscle dysfunction, **acquired ventricular septal defect**, **LV aneurysm** formation, **mural thrombi** formation causing thrombotic episodes, and **post-MI unstable angina**.

What is the Killip Classification?

The Killip classification is used to risk stratify patients after MI. It is a **clinical classification based on physical signs of LV dysfunction on examination**. There are 4 classes.

Class I are patients without heart failure and with normal blood pressure. Killip **class II** includes patients with mild to moderate heart failure evidenced by a third heart sound (S3).

bilateral basal crepitations less than $\frac{1}{2}$ the posterior lung field, or elevated JVP, and respond well to medical management of LVF. Class III includes patients with overt LVF. Class IV describes patients with cardiogenic shock and has the worst prognosis.

What is the blood supply of the heart?

The heart is supplied by two coronary arteries, the left and the right coronary arteries, which arise from the left and right aortic sinuses. They are end arteries. The right coronary artery is a long artery which travels down the right atrioventricular groove, and supplies the right ventricle and part of the left ventricle. The left coronary artery has a short main stem and divides into the left anterior descending (LAD) artery and the circumflex artery. These supply the left ventricle predominantly. The LAD artery is the main vessel supplying the anterior surface of the heart. Thus, in practice, the heart is considered to have 3 principle vessels supplying it, leading to the terms double vessel or triple vessel disease. The posterior descending artery supplies the ventricular septum. It arises from the right coronary artery in 70%, from the left circumflex artery in 10%, and from both of these in the remainder. The term coronary artery dominance is used to describe which artery supplies the posterior descending artery. If it is supplied by the right coronary artery it is referred to as right dominance. If it is by the left then it is called left dominance and if by both, co-dominance. In the normal heart, the arteries have no collaterals, but when ischaemia is present, collaterals develop.

How does one get a heart attack?

The basic pathological problem is atheroma, i.e., the formation of atheromatous plaques on the inside of the coronary vessels. These have a lipid rich core and a fibrous cap. The triggering event in an MI is plaque rupture. When the plaque ruptures, the lipid rich core, which is highly atherogenic, is exposed. This results in the formation of a thrombus on the ruptured plaque. If this is a

non-occlusive thrombus, the patient develops unstable angina. If it occludes the vessel, the area distal to the occlusion gets infarcted, and this results in myocardial infarction.

Are there any further investigations that this patient needs?

He has had what sounds like a TIA in the past. Thus he will need to have a carotid Doppler to identify if there are any carotid artery plaques. If there is significant carotid stenosis this may need revascularization if he is having cardiac revascularization at the same time to reduce the risk of further stroke. With long-standing hypertension and hypertensive changes in the eye I would arrange an ultrasound scan of the kidneys to see whether there is radiological evidence of renal involvement due to hypertension.

What is the pathophysiological basis of developing pulmonary oedema?

It is usually due to ischaemic damage of left ventricle leading to the left ventricle failing to pump blood out of the heart in to the systemic circulation. There is a resultant increase in pulmonary venous pressure, which results in transduction of fluid into the interstitium of the lung. Breathlessness occurs due to increased stiffness of the lungs, and in extreme situations due to flooding of the alveoli causing impaired gas transfer.

When would you discharge him from hospital?

I would keep him in hospital for 5-6 days if he does not develop any complications. I will start weaning him off oxygen and gradually mobilizing him, helping him to get back home, pain free, with medications optimized. I understand he has a busy time ahead with his daughter's wedding and would advise the importance of adhering to medication, graded exercise and not smoking or drinking excessively. Ideally a limited exercise ECG should be performed prior to discharge, but this is not always practical.

What is the long-term follow up?

Mr SJ should be followed up in 2 weeks, and regularly thereafter. He is best followed up by the cardiologist and I will refer him if possible. His ischemic burden should be evaluated, along with possible benefit of revascularization. He should have an echocardiogram after 6 weeks to look at left ventricular function and for persistent segmental wall motion abnormalities like LV aneurysm formation and mural thrombi. He should also ideally have a stress test by way of exercise ECG or stress echo, to determine whether there is ongoing ischaemia. In a tertiary center it maybe possible to organize a thallium scan, cardiac MRI scan, or coronary angiogram as appropriate, considering availability and indications.

When can he return to work/driving and sexual activity?

Mr SJ had an uncomplicated MI and it should be safe to drive his car/motor cycle after one month. He works as a clerk. I would advice him to get back to work after 2-3 months. Mr SJ should start with less challenging duties at first, with additional rest periods if tired, and to gradually get back to his normal routine over about 2-3 weeks.

It is safe to postpone sexual activities for few weeks until he is able to walk without chest pain. If there is chest pain with sexual activity, or if there is sexual dysfunction, this should be discussed at his follow-up clinic visit. Sexual dysfunction could be due to emotional stress or due to side effects of medications, like beta-blockers causing impotence.

Case 2

Mrs KK, a 76-year-old woman, presented with fever and cough for three days, and shortness of breath for one day. She had had high fever, although she had not measured her temperature. The fever had been intermittent over the past 3 days, associated with headache, bodyaches and loss of appetite. She also complained of intermittent cough, and had been producing small amounts of sputum for the same duration. Her cough did not vary with the time of day, and was not postural. There was no chest pain or haemoptysis. She had had slight right upper abdominal pain over the last two days. This was not related to meals, and there was no nausea, vomiting, yellowish discolouration of her eyes, or change in bowel habits. She did not complain of dysuria, haematuria, frequency, nocturia or lower abdominal pain.

On the day of admission she developed sudden onset shortness of breath while lying in bed, which progressively worsened until she was brought to the hospital. There was no associated chest pain, palpitations or pink frothy sputum at the onset, but she sounded very wheezy, according to her relatives. After admission she was given oxygen and several injections, and was nebulized. She felt much better the next day, had no fever or cough, and only very slight breathing difficulty at the time I saw her.

Mrs KK had been suffering from painful swelling of both knee joints which started in the right knee four years ago, and progressed to involve the left knee about one year back. She was

investigated with blood tests and an x-ray of the knee joints, and was treated with an injection into the right knee joint. The pain in her knee joints was less on waking, and worsened throughout the day. There was no involvement of other joints, or morning stiffness. She was registered in the rheumatology clinic but she did not regularly attend. She had been continuing the analgesics initially prescribed from the clinic. She had been diagnosed to have hypertension around 3 years ago, and started on treatment. She was being regularly followed up in the general medical clinic, and appears to have been compliant with treatment. Mrs KK had noticed intermittent tightening-type central chest pain on exertion, relieved by rest, for the last 2 years but had never considered it to be severe enough get admitted to hospital for investigations. She had been investigated as an outpatient with an echocardiogram and an exercise ECG, and had been told that she had heart disease, but was not aware of the exact condition. One year ago she had had an episode very similar to the current presentation. Her exertional dyspnea had worsened since then. She was unable to climb more than a single flight of stairs, and was out of breath when walking 20 metres. She also complained that she felt breathless when lying flat, and had to prop herself up with two pillows. There had been no instances of paroxysmal nocturnal dyspnoea however. She had also noted bilateral ankle swelling, but had not noticed any facial puffiness on waking. She did not have diabetes or hyperlipidemia, and had no history of asthma.

to her activities of daily living. She is accompanied by one of her children on her clinic visits.

Can you summarize your history?

Mrs KK is a 76-year-old lady presenting with fever and cough for three days and shortness of breath for one day, associated with poor appetite, headache, bodyaches and right upper abdominal pain. She had had hypertension for three years and was suffering from exertional chest pain for around 2 years, and exertional dyspnoea, orthopnoea, and dependent oedema for 1 year. Apart from these symptoms, she had bilateral knee joint arthritis, with symptoms suggestive of osteoarthritis. She had had a previous hospital admission for similar symptoms, and she is generally complaint with medications. She had good family support and was managing her activities of daily living independently.

What are the differential diagnoses at the end of your history?

This is an elderly woman with a history suggestive of ischaemic heart disease (tightening chest pain on exertion, had been told that her echo and exercise ECG were not normal, no history to suggest valvular heart disease), possible congestive heart failure (hypertension, exertional dyspnea, orthopnoea), presenting with fever, cough and constitutional symptoms. The current presentation appears to be due to chest infection on a background of heart failure. Analgesic use for the knee joint problem might have contributed to fluid retention. There have been no features to suggest a primary respiratory problem, there is no history of asthma, and although I omitted to mention it, she is a non-smoker.

I would like to consider lower respiratory tract infection (pneumonia or bronchitis), in view of the fever and productive cough. However, she clearly has features suggestive of heart failure, and it is likely that the chest infection has resulted in an exacerbation of heart failure. Although an infective exacerbation of chronic lung disease could be considered in the differential

diagnosis, this is less likely as the patient has no history of lung disease. Other reasons for worsening heart failure which should be considered include acute coronary syndrome and infective endocarditis. In view of the fever, I would bear in mind the possibility of other febrile illnesses and bacterial sepsis.

You mentioned that she had developed right hypochondrial pain. What could this be due to?

This could be due to congestion of the liver. Other possibilities are that there is an independent process going on in the liver or gall bladder resulting in fever – this is less likely given the features of the case.

In heart failure, venous congestion occurs as a result of an increase in venous hydrostatic pressure as well as fluid overload. This could lead to congestion of the liver, and stretching of the liver capsule can result in discomfort or pain. Given that there is fever, there is a possibility of a liver or gall bladder pathology, but I think this is less likely.

What is the mechanism of paroxysmal nocturnal dyspnoea?

In paroxysmal nocturnal dyspnoea, the patient goes to sleep, but wakes up suddenly in the night with severe dyspnoea, which is relieved by sitting up. During sleep, blood is redistributed from the legs to the upper body, resulting in an increase in central and pulmonary blood volume. This increased venous return in a patient with congestive heart failure results in increasing pulmonary oedema, which goes unnoticed for some time because of reduced awareness during sleep. At one point it wakes the patient up in a state of severe breathlessness. Other contributory mechanisms are thought to be the compression of the bronchial tree due to increased pressure in the bronchial vessels, and also the fact people who are propped up slide down to the flat position during sleep.

Shall we proceed to the examination findings?

Mrs KK is dyspnoeic at rest and looks ill, and is propped up in bed. She is afebrile, not pale or icteric, not cyanosed or clubbed. There is bilateral pitting ankle oedema. Both knee joints showed soft tissue swelling but no warmth or effusions. There was crepitus in both knee joints and limitation of range of movement in flexion. There was no muscle wasting around the knee joints. The other joints were normal.

Her pulse was regular, collapsing, with a rate of 84/minute. Blood pressure was 160/60mmHg. All peripheral pulses were present. Over the femoral arteries 'pistol-shot' sound and 'Duroziez's sign' were present. Jugular venous pressure was raised. The cardiac apex was in the sixth intercostal space at the left anterior axillary line. It was thrusting in nature. The pulmonary second heart sound was loud. I could hear two murmurs: a pan systolic murmur best heard over the mitral area, and an early diastolic murmur best heard over the aortic area. The respiratory rate was 18/min, and the trachea was in the midline. Her chest expansion, vocal fremitus and percussion of the chest were normal. There were bilateral fine crackles over both lung bases. There was smooth tender 3cm hepatomegaly, and the spleen was not palpable. The upper border of the liver was not shifted down. There was no clinical evidence of ascites. Neurological examination was unremarkable, and her fundi were normal apart from the presence of silver wiring.

According to your history and examination what are the cardiovascular problems she is likely to have?

She has cardiomegaly and both systolic and diastolic regurgitant murmurs, with peripheral signs of aortic regurgitation (collapsing pulse, wide pulse pressure) and congestive heart failure. This is most likely due to...

possible that she has rheumatoid arthritis, which is known to cause valve incompetence in some cases? This is less likely, because she has none of the other features of rheumatoid arthritis, i.e., polyarticular involvement, morning stiffness.

It is likely that her symptoms are due to heart failure, probably made worse by a chest infection. She has signs of biventricular heart failure and both mitral and aortic regurgitation. One possibility is that her hypertension resulted in left ventricular strain, hypertrophy and subsequent dilatation, resulting in valve incompetence. It is also possible that she had valvular heart disease to begin with, later resulting in heart failure, contributed by hypertension. It is not possible to determine the cause of the valve lesion from the history and examination.

What are the causes of mitral regurgitation?

Mitral regurgitation could be acute due to ischemic heart disease causing damage to chordae tendinae or papillary muscle rupture. Chronic mitral regurgitation occurs due to rheumatic heart disease, previous infective endocarditis, myxomatous mitral valve that occurs with mitral valve prolapse, cardiac dilatation as a result of ischaemic heart disease or hypertension, or dilated cardiomyopathy. Her joint problem is not suggestive of rheumatic heart disease. Rheumatoid arthritis can cause valve incompetence, both mitral and aortic, however she has none of the classical features of rheumatoid arthritis...

....and what are these classical features?

Well, morning stiffness and other joint involvement, or a history of being diagnosed with rheumatoid arthritis.

You did not mention about her weight or build. Can you tell something about that, and why is it relevant?

Although she has oedema, she appears to have reduced muscle mass. I did not measure her weight as she was reluctant to get

down from bed; however it is important to measure her weight in order to monitor response to diuretic therapy. Patients with severe chronic heart failure develop wasting, and this is known as cardiac cachexia. There are many causes for this.

Such as?

In congestive heart failure there can be gut oedema, which impairs gastrointestinal absorption and results in nutritional deficiency. The work of breathing is also greater in heart failure, and more energy is expended. Cytokines can increase the metabolic rate, which also increases catabolism.

What is the mechanism of oedema in heart failure?

Oedema is caused by either increased hydrostatic pressure or reduced colloid osmotic pressure (oncotic pressure) in the capillaries. In heart failure it is mainly due to increased hydrostatic pressure. When there is reduced cardiac output there is increased backpressure leading to raised hydrostatic pressure. Also, in heart failure renal perfusion is affected, and as a result there is increased renin secretion; this is also supported by sympathetic activation. Renin converts angiotensin I to angiotensin II, which in turn stimulates aldosterone secretion. Therefore there is secondary hyperaldosteronism. Aldosterone increases sodium reabsorption in the kidney, leading to increased intravascular volume and hydrostatic pressure.

Based the history and examination what do you think is the reason for her acute presentation?

I think the most likely cause is acute exacerbation of chronic heart failure resulting from respiratory tract infection. But there could be other precipitating factors....

What other factors could cause de-compensation of chronic heart failure?

Any infection will result in stress and increased workload on the heart. Other causes include acute coronary syndrome, or cardiac arrhythmias, changes in drug regimen, non-adherence to medications, and taking medications which increase fluid retention, in particular NSAIDs. Binge drinking can also make heart failure worse. Infective endocarditis is another cause.

What are the common causes for heart failure? What do you think is affecting her?

Ischaemic heart disease is one of the commonest causes. Chronic hypertension can lead to heart failure, initially diastolic failure, but later on cardiac dilatation occurs and systolic failure can develop. There are several different types of cardiomyopathies which can result in heart failure. These are classified as restrictive, obstructive or dilated cardiomyopathies. Dilated cardiomyopathy could be autoimmune in origin, or could follow viral infections. Long standing valvular heart disease can also result in volume or pressure overload and heart failure.

But this patient does not give a history of acute myocardial infarction....

Yes, but chronic cardiac ischaemia can result in long-term

Long-standing medical problems include:

- hypertension
 - chronic heart failure
 - mitral and aortic regurgitation
 - bilateral knee joint osteoarthritis
- Her psychosocial problems include:
- Poor understanding of the illness
 - Deteriorating functional status

In the acute setting, how would you investigate her?

I will start with basic investigations - full blood count, c-reactive protein or ESR, serum creatinine and electrolytes, troponin or cardiac enzymes, ECG and chest radiograph. The full blood count will tell me whether she is anaemic (which can worsen heart failure), and a raised white cell count with neutrophil leukocytosis and raised ESR/CRP will suggest bacterial infection. A positive cardiac troponin will indicate that she has acute coronary syndrome,



which will require appropriate management in addition. Chest radiograph will show whether there is evidence of pneumonia, pleural effusions and also features of heart failure. The ECG may show evidence of cardiac arrhythmias, or new ECG changes indicating acute coronary syndrome. The ECG is nearly always abnormal in heart failure. An echocardiogram will be helpful in confirming heart failure but is not essential to make a diagnosis. It will be useful to know her renal and liver functions, the latter in particular because of the enlarged and tender liver. Electrolytes should be monitored in patients receiving heart failure medications.

This is her chest radiograph. What is your impression?

The typical features seen in acute heart failure that I will look for are cardiomegaly, which is seen as increased cardiothoracic ratio (the normal being 1:2), upper lobe diversion of blood (normally the ratio between the caliber of blood vessels in the upper and lower parts of the lung is 1:4. If the caliber is equal in upper and lower zones, this is considered to be upper lobe diversion), perihilar congestion (bat-wing sign), Kerley B lines, and pleural effusions. In this patient I would also look for lobar consolidation suggestive of pneumonia.

There is cardiomegaly, upper lobe diversion and perihilar congestion. I cannot be sure whether there is also evidence of infection.

How would you manage this patient during the acute stage?

I will get her to an acute bed, near the nurses' station. I will allay her anxiety, and connect to a cardiac monitor if available. I will inform my seniors that this is an ill patient. Since she has no history of COPD, I will give her oxygen by mask, the highest concentration I can achieve, to maintain her pulse oxygen saturation over 94%. I will obtain IV access, and take basic blood tests, including cardiac troponin. Since clinically she is in pulmonary oedema, I will give her furosemide 40-80mg IV as a slow bolus, followed by repeated

doses as necessary. I will consider starting a furosemide infusion also if necessary.

Why do you want to give furosemide as a slow bolus? How slow?
If furosemide is given too fast it can result in oto-toxicity. The recommended rate is 4mg/min, so 40mg should be given over 10 minutes.

How does furosemide work?

Furosemide is a diuretic, but it also has vasodilatory properties, and when it is given it causes pulmonary venodilatation. This reduces the pre-load on the heart, which is useful in heart failure. The diuretic effect takes longer to start. Thus when furosemide is given it ameliorates heart failure rapidly.

Go on....

I will consider giving morphine, 2.5-5.0mg IV bolus, with metoclopramide 10mg IV to prevent vomiting. Other drugs which can be given include nitrates and inotropes which will be decided based on the response to initial therapy and her blood pressure. If the response to these is not enough and blood pressure is high, nitrates like glyceryl trinitrate can be given as an infusion. In patients with relatively low blood pressure, inotropes should be started.

Since the most likely cause for her acute deterioration is a superadded chest infection, I will start her on intravenous antibiotics, after taking blood and sputum cultures.

In a patient who is not responding to any of the above measures what are the other possible interventions?

Pressure support for breathing with non-invasive ventilation will cause improvement in pulmonary oedema. Continuous positive airway pressure via a tight fitting mask can be applied. Otherwise intubation and ventilation can be done.

Other than the above measures there are some modalities that are not commonly used in Sri Lankan setting. They include balloon counterpulsation and ventricular assisting devices. Also haemofiltration will clear fluid out from the intravascular compartment and can be used even in patients with normal renal function.

Your patient was nebulised in the ward. Do you agree with that?

Left ventricular failure (LVF) can mimic asthma, hence in the old days it was known as cardiac asthma. Mucosal oedema occurs in LVF and can cause airway narrowing. However there is no proven benefit with nebulization using bronchodilators, and furthermore, salbutamol can cause tachycardia, which can worsen cardiac failure by shortening diastolic filling time. Sometimes, in the acute stage, when wheezes are heard it is difficult to be sure whether there is an element of bronchoconstriction or not, and this is probably the reason why the doctors nebulized her.

There are various methods of classifying severity of chronic heart failure. How will you stage this patient?

There are several methods of classifying the severity of heart failure. One system is the New York Heart Association functional classification, which has four classes. This is described to grade the severity of the disease based on the functional state of the patient depending on the symptoms. This classification is used for patients with chronic heart failure and should not be used on other patients, or during acute deterioration.

In class I the patient does not have symptoms with ordinary activities. In class II the patient has fatigue, palpitations, dyspnoea or angina with normal day-to-day activities. In class III the patient has symptoms with less than ordinary activities. In class IV patient cannot do any physical activity.

There is another classification given in the American Heart Association guidelines, with grading from A-D. In Stage A the patient is at risk of heart failure, but there are no structural disorders of the heart. In stage B there are structural disorders of heart without symptoms. In stage C the patient has structural heart disorders with present or past symptoms. Stage D indicates end - stage disease.

Prior to admission, Mrs KK had shortness of breath during activities less than ordinary activities, but was not dyspnoeic at rest. Therefore she had NYHA class III heart failure. According to the American Heart Association guidelines she is in stage C, as she has cardiac symptoms with structural heart disease.

Why do you say that she has knee joint osteoarthritis?

She gives a history of painful swelling of both knee joints. The pain is mainly after walking, suggestive of a mechanical (rather than inflammatory) cause. Her symptoms started after menopause, involving the knee joints only, with no history of joint stiffness – these all suggest osteoarthritis, which is common. Furthermore, the examination showed no involvement of other joints; the knee joints were swollen without features of active inflammation, suggesting osteoarthritis.

Note that although osteoarthritis is not typically an inflammatory condition, there can be an inflammatory phase. At times patients with osteoarthritis can develop severe pain, stiffness and warm, tender joints.

How can her use of analgesics affect the management her cardiovascular problems?

It is possible that she uses NSAIDs for arthritis. While paracetamol is safe, other COX inhibitors can cause fluid retention and can precipitate or worsen heart failure. Opiates are safe in this context.

What are the changes you expect in her knee joint x-rays?

Narrowing of the joint space, subchondral sclerosis and osteophyte formation are the main x-ray changes seen osteoarthritis.

How would you manage this patient's knee joint osteoarthritis?

There are pharmacological and non-pharmacological methods to manage knee joint osteoarthritis. In obese individuals, weight reduction helps, but this patient is not obese. Exercise aimed at strengthening muscles is of use, and I will teach her quadriceps strengthening exercises. Walking is good, but climbing stairs and running is not. If possible, I will refer her to the physiotherapist for a planned exercise programme. Infrared and ultrasound therapy may be of some use. Analgesics like paracetamol, local NSAID gels (such as diclofenac gel) can be used, and opiate analgesics (tramadol, codeine) are safe. Glucosamine and chondroitin sulphate are often prescribed, but there is little evidence to support their use; they are harmless however and some studies have shown symptomatic improvement. Injection of steroids into the joint (intra-articular steroids) can be used if pain and swelling is severe, and the effects can last for a few months. In extreme cases, knee joint replacement may become necessary.

Moving back to her heart condition, what are the long-term objectives in her management?

The objectives of management are to improve her symptoms, prevent further deterioration in heart function, prevent exacerbations, and reduce the risk of death.

What drugs would you use in the long-term management of this patient?

Furosemide is an essential drug in the symptomatic management of heart failure. There are many other drugs which will provide symptomatic and survival benefit in heart failure. ACE inhibitors, commonly captopril, enalapril or ramipril, are of survival benefit

and are generally prescribed to all patients with heart failure, if no contraindications exist. ACE-inhibitors are also effective in lowering the blood pressure, which would be a good thing in this patient.

What are the side effects and contraindications of ACE inhibitors?

Cough is the commonest side effect, and usually presents as a dry irritating cough originating in the throat. If this occurs, an angiotensin receptor blocker can be used instead. While ACE inhibitors are used to retard progression of renal failure, they can also make renal failure worse, and therefore it is important to monitor renal function. They also can cause hyperkalaemia. First-dose hypotension is also known to occur. Anglo-oedema is another uncommon side effect of ACE inhibitors.

What other drugs are useful?

Beta-blockers are of survival benefit in heart failure, commonly carvedilol, which has combined alpha and beta blocking properties, and bisoprolol.

You are right, but beta-blockers are negative inotropes; how come they are used in heart failure?

Although beta-blockers initially reduce cardiac output and can cause worsening of symptoms when introduced, in the long term they improve symptoms and mortality. I will not start a beta-blocker in Mrs KK at this stage, but would consider adding it later on once her condition is more stable.

Any other drugs?

Spironolactone, an aldosterone antagonist, has been shown to improve symptoms and survival. It acts on the second part of the distal convoluted tubule in the kidney. I can also consider giving digoxin.

She is in sinus rhythm according to your assessment. Do you still want to give a digoxin?

Maybe. Clinical trials have shown that digoxin is useful in patients with heart failure even if they are in sinus rhythm. Though the drug does not have a mortality benefit, due to its positive inotropic effect it will increase cardiac output. As a result it can reduce symptoms and hospitalization. In patients with atrial fibrillation, digoxin should be started for rate control early.

How are ACE inhibitors beneficial in heart failure?

In heart failure, as a result of reduced cardiac output and impaired systemic circulation, there are many compensatory neuro-hormonal effects taking place. These include increased sympathetic activation, sodium and water retention, and increased contractility and heart rate to maintain the blood pressure. Angiotensin II is one main mediator, which has vasoconstrictor effects, and it stimulates the production of aldosterone and also increases sympathetic drive. Although these effects are useful in the short term, they increase the stress on heart and result in myocardial remodeling and more damage to the heart in the long term. Antagonizing these effects is beneficial.

ACE inhibitors block angiotensin converting enzyme which converts angiotensin I to angiotensin II. Thereby they prevent vasoconstrictor effects of angiotensin II. As a result the afterload is reduced and the workload on the heart is reduced. When fluid and sodium retention is reduced, venous congestion is reduced. Thus these drugs will reduce oedema and shortness of breath. Sympathetic activation is also reduced and this also results in reduction in cardiac workload. When the stress on heart is reduced, cardiac remodeling will be less. Thus these drugs provide both symptomatic and survival benefit.

How do beta-blockers help?

In heart failure, there is increased sympathetic activity, resulting in increased heart rate. It is thought that beta-blockers help by reducing sympathetic overactivity.

What general measures would you recommend in this patient?

I will educate her and her family regarding her cardiac condition, focusing on the fact that this is a chronic condition which will need long term treatment and care. I will reiterate the importance of avoiding possible precipitants (avoiding infections, fluid management, diet). Salt restriction is of particular importance. Pneumococcal and influenza vaccination should be considered. I would encourage physical activities at a level which can be tolerated. Given her stage of disease, strenuous exercise will not be possible. Although there is a possible place for valve replacement in this patient, I am not sure whether she is a suitable candidate for this right now. I will discuss this with my seniors and the cardiologist.

Her ECG shows wide QRS complexes. What other therapeutic measure may improve her outcome?

Prolonged QRS complex in heart failure indicates that there is abnormal interventricular and intra-ventricular conduction resulting in dys-synchronous ventricular contraction. She may benefit from cardiac resynchronization therapy (CRT), which involves biventricular pacing. However, this is a specialist decision which should be taken by a cardiac electrophysiologist.

Is there another device that may improve survival?

Implantable cardiac defibrillators (ICD) can be combined with CRT, and these will automatically provide cardioversion or defibrillation if the patient develops an arrhythmia like ventricular tachycardia or ventricular fibrillation. Since arrhythmia is the main cause of sudden cardiac death in heart failure, this can improve survival.

Case 3

Miss PM, a 17-year-old schoolgirl, presented with progressively worsening swelling of the body and face. She had been previously well and had been attending school, preparing for the advanced-level exam. Two weeks before admission she developed swelling of her face, which was more obvious on waking up in the morning. As time went by the swelling worsened and involved her whole body. She noticed her urine was frothy but did not notice any change in urine colour. The amount of urine produced per day was gradually getting less. Around the same time she noticed that she was becoming short of breath. This was initially only felt on exertion, but worsened with time, and on admission she was breathless at rest. She had no orthopnoea. She had no chest pain at rest or on exertion. She had lost her appetite over the past 3 days. On admission she complained of a headache.

Two days ago she sought medical advice from a general practitioner and she was prescribed some medications, and had a urine test. She was not aware of the exact results, but was told it was abnormal.

She had had a sore throat three weeks before the symptoms started, for which she had not taken any treatment. She had also had an itchy skin rash over her left foot, which she had ignored. She did not give any history of fever. She had no history of joint pains, irritation of the skin on exposure to sunlight, or facial rash.

Her last regular menstrual period was 3 weeks back. She gave no history of other significant medical illnesses or allergies, and was not on any medications. There was no history of recent travel. She lived with her parents and younger brother. Her father was a mason and her mother an unskilled worker in a garment factory. She had never consumed alcohol or recreational drugs.

On examination, she was short of breath at rest, with facial puffiness and leg oedema extending up to mid-thigh level. There was no central or peripheral cyanosis, and she was not pale or icteric. There were no palpable lymph nodes. She had an eczematous rash on her left foot which appeared to be active. Her heart rate was regular at 80/min, blood pressure 150/90mmHg, jugular venous pressure was elevated, and heart was in dual rhythm with no cardiac murmurs.

Her respiratory rate was 22 cycles per min and oxygen saturation 95% on air. Both lung bases were dull to percussion, with reduced intensity of breath sounds. No added sounds were noted. The abdomen was distended and tender in the right hypochondrium. There was no renal angle tenderness, and the liver, spleen and kidneys were not palpable. Shifting dullness was noted on percussion. Neurological examination, including optic fundi, was within normal limits, and so was the examination of large and small joints.

Can you Summarize your Findings?

A 17-year-old previously healthy schoolgirl presented with progressively worsening generalized oedema of 2 weeks duration. She also had frothy urine and reduced urine output, but no haematuria. Three weeks before the onset of symptoms she had a sore throat, and had a rash on her left leg. She also complains of breathing difficulty, with no evidence of orthopnoea.

She was dyspnoeic at rest, not pale, and had an eczematous rash on the left foot. She had generalized oedema with elevated

blood pressure and jugular venous pressure, tender hepatomegaly, bilateral pleural effusions, and mild ascites. She did not have any symptoms or signs of uraemia.

Can you give a Diagnosis or Differential Diagnosis?

Generalized oedema could be due to renal, cardiac or hepatic conditions. There are some other causes of generalized oedema like kwashiorkor due to malnutrition, and drugs, which are less common. This patient has features to suggest both renal and cardiac involvement. Frothy urine and oliguria together with hypertension suggest a renal aetiology, while dyspnoea, bilateral pleural effusions and elevated JVP suggest that the patient is in heart failure. In such a situation one should first consider common syndromes which will explain all those presentations, before considering a dual pathology. Fluid retention occurs in renal conditions, and volume overload can give rise to features of heart failure.

This patient has oliguria and proteinuria suggesting a renal cause, and she also has shortness of breath and bilateral pleural effusions, which could be due to fluid overload and possibly an element of heart failure.

What Renal Condition Could Explain her Clinical Presentation?

With proteinuria and fluid overload, nephritic syndrome or nephrotic syndrome are the two broad entities which one should consider. Acute kidney injury can also be considered, but there are no features of renal failure, and this should not be mentioned as a primary diagnosis; however it could be mentioned that there is a possibility of acute renal impairment in addition. Nephrotic syndrome is defined as massive proteinuria, hypoalbuminaemia, gross oedema with or without hyperlipidaemia. Nephritic syndrome consists of haematuria, proteinuria, oliguria and oedema, with

nephritic syndrome rather than nephrotic syndrome. Frothy urine often suggests proteinuria, but one should not assume that the presence of frothy urine is diagnostic of proteinuria.

I would consider nephritic syndrome or nephrotic syndrome, with possible acute kidney injury. The presence of hypertension and evidence of heart failure suggests a diagnosis of nephritic syndrome.

What are the Causes for this Presentation, and what would you Consider in Miss PM?

Both nephritic and nephrotic syndromes are caused by glomerulonephritis. Acute glomerulonephritis is the underlying pathology in nephritic syndrome, Aetiology wise it could be idiopathic or secondary to some other underlying medical condition. The commonest in this age group, especially in view of the history of skin sepsis, is post-streptococcal glomerulonephritis, i.e., acute diffuse proliferative glomerulonephritis. With the history suggestive of a streptococcal skin infection or throat infection this is likely; there can be other causes such as staphylococcal infection, hepatitis virus infection etc. Acute glomerulonephritis can also occur in patients with infective endocarditis, infected ventriculoperitoneal shunts, visceral abscesses etc. Other pathological entities such as mesangioproliferative glomerulonephritis as in IgA nephropathy, and membranoproliferative glomerulonephritis, can present as nephritic syndrome. Lupus nephritis, other vasculitis should also be considered in this patient.

The most likely cause in this case is acute diffuse proliferative glomerulonephritis secondary to streptococcal skin infection.

What Investigations do you wish to do?

I will investigate her with a view to confirming the diagnosis, identifying the aetiology, and detecting complications. I will request urine full report, ESR, full blood count, serum albumin, urea,

creatinine and electrolytes, serum cholesterol, chest radiography, ASOT, ANA and serum complement (C3, C4) levels.

I will look for the presence of red cells and proteins in urine. I would expect there to be microscopic haematuria and proteinuria below the level of nephrotic range. In nephritic syndrome there can be transient renal impairment. Thus I would check whether creatinine is high and also to find out if she is hyperkalaemic. The serum cholesterol is to see whether there is hyperlipidaemia....

....Why Hyperlipidaemia?

In nephrotic syndrome, because albumin leaks out in the urine, there is an increase in albumin production in the liver. Activation of synthetic enzymes results in an increase in cholesterol synthesis.

Since she has shortness of breath, to look for any evidence of pulmonary oedema, I will do a chest x-ray. ASOT will give supportive evidence of recent streptococcal infection if the titre is high. ESR, FBC, and ANA will be done to look for features suggestive of any other secondary pathology leading to glomerulonephritis other than streptococcal infection, particularly connective tissue disorders. Complement levels are low in lupus nephritis.

In the urine full report albumin is trace, there are 6-8 pus cells and 8-10 red cells. ASOT is less than 200. Can you comment on these finding?

Even following severe streptococcal infection only 70-80% develops positive ASOT titres. Therefore its absence does not rule out recent streptococcal infection. Post streptococcal glomerulonephritis can occur following pharyngitis or skin infection due to group A beta-haemolytic streptococci. Only the nephritogenic strains cause glomerulonephritis. Though this is more common in children up to 12 years, adults also develop the illness. So in this type of a patient other underlying aetiologies also should be kept in mind.

Though ASOT is not significant, with the history and urine full report suggesting nephritic pattern I would still consider post streptococcal glomerulonephritis in her.

What is the Pathophysiology of Nephritic syndrome?

Acute glomerulonephritis is due to an immune response, and the latent period between the infection and nephritic syndrome is due to the time taken for the development of the immune reaction. This results in diffuse inflammation of the glomeruli where damage is caused by activation of complement system in association with cell mediated injury.

Following streptococcal infection, the body's immune mechanism produces circulating antibodies which react with bacterial antigens and produce antigen-antibody complexes which deposit on the glomerular capillary walls. This leads to glomerular injury.

What causes oedema in nephritic syndrome?

The commonest reason for oedema in nephritic syndrome is salt and water retention. Glomerular hypercellularity encroaches on the glomerular capillary cross sectional area and compromises intraglomerular blood flow. As a result there is reduced fractional excretion of sodium in the urine. This leads to increased hydrostatic pressure, and then oedema. Sodium and fluid overload can result in hypertension, heart failure. Inflammatory damage to the filtration surface leads to passage of red cells into tubules resulting in haematuria. Oedema is due to salt and water retention resulting from diminished water and electrolyte clearance by the kidney.

How will you manage her in the ward?

Monitoring and looking for development of complications such as acute kidney injury, hypertensive encephalopathy, acute heart failure

effective in improving glomerulonephritis, but a course of penicillin is usually given to clear any residual infection. Adjusting the fluid intake according to urine output is necessary to avoid fluid overload. Usually the previous day's urine output + 500 ml is given as the intake for a day. To reduce oedema, a loop diuretic such as furosemide is used. Albumin may be given. Hypertension is treated with a calcium channel blocker such as amlodipine or nifedipine. If there is hypertensive emergency, intravenous antihypertensives are given. There is no place for steroids or any other immunosuppressants. It is essential to mention about diet, patient education and the follow up plan.

Ward management includes monitoring and continued clinical assessment, antibiotic treatment, fluid management, and other drug therapies. I will monitor her urine output, blood pressure, daily weight, renal functions and electrolytes, and assess for heart failure. Oral penicillin is given to clear any residual streptococcal infection. I will balance the fluid intake according to the urine output, i.e., the intake should be the previous days urine output plus insensible water loss – however I will be careful not to let the patient get dehydrated, and would vary this according to clinical findings. I will start antihypertensives and diuretics. If there is significant renal impairment she will need dialysis.

What advice will you give her on diet?

In the acute stage I will restrict salt since there is fluid overload. If there is renal impairment she will need reduction of protein intake and also potassium restriction.

Will you arrange a renal biopsy for this patient?

Post streptococcal glomerulonephritis is a clinical diagnosis. Renal

persisting for more than 6 months or microscopic haematuria persisting for more than 18 months, then biopsy should be considered.

In post streptococcal glomerulonephritis a renal biopsy is not indicated routinely. But I will discuss with my seniors to see whether she needs to undergo a renal biopsy.

If the consultant has decided that she needs a renal biopsy how will you, as the house officer, prepare the patient?

I will discuss the need for biopsy with her, together with risks and benefits, and obtain consent. I will make sure that she does not have any contraindications for the procedure by maintaining her blood pressure below 160/90 and excluding coagulopathy from the history and performing prothrombin time and checking her platelet count. She needs to undergo ultrasound scan of the kidneys to make sure that she has two kidneys, and also that the kidneys are not contracted (which would indicate chronic kidney disease); in the latter situation, biopsy would be technically difficult and the specimen is unlikely to provide useful information (it will just show scar tissue). I will send blood for grouping and cross matching. I will make sure the equipment for the procedure and the solution to send the sample to laboratory are ready.

What would be the post procedure care for the patient?

She should be kept on bed rest for 24 hours. Pulse, blood pressure and urine colour should be monitored. She should be hydrated adequately and paracetamol can be given for analgesia.

Four hours after renal biopsy her mother complains that the patient has developed haematuria.

Complications of renal biopsy include macroscopic haematuria, which occurs in 10-20% of the patients. Most of the time this is not severe and is self-limiting, but in 1-3% this may need blood transfusion, and a minority will need procedures to stop bleeding.

such as occlusion of the bleeding vessels or even nephrectomy. Other complications are infections, peri-renal haematoma formation and arteriovenous aneurysm formation.

She was discharged after recovery and her renal biopsy report comes as acute diffuse proliferative glomerulonephritis suggestive of post streptococcal glomerulonephritis. Her mother asks you about her prognosis and whether she needs any follow up. What will you tell her?

Though prognosis is very good in paediatric patients with post streptococcal glomerulonephritis, a small number of adults develop persistent hypertension and proteinuria even after full recovery. A minority also progress to chronic kidney disease. Blood pressure, urine protein and serum creatinine should be monitored even after full recovery. Recurrent disease is rare even in the presence of bacterial infection, unlike rheumatic fever.

I will reassure her that this is an acute illness and she has fully recovered, so that her prognosis is likely to be good. However I will emphasize the need for follow-up.

Case 4

Mr SM, a 70-year-old farmer, presented with on-and-off fever over the past 2 months. He had noticed twice-daily peaks of fever during that period, and these were not associated with chills or rigors. He had not measured his temperature. His appetite was poor, and his family members had noticed that he had lost weight significantly. He often felt tired. He also complained of occasional abdominal bloating and had recently noticed painless swelling of both his ankles which worsened towards the end of the day. He had not noticed puffiness around the eyes or abdominal distension. On direct questioning he mentioned that he had generalized pruritus which interfered with his sleep. His family had also noticed that his eyes were yellow. His bowel habits and stools were normal, and he had no abdominal pain. He did not have a significant cough, and was free of chest pain and shortness of breath on exertion. He had no night sweats. He had no urinary or neurological symptoms, or bone, joint or back pain. He had no bleeding manifestations or history of recurrent infections, such as sore throat or recurrent skin ulcers.

He appeared to have been healthy in the past, and had no notable family history. He had not undergone any form of surgery or received blood transfusions, and was not on any regular medications, including ayurvedic treatment. He occasionally consumed alcohol and smoked cigarettes, but had stopped during

his illness. He denied high risk sexual exposure and the use of recreational drugs.

He had been working as a farmer until his illness and rarely used recommended personal protective equipment when using agrochemicals. He had been separated from his wife for the past 10 years and was living with his brother. He had no contact with his two sons. He was admitted to hospital one week ago, and prior to that had taken several medications from a general practitioner. He had undergone several blood investigations, and some imaging studies suggestive of ultrasound and CT scan after admission.

On examination, he was of average build and appeared to be comfortable. Weight was 59kg. He had scratch marks on his skin. He was afebrile, icteric and pale. There was no lymphadenopathy. Throat and gums were normal. He did not have peripheral stigmata of chronic liver disease, such as spider naevi or palmar erythema, and hepatic flaps were absent. There was bilateral pitting ankle oedema.

His abdomen was distended. A non-tender hard mass that moved with respiration was felt in the right hypochondrial and epigastric areas. The mass was nodular and had an irregular border. The spleen was not palpable and there was no free fluid in the abdomen. There was no hepatic bruit.

Examination of the heart, lungs and nervous system was normal.

Can you summarize the history and examination findings of your patient?

This 70-year-old previously healthy farmer presented with fever, abdominal fullness, bilateral ankle oedema, loss of appetite and loss of weight over a two-month period. His clinical history was suggestive of obstructive jaundice with no symptoms related to other systems. He had consumed alcohol occasionally and did

not have any risk factors for sexually transmitted or blood borne infections. Mr SM had been exposed to agrochemicals, and never used any personal protective equipment when using agrochemicals.

There were features of obstructive jaundice and dependent oedema, without evidence of chronic liver disease. There was a palpable non-tender irregular hard liver with no bruit, and ascites was not detected clinically.

What differential diagnoses would you like to consider in Mr SM?

I would consider neoplastic conditions as the first diagnosis. This could be a primary hepato-cellular carcinoma, cholangiocarcinoma or a carcinoma of the head of pancreas, lymphoproliferative malignancy like lymphoma or secondary liver metastasis from lung or bowel malignancy. Secondly I would consider infections such as liver abscess, viral hepatitis and chronic malaria. Thirdly I will consider alcoholic cirrhosis, or non-alcoholic cirrhosis possibly related to prolonged exposure to agrochemicals; however the irregular hard non-tender liver cannot be explained by the latter.

How will you investigate Mr SM?

Mr SM should be investigated to assess his general status, to arrive at diagnosis and to look for complications. I will do a full blood count to look for anemia that can occur due to chronic disease, and low platelets and white cells that can occur if there is portal hypertension. If the underlying condition is infective or inflammatory, leucocytosis maybe present. Serum creatinine and electrolytes will be done with a view to excluding renal impairment, which could be pre-renal due to his poor oral intake and fluid loss from fever, or it could be due to hepato-renal involvement in end-stage liver disease; it is also important to note what his baseline renal function is like.

gamma GT and coagulation profile including prothrombin time. This will help recognize acute liver injury due to toxins like agrochemical or paracetamol. Prolonged prothrombin time, elevated transaminases and reversed albumin: globulin ratio will suggest chronic liver damage. Hepatic cancer is more likely to arise on a background of cirrhosis.

I will initially arrange an ultrasound scan of the abdomen as it can be arranged quickly, and will help identify an abscess or tumour. Based on this I can plan further imaging, like CT scan or MRI. Ultrasound will also help identify para-aortic nodes and ascites, if present.

US scan abdomen reveals a hypoechoic lesion in segment V of the liver. How will you proceed?

Since the US scan showed only an isolated lesion I will consider the possibility of primary or secondary tumor which could be benign or malignant. Considering that Mr SM has significant loss of weight and appetite, I will consider primary hepatic malignancy to be more likely. Liver abscess, granulomas and secondaries are more likely to be multi-focal. The next step would be therefore to arrange a CT scan of the chest, abdomen and pelvis, with quadruple phase imaging of the liver.

I will also do tumour markers - α -fetoprotein levels, carcino-embryonic antigen levels, CA 125 and CA 19-9 that will help diagnose cancer. Hepatocellular carcinoma could be secondary to chronic active hepatitis or any form of cirrhosis. I will send off hepatitis B and hepatitis C serology, and also EBV and CMV,

The CT scan abdomen done earlier shows a focal lesion in segment V of liver suggestive of primary hepatocellular cancer. There is no evidence of cirrhosis. How will you confirm the diagnosis?

Biopsy is not recommended for primary hepatocellular carcinoma as the tumour can spread along the biopsy track. For confirmation quadruple phase CT scan or contrast MRI scan should be done. Elevated α-feto protein level will help, as he has no evidence of cirrhosis or hepatitis. If this is very high, the diagnosis will be confirmed. Biopsy is recommended only when the imaging results are uncertain.

How will you prepare this patient for liver biopsy, if you were to do one?

Before doing a liver biopsy on a patient, I will discuss the reasons for the procedure, benefits and the risks of having the procedure. Biopsy is best done under ultrasound or CT guidance.

If the platelet count is less than 100,000/mm³ or prothrombin time is prolonged, he will need correction with platelet transfusion or FFP transfusion respectively soon before the procedure. All medications that increase bleeding like clopidogrel must be stopped at least one week before the procedure. Prior to liver biopsy the patient should be kept fasting for 6 hours. The patient should be monitored for features of internal bleeding post-operatively.

Do you know methods of doing liver biopsy other than the routine percutaneous method?

It can be done by the transjugular approach, or laparoscopically. The transjugular method is used in patients with an increased risk of bleeding. ERCP can also be used for diagnosis when a biliary pathology is suspected, or when there is a need to insert a stent to relieve biliary obstruction.

Can you mention the possible complications following liver biopsy?

Minor complications include pain at the site and pain referred to the right shoulder, mild hypotension due to vagal stimulation, and formation of small haematomas. More serious complications are intraperitoneal bleeding, sepsis, pneumothorax, haemothorax, haemobilia, and biliary tree injury, and seeding of tumour along the biopsy track.

What are the common malignancies that give rise to liver metastasis?

The commonest are bowel and lung carcinoma in both genders and breast carcinoma in women, and also local extension from cholangiocarcinoma, pancreatic carcinoma, and lymphoma.

What are the mechanisms of developing jaundice in hepatocellular carcinoma?

This can be due to many reasons. Common causes are associated underlying advanced liver failure due to cirrhosis, diffuse tumor infiltration of the liver, and hilar invasion.

Can anything be done to relieve biliary obstruction?

It may be possible to stent the obstruction, by a retrograde or anterograde approach. This procedure is usually done by an interventional radiologist.

What are the treatment options available in hepatocellular carcinoma?

At undergraduate level one would not be expected to know how to treat HCC in detail. Having a basic idea about treatment modalities and being aware that selecting the treatment modality is based on both extent of the malignancy as well as the degree of underlying liver disease is adequate.

HCC has a poor prognosis, and mean survival can be as short as 6 months. Treatment depends on the site, size of the lesion, number of lesions and underlying liver function. Surgical modalities are surgical resection of the lesion, which is partial hepatectomy or liver transplantation with complete hepatectomy. Trans-arterial chemo-embolisation, with injection of ethanol or a chemotherapeutic agent into the tumour, is a relatively effective therapy, at least in the short term.

What are the risk factors for hepatocellular carcinoma? Does this patient have any?

Chronic hepatitis due to hepatitis B and C infection, non-alcoholic steatohepatitis, cirrhosis due to any cause, hereditary haemochromatosis are well known to be associated with HCC. Other risk factors include aflatoxins, and drinking water contaminated with blue-green algae, tobacco, alcohol and betel nut chewing. I could not identify any obvious risk factors in this patient, apart from agrochemical exposure.

What would you tell Mr SM?

I will sit with him and a staff nurse and ask if he wants his family to be present. I will ask him what he has understood from what we have said so far and how much he wants to know about his current medical condition. If he wants to know further, I will explain to him that it appears that he has a liver tumour, which is blocking his bile duct, which is why he is yellow. I will also explain that this may not be curable, but that certain therapies can be done to make him feel better, and possibly reduce the size of the tumour.

If he wants to know the prognosis I will say it will probably be months rather than years, and that it is possible that he may get worse. However, I will make arrangements for him to get more information from my seniors or oncologist team because I have less experience with this sort of cases.

Case 5

Mr AL, a 41-year-old manual worker, presented to the ward with worsening bilateral leg swelling over the last week. The swelling was painless and worsened towards the end of the day. There was no difficulty in movement. He had not noticed facial puffiness or abdominal distension. He had not experienced similar symptoms before. He had noticed some reduction in his physical activity with easy fatigability. His urine output was normal in volume and he had not noticed froth or change in colour in his urine. He had no abdominal pain, haematemesis or melaena and his bowel habits were normal. He did not complain of chest pain, shortness of breath on exertion or when supine or waking up from sleep with difficulty in breathing. He had no symptoms related to other systems. Neither he nor his associates had noticed any yellow discolouration in the eyes. There was no history of fever.

He had been hospitalized seven years ago for pneumonia, but other than occasional dyspeptic symptoms he was healthy. He did not have any medical problems including diabetes or hypertension, had not undergone any surgeries, had no history of blood transfusions and was not on regular medications.

His brother had been diagnosed with hypertension at the age of 36 years. Mr AL is married with four children. His wife is a housewife and there was no fixed family income. He had consumed ½ a bottle of spirits and smoked 5 cigarettes daily for

the past 15 years. He denied high risk sexual behaviours and the use of recreational drugs.

Can you summarize your history before proceeding into examination?

A 41-year-old manual worker presented with painless bilateral leg swelling and reduced exercise tolerance without significant dyspnoea, orthopnoea, chest pain or urinary symptoms, for one week. The history did not reveal any significant co-morbidity, similar past episodes or contact history. He had been consuming alcohol, around 12 units a day for 15 years, and smoked 4 pack years.

At the end of your history what is your differential diagnoses for Mr AL?

It is best to give a classification to make your answer more structured. However, there are some other important causes of oedema that people tend to forget though they are not high in the list in this patient. They include hypothyroidism and drug induced oedema (e.g. nifedipine, amlodipine etc). Severe hypoproteinaemia due to dietary insufficiency or protein loss as in bowel pathologies can also lead to oedema. That is why it is crucial to ask about dietary habits and bowel habits in these patients. In the differential diagnosis however, you should give the common and likely causes.

His bilateral lower limb swelling could be due to a localized pathology or systemic pathology.

Systemic pathologies causing generalized oedema can initially present with dependent oedema. The causes could be renal pathologies such as renal failure, nephrotic syndrome, nephritic syndrome, a cardiac pathology like congestive cardiac failure, or liver pathology like cirrhosis. Severe anaemia can also lead to oedema.

Under localized conditions I will consider lymphoedema, venous obstruction due to some pelvic pathology, and deep vein thrombosis in the more proximal veins. These conditions are more likely to cause unilateral oedema and are unlikely in Mr AL who has bilateral oedema.

What is the most likely cause of oedema in this patient?

The history doesn't provide enough information to decide which system is involved. His urine output is normal and urine is clear, which are against a renal cause, although this is still possible in the absence of any symptoms. In heart failure, shortness of breath and orthopnoea are prominent features. He did not have a significant past medical history of cardiac risk factors either. In the absence of localizing symptoms, and with history of heavy alcohol consumption I will consider cirrhosis due to alcohol at the top of my differential diagnosis.

Can you now present your examination findings?

He was of average build, icteric and pale with sparse body hair. He had no clubbing or gynaecomastia, spider naevi, palmar erythema or flapping tremors. There was bilateral pitting ankle oedema. The abdomen was distended with non-tender hepatomegaly of 8cm in the mid-axillary line and 3cm in mid-clavicular line. The upper border was not shifted down. The tip of the spleen could be felt. There were no other lumps in the abdomen. There was free fluid in the abdomen. There was no hepatic bruit and bowel sounds were normal. Examination of the external genitalia and rectum was normal. Pulse rate was 80/minute and blood pressure was 120/70mmHg. No abnormalities suggestive of haemochromatosis or Wilson's disease, such as pigmentation or KF rings in the eyes were noted, and examination of other systems were clinically normal.

At the end of your clinical examination can you narrow down your differential diagnoses and come into a final diagnosis?

There is sufficient clinical evidence to give a diagnosis as cirrhosis probably due to alcoholic liver disease, with evidence of liver decompensation. Cirrhosis by definition is a histological diagnosis with diffuse hepatic process characterized by fibrosis and nodular regeneration distorting the liver architecture. However, it is reasonable to give a clinical diagnosis of cirrhosis. The reason you consider him to be decompensated is because of the presence icterus and oedema. Usually, the presence of icterus, oedema, and hepatic encephalopathy are considered features of decompensation.

Decompensated cirrhosis most likely due to chronic alcohol use. The presence of icterus, lack of normal hair distribution hepatosplenomegaly with ascites, and the absence of features to suggest cardiac involvement together with normal blood pressure support this diagnosis. Nonetheless I will investigate him to rule out other possibilities.

Describe the pathophysiological mechanisms of oedema in cirrhosis?

Oedema in cirrhosis has several mechanisms. There is obstruction to hepatic venous outflow and expansion of the splanchnic system. This in turn will result in reduction in venous return. As a result the renin angiotensin aldosterone system gets activated and there will be salt and fluid retention. There is also

- ② reduced metabolism of aldosterone contributing to this. When the hepatocytes are damaged, the ability for hepatic synthesis of albumin will diminish, so that plasma oncotic pressure will fall. Due to reduced plasma oncotic pressure and increased hydrostatic

enlarged due to nodular regeneration as an attempt of the liver to maintain its functions.

No. With fibrosis the liver is shrunken and will not be palpable. But in early cirrhosis it can be palpable.

What are the common causes of cirrhosis?

Cirrhosis could be caused by alcohol, drugs, and infective, autoimmune, genetic causes, or be idiopathic. Chronic alcohol abuse is one of the commonest causes for cirrhosis worldwide. Other substances include paracetamol over dose, methotrexate, and herbal products. Chronic hepatitis B and C infections are also known to cause cirrhosis. Autoimmune causes are primary biliary cirrhosis, primary sclerosing cholangitis and chronic autoimmune hepatitis. Hereditary haemochromatosis, Wilson disease and α_1 antitrypsin deficiency are the genetic causes. Non-alcoholic fatty liver is also a common cause of cirrhosis which is now being detected more frequently, due to diabetes mellitus and obesity. In a proportion of patients when the etiology is not known, it is considered to be cryptogenic cirrhosis.

What are the likely mechanisms for splenomegaly and free fluid

Portal hypertension increases fluid accumulation into the peritoneal cavity. The other mechanism is reduced systemic arterial filling in patients with cirrhosis due to increased splanchnic circulation. This results in activation of the renin-angiotensin-aldosterone mechanism and the sympathetic system which will eventually lead to sodium and water retention. This will also lead to increased fluid accumulation in the peritoneal space.

Why do people with liver cirrhosis get gynaecomastia and palmar erythema?

Both of these manifestations are due to increased oestrogen levels in blood, due to reduced hepatic metabolism. It also explains why they lose facial and chest hair.

What investigations would you do?

The full blood count can provide certain indications of chronic liver disease. Hypersplenism can result in thrombocytopenia, and sometimes anaemia and leucopenia. Macrocytosis (high MCV) occurs due to alcohol or nutritional deficiency of folate and vitamin B12; poor diet could contribute to this. Chronic bleeding due to oesophageal varices, portal gastropathy, or alcoholic gastritis could give an iron deficiency picture or a mixed blood picture.

The ESR may be elevated in autoimmune hepatitis.

Serum creatinine will be done as a baseline, and to see if there is any renal impairment, which could indicate the development of hepatorenal syndrome.

Serum electrolytes are very important for many reasons. There can be dilutional hyponatraemia in cirrhosis due to fluid overload. This is a poor prognostic marker. On the other hand hypokalaemia can precipitate hepatic encephalopathy. Electrolyte levels should also be known before starting diuretics.

Because of the impairment of synthetic functions of the liver serum albumin will be low and the

be reversed. AST and ALT can be high. In alcoholic hepatitis, characteristically AST is greater than ALT. However by the time cirrhosis is established, as the number of viable hepatocytes decreases, the transaminases may be low. Serum bilirubin is often raised due to impaired ability of the liver to conjugate and excrete bilirubin, giving rise to icterus.

Prothrombin time is elevated due to impaired synthesis of clotting factors and due to vitamin K deficiency.

Ultrasound scan of the hepato-biliary system is useful to confirm portal hypertension and also exclude complications like hepatocellular carcinoma, unexpected findings like hepatic vein thrombosis or Budd-Chiari syndrome, and metastatic liver disease.

Upper GI endoscopy is needed if there is suspicion of portal hypertension, to identify varices. It is essential if there is a GI bleed, and, if varices are present, banding or sclerotherapy can be done at the same time.

Liver biopsy will be diagnostic, but is not routinely done as it is risky. With a clear history of alcohol abuse and no other medical condition I would not do a liver biopsy for this patient.

Investigating for viral hepatitis B and C, autoimmune hepatitis with auto antibodies like ANA, anti smooth muscle antibodies, anti-liver-kidney microsomal antibodies.

and spontaneous bacterial peritonitis. It is calculated based on the following criteria: hepatic encephalopathy, ascites, serum bilirubin, prothrombin time and serum albumin. It is also used to determine the need for liver transplantation. However this is being replaced by a new clinical staging method called 'model for end stage liver disease (MELD)'.

What are the principles of management of Mr AL?

Correcting the causative factor is generally of benefit in preventing progression. Steps should be taken to arrange alcohol cessation therapy. Psychiatry referral may be needed since this patient is alcohol dependent.

Thiamine deficiency is known to occur in chronic alcoholics and is more common with concomitant liver disease, malnutrition, etc. Therefore it is necessary to empirically start thiamine. Patients with alcoholic liver disease can have hypoglycaemic episodes. Thiamine should be given before giving glucose since replacing glucose can precipitate Wernicke's encephalopathy.

General management includes diet with low salt supplementation of vitamins B complex and thiamine to prevent Wernicke's encephalopathy.

For symptomatic therapy of oedema and ascites, diuretics are given. Usually furosemide and spironolactone combination is given at a 40:100 ratio.

Adequate hydration, preventing constipation, identifying and correcting electrolyte imbalance are important. As mentioned earlier, upper GI endoscopy should be done to identify and treat varices.

Do you want to restrict protein in his diet?

Current recommendations do not advise protein restriction. Traditionally it was thought that vegetable protein with branched chain amino acids is better since it is not metabolized in the liver.

However, that hypothesis does not have any evidence, and large amounts of vegetables will have to be given to provide adequate amount of proteins.

No. Though there is fear about hepatic encephalopathy being precipitated by a high protein diet, dietary protein alone usually does not cause it. On the other hand, chronic alcohol abusers are malnourished and baseline protein intake might also be quite low. So if I try to restrict his proteins it could worsen muscle breakdown, and increase the ammonia load. Currently Mr AL has no evidence of hepatic encephalopathy. I will allow him to have good protein intake and if he shows any evidence of encephalopathy I will restrict it accordingly.

Considering the history of alcohol abuse in this patient, is there anything else that you have to consider while he is in the ward?

There is a risk of alcohol withdrawal since the patient will not have access to alcohol while in the hospital. I will observe for evidence of features of alcohol withdrawal, such as tremors, anxiety and agitation, insomnia, seizures and delirium tremens. However, I will be cautious about starting benzodiazepines in view of his chronic liver disease, as it could push him into hepatic encephalopathy.

Yes. It is likely that large varices would have been banded at the time of endoscopy. I will start a beta-blocker like propranolol to reduce the risk of variceal bleeding by reducing the portal pressure..

After starting treatment he improves and is discharged forward. One month later he presents with worsening abdominal pain and swelling with fever. What is your approach?

I will consider spontaneous bacterial peritonitis (SBP) as it is known complication of cirrhosis, and treatment improves outcome. The diagnosis is established by positive ascitic fluid bacterial culture with or without neutrophils $>250/\text{mm}^3$ on diagnostic paracentesis.

Any intra-abdominal infection will cause pain and swelling associated with fever. On the other hand any other infection causing fever might lead to worsening ascites with associated discomfort. However in the setting of cirrhosis and ascites, SBP has to be considered high on the list.

At the same time you realize that patient has altered sleep pattern with slight disorientation. What is the most likely cause?

It could be due to hepatic encephalopathy

How will you determine severity of hepatic encephalopathy? I will stage it according to West Haven criteria. According to the given details he is in stage 1 encephalopathy with reversed sleep-wake cycle, impaired attention and mild confusion. If there is drowsiness, flapping tremors or slurred speech it will be considered to be stage 2. Drowsiness, flapping tremours or slurred speech with gross disorientation, with somnolence and hyper-reflexia is stage 3. In stage 4 patients are in coma.

What will precipitate hepatic encephalopathy in a patient with cirrhosis?

Any infection also can precipitate hepatic encephalopathy. Drugs such as sedatives, diuretics, electrolyte imbalance such as hypokalemia and hyponatremia, dehydration, upper gastrointestinal bleeding, constipation, hypovolemia and, surgery are some other causes. Other iatrogenic causes are massive paracentesis and portosystemic shunting procedures.

How will you manage hepatic encephalopathy?

There are several aspects in managing this patient. Managing the infection with IV antibiotics will treat the precipitating cause and help to improve encephalopathy. Supportive therapy with good nursing will help irritability and disorientation. If there are other concurrent precipitating factors such as electrolyte imbalance I will treat them. At the same time I will look for any other cause of encephalopathy even unrelated to his cirrhosis such as CNS infection, intracranial bleeding, etc. Lactulose will be prescribed to maintain 3-4 bowel openings per day. Enemas are of benefit. Oral metronidazole or rifaximin is given to reduce the gut organism load.

If Mr AL presents to the medical casualty with several episodes of haematemesis and is found to be pale having a blood pressure of 90/70 and pulse rate of 112/min, how will you manage him?

Initially I will do a quick assessment- brief history and examination -while resuscitating him. Provided he is conscious and able to maintain a good airway and breathing, I will arrange for urgent vascular access with two wide bore cannulae. Blood will be drawn for full blood count, prothrombin time, electrolytes and grouping and cross match.

Since he is haemodynamically compromised, I will give him IV 500ml of normal saline over 30 minutes, and if he does not respond consider giving colloids.

I will arrange for **urgent blood transfusion** for Mr AL if he is tachycardic or hypovolaemic.

I will start Mr AL on **IV terlipressin** or **IV octreotide**, beginning with a **bolus dose** and followed by **maintenance doses**.

I will start **IV antibiotics**; ciprofloxacin, or a cephalosporin, as this is known to **reduce mortality in GI bleed and cirrhosis**. This should be **continued for 7 days**.

Once the patient is stabilized hemodynamically, I will plan for **urgent upper GI endoscopy** for **diagnosis and treatment**. **Varices** are treated with sclerotherapy or variceal banding therapy.

The Rockall score and the Glasgow-Blatchford score are used to identify patients at risk of adverse outcome following upper GI bleeding.

Case 6

Mr MS is 47-year-old carpenter with diabetes mellitus. He was diagnosed with chronic kidney disease six months previously. His main presenting complaint was worsening shortness of breath and loss of appetite for three days. He also noticed bilateral ankle swelling and abdominal distension over the previous week. He did not complain of chest pain, fever, cough or wheeze. His breathing worsens when lying flat and during sleeping. For the past two days he had felt nauseous and had vomited once. He had no abdominal pain, and his bowel habits and stools were normal. His urine output was adequate, and he had not noticed frothy urine or dysuria. He also complained that he felt tired and weak and did not show much interest in personal or social activities.

Six months ago he was diagnosed to have kidney disease when he presented to a doctor with bilateral leg oedema, lethargy and shortness of breath. Three months ago he was started on regular dialysis after his symptoms worsened. He was on regular dialysis twice a week via a neck line, and his last dialysis was a week ago; he had missed his last dialysis session because of financial difficulties in arranging transport to hospital. He had been on treatment for diabetes mellitus for the past 14 years with poor adherence to follow up, medicines and diet. He checked his fasting blood sugar levels only occasionally, and these were usually in the range of 200-300mg/dL. He had been taking oral drugs from the dispensary using an old prescription until 6 months

back. Since then he is on insulin, which is stored in his neighbour's refrigerator and injected by his wife. He was blind in his right eye and had undergone laser photocoagulation treatment to the left eye. He had developed numbness of both his lower limbs over past three years. He did not complain of episodes of chest pain, lower limb pain on walking, or episodes of limb weakness or speech difficulty. He had never undergone any surgery. His elder brother and mother have diabetes mellitus, but neither have renal disease. His mother had hypertension for about 10 years.

He had never smoked or used recreational drugs, and only consumed alcohol occasionally. His wife was a seamstress and their two children were schooling. They had had a stable family income, but money had been scarce during the past 3 months as both he and his wife had been unable to work due to his CKD. They were educated about the prognosis of the illness and the need for chronic dialysis or transplant. His wife was very anxious and wanted him to undergo a kidney transplant.

Can you summarise your history before continuing with examination?

A 47-year-old male with poorly controlled DM for 14 years and CKD diagnosed 6 months ago, presenting with worsening oedema, shortness of breath, and general ill health over 3 days. He was on regular twice weekly hemodialysis for the last 3 months, and had missed the last session. He does not give a recent history of reduced urine output, dysuria or fever. He has developed eye complications and possible neuropathy due to DM, but had no clinical evidence of diabetic macrovascular complications. He is from a poor socioeconomic background, and his financial circumstances had worsened of late.

According to your history what is the reason for his current presentation?

Most probably his symptoms have worsened due to lack of dialysis.

Tell us your examination findings.

He was dyspnoeic at rest and had facial fullness. He was pale, and had thin dry skin with some scratch marks. There were no flapping tremors. Bilateral ankle oedema was present. His pulse rate was 92/minute, regular and all peripheral pulses were present. The blood pressure was 140/90 in the supine position, and fell to 130/70 on standing. The jugular venous pressure was 7cm. The cardiac apex was in the 6th intercostal space, 1cm lateral to the mid-clavicular line. His heart was in dual rhythm, regular, and an ejection systolic murmur was heard in the aortic area. The respiratory rate was 24/min. Examination of the lungs revealed bi-basal fine crackles. Abdomen was clinically normal. Bilateral hard exudates were noted on fundoscopy and changes of proliferative retinopathy seen in both eyes with laser burns in the left eye. Vibration sense and joint position sense were diminished up to the knee in both lower limbs.

What are the problems that you have detected in your patient?

His acute medical problems are

- Fluid overload and uraemic symptoms such as nausea, vomiting and itching
- Postural hypotension, indicated by a diastolic drop of 20mmHg
- Anaemia which might have contributed to his symptoms
- Having missed his dialysis with no clear plan for long-term renal replacement therapy

His longstanding problems are

- Type 2 diabetes mellitus with poor diet and poor adherence to medications
- CKD stage V on twice-a-week dialysis
- Peripheral neuropathy due to long standing DM
- Blind in the right eye with proliferative retinopathy and laser treatment given to left eye.

He also has social problems due to poor financial status, lack of easy access to healthcare, and poor psychosocial support.

You have mentioned that he is in stage 5 of CKD. What do you mean?

To guide management, CKD is staged. This also helps in determining risk of progression and complications of CKD. The commonly used staging considers 6 categories of GFR or G staging, and 3 categories of albuminuria based staging. In GFR staging G1 is $>90 \text{ ml/min}/1.73\text{m}^2$ which is normal, G2 $60-89 \text{ ml/min}/1.73\text{m}^2$ which is mildly decreased, G3a $45-59 \text{ ml/min}/1.73\text{m}^2$ mild to moderately decreased, G3b $30-44 \text{ ml/min}/1.73\text{m}^2$ moderate to severely decreased, G4 $15-29 \text{ ml/min}/1.73\text{m}^2$ severely decreased, G5 $<15 \text{ ml/min}/1.73\text{m}^2$ add D if treated by dialysis. Albuminuria stages are A1 $<30 \text{ mg/day}$ normal to mildly increased, A2 $30-299 \text{ mg/day}$ moderately increased, A3 $\geq 300 \text{ mg/day}$ severely increased. In usual practice the GFR staging is used.

Chronic kidney disease is classified based on glomerular filtration rate (GFR) values. The eGFR is used in place of GFR in clinical practice. Stage 5 is when GFR is less than $15 \text{ ml/min}/1.73\text{m}^2$. Though I do not know his GFR, since Mr MS is dialysis dependent it is likely to be below 15. Based on that I think he is in stage 5.

When a patient with CKD presents with acute shortness of breath, what could be the causes?

There are many causes of acute shortness of breath in a patient with CKD. One common cause is pulmonary oedema due to fluid overload. This might be due to gradual deterioration of renal function and lack of dialysis, or there might be a component of acute on chronic renal failure. Another common cause is metabolic acidosis, which will result in increased respiratory rate to compensate for acidosis by washing out CO₂.

These are the two most important reasons for shortness of breath in CKD. There are several other causes that are possible in these patients. These can be divided into causes directly related to CKD alone, those due to associated co-morbidities like diabetes mellitus and hypertension, and unrelated causes. Therefore, acute coronary syndrome has to be considered as a cause since it will cause acute heart failure. In particular, they can have silent myocardial infarction. They are also at higher risk of infections including pneumonia, which could be the cause for shortness of breath.

Causes like anemia, and uremic cardiomyopathy can also contribute to shortness of breath of insidious onset. There are some complications of CKD like fibrinous pleuritis that can cause shortness of breath. Pericardial effusion can also occur, and this could be transudative, exudative or even haemorrhagic.

What investigations you will arrange for?

At the initial stage my aim is to find out the cause for his acute worsening of shortness of breath and start appropriate treatment. The most likely cause for this is lack of dialysis. The investigations would aim to identify whether he has other indications for urgent dialysis, apart from fluid overload. I will check his serum creatinine and compare it with previous records. I will also do serum sodium and potassium to see whether they need correction.

In particular, if hyperkalemia is present, I will have to treat it as a medical emergency. I will do a venous blood gas analysis to check whether there is metabolic acidosis.

To rule out the other common causes of shortness of breath I will arrange for a chest radiograph, cardiac troponin and ECG. These will indicate whether there are any acute coronary events, heart failure or chest infections. I will also do a full blood count mainly to check his haemoglobin since he is pale, and at the same time to look for any evidence of infection that might have produced acute worsening of his renal condition. I will also arrange a urinalysis to find out if he has concomitant UTI. At the same time I will check his blood sugar levels and optimize with insulin if needed.

What is your blood pressure target for this patient?

A lower target blood pressure is preferred for patients with diabetes and CKD. However the recent JNC 8 guidelines suggested that a target of 140/90mmHg is adequate for such patients. This is still controversial, and older guidelines suggest a target of <125/75mmHg

He has diabetes and CKD both. A lower target blood pressure is preferred, at least below 140/90, preferably lower, although there is some controversy on this.

You have mentioned that he is pale. What are the causes of anaemia in CKD?

Anaemia in CKD is due to many reasons, of which the erythropoietin deficiency is the most important cause, since the kidney is the main source of the erythropoietin which drives red cell production. Lack of erythropoietin acts as the major contributory cause for anaemia. Other causes include reduced red cell survival on a background of uremic bone marrow suppression. There is often also iron, B12 and folic acid deficiency due to the loss of appetite, poor absorption and over enthusiastic dietary restrictions. CKD

is considered a state of chronic inflammation and the body is unable to utilize iron in a manner similar to anemia of chronic disease. There is also bone marrow fibrosis, which will reduce red cell production. Also these patients are at increased risk of bleeding, especially gastrointestinal bleeding due to medications like aspirin and clopidogrel. This will also contribute towards iron deficiency anemia.

How will you investigate Mr MS's anaemia?

Initially I will do full blood count to confirm my clinical diagnosis of anemia, exclude other common causes of anemia and look for contributing factors to treat. The red cell indices will provide certain clues. For example, in CKD a normocytic normochromic anemia is expected. However there might be other contributory factors. A blood picture and reticulocyte count will be the next step. Low reticulocyte count will be seen due to erythropoietin deficiency and nutrient deficiencies. If the blood picture shows any abnormalities beyond what is expected we will have to further investigate accordingly. Serum ferritin to look at body iron stores and serum iron and transferrin to assess iron status needs to be done. If clinically indicated, according to red cell morphologies, we will have to test folic acid and B12 levels. This is important because we have to correct these deficiencies before erythropoietin therapy.

Could you mention a few problems with erythropoietin treatment?

Patients can have uncontrolled hypertension with erythropoietin injections which can lead to hypertensive encephalopathy. Some people can have hypersensitivity to the products causing reactions. Over-correction of anemia can happen if the patient is not monitored during treatment. In patients with CKD, having hemoglobin values above 12g/dL is also associated with increased cardiovascular risk, due to higher chance of thrombosis.

What are the complications of CKD, other than anemia?

There are complications pertaining to almost all systems. In relation to fluid and electrolyte homeostasis, there is increased extracellular fluid volume and hyponatremia. In later stages there can be hyperkalemia, and reduced phosphate clearance leading to high phosphate level. Metabolic and endocrine complications include metabolic acidosis, impaired glucose tolerance and reduced plasma sex hormone levels. There is higher risk of hyperlipidemia. Due to urate retention the patient can develop acute gout.

Complications pertaining to the skeletal system in CKD are adynamic bone disease, hyperparathyroid bone disease and osteomalacia.

There are cardiovascular complications of CKD, which lead to increased cardiovascular morbidity and mortality. These are due to many reasons, such as hypertension, cardiac hypertrophy, cardiomyopathy and coronary artery calcification. Another complication is uremic pericarditis. Neurological manifestations include gradual decline of cognitive functions, seizures, autonomic dysfunction, peripheral mononeuropathies like carpal tunnel syndrome, polyneuropathy, and restless leg syndrome.

Skin complications are pruritus and pigmentation. Gastrointestinal complications are peptic ulcer disease, gastritis, nausea, vomiting and constipation.

They can have severe nutritional effects due to dietary restrictions, as well as catabolic state of CKD. In later stages these patients can develop protein energy malnutrition.

You have mentioned several complications related to the skeletal system in CKD. What is the underlying pathophysiology?

There are several types of bone disease which occur in CKD. One entity is hyperparathyroid bone disease. Hyperparathyroidism is due to several reasons. One-alpha-hydroxylase is produced by kidney, which converts vitamin D to its active form. So, in

CKD there is reduced activation of vitamin D. As a result there is reduced absorption of calcium from the gut. Due to reduced excretion by the kidney there is phosphate retention in CKD. Low calcium, low active vitamin D and high phosphate act on the parathyroid gland and stimulate the gland to produce more PTH. This results in secondary hyperparathyroidism. Increased PTH acts on bones and increases osteoclastic activity, cyst formation and bone marrow fibrosis. This is called osteitis fibrosa cystica.

Osteomalacia also occurs in CKD due to hypocalcemia and vitamin D deficiency leading to reduced mineralization of bone. Aluminium inhibits osteoblasts and high aluminum levels due to drugs and dialysis also plays a role in reducing bone mineralization.

Another condition called adynamic bone disease occurs, where bone volume and mineralization both are impaired. This is caused by overtreatment with vitamin D and calcium, and also due to the chronic inflammatory state. Osteomalacia and adynamic bone disease are low turnover bone disease.

The above explanation of bone disease is quite comprehensive. Many of these mechanisms can occur simultaneously. Later-on the patient can develop tertiary hyperparathyroidism, when the parathyroid glands become hyperplastic and autonomous.

What are the types of neuropathy associated with diabetes, and what have you found in this patient?

Diabetic neuropathy can affect somatic nerves, autonomic nerves or both. Somatic neuropathies include distal symmetrical sensory polyneuropathy, acute painful neuropathy, mononeuropathy (commonest involved is third cranial nerve), mononeuritis multiplex and diabetic amyotrophy. Diabetic amyotrophy is a type of diabetic polyradiculopathy. Autonomic neuropathy is the other type of nerve involvement in diabetes.

This patient has distal symmetrical polyneuropathy. He is symptomatic and complains of sensory loss. He has objective evidence of loss of vibration sense and proprioception. Since he has postural hypotension it is possible that he has autonomic neuropathy.

But postural hypotension could be due to other causes like antihypertensives and fluid loss. What are the other features of autonomic neuropathy you checked in him?

In the cardiovascular system, resting tachycardia and lack of sinus arrhythmia occurs. Nocturnal diarrhea, and vomiting due to gastroparesis can occur. Incomplete bladder emptying may occur. They can develop erectile dysfunction. Hyperhidrosis of the upper limbs and anhidrosis of the lower limbs also can be seen. My patient did not have many of these features, except for vomiting which could be a feature of uraemia.

You mentioned that he has changes of proliferative retinopathy. What are these changes and how do they occur?

In diabetic retinopathy initially there is retinal ischemia. As a response neovascularization (new vessel formation) takes place. These new vessels can be seen on fundal examination. Since these vessels are fragile they also can cause bleeding which lead to fibrosis and retinal detachment.

Diabetic eye disease comprises of retinopathy, which starts as non-proliferative retinopathy, and can progress into proliferative retinopathy and maculopathy. The earliest feature of maculopathy is macular oedema. In non-proliferative retinopathy dot hemorrhages, blot hemorrhages, hard exudates and cotton wools spots can be seen. Neovascularisation of the iris can also occur, leading to glaucoma. Cataracts may also develop.

Why do you think he was changed over to insulin?

I think it might be due to poor glycemic control as well as the presence of CKD. He was on metformin, which should be avoided in patients with eGFR less than 30ml/min/1.73m². Though he can be started on other oral hypoglycemic agents, because of his high blood sugar levels he might have been converted to insulin.

There are criteria to decide when to use insulin for patient with type 2 DM. They include acute intercurrent illness, perioperative states, and poor glycemic control despite good oral drug therapy. But in clinical practice it is a difficult decision to convert to insulin specially when there is possibility of trying with oral drug combinations. This patient's poor glycemic control might be due to poor adherence rather than any other cause.

What are the problems related to insulin therapy that you have identified, and that you anticipate in this patient?

He has already got problems related to administration and storage of insulin. He doesn't have a refrigerator of his own and stores his insulin in his neighbours fridge. He has impaired vision and he has to depend on his wife to administer his insulin.

An important aspect of insulin therapy is monitoring of glycemic control, using self-monitoring of blood glucose (SMBG). He does not have a glucometer and has difficulty having his blood sugar checked frequently in the private sector. Therefore he can't have his treatment titrated well and is at risk of hypoglycemia. He needs close monitoring since he has autonomic neuropathy and hypoglycaemic symptoms maybe masked. Other side effects of insulin are common to all patients, like poor technique, injection site reactions, lipoatrophy and lipohypertrophy and weight gain.

This patient underwent ultrasound scan of the abdomen, and was found to have normal sized kidneys. What do you think of this?

In diabetic nephropathy the kidneys are enlarged initially, as a result of glomerular hyperfiltration. Normal size kidneys indicate that the kidneys have actually shrunken, and that he has CKD.

Usually in CKD kidneys are small except for few instances. One is diabetic nephropathy. In amyloidosis and HIV nephropathy also kidneys are normal in size. In polycystic kidney disease kidneys are large due to cysts.

Will you plan for renal biopsy to confirm your diagnosis and underlying etiology?

No. Renal biopsy is not indicated in him, and it is risky as well. He definitely has chronic kidney disease even if the underlying etiology is not definite. His kidneys are likely to be scarred. Therefore the chances of getting diagnostic tissue samples are minimal, and also it will not change the management in him at this point, since his renal failure is advanced. Also, renal biopsy carries a high risk of bleeding in shrunken kidneys.

What are the basic steps in his long-term management?

One of the main components of his long-term management is arranging for renal replacement therapy, either with chronic dialysis or renal transplantation. He also has to be kept symptom free. Even though his renal failure is advanced, optimal glycemic control and good blood pressure control may help retain residual renal function. He already has eye and nerve complications. So it is necessary to refer him to the relevant specialists for proper follow up. To achieve these things he has to be managed by a multidisciplinary team, which includes medical and renal specialists, social support personnel, diabetic nurses, dietician, physiotherapist and podiatrists. Mr MS should be seen by an

ophthalmologist and a diabetologist. He and his family should be counseled on the future management plan, the need for good follow up and compliance with treatment, and how to protect eyes and feet. In order to achieve these goals, we should arrange good social support for him. It might be better to refer him back to the closest hospital with dialysis facilities, to improve adherence.

If his CKD was detected early, what measures could have been taken to prevent or slow its progression?

Good glycemic control and the use of antihypertensives to achieve target blood pressure might have helped prevent progression of his disease. Control of systemic and intra-glomerular pressure is very important measures in this aspect. Proteinuria is known to cause further renal damage and therefore preventing proteinuria is a major aim in preventing further progression. Increased intra-glomerular pressure increases protein filtration, thus increasing proteinuria. ACE inhibitors and ARBs will inhibit efferent arteriolar constriction and thus reduce intra-glomerular pressure. Therefore these drugs are beneficial in both reducing proteinuria and in controlling systemic blood pressure.

Also, smoking cessation and reduction of protein intake to 0.5-1mg/kg/day of high quality protein are known to prevent progression of the illness. Avoidance of nephrotoxic agents like radio-contrast and NSAIDs is also important.

What is the investigation that could have been done to detect his renal involvement early?

Urine for microalbumin. This is an early marker of renal involvement.

Case 7

Mrs NB, a 33-year-old right handed caterer presented to the ward at 10 am with sudden onset weakness and numbness of the left upper and lower limbs. She was making breakfast for the family around 7.30 am, when she felt her left arm and leg go numb and weak. She fell to the ground and was unable to stand up without help from her maid. She remained conscious and was able to speak clearly. The onset of symptoms had not been associated with vertigo, headache, nausea or vomiting. Her symptoms had persisted at the same intensity since onset. She had not passed urine or stools during the incident, and had not noticed any problem with her vision.

She did not have a bleeding tendency, although her last menstrual cycle had been exceptionally heavy and had lasted 10-11 days. She had had no skin rash, joint pains or chronic headaches. She gave no history of trauma to the neck. There was no history of chest pain on exertion, shortness of breath, palpitations, or pain in her calves when walking, previously. This was the first time she had experienced symptoms of sudden focal loss of function. She had had a first trimester miscarriage nine years ago, and a ectopic pregnancy two months back. Her fasting blood sugar, serum cholesterol and blood pressure had been checked a few months ago, and had been normal.

As a child she had febrile fits, but had not had seizures after the age of 5 years. She had used an inhaler for asthma until she was 10 years of age. A year ago she was investigated for back pain and was noted to have a vertebral disc prolapse at the L4/L5 level with compression of the L4 nerve root. This was managed conservatively. She was not taking any medications, nor was she on any form of contraception. She had once developed urticaria after using amoxicillin.

Her mother had died in a road traffic accident when she was a child. Her other family members were healthy. She had been running her own catering service for the past 7 years and had a steady income, which was adequate for their needs. Her husband was a police officer and they have a 4-year-old son. They live in official police quarters. She has never smoked, taken alcohol or used any recreational drugs.

On examination her Glasgow Coma Scale was 15/15. She was obese, afebrile, not pale or plethoric. She had a few bruises on her right thigh and right arm, which she could not explain. There were no skin rashes or oral ulcers. Her pulse rate was 73/min, regular, and blood pressure was 130/80mmHg. Both blood pressure and pulse volume were equal on both arms. The heart was in dual rhythm, regular, and there were no murmurs. There was no carotid bruit. No abnormalities were found on examination of the respiratory system and the abdomen.

On neurological examination her pupils were equal and reacted to light, and optic fundi were normal. Eye movements were full, with no diplopia, but she had horizontal nystagmus on left lateral gaze. Visual fields were full, with no visual inattention, and her speech was normal. The other cranial nerves were normal. Tone was reduced in her left arm and left leg, and power was 3/5 in both upper and lower limbs on the left. Biceps, triceps and supinator reflexes were diminished on the left side. Lower limb reflexes were normal on the left side and the left plantar reflex was equivocal. Co-ordination was difficult to examine for on the left

side, but had normal heel-shin and finger-nose tests on the right. The right arm and leg were neurologically normal. There was loss of pain, touch, and joint position sense of the left arm and leg.

Can you summarize the history and examination findings?

A 33-year-old right-handed female was admitted with sudden onset left upper and lower limb weakness and numbness for two and a half hours, which remained static. There was no headache, loss of consciousness, or seizure activity at the onset. She gave a history of febrile fits, childhood asthma, a miscarriage 9 years ago, lumbar disc prolapse 1 year ago and an ectopic pregnancy 2 months back, with a heavy menstrual period last time. She was otherwise well, with no significant family history of any vascular disease.

She was obese, fully conscious and alert with GCS of 15/15. Left upper and lower limb tone was reduced and power was 3/5 with loss of sensation. Reflexes were diminished in the left upper limb while there were normal reflexes in lower limb with equivocal plantar response. Except for horizontal nystagmus on left lateral gaze, cranial nerves were normal. Cardiovascular, respiratory systems and abdominal examination was normal. Blood pressure was 130/80mmHg, no carotid bruits, and normal fundi.

What is your differential diagnosis for her acute presentation?

She has presented with sudden onset left sided hemiparesis and hemianesthesia. Most likely diagnosis is a stroke or transient ischemic attack. The other possibilities are post-ictal phase after a seizure, hemiplegic migraine, large artery dissections, or a space occupying lesion of the brain, although these are less likely.

What diagnosis would you favour?

Left sided anterior circulation TIA or stroke if weakness continues for more than 24 hours

When giving a diagnosis you must try to give a complete one. The complete diagnosis consists of several components, which are mentioned below.

- Anatomical diagnosis —
- Pathological diagnosis —
- Aetiology —
- Complications —
- Disability —

Especially when it comes to neurological conditions you should pay particular attention to two crucial questions, which cover the first two components in above list. The questions are 'where is the lesion?' and 'what is the lesion?'

In the answer given above the pathology of the lesion is discussed. Sometimes it might be important to be more specific in your answer if you are confident enough; however trying to be too specific will put you in trouble. For example, one might be tempted to comment whether this is an ischaemic stroke or a haemorrhagic stroke, which cannot be decided reliably clinically. In such a situation it is safe to avoid commenting on it unless the examiner specifically asks you.

The site of the lesion can be determined based on the clinical presentation. When there is involvement of both upper and lower limbs you should consider a level higher than the innervations of both. So in this case you should think of a lesion above the spinal segment for C5. Possible sites are the cerebral cortex, internal capsule, brain stem and upper cervical cord. Also when possible try to identify the structures that are involved in the horizontal level. For example, when describing a cervical cord lesion mention whether dorsal column, spinothalamic column or posterior column is involved. The clinical classification of strokes is described in Oxford-Bamford classification for stroke:

- Total Anterior Circulation Syndrome (TACS) - there is involvement of all cortical functions with unilateral weakness and/or sensory loss
- Partial Anterior Circulation Syndrome (PACS) - All cortical functions are not involved but has unilateral weakness and/or sensory loss
- Posterior Circulation Syndrome (POCS) - cerebellum and/or brain stem is involved, or isolated homonymous hemianopia.
- Lacunar Syndrome (LACS) - No loss of cortical functions, brain stem or the cerebellum is involved. Only subcortical areas involved, causing unilateral weakness and/or sensory loss.

What are the common causes for strokes?

Stroke can be due to ischaemia or haemorrhage. Ischaemic strokes can be due to atherosclerosis, hypertension, diabetes mellitus, smoking, high cholesterol and non-modifiable risk factors like age. They could also be cardioembolic, commonly due to atrial fibrillation. Haemorrhagic strokes can be due to hypertension, amyloid angiopathy, arteriovenous malformations or aneurysms.

Clinically is this more in favor of haemorrhagic stroke or ischaemic stroke?

It is difficult to comment reliably on clinical features alone. But it is more likely to be an ischaemic stroke in the absence of severe headache, nausea and vomiting, seizures, or deteriorating level of consciousness. However, I need to arrange an urgent non-contrast CT scan of the brain to exclude an intracerebral bleed.

What are the problems you have identified in this woman?

- The current acute problem is sudden onset weakness on the left side indicating an acute stroke

- Heavy per-vaginal bleeding in a woman who had an ectopic pregnancy 2 months back
- History of febrile fits
- Childhood asthma treated with inhaler until the age of 10 years

It is better to classify the problems either on a time scale (acute and long term), or based on several categories such as medical, psychological, and social so that you will not miss important problems, and the examiner understands that you can manage the case in an organized way. In this case it is better if you identify problems other than the above mentioned medical ones. They include her psychological state with regards to having a stroke at a young age, impact on her child and her work. These issues are quite important in planning out long-term care and providing her rehabilitation.

What about her disability? Did you do a disability assessment?

In the management of a patient with stroke, disability assessment is important. With rehabilitation, our aim is to make the patient independent as much as possible, so that she can perform her activities of daily activities (ADL) on her own. These include bladder and bowel control, grooming, toilet use, feeding, transfer, mobility, dressing, bathing etc. In an active young woman like this, instrumental activities of daily living (IADL), which refer to activities beyond ADL, are important. These include cooking, shopping, managing her finances, driving, using the computer or telephone, managing medication etc. These are important in bringing back normal or near normal life after the stroke.

There are several scales that are used to assess disability in patients following stroke. The commonest are the Barthel index and modified Rankin scale. These are generally done initially and then at regular intervals to assess the progress. Though you don't

have to know these by heart, it is important to be familiar with their components. The Barthel index scores on feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers (bed to chair and back), mobility on level surfaces, and climbing stairs. The modified Rankin scale is shown below:

0. No symptoms at all
1. No significant disability despite symptoms; able to carry out all usual duties and activities
2. Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3. Moderate disability; requiring some help, but able to walk without assistance
4. Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6. Dead

Why do you classify her as having a 'young stroke'? What is the clinical significance?

Mrs NB is 33 years of age and has no cardio-vascular risk factors or family history of vascular disease. Therefore I called this a young stroke. This has clinical relevance because the risk factor profile as well as the social and psychological impact of her illness are different in this age group.

There is no exact cut-off for the definition of young stroke but usually it is taken as 45 years of age. It is important to consider biological age rather than the chronological age. The risk factors in young people are different to that in the older population. For

example, haemorrhagic strokes are more common in younger patients (around 50%). Ischaemic strokes may be due to large vessel dissection, vasculitis, infective endocarditis, thrombophilia, or recreational drug use rather than due to atherosclerotic disease. The commonest cause for cardio-embolic stroke is atrial fibrillation in all ages. This has to be kept in mind when planning the investigations and managing this patient, especially with regards to secondary prevention. The psychological, social and financial impact is greater when a younger patient is disabled with residual weakness from stroke.

If you are the doctor seeing her on admission, what will your initial work up be?

Since she presented early, she is a suitable candidate for thrombolysis, provided that there are no contraindications. I will first exclude haemorrhage by doing an urgent non-contrast CT scan of the brain. If there is no haemorrhage, I will refer her for thrombolysis as soon as possible. Thrombolysis is offered for moderately severe stroke, and I would contact the stroke team to assess the severity using National Institute of Health Stroke scale (NIHSS). I will keep her nil-by-mouth as the stroke can affect the swallowing, insert a cannula, take blood for basic investigations and start on a normal saline infusion to prevent dehydration. I will monitor her random blood sugar and blood pressure.

Thrombolysis is proven to be beneficial when performed within 4.5 hours from the onset of symptoms. Therefore the exact time of symptom onset should be available and there should be a definitive neurological deficit. Patients are selected judiciously by doing a National Institute of Health stroke scale (NIHSS). If the score is too low (<5) it is considered a mild stroke which will recover without significant residual weakness and thrombolysis is not offered. If the NIHSS score is very high (>25) it is considered a major stroke and thrombolysis is not offered, as it is unlikely to benefit the patient. This is only a general guidance, and we need

to consider the overall effects on the individual rather than the numbers. Also if the neurological deficit is rapidly improving, or they have contraindications, thrombolysis is not given. The following are some exclusion criteria:

- Blood pressure $>185/110 \text{ mmHg}$ despite antihypertensive treatment
- Rapidly improving or minor stroke symptoms
- Stroke or serious head trauma within 3 months
- Major surgery within 14 days
- Prior intracranial haemorrhage
- Gastrointestinal or urinary tract haemorrhage within 21 days
- Platelet $<100000/\text{mm}^3$ or prothrombin time $>15\text{s}$ or haematocrit $<25\%$ or glucose $<50\text{mg/dL}$ or $>400\text{mg/dL}$
- Menstrual bleeding is generally not considered a contraindication.

Thrombolysis is done using IV r-tPA 0.9mg/kg (maximum 90mg bolus dose (10%) followed by an intravenous infusion for 1 hour (90%).

If she presented 6 hours after the onset of weakness what would be the plan of management?

When more than 6 hours have passed since the onset of symptoms, thrombolysis is not recommended. Therefore I will manage the patient addressing the following aspects: acute management, secondary prevention, and rehabilitation.

For acute management I will insert a cannula, take bloods for basic investigations including random glucose, full blood count, ESR, lipids, renal function, and start a normal saline infusion. I will ask the patient not to take anything orally until a trained

person has assessed safety of swallow. I will arrange for an ECG and a non-contrast CT scan of the brain to exclude haemorrhage. As the admitting medical officer I will inform the patient that she has had a stroke, and that she needs assessment by other experts. If available, I will admit her to the stroke unit.

CT scan has excluded a haemorrhage; how would you manage Mrs NB?

Since she is within the thrombolysis window I shall arrange treatment without delay, as the earlier the treatment is given the better the outcome.

If there is no thrombolysis facility, I will optimize cerebral perfusion to prevent further damage to the surrounding ischaemic penumbra. I will give oxygen by mask if the saturation is below <94%, and give her aspirin 300mg stat. Mrs NB is normotensive at presentation and was not on any antihypertensives. I will check for temperature and give antipyretics, paracetamol if she is febrile. Her blood sugar levels should also be maintained within normal range. She has no history of diabetes mellitus. She would benefit from a statin.

Why don't you try to achieve normotensive blood pressure targets in patients immediately after stroke?

If the blood pressure is lowered too fast, the blood flow to the brain can be impaired and the ischaemic penumbra can be affected, resulting in extension of the stroke. If blood pressure remains high in hospital after the acute period I will start on antihypertensive to control the BP slowly.

Within the ischemic brain, collateral blood flow is dependent on blood pressure. Hence acutely lowering blood pressure will impair cerebral perfusion. If the blood pressure is above 220/120mmHg in ischaemic stroke or 185/105mmHg in haemorrhagic stroke you might give antihypertensives to lower the blood pressures to the

above levels. If the patient was on anti-hypertensives before the onset of stroke, then these should be continued, but antihypertensives are generally not started during the acute phase. Other indications for lowering blood pressure are concomitant myocardial infarction, dissecting aneurysm, or for thrombolysis when blood pressure is above 180/110mmHg.

What are the steps that you should take in secondary prevention?

I would arrange for a MRI scan of the brain to confirm the diagnosis. MRI with DWI should show acute lesions and changes will be there for about 10 days. It is important to confirm the diagnosis in this young woman without any risk factors. This will also exclude demyelination, carotid dissection, etc.

I will review the results of ECG (for evidence of atrial fibrillation), random glucose, ESR, lipid profile.

If the ECG is normal I will arrange for continuous ambulatory ECG monitoring for at least a week, as paroxysmal atrial fibrillation is the commonest cause of cardioembolic strokes in people with no other risk factors.

Carotid duplex scan should be arranged for all non-disabling strokes and if there is significant stenosis they should be referred for carotid endarterectomy. If the carotid duplex scan suggests carotid dissection, CT angiogram or MR angiogram should be arranged to further evaluate this.

Considering her miscarriage, if it was in the first trimester it could have been due to an autoimmune condition like antiphospholipid syndrome or SLE. Therefore in addition to full blood count, ESR, ECG, liver and renal profiles I will do autoantibody and thrombophilia screen, which include ANA-DsDNA, ENA, ANCA, complement C3/C4 level, rheumatoid factor, prothrombin time, APTT, lupus anticoagulant, anti-phospholipid antibodies (anti-beta-2-glycoprotein-I antibody).

anti-cardiolipin antibody), homocysteine level and VDRL.

I will arrange for an echocardiogram, and if this is normal I will consider a contrast echo to look for patent foramen ovale (PFO).

If investigations show any specific cause I will address it accordingly. Otherwise, routine secondary prevention measures include antiplatelet therapy with aspirin and long acting dipyridamole or clopidoprel and treatment with a statin.

Should Mrs NB be managed in a stroke unit?

Since she is not severely disabled she can be managed outside.

That isn't quite correct. Ideally all patients should be managed in a stroke unit. However, there are constraints in doing this.

It is a misconception held by many that patients without severe disability can be managed outside a stroke unit. The most recent guidelines recommend that all the stroke patients irrespective of severity should be managed in a stroke unit. This is not practiced in all settings due to lack of availability of specialized stroke units to serve all stroke patients. Stroke units are staffed by coordinated multidisciplinary teams with a special interest in stroke care. The team includes medical, nursing, physiotherapy, occupational therapy, speech and language therapy, psychology and social work staff members. These teams of individuals arrange regular meetings (multidisciplinary team meetings) to plan rehabilitation goals, both short term and long term, for the patient. It is important for a young woman with a small child and business of her own to be able to return to her pre-stroke level of independence. There is substantial evidence to prove that rehabilitation outcome is significantly greater when a patient is managed at a stroke unit.

What complications can occur after stroke?

Medical complications include respiratory infections (aspiration pneumonia, orthostatic pneumonia and hospital acquired pneumonia), constipation, urinary retention, urinary incontinence and urinary tract infections, recurrent strokes, pressure ulcers, malnutrition, venous thromboembolism, post - stroke headache. Electrolyte imbalance like hyponatraemia, metabolic derangements like hypoglycaemia in diabetic patients, and poor recovery with residual disability. Psychological problems include depression and anxiety. Mechanical complications should also be considered - falls, fatigue, spasticity, shoulder subluxation, post-stroke neuropathic pain.

When will you start rehabilitation in this patient?

Once the initial medical problems are sorted out I will start rehabilitation.

Actually, it is better to start as early as possible.

Early rehabilitation is vital in stroke care and it starts from the initial contact of the patient with the healthcare staff. Rehabilitation is a broad concept where you plan all aspects of your management in a way that allows proper rehabilitation, and you optimize the medical and psychological status of the patient to enable active participation in rehabilitation. Early mobilisation is a key principle in stroke care to avoid many of the post stroke complications including venous thromboembolism, constipation and pressure ulcers. Therapeutic positioning is another principle that has to be taken into consideration from the beginning. If the medical conditions permits this, the patient is positioned in upright sitting position to promote optimal recovery (by modulating muscle tone, improving sensory stimulation and increasing spatial awareness) while minimizing complications. Nutritional and swallowing assessment, assessment of continence, activities of daily living, posture and movement have to be done.

hand in hand with medical management, and necessary activities and interventions should be planned out.

Are there any lifestyle advices that should be given to a patient who has developed a stroke?

With regard to diet they should be advised to take a diet with low total and saturated fat content, with adequate amounts of fish, fruit and vegetables. If there is hypertension, reducing salt content is important. For overweight and obese patients a plan to reduce weight should be offered. Smoking cessation and cutting down alcohol consumption are two other important aspects. The patient should be encouraged to participate in exercises and return to normal life.

How do you explain her nystagmus?

The presence of nystagmus means there is additional involvement of the cerebellum. Other symptoms and signs of the stroke points to a lesion in the subcortical area like the internal capsule. I will recheck my physical sign as I have not elicited any other sign related to cerebellum. I do know that if horizontal gaze is checked too far it could give rise to few beats, which is not due to cerebellar lesion. If it is present it may indicate two lesions. MRI scan of the brain should help exclude old stroke or other stroke mimics like demyelinating conditions.

If the symptoms had completely resolved within 2.5 hours what will be you do?

The most likely diagnosis in that case is transient ischaemic attack. This is defined based on resolution of symptoms in less than 24 hours according to the WHO 2005 definition. But still I will arrange the investigations to look for risk factors to reduce the risk of a stroke; I will arrange a carotid Doppler scan as the TIA is involving the anterior circulation, 24-hour ECG monitor.

aspirin 300mg orally for 2 weeks and then convert to clopidogrel monotherapy.

There is an arbitrary cutoff of 24 hours to define TIA. But now it has been clearly shown that there is some degree of infarction in some of the TIAs. If better imaging such as MRI diffusion weighted imaging (DWI) is performed these changes can be detected. The future risk of stroke TIA can be predicted using a score like the ABCD2 score, and based on the risk you can decide whether to admit the patient for investigations, or investigate the patient as an outpatient. If the score is ≥ 4 there is a high risk of developing a stroke within 2 days. Such patients should ideally be seen in a high risk TIA clinic within 24 hours and risk factors should be assessed and treated, and carotid imaging should be done and reviewed.

Case 8

Mr RR, 53-year-old man, presented with cough, wheeze, and fever for 5 days. Over the previous 5 days his cough had progressively worsened, and become productive with yellowish sputum. Only a small amount of sputum is passed at a time, and he has had cough throughout the day. He had not noticed any blood in his sputum. He also had difficulty in breathing and a wheeze, which was persistent throughout day and worsened with mild exertion. However, he did not complain of orthopnoea, paroxysmal nocturnal dyspnoea, body swelling or chest pain. He also complained of fever with chills and rigors over the same period. He had fatigue, lethargy and anorexia, but no nausea or vomiting. He did not complain of any chest pain, urinary or bowel symptoms, headache or photophobia.

Two weeks prior to this episode he had coughed up a small quantity of blood stained sputum once. His appetite had been normal previously, and he had not been losing weight. He had noticed that he had been passing large volumes of urine, and had to wake up 2-3 times at night to pass urine, with excessive thirst.

Over the last 10 years he had noticed gradually worsening shortness of breath and cough with small amounts of sputum, and reduced exercise tolerance. He had had several exacerbations of dyspnoea, wheeze and productive cough, for which he had been admitted to hospital. On these occasions he was treated with oxygen by mask nebulization and sometimes i-

He used to smoke 15-20 cigarettes per day for the past 35 years, and had been advised many times to stop. He eventually stopped smoking 5 years ago. He had been using inhalers for the past 5 years, though he was not aware of their names. His adherence to treatment was good.

He was diagnosed to have type 2 diabetes mellitus 8 months ago, at which time he had noticed increased urinary frequency, thirst and nocturia. He had been given oral hypoglycaemic drugs at the medical clinic. He gave no history of tuberculosis, heart disease, hypertension or hypercholesterolaemia. He had no visual impairment, pain or numbness in the feet, or episodes of sudden body weakness, numbness or inability to speak. He had never had an eye examination or education on foot care or lifestyle changes pertaining to diabetes management. He could not remember his last blood glucose report, but said the doctor had told him his blood glucose was ok.

His father had died of liver disease at the age of 60 years. His elder brother had successfully completed a course of treatment for pulmonary tuberculosis 8 years earlier. His mother is 75 years old and is not on any medications.

He used to drink a quarter of a bottle of spirits on 4 days of the week for about 15 years, but had stopped drinking 2 years ago. He denied using recreational drugs. He had worked as a manual labourer until 5 years before, when he stopped work due to his poor health. His wife was unemployed. Four of their children were married and living separately. The fifth child was living with his parents and was a watch repairer. He did not have a pet, they used a gas cooker to prepare meals, and he had not been exposed to animals or toxic fumes during his working life.

Can you summarise your history before presenting your examination findings?

Mr RR, a 53-year-old man, was admitted with worsening of shortness of breath, cough with yellow sputum and wheeze for one week. There was associated fever with chills and rigors, lethargy and anorexia. He gives a history of one episode of haemoptysis two weeks back. He has had type 2 DM for 8 months and recurrent chest symptoms for the last 10 years. He has polyuria and nocturia and is not aware of what his glycemic control is like. He is married, stopped smoking 5 years ago after 30 pack years of smoking, and is unemployed for 5 years because of his current illness. There is no history of weight loss or exposure to industrial dust, toxic fumes, birds, or animal fur. He has a contact history of TB.

Shall we try to identify his problems based on your history?

His acute medical problems are:

- fever with cough, sputum and shortness of breath
- haemoptysis, with contact history of tuberculosis
- polyuria, nocturia and polydipsia

His long standing medical problems are,

- progressive shortness of breath with cough and wheeze for 10 years
- diabetes mellitus for 8 months

His socioeconomic problems include

- lack of income due to illness
- limited family support

When a patient presents with episodic shortness of breath, cough and wheezing what are your main differential diagnoses?

Asthma and chronic obstructive pulmonary disease (COPD)

From the history, what features differentiate two? What is more likely in this patient?

Age of onset is helpful. **Asthma more commonly** starts from childhood, although there is a type called **adult onset asthma**. **COPD presents commonly in the adult** population since it usually occurs following prolonged exposure to a noxious substance, commonly cigarette smoke. **In most patients with COPD there is history of cigarette smoking or exposure to a toxic fumes, dust, or animal fur.** In asthma, patients often demonstrate **worsening of symptoms following a particular exposure, or climate change**. Patients with asthma are almost asymptomatic between episodes because of complete reversibility of airways obstruction. However, **COPD patients have persistent shortness of breath, which worsens even with mild exertion leading to exercise intolerance**, and the condition progresses chronically. Patients with asthma will have **good response to inhaler therapy, which is not so well noticed in patients with COPD.**

Thus, considering his older age of onset, and progressive nature of the symptoms in a patient who has smoked 30 pack years, this patient is most likely to have COPD.

What is meant by the term COPD?

COPD is a condition where there is progressive airflow limitation **which is not fully reversible with bronchodilators, and is associated with an abnormal inflammatory response of the lung to noxious particles and gases.**

Present your examination findings, please

On examination he looked ill and wasted, was dyspnoeic, breathing with pursed lips, and had an audible wheeze. He was afebrile, not cyanosed, and was neither pale nor plethoric. First degree digital clubbing was present. There was no lymphadenopathy, flapping tremor or ankle oedema.

His respiratory rate was 28 cycles per minute. His chest was barrel shaped. He was using his accessory muscles of respiration, and had intercostal recessions. Chest expansion was reduced bilaterally. On auscultation breath sounds had a prolonged expiratory phase. Bilateral polyphonic rhonchi were heard, and coarse crepitations were present in all zones, more on the right side. The cardiac and liver dullness were reduced. Heart rate was 92/min, blood pressure 120/70mmHg. JVP was not elevated and heart sounds were normal. Abdomen, neurological, and musculoskeletal systems were normal.

Did you get a chance to have a look at his sputum cup? Do you think it is important?

I did not have time to look at his sputum cup. But it is very important to do so.

Examination of sputum yourself gives lot of valuable information in a patient complaining of sputum production. For example, in a patient with bronchiectasis you might see copious amounts of purulent sputum. Pink frothy sputum is seen in severe pulmonary oedema. Yellow or green sputum indicates infection. When there is blood in the sputum one has to consider malignancy or TB. There might be black specks in sputum due to heavy smoking.

You mentioned that he is on inhalers. Did you check his inhaler technique?

The inhaler was not available with the patient during the clinical interview. However, from what he describes, it appears that he is

aware about the correct technique of inhaler use.

Inhaler technique is a commonly overlooked aspect in management of patients with obstructive airway disease. There are many patients whose disease is inadequately controlled because of poor inhaler technique. Therefore it is important to ask patients to demonstrate the technique in front of you. The inhalers are sometimes colour coded. For example, blue inhalers are short-acting bronchodilators, like salbutamol, and brown is for corticosteroids.

You mentioned about first degree clubbing. Tell us its significance.

I was able to elicit fluctuation in the nail beds, and the angle between nail bed and the nail fold was obliterated, but there was no increased curvature or diameter of the nail.

Clubbing of the nail is seen in many conditions related to several systems. Respiratory causes include lung carcinoma, idiopathic pulmonary fibrosis and suppurative lung conditions like lung abscess, empyema and bronchiectasis. Cardiovascular conditions are infective endocarditis, congenital cyanotic heart disease and atrial myxoma. Gastrointestinal causes include inflammatory bowel disease and primary biliary cirrhosis. Some people have primary clubbing where there is no demonstrable secondary cause. This could be congenital clubbing or idiopathic clubbing.

The mechanism of clubbing is not very clear but it is believed to be due to hypoxia of the peripheries leading to formation of cytokines like platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) which cause increased proliferation of tissue in the nail bed.

Clubbing is recognized by the presence of a fluctuating, boggy feeling in the nail bed, increased angle between the nail and nail fold, which is normally less than 160° , and increased curvature of

Case 8

the nail. This can be demonstrated by keeping the dorsal surfaces of two fingers together and looking for the kite - shaped gap, which is lost in clubbing.

Grading of clubbing has little clinical significance, but for interest's sake is given below:

Grade 1- Fluctuation and increased angle between nail and nail bed

Grade 2- Increased diameter of the nail

Grade 3- Increased pulp tissue with drumstick appearance

Grade 4- Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy is not seen in all cases of clubbing. It is seen in some patients with lung cancers.

You have noticed pursed lip breathing in him. What is the reason for this?

There is pathological loss of airway recoil pressure in COPD. Airway recoil pressure is needed to maintain airway patency during expiration; without it, the airways collapse during expiration. By pursed lip breathing patients increase their airway pressure as a result the small airways remain open.

I would look for lung carcinoma and bronchiectasis. However, he does not produce copious amounts of sputum, suggestive of bronchiectasis.

I would have to consider tuberculosis also as a possibility, given his contact history.

This patient has presented with progressive shortness of breath and cough. You have also found clubbing in him. Though sputum production, wheezing, and coarse crepitations are there, you should also think of interstitial lung disease.

This patient was recently found to have high blood glucose readings. What are the possibilities?

It is likely that he has type 2 diabetes mellitus. With a history of repeated hospital admissions and possible corticosteroid use, I would also consider secondary diabetes. He has no other features of Cushing's syndrome. Another possibility is chronic pancreatitis due to heavy alcohol use, although he doesn't have other features to support this, such as steatorrhoea and backache.

How will you investigate Mr RR?

My initial investigations will be focused on diagnosing the acute problem, and assessing him in relation to glycemic control and cardiorespiratory status. I will go through his old records to find out if any diagnosis had been made previously. I will do a chest radiograph to look for evidence of consolidation, lung abscess, lung tumour, or tuberculosis. The x-ray will be useful in excluding concomitant pneumothorax, and also heart failure as causes for worsening shortness of breath. It will also show evidence of COPD. I will do a full blood count to look for any polycythaemia, and look at his white cell count to see whether there is any evidence of respiratory tract infection. I will check his random blood sugar to get an idea about glycemic control. Serum electrolytes will be done to look for any impairment due to acute illness. An ECG will

show whether there are any ischaemic changes or changes due to cor pulmonale. Sputum will be sent for acid-fast bacilli, culture and ABST. If pulse oximetry shows low oxygen saturation I will arrange an arterial blood gas level to determine his requirements for oxygen therapy.

Once the acute management is established I will further evaluate him after going through his old records to establish his diagnosis if not already done and to complete his workup in relation to diabetes mellitus. In particular, given his history of haemoptysis and clubbing, I will look for any suspicious areas in the chest radiograph suggesting bronchiectasis or lung cancer. A CT scan of the thorax may be needed. At the same time I would do a Mantoux test for tuberculosis. If he has never undergone lung function tests they have to be performed to establish the diagnosis and grade disease severity. Echocardiogram is also helpful in looking at his cardiac status and to rule out the possibility of cor pulmonale. I will review the ward test urine done, and if there is no protein noticed will send urine for microalbuminuria. Other tests include serum creatinine, lipid profile and HbA1c.



FBC
X-ray
SE
ECG } cor pulmonale
ECO }
LFT - establish diagnosis
Grade disease severity

This is his chest x-ray. What are your comments?

This chest appears hyperinflated, with a long narrow mediastinum. The ribs are more horizontal than normal. His seventh rib crosses the diaphragm anteriorly. The diaphragm is flattened. I can't see any emphysematous bullae however.

The features in the chest radiograph which suggest emphysema are

PA view:

- Hyperinflated lung fields. Reduced vascular markings. hyperlucent lung fields
- Ribs more horizontal
- Pushed down diaphragm: usually the 6th rib crosses the diaphragm anteriorly - in emphysema the 7th or lower rib crosses the diaphragm anteriorly
- Narrow elongated heart shadow

Lateral view:



- Increased anteroposterior diameter
- Flattening of the diaphragm (best seen on lateral X-ray)
- Increased retrosternal and infra-cardiac air (left hemidiaphragm seen in its entirety)

You have been mentioning about controlled oxygen How will you manage his acute exacerbation of COPD?

Acute management includes positioning the patient in a comfortable posture, i.e., propped up, and providing him controlled oxygen via venturi mask. I will then arrange to nebulise him with bronchodilators, both salbutamol and ipratropium. I will start him on steroids- intravenous hydrocortisone to begin with, followed by a short course of oral steroids, say oral prednisolone for 5 days. I will monitor his blood sugar regularly and watch for hyperglycemia. Since there is high suspicion of infection I will also give him antibiotics. While providing these measures I will check his oxygen saturation and arterial blood gas to avoid hypoxia as well as hypercapnoea. I will aim for an oxygen saturation between 88-92%. Oxygen can be gradually increased if there is no significant rise in pCO_2 , and nebulisation can be repeated. If his oxygen saturation remains low, or he is developing significant CO_2 retention, we will have to consider non-invasive bi-level positive airway pressure ventilation (BiPAP), or perhaps even intubation and mechanical ventilation. Chest physiotherapy is useful in removal of retained secretions.

You mentioned controlled oxygen replacement in acute exacerbations. What is the physiology behind this practice?

There is hypoxia due to V/Q mismatch in patients with COPD. In normal individuals, CO_2 is the main stimulant of respiration, which acts on both central and peripheral chemoreceptors. But in patients with chronic hypercapnoea, these receptors become insensitive to CO_2 , and ventilation is driven by hypoxia. Therefore attempts to abolish hypoxia completely by administering oxygen can reduce respiratory drive and lead to hypercapnoea. Also, a small increase in inspired oxygen can cause an increased SpO_2 in blood that is adequate to cause a significant increase in oxygen saturation. Therefore it is safe to start with lower percentage and titrate up if necessary.

But do not forget that hypoxia is dangerous and patients can die easily when enough oxygen is not administered. Patient should be closely observed, and if there is persistent hypoxia, or rise in CO₂ partial pressure, ventilatory support will be needed.

What are the steps in the long-term management of COPD?

Long term management includes close monitoring and follow-up with good pharmacological and non pharmacological support. The most important step is smoking cessation, and where required, support should be arranged for this. Patients need regular follow up and assessment of progression of the illness. They are usually given annual influenza vaccine and pneumococcal vaccine to prevent further deterioration due to infection. Pulmonary rehabilitation includes education and cardiovascular conditioning of the patients.

Pharmacotherapy includes inhaled bronchodilators, which could be anticholinergic drugs such as ipratropium or tiotropium, and short acting beta-agonists such as salbutamol. Long acting beta agonists like salmeterol are also used but usually combined with inhaled corticosteroids. Early recognition and prompt treatment of infections reduces further lung damage.

Another pharmacological therapy is long-term oxygen supplementation. It is of proven benefit, but the equipment is costly.

Physiotherapy, in particular respiratory muscle training, is of benefit.

Lung reduction surgery and lung transplantation are performed in selected patients to improve outcome.

What are the cardiac complications you anticipate in the patient?

Cor-pulmonale is one complication anticipated in COPD. Long standing severe COPD leads to pulmonary hypertension, whi-

will cause right ventricular hypertrophy and eventually right heart failure.

Ischemic heart disease is another potential complication in this patient. He was a heavy smoker and has diabetes. Furthermore, COPD is also known to increase the risk of ischaemic heart disease as it gives rise to a chronic inflammatory state.

Have you heard of any scores used to assess severity of COPD?

The Global Initiative in Obstructive Lung Disease (GOLD) criteria uses spirometry findings and symptoms for severity assessment. Another simple severity scoring system is Medical Research Council (MRC) grading which uses the degree of breathlessness. But there are other new systems, which are more sophisticated.

What advice would you give regarding nutrition?

This patient has poorly controlled diabetes and evidence of malnutrition. While optimizing medical management and ruling out secondary causes like lung cancer as a cause for wasting, I will plan to optimize his nutrition. I will obtain a nutritionist's input. Basic concepts will include having three main meals and two snacks a day regularly, with restriction of carbohydrates and fats. I will advise him to take the required amount of carbohydrates mainly as complex carbohydrates. I will also focus on the need for high quality protein, like fish and eggs.

Case 9

Mr AA, 26-year-old male who is being treated for epilepsy from the age of 10 years was admitted following an episode of abnormal movements of the body lasting five minutes. The history was taken from the patient and a bystander.

The previous night he was out having dinner with his friend when he felt 'funny', with generalized aching headache. He was unable to concentrate on the surrounding environment. He had had similar episodes in the past, which were generally warning signs of an impending seizure. He had then slumped back in his chair. His friend noticed right-sided jerky movements of the upper and lower limbs and face. His mouth was deviating to the right side. There was no preceding rigidity of the limbs. He did not have faecal or urinary incontinence; his eyes did not roll upwards, nor there was frothing at his mouth. He had not sustained any injuries or tongue bites. There was a brief period of clouding of consciousness and unresponsiveness. The abnormal movements persisted for about five minutes and stopped before he was admitted to hospital.

Following this he had severe headache and drowsiness. There was no confusion or loss of consciousness. The episode was not associated with sweating, palpitations, chest pain, dizziness or vertigo. He had had his lunch about 3 hours earlier. He had not

taken alcohol or recreational drugs. He was not on any treatment, and had not been under any psychological stress. He had not had any sleep deprivation. He was adherent to his treatment.

He was diagnosed as having epilepsy at the age of 10 years. These episodes comprised right-sided jerky movements with loss of consciousness lasting about 10 minutes, with tongue biting, incontinence of urine and frothing at the mouth. He had had several episodes per year even after starting treatment. There had been one admission to ICU, probably due to status epilepticus. He had been investigated with blood tests, EEG, CT and MRI brain, but claimed to be unaware of the results of the investigations. He was initially started on sodium valproate. Later on, this was changed to phenytoin sodium. One year ago he was changed over to carbamazepine, after which there had been a reduction in the frequency of seizures. The last seizure was three months back, and had been triggered by smoking marijuana. Unlike in childhood his recent episodes were less severe, with shorter duration, and without loss of consciousness.

He did not have any symptoms in relation to his cardiovascular, respiratory, gastrointestinal or genitourinary systems. He had no fever, skin rashes, joint pain or swelling, unsteadiness, double vision or yellow discoloration of eyes.

There was no history of childhood brain infections, head trauma or episodes of sudden onset body weakness in childhood. There was no history of any other illnesses, and had not undergone any surgeries. There was no history of food or drug allergies. None of his family members have epilepsy.

He is single, educated up to the GCE ordinary level. He works as an attendant in the hospital. There is no exposure to any at-risk activities such as climbing heights, drawing water from deep wells, working with heavy machinery. He does not drive. He lives with his parents and a younger sister. Both he and his family are aware of his seizures and what to do and not to do during these

episodes. He is aware of the need for regular medication and the avoidance of precipitating factors. However he consumes alcohol about once a week and smokes 1-2 cigarettes per day. Occasionally he smokes cannabis.

On examination he was fully conscious and oriented. General examination did not reveal any abnormalities. Cardiovascular system examination was normal with a pulse rate of 80/min and a blood pressure of 120/70mmHg. Respiratory system and abdomen examination were normal. Neurological examination including cranial nerves, fundoscopy, upper and lower limbs did not reveal any abnormality.

Can you summarise the history and examination?

My patient is a 26-year-old male with epilepsy from the age of 10 years, presenting with an episode of abnormal jerky movements of the right side of the body with deviation of the mouth to the right side, preceded by an aura and headache. He had transient loss of awareness, and the episode lasted for 5 minutes. There was drowsiness and headache after the episode. He had been fully investigated since childhood, and is currently on carbamazepine. There are no identifiable trigger factors and he has not experienced any significant side effects of the drug. He gets about 3 to 4 seizures per year and is well adapted to living with the disease. He does not drive. Examination findings were normal.

Tell us how the disease has affected his lifestyle?

He is compliant with medications, and has a good understanding of his disease, and what to do and what not to do. He copes well with the disease, but has had to take time off work because of occasional hospital admissions. He does night shifts once in two weeks, but sleeps the next day, and has had no seizures as a result of breaking rest.

The objective of a good social history is to find about the impact of the disease on his life and how his lifestyle has affected the course of illness rather than collecting information blindly. Particularly in a chronic illness like this, one should go into detail regarding the social history with respect to those concerns, so that the management plan can address any issues. When you are talking about the effect of the disease on his life, whether his day-to-day activities, occupation, marriage, education were affected by the illness have to be discussed. The need to have special safety measures, regular medicine, and avoidance of sleep deprivation, the need for regular clinic follow up, and how the medications may affect his life in relation to above aspects. Also financial aspects are relevant, especially if he has to pay for his medicines.

On the other hand, his level of education, family support, financial status, and his job might affect how he is complying with medicine, lifestyle measures and follow up. In this patient who is working as a hospital attendant there might be sleep deprivation due to night shifts. Availability of resources to seek medical advice in an emergency is another important aspect. Whether he uses alcohol, cigarettes or other recreational drugs that can affect his health is very important.

You mentioned that you could not identify a triggering factor for this episode. What are the triggers for a seizure episode?

Sleep deprivation, alcohol, flickering lights, missing meals and missing drugs are common triggering factors. Any physical stress like infection, fever or trauma as well as psychological stress can trigger a seizure episode.

You also mentioned that he does not have any side effects from carbamazepine. What are the usual side effects?

There are neurological side effects such as ataxia, dizziness, vertigo and diplopia. Minor side effects include dry mouth, headache, nausea, vomiting and drowsiness. It can also cause side effects like

dermatitis, urticaria and haematological abnormalities. Serious but rare side effects include Stevens-Johnson syndrome, aplastic anaemia, water intoxication and hepatitis.

You gave a detailed description of the onset and progress of the seizure. How does it help you in managing Mr AA?

In some patients with focal motor seizures, abnormal movements start on a specific localized area like the fingers and then progresses to the other parts of that extremity. This is called 'Jacksonian march'. This may indicate that the seizure activity progresses over a region of that particular cerebral hemisphere. It is important to rule out a structural lesion in this sort of case, however this has been done previously and nothing has been found.

For his acute presentation, what is your differential diagnosis?

In view of a well-established diagnosis of epilepsy and the history I would consider a seizure episode as the most likely diagnosis. I had to take the history from an eyewitness, and the details of the event were confirmed. I would also like to go through the records to make sure that a structural lesion has been ruled out. The clinical features strongly support focal seizures with secondary generalization. The preceding abnormal sensation, loss of consciousness, jerky movements for five minutes and post ictal headache and drowsiness support this diagnosis.

Another differential diagnosis is pseudoseizure, also called non-epileptic attack disorder (NEAD). This can be commonly mistaken for seizures. But they are seen commonly in females and have more pronounced dramatic movements, especially in the setting of a stress or social distress. This is less likely in this

post-ictal features also make this diagnosis unlikely.

Syncope is unlikely given the associated features, although a few jerky movements can be seen during episodes of syncope.

When a patient is not responding to medicine you have to consider alternative diagnosis, but do not forget there are many patient who will not respond to monotherapy. On the other hand one should keep an open mind. There are many patients with NEAD who were erroneously diagnosed as having epilepsy by specialists. So you have to be open in your approach. Also patients with true epilepsy can have NEAD and they can mimic true episodes and produce diagnostic challenge to the clinicians.

Have you heard of any blood investigations that can help to differentiate seizures from NEAD?

Serum prolactin levels can help in differentiating the two. In patients with true epilepsy, prolactin levels are elevated soon after the episode. If the levels are normal soon after the episode it is more in favour of a NEAD.

Unfortunately in certain forms of epilepsy like simple partial seizures and when seizures do not involve the mesial temporal areas prolactin will not rise. On the other hand sometimes with simple syncope prolactin levels can rise. Other serum markers like CPK, serum lactate, white blood cell count and serum cortisol level are of limited value.

A video-EEG is the gold standard to diagnose epilepsy and to differentiate NEAD. Sometimes provocation like sleep deprivation are used to trigger seizures.

If you take this episode of seizure, what type of a seizure did your patient have?

I think it is a complex partial seizure. Since there was abnormal movement of only one side of body and there was preceding abnormal sensation with transient loss of consciousness.

All seizures cannot be classified based on clinical features. When a patient is treated with anti-epileptics, the features of the seizure can get modified. In such cases it is difficult to classify a seizure under the usual classification. The International League against Epilepsy (ILAE) has revised the classification of seizure types. The two main categories are focal and generalized seizures. The term 'partial seizures' was removed. Also focal seizures are categorized into focal seizures with dyscognitive features and without dyscognitive features. This has replaced the 'simple and complex partial seizure' terminology, although the older terms are still used.

His epilepsy was diagnosed at the age of ten years. At that age, what are the important underlying causes for epilepsy? How does this differ when a 65-year-old male is newly diagnosed to have epilepsy?

Adolescence is the time period in which idiopathic and genetic epilepsy syndromes present. However other causes including CNS infections such as meningitis and encephalitis, head trauma, brain tumors and structural development abnormalities in the brain can also manifest at that age.

Idiopathic epilepsy is rare to present for the first time in the elderly. Common causes for new onset seizures in the elderly include cardiac arrhythmias, drug interactions causing hypotension, and prolonged syncope, electrolyte disturbances like hypernatremia, hyponatremia, hypocalcaemia, metabolic derangements like hypoglycemia, hyperglycemia, hypertensive encephalopathy, ischemic changes due to old strokes and neurodegenerative disorders like Alzheimer's disease. In particular, in the elderly, space occupying lesions, either primary or secondary brain tumours, should be considered.

Causes such as brain tumors, trauma, and cerebral infection like meningitis encephalitis, cerebral abscess formation, or primary or secondary brain tumour can manifest at any age.

You have found that he is sufficiently well educated regarding the disease. What aspects are you interested in?

First of all he should have a good general understanding about epilepsy, i.e., what epilepsy is, why it happens and the prognosis. Another important aspect is education regarding the drugs, which includes the name of the drugs, dosage forms, how to take, when to take, potential side effects, and drug interactions. There is often variation between the efficacy of different preparations of the same drug, and patients are advised to stick to the same preparation or brand. The importance of adherence to drugs has to be emphasized. He should also be aware of the potential triggers for seizures.

Another important aspect is for his relatives and friends to be aware of first-aid measures to be taken during these episodes, such as turning him to his side, allowing secretions to drain freely, and keep the airway clear. It is inadvisable to put anything inside his mouth, and if there is any food in the mouth this should be removed. It is important to tell the family or friends to take him to a hospital if the seizure does not stop within 5 minutes, or if he develops recurrent seizures. He should be educated on the importance of lifestyle measures to avoid personal injury during these unpredicted episodes. He should also be aware about the psychosocial impact of the disease, including stigma, and be reassured that he can have a near normal life despite certain restrictions.

What advise will you give this patient on lifestyle measures?

I will advise him to avoid triggering factors. He should avoid sleep deprivation, thus will need to preferably avoid doing night shifts. He should avoid alcohol and smoking, avoid strong flickering lights, as these are well known trigger factors. He should avoid driving, swimming, climbing heights, bathing alone in river or sea, drawing water from deep wells. At the same time I will advise him regarding the things that he can do safely, like walking, running.

I will advise him that the disease is not a restriction towards living a normal life in most ways, and that he can marry and have children - it is particularly important to tell him that epilepsy is generally not genetically transmitted.

Do you know why he was started on phenytoin sodium?

From my history I could not find exact reason. I need to go through his records and find out. But I believe that it might have been due to poor response, or due to adverse effects, with sodium valproate.

What would be the correct approach if the patient is not responding to the initial antiepileptic drug?

Having ruled out an alternative diagnosis, we would have to look for reasons for his poor response. This includes any trigger factors or poor adherence to treatment. Once these are addressed we have to determine whether the given treatment, dosage and frequency are correct with regard to the epilepsy syndrome and the patient. If the drug is correct we should increase the dose to maximum recommended dose. We have to check whether there are any other drugs which interfere with anti epileptics making their bioavailability lower. When the patient is on the maximum tolerated and safe dose, and the response is still not adequate, one approach is to switch to another first line drug while gradually tapering over the first drug. If good control still can't be achieved, combination therapy is considered.

This is the recommended method to approach a patient with epilepsy who is not responding well to treatment. What you have to understand is increasing drug dose, changing drugs or combination therapy are done only after careful assessment of the other aspects. In some patients who are responding significantly but not achieving adequate control, it is reasonable to add a second drug.

How do you assess the adherence to treatment in this patient?

The simplest method is directly questioning from the patient regarding his adherence. Most patients give a reasonable estimate on their adherence. In some settings pill counting, where the number of pills remaining with the patient is counted, is employed, especially in elderly patients. Monitoring drug levels in the blood is another method used to determine adherence to treatment. With the given dose if the patient has not achieved the expected concentration, it is possible that his adherence is poor. We also have to think of other possibilities like poor absorption, differences in drug metabolism, and drug interactions.

He has undergone EEG earlier. What is the place of EEG in a patient with seizures?

It helps in the diagnosis, classification, and prognostication of the disease. An EEG taken during seizure activity is likely to show electrical seizure activity that is valuable in establishing the diagnosis. But its absence does not exclude epilepsy, and it is very difficult to perform EEG during an episode since they commonly happen at unpredictable times. Most of the time EEG is performed during inter-ictal periods, and can show epileptiform activity that supports the diagnosis of epilepsy.

It is also useful in classifying the seizure type and specific epilepsy syndromes, which helps in deciding on treatment. Patients with epilepsy whose EEG is abnormal have a poorer prognosis. When a patient presents with first seizure, and the EEG is abnormal, the likelihood of a second episode is high. In such situations it is commonly decided to start on antiepileptics early.

In the initial assessment of a patient presenting with seizure what other investigations will you do?

Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scan of the brain is done to look for underlying structural

brain lesions. It is not routinely done in all patients specially if there is clear clinical evidence of a generalized epilepsy syndrome. But in my patient it was necessary since he had a focal seizure. Other investigations are done to look for uncommon but treatable secondary causes. Random blood glucose levels are done to look for hypoglycaemia as a cause of seizure. Electrolyte abnormalities also cause seizures. Therefore serum calcium, magnesium, sodium and potassium are checked routinely. If there is any clinical suspicion liver functions and renal functions are also done.

You mentioned that he has a history of status epilepticus. What do you mean?

Status epilepticus is a continuous seizure that lasts beyond 30 minutes, or repeated episodes of seizures without regaining consciousness in between.

As a general definition this is commonly used. But you have to be clear about the following concepts. Status epilepticus has many subtypes, the most important being generalized tonic clonic status epilepticus, which is also called convulsive status epilepticus. There are other non-convulsive status epilepticus subtypes such as simple partial, complex partial and absence status epilepticus.

Furthermore, most seizures (>80%) resolve within five minutes and if a seizure does not resolve within that time there is a high chance that it will continue unless treated. If a seizure continues longer it becomes even more difficult to control. Therefore any seizure that goes beyond five minutes should be treated aggressively and a seizure that goes beyond 15 minutes is considered a potential status.

How would you manage a patient with status epilepticus?

Initial management includes positioning patient in safe way, to avoid injuries and aspiration. The general status of the patient should be managed following the ABCD approach. This is by securing the

Airway- clearing secretion or food; ensuring Breathing- providing oxygen, and if the breathing is obstructive inserting an airway; and monitoring Circulation with vital parameters like blood pressure, pulse rate, respiratory rate and oxygen saturation. I will immediately secure venous access with a large wide bore cannula and take blood for investigations like blood sugar and electrolytes. If rapid assessment of blood sugar is not available I will give intravenous dextrose if there is any suspicion of hypoglycaemia. If the patient is malnourished or there is a possibility of alcohol abuse, I will add thiamine.

Drug management includes intravenous lorazepam 4mg or diazepam 10mg immediately. If the patient is not responding to this, intravenous phenytoin by slow infusion should be given at a rate of maximum 50mg/min. By this time I will arrange senior and expert help since this is going to be a difficult scenario with the potential of brain damage. If the patient does not respond to phenytoin, intravenous phenobarbital 10mg/kg will be given at a rate less than 100mg/min. If the patient is not responding to any of them and continues to have seizures, we will need to intubate and induce anaesthesia with propofol or thiopental.

Sometimes people use rectal diazepam or buccal midazolam instead of intravenous lorazepam or diazepam. What is the importance of this?

When intravenous access is not available buccal midazolam and rectal diazepam is a good alternative depending on its availability. These are safe to administer in the community setting. These drugs when given intravenously, have a higher risk of respiratory depression. Therefore in such instances buccal or rectal routes are preferred.

You mentioned that his previous episode happened while taking cannabis. Is there any relationship between those two?

Cannabis is not known to precipitate seizures. Actually some studies have revealed that cannabis can be helpful to treat seizures if used medically!

What are the health effects of cannabis?

Health effects of cannabis include short-term effects, long-term effects, and dependence. Short-term effects include physical effects like tachycardia, conjunctival injection, and mental effects like euphoria, sedation and cognitive impairment. Long-term effects include mental effects like cognitive deterioration and precipitation of psychotic disorders. Physical effects include precipitation of angina and worsening of ischemic heart disease, and respiratory effects such as chronic bronchitis.

Dependence is also seen, though not as common as substances like alcohol and opiates. Withdrawal symptoms like irritability and sleep disturbance can take place.



Case 10

Mr MM, 54-year-old man, presented with diarrhoea and heat intolerance for one and half months. Over the last one and a half months he developed loose stools with increased frequency, upto 7-8-bowel openings per day. Previously he used to have one to two bowel openings per day. There was no blood or mucous and he did not have nocturnal diarrhoea. Each time he opens bowels the volume of stool is small, with excessive flatus. Diarrhoea was not related to any particular foods, and the stools were not bulky, smelly or difficult to flush. There was cramping lower abdominal pain, and after defecation this pain was relieved. There were no episodes of constipation, tenesmus, abdominal distension, nausea or vomiting. Over the same period he noticed marked weight loss, although he had not weighed himself. His appetite was good and he had increased his food consumption.

He had also started experiencing heat intolerance with excessive sweating. There is insomnia, and he gets up from sleep several times at night. There was no irritability or restlessness. He had noticed tremors of his hands.

He had body weakness with difficulty in standing from sitting position, climbing stairs and lifting weights. There was no neck pain or backache. There was no incontinence, sensory loss, swallowing difficulty, or imbalance. There was no shortness of breath, chest pain, palpitations, cough or wheezing. There were no urinary symptoms, skin rashes, swelling of the body, joint pains or swelling of joints. He had not noticed any neck lumps.

He had been previously well and did not have any history of hypertension, diabetes or hyperlipidaemia. He has never undergone any surgeries, and there are no known drug or food allergies. He does not have a family history of thyroid disorders or autoimmune diseases. Two of his brothers have ischaemic heart disease, hypertension and hyperlipidaemia and his sister has diabetes. He is married with three children aged 21, 28 and 30 years. They are all married. Mr MM was living with his younger son, his wife and their son. He owns a shop, which is now run by his son. He has good family support. He had never smoked and does not take alcohol.

His weight was 73kg and height was 174 cm. Body mass index 24.1 kg/m². He was not dyspnoeic, not wasted and did not appear anxious or restless. He was afebrile and not sweating. There was no exophthalmos, proptosis, lid lag or lid retraction. He was not pale. There was diffuse enlargement of thyroid gland with no nodules or thyroid bruit. There was no retrosternal extension and no signs of thoracic inlet obstruction. There was no cervical lymphadenopathy. He had a fine tremor in both his hands but there was no thyroid acropachy or onycholysis. Hands were warm and sweaty with palmar erythema. There was no pretibial myxoedema or ankle oedema.

Pulse rate was 96/min, regular good volume and collapsing in nature. Blood pressure was 150/60mmHg. JVP was not elevated. His cardiac apex was in the left 5th intercostals space in the mid clavicular line. There were no thrills or palpable heart sounds. First and second heart sounds were normal and there were no murmurs. Respiratory system was normal; there was no evidence of pleural effusions. Abdomen was normal with no hepatosplenomegaly, and normal findings on digital examination of the rectum. Cranial nerves were normal. Limb examination revealed normal muscle bulk, power and tone with exaggerated reflexes in the upper limbs. In the lower limbs hip muscle power

was 4/5 proximally and other findings were normal. Sensory examination was normal. He had no cerebellar signs.

Can you summarise your history and examination?

Mr MM, a 54-year-old previously healthy male, presenting with diarrhoea with no blood or mucous for one and a half month's duration. This was associated with increased appetite and loss of weight, heat intolerance, sweating and insomnia, malaise and body weakness. On examination there was fine tremor of the fingers, sweaty and warm hands, and bounding pulses with hypertension and a wide pulse pressure. There was bilateral proximal muscle weakness in the lower limbs with exaggerated reflexes in the upper limbs. There were no eye signs of thyroid disease. He had a diffusely enlarged goiter.

Would you like to give a diagnosis or do you want to give differential diagnoses?

With all the typical clinical features, and in the absence of any other alternative diagnosis I would clinically diagnose thyrotoxicosis in this patient.

Your clinical diagnosis of thyrotoxicosis is acceptable in this clinical scenario. However you should try to be more detailed in your diagnosis. For example you can try to mention a cause for his thyrotoxicosis under your diagnosis. You could mention that he has no eye signs, and therefore Grave's disease is less likely.

His main complaint was diarrhoea. Why do you get diarrhoea in thyrotoxicosis?

In thyrotoxicosis there is increased intestinal motility. It is not true diarrhoea and is a functional diarrhea due to reduced intestinal transit time.

What are the cardiac manifestations of thyroid disease?

The commonest is sinus tachycardia. The patient usually complains of palpitations. Atrial fibrillation can occur, particularly in elderly.

Other common arrhythmias include supraventricular tachycardia. Patients can have high output cardiac failure due to peripheral vasodilation. In patients with preexisting ischaemic heart disease, thyrotoxicosis can worsen angina by increasing cardiac workload.

Other than thyrotoxicosis what are the conditions that can cause high output cardiac failure?

Severe anaemia and pregnancy can cause high output cardiac failure in a patient with underlying cardiac disease. Other causes are large arteriovenous fistula, wet beriberi and Paget's disease.

What is the mechanism behind tachycardia in thyrotoxicosis?

It is rather complex. Thyroxine increases heart rate, myocardial contractility and therefore cardiac output, and also causes a drop in systemic vascular resistance. It is similar to the effects of beta-adrenergic stimulation, but is probably mediated directly by thyroxine, although it is also thought that thyroxine may increase sensitivity to catecholamines.

What are the possible causes for thyrotoxicosis in this patient?

It could be primary thyrotoxicosis due to Grave's disease, toxic multinodular goiter, or toxic adenoma. With the relatively short history, subacute thyroiditis is also possible. Secondary causes like pituitary adenoma are rare, but have to be considered. With diffuse enlargement of the gland clinically, Grave's disease and thyroiditis are more likely.

What clinical features will you look for in this patient to suggest Grave's disease?

Other than features common to thyrotoxicosis due to any cause, there are specific clinical features of Grave's disease. Grave's ophthalmopathy is one such entity. Symptoms would be eye discomfort, grittiness and excessive tearing. Exophthalmos is the characteristic feature of Grave's ophthalmopathy. There can

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also be diplopia due to swelling of the extraocular muscles, and reduced vision due to optic nerve compression. Proptosis is another feature, which can be complicated by chemosis. Corneal ulceration, papilloedema and ophthalmoplegia are uncommon manifestations. Another manifestation is thyroid dermopathy or pretibial myxoedema. In this, there is 'orange skin' appearance in the skin mainly over anterior aspect of leg. Thyroid acropachy is clubbing seen due to Grave's disease. Thyroid examination will reveal a diffusely enlarged goiter. There can be a bruit over the thyroid due to the increased vascularity, which was not present in Mr MM. A history of autoimmune diseases in the patient or family will support Grave's disease.

Though thyroid ophthalmopathy, dermopathy and acropachy are suggestive of Grave's disease, their absence does not exclude it. Note that lid retraction and lid lag are not features of Grave's disease. They are due to sympathetic hyperactivity and can happen in any condition with thyrotoxicosis.

What are the tests you will do to assess his thyroid status?

I will do TSH, and free T3 and T4 levels.

Why do you want to do serum free T4 and free T3 rather than total hormone levels?

Thyroid hormones secreted from the gland are bound to proteins in the blood, namely thyroid binding globulin, transthyretin and albumin. Only a small proportion of thyroxine is unbound and available to tissues, and that is known as the free hormone. In the negative feedback loop of the thyroid axis, free hormone levels are sensed since this is the component that reaches the pituitary and the hypothalamus. Serum protein levels can vary in cirrhosis, acute illness, with certain drugs, and (although not relevant in this patient) in pregnancy. Therefore, measuring total hormone levels can be misleading.

Investigations have revealed low TSH and high T₄ and T₃. What is the physiology behind this finding?

The thyroid gland produces thyroid hormones, which include thyroxine (T₄) and tri-iodothyronine (T₃). TSH secreted from the anterior pituitary stimulates thyroid hormone synthesis and secretion. Thyrotropin Releasing Hormone (TRH), secreted by the hypothalamus in turn stimulates this. This axis is under negative feedback control. Thyroid hormones inhibit TSH and TRH. Therefore when the primary problem is in thyroid gland, increased thyroid hormones will reduce TSH secretion.

One of your differential diagnoses was subacute thyroiditis. What are the features of subacute thyroiditis? Do they usually present like this?

Usually, there is painful enlargement of thyroid gland, associated with fever. There might be sore throat, or pain referred to jaw or ear. This may persist for a few weeks. The ESR is usually high.

In subacute thyroiditis, which is also called De Quervain's thyroiditis or granulomatous thyroiditis, prominent features include symptoms similar to upper respiratory tract infection, painful enlargement of thyroid and malaise. They usually have features of thyrotoxicosis and can later develop hypothyroidism. The condition is self-limiting in many patients.

Will you do any investigations to find a cause for his thyrotoxicosis?

Thyrotropin receptor antibodies (TRAb) will be elevated in Graves' disease.

Ultrasound scan of the thyroid gland should be done to look for any clinically undetected nodules in thyroid gland.

Thyroid radioiodine uptake scans are used to arrive at diagnosis. In Grave's disease there is homogenous increase in uptake. There is focal increase of uptake in toxic adenoma.

Multi-nodular goiter will show areas with increased and decreased uptake.

What are the therapeutic options available to manage thyrotoxicosis in Grave's disease?

The main options are antithyroid drugs, radioiodine treatment, and thyroidectomy.

Commonly used antithyroid drugs are methimazole, carbimazole, and propylthiouracil. These act by inhibiting the enzyme thyroid peroxidase. Methimazole is generally preferred because it can be given once a day, acts faster, and has fewer side effects. Two different regimens are used. In the titration regimen, the drug is started at a higher dose and then reduced gradually to achieve euthyroidism. Drugs are continued for 18 to 24 months. Another regimen is the block and replacement regimen. Higher doses are given together, with thyroxine to prevent iatrogenic hypothyroidism. This will achieve euthyroidism about in 6 months.

Radio-iodine is another method of treatment, where one dose of I-131 is given; this will gradually destroy the gland, and later on thyroxine replacement may become necessary.

Surgery is another option available to treat Grave's disease. Either total thyroidectomy or subtotal thyroidectomy can be done.

Other than the specific treatment, a non-selective beta-blocker like propranolol is used to treat the symptoms until euthyroidism is achieved.

Which method would you recommend for your patient?

As first line treatment in this patient either antithyroid drugs or radioiodine can be used. Surgery should be considered in relapses and large goiters that cause thoracic outlet obstruction. Mr MM can have oral antithyroid drugs or radioiodine. I will discuss with him the advantages and disadvantages of these two methods and decide on the best treatment.

What are the important side effects of carbimazole?

Skin rash, fever, urticaria, athralgia, headache and distaste are minor side effects. Serious side effects are agranulocytosis, aplastic anaemia and hepatitis and SLE like syndrome.

If you decide to start on carbimazole, what advice will you give him?

I will tell Mr MM that his thyroid gland is working more than necessary and that is why he is having symptoms like diarrhoea, loss of weight and sweating. I will advise him of the need to start him on tablets to reduce his thyroxine levels. These will improve his symptoms. Carbimazole is one such drug and tell him about the dosage and how to take it. I will also tell him the importance of compliance. I will educate him on the side effects of carbimazole, that if he develops skin rash he should stop the drug and seek medical advice so that we can change the drug. I will tell him about more serious side effects like agranulocytosis, which can cause fever, oral ulcers and sore throat. If any of these appear he should stop the drug, obtain a full blood count immediately, and seek medical attention. I will tell him we will regularly monitor him with thyroid functions, and that the carbimazole dose will be titrated accordingly.

It is not recommended to monitor the full blood count when you are treating with carbimazole in contrast to drugs like clozapine or methotrexate. The side effect is very rare (<1%) and it happens abruptly at any time. It is an idiosyncratic drug reaction and does not always occur soon after initiation of the drug. Therefore, it is necessary to check the full blood count only if there is clinical suspicion.

If he is treated with radioiodine treatment what are the special precautions that need to be taken for the protection of the others?

Residual radioiodine isotopes can release radiation, which can cause harm to others. It is excreted by body fluids, principally,

urine for the first few days after treatment. Therefore, he should avoid close contact with family and the public as much as possible, specially children and pregnant women, for upto 3 weeks. Urine and other body secretions should be disposed of carefully, and cups and utensils should not be shared. He should bathe daily to wash away sweat.

**He develops a thyroid crisis following radioiodine treatment.
What might have caused this?**

This is rare, but can occur if the patient was not pre-treated with antithyroid drugs.

How will you manage this complication?

Management of thyroid crisis is largely aimed at supportive therapy and monitoring. They can develop tachyarrhythmias, high output cardiac failure, seizures, coma and hyperthermia. Cooling the patient and careful hydration is essential. The patient should be monitored for the development of these complications. Beta-blockers like propranolol are given to control tachycardia. Propranolol also reduces peripheral conversion of T4 to T3.

Another management strategy is to reduce the synthesis of thyroid hormones. To achieve this, a high dose of propylthiouracil is given. Potassium iodide solution is also given since excess iodide can inhibit the organification of iodide transiently.

Is there any particular reason why you give propylthiouracil over carbimazole in this instance?

Yes. Other than inhibiting thyroid peroxidase, it also inhibits the peripheral conversion of T4 to T3.

In the circulation T4 is found in greater amounts than T3, although the more potent form is T3. The blockade of peripheral conversion of thyroxine is an added advantage in the acute stage.

Case 11

Mr KD, 55-year-old male with hypertension and hyperlipidemia, presented with progressively worsening shortness of breath for 6 weeks, and gum bleeding for 2 weeks.

He had noticed shortness of breath on exertion, which had gradually worsened over time. He was normally able to engage in heavy exertion, including farming and walking long distances. However his exercise tolerance had decreased, and at the time of presentation he was unable to walk 100 meters on flat ground without feeling out of breath. He also complained of palpitations on exertion, malaise and fatigue. He had no chest pain, orthopnoea, paroxysmal nocturnal dyspnoea, swelling of the body, or shortness of breath at rest, or weight loss. There was no cough or wheezing.

Over the past two weeks he had noticed gum bleeding while brushing his teeth. He had never had any oral diseases or gum bleeding earlier. He did not report any other bleeding manifestations, such as skin patches, haematuria, malaena, or blood in his stools.

One month ago he had developed swelling and redness of the left leg, which was slightly painful, associated with fever. This had resolved with oral medicines from his family doctor. He had developed headache and nasal congestion, with fever, two weeks ago, and was given antibiotics by his family doctor; he was told

that he probably has sinusitis. There was no history of oral ulcers, dysuria, abdominal pain or alteration of bowel habits, and his stools were normal. He did not have any joint symptoms or skin rashes, or leg ulcers. He had not been on long-term medications. He was not aware what medications his family doctor had given him to treat his leg problem.

At this point, what possibilities did you consider?

Given that he has features of shortness of breath and fatigue, together with bleeding gums, I would consider anaemia, with associated low platelets to account for his bleeding gums. He has no features to suggest ischaemic heart disease or heart failure, or lung disease. With the history of leg swelling, I would also consider the outside possibility of deep venous thrombosis with pulmonary embolism, although this doesn't quite account for all of his symptoms.

Please go on with your history

He presented to local hospital 1 week ago, and after blood investigations he was told his blood counts were reduced, all cell types, and that he required further evaluation; he was transferred to the teaching hospital for further management. There he underwent blood investigations, several imaging studies and bone marrow biopsy. He was also transfused several units of blood and platelets. He had felt better after transfusion.

He was diagnosed to have hypertension and hyperlipidaemia four years ago and was treated with nifedipine and atorvastatin, which he had been taking regularly. He was being followed up by his family doctor, and had good control of blood pressure. He does not have diabetes, heart disease or previous strokes. He had never undergone any surgeries and did not have any allergies. His father had asthma and his mother had diabetes and hypertension. There was no history of any malignancies or blood disorders within his immediate family.

He is married, has two children who are 12 and 16 years of age, and his wife is a housewife. While working as an instructor in agriculture department, he also works in his own paddy field and has been exposed to agrochemicals. He had smoked about three cigarettes per day for 10 years, and stopped smoking 15 years ago. He takes an occasional drink.

His weight was 75kg and height 163cm. He looked well. He was afebrile and pale, but not icteric. There was no angular stomatitis or glossitis, and oral hygiene was good. He did not have lymphadenopathy, petechiae, bone tenderness or oedema. His legs were not swollen. His pulse rate was 88/min with good volume, blood pressure 120/70mmHg, JVP not elevated. Cardiovascular and respiratory system examination was normal. His abdomen was soft and non-tender, and there was no hepatosplenomegaly or other palpable lumps, and no ascites. There was a surgical dressing over his right posterior superior iliac spine, where he had had a bone marrow biopsy. Genitalia were normal. Neurological examination was grossly normal; there was no evidence of peripheral neuropathy, and his optic fundi were normal.

Can you summarize your findings?

In summary, my patient is a 55-year-old male with well controlled hypertension and hyperlipidaemia, who presented with progressively worsening shortness of breath on exertion for six weeks, and bleeding gums for two weeks. In addition he gave a history suggestive of cellulitis a month ago, and possible upper respiratory tract infection two weeks ago. He had no other associated symptoms, but has a history of exposure to agrochemicals. He has been told that he has low blood counts, and has been transfused blood, following investigations including bone marrow biopsy. On examination he is pale, not icteric and afebrile. There was no lymphadenopathy, skin rashes, petechiae, bone tenderness or hepatosplenomegaly.

What diagnoses would you consider at this point?

His shortness of breath is most likely due to anaemia; I say so because he is pale, has had to have blood transfusions which improved his symptoms, and also because there were no other obvious reasons for his shortness of breath found on history or examination. Furthermore, he has had two recent infections – cellulitis and possible sinusitis, and also has had bleeding gums, and had been told that his blood counts were low. Therefore it is likely that he is pancytopenic.

Could this be some form of haemolytic anaemia?

Unlikely, since he is not jaundiced – with this degree of anaemia, if he had ongoing haemolysis, he would have been icteric.

What are the common infections you see in patients with neutropenia?

Gingivitis and mucosal ulceration is characteristically seen when significant neutropenia is present. With severe neutropenia they can have systemic severe infections, like pneumonia leading to severe sepsis. They also can have systemic fungal infections.

The bulk of neutrophils are contained in the bone marrow pool, and the rest are in the tissues and marginated to the lining of blood vessels. Only a small proportion of neutrophils are actually in the peripheral blood. Therefore the peripheral neutrophil count is not an accurate measure of bone marrow reserve. The main function of the neutrophils is to ingest and kill bacteria, fungi and damaged cells. Out of the bacteria they provide protection mainly from extracellular bacteria. Gingivitis and mucosal ulcers are seen when the bone marrow reserve of neutrophils is poor. In fact, if abscess formation occurs, then it suggests that the bone marrow reserve of neutrophils is good.

What are the causes of pancytopenia?

Pancytopenia occurs either due to reduced or ineffective production of blood cells from the marrow, or due to increased peripheral destruction of cells. Increased cell destruction occurs most commonly in hypersplenism.

What is hypersplenism?

Hypersplenism is a condition which occurs when the spleen is significantly enlarged for some other reason, and sequesters blood cells. This results in pancytopenia, with platelets and granulocytes more commonly affected.

What are the common causes of production failure leading to pancytopenia?

Decreased cell production can occur as a result of true bone marrow failure or as a result of ineffective haemopoiesis. The most important is true bone marrow failure, which occurs in aplastic anaemia. Bone marrow infiltration from malignancies such as lymphoma, leukemia, solid tumours with bone marrow deposits, or disseminated tuberculosis infection are also recognized causes. Paroxysmal nocturnal haemoglobinuria, which is also associated with intravascular haemolysis, can also cause pancytopenia; this is also associated with the other characteristic features of PNH, namely intravascular haemolysis and increased thromboses. Severe vitamin B12 or folic acid deficiency (megaloblastic anaemia) can also result in pancytopenia. Mild jaundice can be apparent here also, as there is some degree of ineffective erythropoiesis. Ineffective haemopoiesis occurs in conditions like myelodysplasia, where there is increased stem cell proliferation but impaired maturation and differentiation. In myelofibrosis there is bone marrow fibrosis, which results in pancytopenia.

Out of the above causes, what is the most likely cause?

In the absence of jaundice, lymphadenopathy, hepatosplenomegaly, features of PNH, or features suggestive of haematological or other malignancy, I would consider aplastic anaemia as the most likely diagnosis. Megaloblastic anaemia presents mainly with anaemia, as the pancytopenia is less profound. Myelodysplasia is less common at this age. However I will also consider acute leukaemia in this patient since they can present with features of pancytopenia alone.

In aplastic anaemia, clinical features are confined to those of pancytopenia. Unless septic, they are generally systemically well, and have no constitutional symptoms, such as weight loss, fever etc. The presence of constitutional symptoms suggests an alternative diagnosis.

Other than features due to pancytopenia what else will you look for in your patient to suggest acute leukaemia?

Fever and constitutional symptoms such as weight loss are seen in acute leukemias. This patient does not give history of fever, other than during the episodes of infection. He does not have lymphadenopathy, hepatosplenomegaly or testicular enlargement, which can occur due to infiltration. There were no features of neurological involvement such as cranial nerve palsies or meningism. He did not have bone tenderness either.

What are the causes of aplastic anaemia?

Causes of aplastic anaemia are primary and secondary. Primary idiopathic aplastic anaemia is the commonest cause. There are also inherited conditions, such as Fanconi anaemia, which can result in pancytopenia.

Where a secondary cause can be identified, aplastic anaemia would be considered secondary. Secondary causes include drugs, such as cytotoxic drugs which cause bone marrow aplasia and other

drugs like chloramphenicol, anti-thyroid drugs, gold, NSAIDs and sulphonamides which cause aplasia as an idiosyncratic reaction. Viral infections such as hepatitis viruses, parvovirus B19 and EBV can also cause aplastic anaemia. Exposure to radiation, chemicals like pesticides and benzene can also cause aplastic anaemia. Systemic lupus erythematosus is a recognized cause.

You mentioned PNH as a cause of pancytopenia. Could you elaborate on this?

Yes. Some patients with PNH have pancytopenia and bone marrow evidence of aplasia. It is less likely in this patient since he did not have features to suggest haemoglobinuria.

Paroxysmal nocturnal haemoglobinuria is an acquired disease where a clone of red cells is sensitive to the complement cascade, resulting in intravascular haemolysis. These patients have pancytopenia and venous thrombosis, and can develop bone marrow hypoplasia due to expansion of the abnormal clone.

Clinical features include those of anaemia, dark urine due to haemoglobinuria, recurrent abdominal pain due to mesenteric thrombosis, and other manifestations related to pancytopenia and thrombosis. Investigations show anaemia, reticulocytosis, high serum LDH, reduced serum haptoglobin, haemoglobinuria and haemosiderinuria. Anaemia can be initially associated with high MCV due to reticulocytosis, but can later become hypochromic and microcytic due to chronic urinary iron loss leading to iron deficiency anaemia. Bone marrow can have normal cellularity or hypoplasia as well as aplasia depending on situation. Earlier the disease was diagnosed using Ham's test; however nowadays flow cytometry is the gold standard. Some patients diagnosed as aplastic anaemia later turn out to have PNH, and vice versa.



How do you establish the diagnosis of aplastic anaemia?

With the above clinical findings I will do full blood count, which will confirm pancytopenia. The reticulocyte count will be very low, and blood picture will not show abnormal cells. Bone marrow trephine biopsy is essential to establish the diagnosis. It will show loss of haemopoietic cells, with replacement of marrow spaces by fat. Mr KD had a bone marrow biopsy, and I would obtain these reports rather than perform the procedure again.

Though this patient initially had symptoms due to anaemia, many patients with aplastic anaemia present with bleeding manifestations. What is the reason?

Red cells survive for 120 days, whereas survival time is about 8 days for platelets and 1-2 days for neutrophils. As a result they develop neutropenia and thrombocytopenia early. Bleeding generally is the earliest to manifest.

He is confirmed as having aplastic anaemia. Do you have any special concerns about aetiological factors in him?

Considering his agricultural background there is possibility of exposure to pesticides. He has not been wearing proper protective equipment during handling these. It is possible that pesticide exposure played a role in causing this patient's condition, but it is difficult to be sure.

What are the important aspects of his management?

As a part of general management measures, it is important to explain to him and his family about the illness, and building a management plan with their active participation. This also needs input from haematology team. Transfusions form the mainstay of management. Precautions to prevent infections, such as reverse barrier nursing, and prophylactic antibiotics and antifungals are given in the case of severe neutropenia. Early and aggressive management of infections and bleeding is important, and the

patient should be educated to seek medical advice early in case of such features. If a cause for aplastic anaemia can be determined this needs addressing.

Specific management has several options, and is based on the age and severity of the illness as well as the presence of potential stem cell donors. Anti-thymocyte globulin (ATG) is the most widely used specific treatment, and this is often combined with ciclosporin. Androgens are sometimes used in treatment.

In younger patients who have a HLA matching sibling donor, stem cell transplant is preferred, if available.

What is ciclosporin?

It is a selective immunosuppressant, which inhibits production of lymphokines by lymphocytes. It spares haemopoiesis and non-selective immune functions like phagocytosis.

What are the important side effects of ciclosporin?

It can cause a rise in serum creatinine, which usually resolves after withdrawal of the drug, although in some cases significant renal impairment can occur. Other side effects include gastrointestinal disturbances, gum hypertrophy, hypertrichosis, and hepatic dysfunction.

As the house officer you need to ensure reverse barrier nursing is properly done for your patient. What are the steps that have to be followed?

If possible the patient should be kept in isolation away from other patients to avoid exposure to infections. Encounters with visitors and staff should be minimized. For example, the family will be advised to stay away if they are suffering from any infection or are exposed to contagious infections like chicken pox. Health care staff will be advised to take universal precautions, and whenever possible patient care should be provided by the same person.

The patient's bed, clothing, equipment and surrounding must be kept clean, dry and well ventilated to minimize colonization of organisms. The patient can wear a facemask to minimize the risk of infections via inhalation. Hand hygiene is one of the most important measures to be followed by the patient, carers and health staff. I will make sure that there is soap and water available, and the proper technique is followed by everyone. He should avoid uncooked vegetables and green leaves; eat fruits which have a thick skin that can be peeled off, like bananas. He should only drink boiled cooled water. I will advise the health staff, the patient, and his family of these precautions, and reinforce them from time to time to make sure they are followed.

What will you tell him and the family regarding the prognosis of the disease?

I will tell Mr KD that the reason he finds it difficult to breathe, and his recurrent infections and bleeding gums, are because his body is not producing sufficient blood cells to protect him. I will also tell him that although this condition is not an infection, his resistance to infections is poor, and he needs to take precautions regarding this. With the investigations done so far the root cause for the disease has not been found, but there is a possibility that this could be related to agrochemical exposure. I will also gently break the news to him that this is a serious illness, with poor chances of complete recovery. We have requested a consultation with the haematologist who may be able to advise him about the treatment options. Currently we are monitoring him to see whether there is infection, bleeding, or anaemia, and treating appropriately.

Aplastic anaemia has a very poor prognosis without treatment, and death occurs due to infection or haemorrhage. Only a minority have spontaneous recovery. Stem cell transplant gives hope for cure. With immunosuppression people can have remission but there is high chance of relapse or even development of PNH, myelodysplasia or acute myeloid leukaemia later on.

Have you heard of a term called pure red cell aplasia?

Yes. In these conditions patients have anaemia with normal platelet and white cell counts due to decreased red cell precursors in bone marrow. This also could be congenital or acquired. The acquired form is transient in some patients. One common example is parvovirus B19 infection in patients with pre-existing haemolytic diseases such as hereditary spherocytosis or sickle cell anaemia. A chronic acquired form can occur without an obvious cause.

Case 12

Master TT is a 16-year-old previously well schoolboy. He presented with diarrhoea for 1 months duration. The stools were loose in consistency, with mucus but no blood. Previously, his usual bowel habits had been 1-2 normal consistency bowel openings per day, which had changed to loose stools 4-5 times a day. He now typically has to open his bowels following each meal, but has not noticed any particular type of food to aggravate his symptoms. He also had episodic mild right lower abdominal pain, loss of appetite, and had lost weight considerably. He had experienced lethargy and easy fatigability for the same duration. He had no vomiting or abdominal distension, and had not had fever. He did not complain of any urinary symptoms such as dysuria, frequency or hematuria. He had not had any rashes, joint symptoms, bleeding manifestations, shortness of breath, cough, sputum or wheezing. He was well until the onset of this illness and was not on any drugs. He had never undergone any surgeries in the past. He usually has homemade food, but intermittently has meals from the school cafeteria. After the onset of the illness his food intake had markedly reduced to few snacks a day, mainly because he was afraid of having to open bowels if he eats. However, his fluid intake was adequate. He did not have any drug or food allergies. None of his family members or friends had complained of similar illness. He had no family history of malignancy. He had been

in the ward for the last three days; prior to this he had had some basic blood and stool investigations, and had had an ultrasound of the abdomen, but had been told that a definite diagnosis had not been arrived at yet. He was worried about the condition, as well as the fact that he had missed several days of schooling. He was preparing for the O/ Level examination in a few months. His father is an executive officer in a government office and mother is a housewife, and he has a younger brother who was in good health. His father had had to take leave from work to stay with him in hospital.

On examination he was wasted, weight 34 kg and height 155cm. His BMI was $14.2\text{kg}/\text{m}^2$. He was pale, afebrile, not icteric, and well hydrated. He did not have oral ulcers, lymphadenopathy, skin rashes, arthritis, clubbing or oedema. His pulse rate was 112/min with a blood pressure of 100/60mmHg. There were no cardiac murmurs, or any other abnormalities on cardiovascular or respiratory examination. There was mild tenderness in right iliac fossa, but no organomegaly or lumps. There was clinically no ascites, and digital rectal examination was normal. Neurological examination was unremarkable.

Can you summarize your history and examination?

This 16-year-old previously well schoolboy presented with mucous diarrhoea for 1 month, associated with loss of appetite and loss of weight and mild intermittent right iliac fossa pain. He had lethargy and easy fatigability for the same duration. He had no other symptoms pertaining to other systems and was afebrile. There was no significant drug history, past medical history or family history. He was pale and grossly underweight, and apart from mild right iliac fossa tenderness, his abdominal examination was normal. No other abnormalities were found on examination of the other systems.

What problems did you identify in this patient?

His main medical problem that led to hospitalization was chronic mucous diarrhoea. In terms of social problems, he was missing school, and his family was affected by having to care for him in hospital. He was also very concerned about his illness.

Can you outline, in general, the causes of chronic diarrhoea?

Diarrhoea lasting four or more weeks is generally called chronic diarrhoea. There are many causes, and it is convenient to classify them according to their mechanism.

Secretory causes of diarrhoea include the use of stimulant laxatives, alcohol abuse, hormone releasing tumors such as VIPoma, carcinoid tumors and bowel resection. Sometimes infections can also produce diarrhoea by producing toxins that bind to structures in the gut and increase secretion of fluid into the gut lumen.

Osmotic causes include ingestion of osmotic laxatives, carbohydrate malabsorption syndromes such as lactose intolerance.

Inflammatory causes of chronic diarrhoea are inflammatory bowel disease (IBD), infective causes and opportunistic infections in primary or secondary immunodeficiency syndromes.

Gut motility disorders also can lead to diarrhoea in cases such as irritable bowel syndrome, hyperthyroidism and autonomic neuropathies.

Chronic diarrhoea with steatorrhoea occurs with pancreatic hormone insufficiency and diseases such as coeliac disease and Whipple's disease.

Though it is convenient and organized to classify causes of chronic diarrhoea under a classification as done above, in many conditions several of the above mechanisms act to produce the clinical features. For example in inflammatory bowel disease there

is inflammation of the bowel mucosa, which results in damage to enterocytes, leading to malabsorption and secretion of fluid and electrolytes into the bowel lumen.

From the history in this patient, which type of diarrhoea is most likely?

He has loose stools with mucous, but not blood. Steatorrhoea is less likely with this presentation. Although inflammatory conditions typically causes blood and mucus diarrhoea, this may not be evident all the time. The presence of marked constitutional symptoms suggests an inflammatory aetiology.

While there are many clinical features which will help to determine the type of diarrhoea, these are not obvious in many cases. Secretory diarrhoea often results in large volumes of watery stools, which does not resolve even with fasting. This is because even during fasting, secretion of fluid into the gut lumen continues to take place. In contrast, osmotic diarrhoea improves with fasting or discontinuation of the offending food item. In inflammatory diarrhoea there is often blood and mucus and sometimes pus as well. Constitutional symptoms, such as fever, lethargy, and weight loss are seen in inflammatory diarrhoea. In dysmotility diarrhoea the stool volume is usually normal while stool frequency increases. In malabsorption, steatorrhoea occurs, which is the presence of foul smelling, fatty, bulky stools that are difficult to flush because of the oily nature.

What are the differential diagnoses that you will consider this patient?

Although his diarrhoea is not associated with blood or pus, I would consider inflammatory causes high up in the list because of associated systemic symptoms like loss of appetite, loss of weight, lethargy, fatigability and anaemia. Therefore, inflammatory bowel disease, i.e., Crohn's disease or ulcerative colitis would be my favoured diagnoses. The presence of right iliac fossa pain

tenderness suggests Crohn's. Chronic infections such as giardiasis, amoebiasis, and intestinal tuberculosis are other possibilities. Finally, because there is loss of weight and diarrhoea occurring together I would like to consider hyperthyroidism also, although there are no other suggestive features.

Why don't you consider irritable bowel syndrome in him?

In patients with irritable bowel syndrome, loss of weight is extremely rare. Also anaemia cannot be explained by irritable bowel syndrome.

Are there any clinical features outside the gastro-intestinal tract that you would look for in inflammatory bowel disease?

Oral ulcers can occur, more commonly in Crohn's than in ulcerative colitis. There can be skin lesions; erythema nodosum may be seen in some patients, again more commonly in Crohn's. Pyoderma gangrenosum is rare, but is more commonly seen with longstanding ulcerative colitis. Episcleritis and more rarely uveitis can occur. Arthralgia is common, and arthritis is seen in about 5% of patients with IBD, more commonly with Crohn's colitis.

What investigations will you perform?

My plan of investigations will be focused on making a diagnosis, and assessing his general condition and any complications. Since he has lost appetite and weight, I will look for associated nutritional deficiency.

I will start with basic investigations such as full blood count, CRP and ESR, blood picture, urea and electrolytes, albumin, stools analysis and stools culture. Blood counts and blood picture will give an indication of the type of anaemia (microcytic hypochromic or macrocytic or mixed). Neutrophil leukocytosis will suggest infection, or an ongoing inflammatory process, and the CRP and ESR would be also raised in these conditions. Eosinophilia may be seen in parasitic infections, or allergic conditions. Hypokalaemia

may be present in chronic diarrhoea of secretory origin. Serum albumin can be low in chronic inflammatory conditions and also in malabsorption. Although thyrotoxicosis is low on my list, I would still do a TSH test to rule it out. Stools analysis is useful to detect amoebic cysts, ova, parasites and leucocytes; a completely normal stools test is unusual in inflammatory bowel disease.

Following this workup, colonoscopy would be the next step. This will directly visualize the bowel up to the ileum, and any suspicious lesion could be biopsied for histological confirmation. This will help to diagnose inflammatory bowel disease and intestinal tuberculosis.

A colonoscopy was done, and histology confirmed Crohn's disease. Could you tell me what sort of histopathological changes are seen in Crohn's?

Crohn's disease can involve any part of the alimentary tract starting from mouth to anus. The most commonly involved areas are the terminal ileum and proximal colon. It typically has segmental involvement with skip lesions, with normal areas of bowel in between. The disease can involve the entire thickness of the bowel wall. Aphthous ulcers can be seen on the mucosal surface. When severe, there are stellate ulcers, and these fuse producing the classical cobblestone appearance. There are pseudopolyps seen. With recurrent inflammation causing transmural involvement, there could be fistula formation. Later on, with healing, this leads to stricture formation of the bowel wall. On the serosal surfaces there is a 'creeping fat appearance' due to thickening of the mesentery.

On microscopic examination there are aphthoid ulcerations and crypt abscesses. The pathognomonic feature of Crohn's disease on microscopy is the presence of non-caseating granulomata. Lymphoid aggregates can also be seen on histology.

What are the differences between Crohn's disease and ulcerative colitis?

The sites of involvement are different. In Crohn's disease any part of the intestinal tract from the mouth to anus can be affected, although the ileum and proximal colon are most commonly involved. In UC the rectum and colon are affected. Bowel proximal to the colon is not affected, except in backwash ileitis. In CD there is transmural involvement whereas in UC only mucosal and submucosal involvement is seen. Superficial ulcers are seen in UC and deep ulcers are seen in CD. Granulomata are seen in CD are but not in UC. Fistulae, strictures and sinuses are commonly seen in CD. Perianal involvement is also common in CD.

Though there are many similarities and differences that are listed in textbooks, the two diseases are sometimes considered to be in a spectrum of inflammatory bowel disease, and therefore there is a group with features that are not clearly suggestive of one entity. This is called indeterminate colitis.

Can you tell me something about the pathogenesis of inflammatory bowel disease?

The pathogenesis of IBD is not clearly understood, but is thought to be multifactorial, involving both exogenous and host factors. Food antigens are thought to play a role in the development of IBD, although specific antigens have not been identified. A western style diet (sugary, fried or processed food) is thought to be associated with an increased risk of IBD, especially Crohn's. An imbalance in the normal flora of the gut is also thought to play a role. Drugs that influence gut flora, such as antibiotics and NSAIDs may increase the risk of IBD. It has been suggested that appendicectomy may prevent the development of IBD, but the mechanism of this is unknown. Smoking is a risk factor for CD while it is considered protective in UC.

What are the basic aspects in the management of this boy with Crohn's disease?

This is a chronic debilitating illness with significant morbidity. His management needs to be discussed with him and his family, the gastroenterologist, surgeon, his family doctor, and the dietician. The goals of management include inducing remission and maintaining remission of his disease activity, looking for complications and extra-intestinal manifestations, prevention and management of these, achieving good nutrition, counseling, and arranging a long term follow up plan, and arranging support necessary for him to live a near normal life. Initial medical management is based on the severity of the disease, after which treatment is guided by the response to treatment.

What are the drugs used in treating Crohn's disease?

Steroids can be given systemically as oral or intravenous preparations, and locally as enemas. 5-ASA (5-aminosalicylic acid) containing drugs are often started in mild to moderate disease. Sulphasalazine is a pro-drug combination of 5-aminosalicylic acid and sulphapyridine, which is reduced by bacterial enzymes in the colon to the two components. Sulphapyridine is responsible for the side effects of sulphasalazine. Mesalazine is the active 5-ASA, has fewer side effects, and is preferred, unless there is arthritis, in which case the sulpha containing drug may be of benefit. Azathioprine and methotrexate are other immunosuppressant drugs used in the treatment of Crohn's disease. Infliximab, which is an anti-TNF antibody, is used in refractory cases.

Antibiotics are also useful in treating Crohn's disease, especially peri-anal conditions; ciprofloxacin, metronidazole, rifaximin and clarithromycin are used.

While on treatment, his bowel symptoms improve. However he complains of a severe low backache, which is worse in the morning and associated with stiffness. Do you see any relevance to his current problem?

This is suggestive of inflammatory type backache, although I can't come to a definite conclusion without full assessment. Inflammatory bowel disease is associated with seronegative spondyloarthropathies.

Inflammatory bowel disease is associated with several rheumatological manifestations, mainly seronegative arthropathies. Rheumatoid factor is negative in these. There can be different patterns of arthritis – features of ankylosing spondylitis, which affects the lumbosacral spine and pelvis, and sacroilitis, with backache and morning stiffness, is the commonest. In some people asymmetrical large joint arthritis can occur. There is an association with ankylosing spondylitis and HLA B27.

Do you know of any other extraintestinal manifestations of Crohn's disease?

Apart from the ones I mentioned earlier, primary sclerosing cholangitis can occur, which causes extra and intrahepatic bile duct inflammation and fibrosis. This can lead to cirrhosis and liver failure.

They are also at a higher risk developing renal stones, osteoporosis, osteonecrosis, secondary amyloidosis, venous thrombosis, cardiac involvement, interstitial lung disease and pancreatitis.

Do you know the cause for urinary stones in Crohn's disease?

Usually, dietary oxalates combine with dietary calcium and form insoluble calcium oxalate, which is passed out with the stools. In Crohn's disease, due to ileal dysfunction, fatty acid absorption is reduced. These fatty acids bind to luminal calcium. When less calcium is available in the gut lumen, dietary oxalate is absorbed

in excess and passed with urine causing hyperoxaluria. This causes oxalate stones.

What gastro-intestinal complications could occur in Crohn's disease?

Since transmural inflammation occurs in Crohn's disease, this can result in the formation of sinus tracts, which can penetrate the serosa to result in fistulae. These fistulae can be enteroenteric (bowel to bowel), enterovesical (bowel to the bladder), enterovaginal (bowel to vagina) or enterocutaneous (bowel to skin). These can result in various complications, such as recurrent urinary tract infections, cutaneous or vaginal discharge of flatus or faeces, and the formation of palpable masses in the abdomen. Some sinus tracts result in inflammatory abscesses, known as phlegmon. Perianal complications are also common – perianal abscesses, pain and discharge from large anal skin tags, anal fissures, and perianal fistulae. Severe aphthous ulceration can also occur. Involvement of the small bowel can result in malabsorption.

Can you outline the indications for surgery in Crohn's disease?

When medical therapy fails, surgery maybe required. Intestinal obstruction from strictures, abscesses, fistulae, intestinal perforation, and bleeding are indications for surgical intervention.

When a stricture is found on colonoscopy it is more significant in UC than in CD. Can you explain why?

Strictures are commoner in Crohn's disease compared to ulcerative colitis since transmural involvement occurs in Crohn's. On the other hand, the risk of malignancies is higher in ulcerative colitis. Therefore a stricture in ulcerative colitis could be a malignant stricture.

Case 13

My patient is Mr JF, a 25-year-old police sergeant who presented to his local hospital with fever of five weeks duration. He developed acute onset high fever with chills and rigors five weeks ago, which was intermittent, though not observed to be of a particular pattern. There were associated generalized bodyaches, headache and malaise. Following inpatient management he became fever-free three weeks after the onset, and was discharged from the local hospital. However, after a week of being afebrile, his fever reappeared. He had no chills or rigors, and no headache, but had myalgia. He also had severe loss of appetite and loss of weight of about 10 kg over this period. He didn't have nausea, vomiting, altered bowel habits, jaundice, cough, sputum, chest pain, shortness of breath, sore throat, breathlessness, dysuria, loin pain or lower abdominal pain, swelling of any joints, photophobia or limb weakness. He didn't have any bone pain or bleeding manifestations. There were no rashes, or hair loss. He had had multiple sexual contacts, but had used protection always. He had never used intravenous drugs. He was not on any regular medications prior to the onset of illness. When his fever recurred, he had completed the course of treatment given to him on discharge from hospital. He gave no history of travel outside the country, or close contact with a patient having tuberculosis. There was no history of heart problems in childhood. He had no family history of connective tissue disorders or malignancy. He smokes 1-2 cigarettes per day and consumes alcohol occasionally. He was working as a police sergeant. He is contemplating marriage in two months time and currently lives

with his parents. There is good support from his family members. He has been extensively investigated with blood, urine and stool samples, and also had an ultrasound scan of the abdomen. The diagnosis card from the local hospital stated that he was treated with intravenous antibiotics for urinary tract infection.

Can you summarize the history?

A 25-year-old policeman with fever for five weeks duration, initially treated as for a UTI, with recurrence of fever. After a week without fever, his symptoms recurred. The fever was intermittent high grade, with chills and rigors initially associated with bodyaches, headache and malaise. There is loss of appetite and loss of weight of about 10 kg. He had no travel history, contact history of tuberculosis, childhood cardiac problems, or family history of any related illnesses.

What did you look for in the examination?

In general examination looked for pallor, icterus, oral ulcers, lymphadenopathy, skin rashes, arthritis, peripheral stigmata of infective endocarditis, bone tenderness and any abnormalities in the optic fundus.

In the cardiovascular examination I carefully listened for murmurs, to suggest previous valvular or congenital heart disease or new onset murmurs which may occur in infective endocarditis.

In the respiratory examination I looked for any evidence of consolidation, fibrosis, cavitation, or pleural effusions. Poorly resolving pneumonia is an important cause of prolonged fever and constitutional symptoms. Fibrosis and cavitation can be due to tuberculosis, one of the commonest reasons for this type of presentation. Also, connective tissue disorders can give rise to lung signs.

In his abdomen I checked whether there is tenderness, hepatosplenomegaly, or any other palpable lumps such as palpable

kidneys. Hepatosplenomegaly can be found in haematological malignancies and in several infections. I looked for free fluid in the abdomen. I did a digital examination of the rectum to look for prostatomegaly and prostatic tenderness.

I also did a neurological examination to look at any focal deficit, due to abscesses or tuberculosis .

Are there any positive findings?

No

What is your working diagnosis?

This patient has had fever for 5 weeks, with no clear cause identified following routine investigations. I would call this a fever (or pyrexia) of unknown origin (FUO or PUO).

It is justifiable to consider him as having PUO under the definition which has been in place for decades (Petersdorf and Beeson, 1961) as, 'temperature above 38.3 °C on several occasions for > 3 weeks and failure to diagnose despite one week inpatient investigations'. On various occasions changes to this definition have been proposed. For example, it is no longer essential to have a patient admitted for a week to perform investigations. A more appropriate definition would be 'fever higher than 38.3 °C on several occasions lasting for at least three (some use two) weeks without an established etiology despite intensive evaluation and diagnostic testing'. Also PUO can be classified according to the setting.

Do you know of any classification of FUO?

FUO is classified as classic FUO, nosocomial FUO, neutropenic FUO and FUO associated with HIV infection.

This classification is of value since the approach to diagnosis and treatment differs significantly among those categories. In all categories, fever >38.3°C on several occasions is the predominant feature. Classic FUO is defined when there is fever for > 3 weeks

with no diagnosis despite 3 outpatient visits or 3 days of in-hospital stay. In nosocomial FUO, fever, as defined earlier, is present in a hospitalized patient who was not manifesting or incubating infection on admission. Three days of investigations including 2 days incubation of cultures should have been performed, with no cause identified. Neutropenic FUO again is fever with the same characteristics present in a patient who has a neutrophil count of $<500/\mu\text{L}$ or is expected to fall to that level in 1-2 days. A specific cause should not have been found despite investigations meeting the above criteria. HIV associated FUO is fever >4 weeks for outpatients and >3 days for in-hospital patients with HIV infection, where a cause for fever has not been revealed despite investigations fulfilling the criteria mentioned above.

What are the differential diagnoses you will consider in this patient?

In this patient, infections come higher up in the list of differential diagnoses considering his age, and the duration of fever (fevers of less than 3 months are more commonly due to infection, though this is not an absolute rule). In the local setting I would consider tuberculosis (pulmonary or extra-pulmonary), visceral abscesses, enteric fever, infective endocarditis, urosepsis, viral infections such as glandular fever, and HIV. I will also consider neoplastic conditions such as leukaemia or lymphoma, and connective tissue disorders like adult Still's disease in this young man.

There are many conditions that will manifest as prolonged fever which are classified under different categories.

- Infections:** *Bacterial- tuberculosis, Infective endocarditis, enteric fever, localized pyogenic infections. Such as liver abscesses, renal and retroperitoneal abscesses, rickettsial infections, brucellosis*
- Viral-** *Glandular fever, HIV, viral hepatitis*
- Fungal-** *histoplasmosis, cryptococcosis*

Parasitic- malaria, toxoplasmosis, amoebiasis, visceral leishmaniasis,

*Neoplastic: Haematological- leukaemia, lymphoma
Solid tumors- renal cell carcinoma, sarcoma*

Connective tissue disorders: SLE, rheumatoid arthritis, adult Still's, giant cell arteritis

Granulomatous diseases: Crohn's disease, sarcoidosis

*Other: Drug fevers
Endocrine- thyrotoxicosis
Factitious*

You mentioned that he hasn't travelled anywhere – what is the significance of a travel history in PUO?

Certain infections are endemic to certain geographic areas. In patients with a history of travel to such areas with compatible clinical features and timing, such infections have to be considered. For example if there is a history of travel to malaria endemic areas, I will arrange for blood smears for malaria parasites. Rickettsial infections are commonly seen in certain parts of Sri Lanka. Travel outside the country is also important, for malaria, visceral leishmaniasis.

Do not forget malaria in patients who have recent foreign travel. However since 2012 there have been no locally transmitted malaria cases and therefore areas traditionally considered to be endemic for malaria within Sri Lanka are no longer considered significant in the travel history.

How will you investigate Mr JF?

I would first review the results of the investigations done so far, and plan further investigations based on this. I will start with basic non-invasive tests and then proceed towards more complicated and invasive tests. Full blood count and blood picture will show whether there is any suppression of cell lines and also any evidence

of an infective process. ESR and C-reactive protein will help inflammatory markers; although they are non-specific, very high values will suggest the possibility of TB or autoimmune disease. Urinalysis will show whether there is any urinary tract infection and the presence of casts or red cells will indicate glomerular pathology. Liver enzymes, bilirubin, serum protein levels, CPK, creatinine and electrolytes will be done as baseline and also to see whether there is any impact on organ systems.

I would repeat a septic screen, with blood cultures, preferably more than twice from different sites. Since his fever is intermittent, I would arrange for blood cultures to be repeated immediately after a fever spike. Urine will also be collected for culture. I will do a Mantoux test...

How useful is the Mantoux test?

If the mantoux test is strongly positive (in a country with high prevalence, 10mm or more) it is very suggestive of tuberculosis, either pulmonary or extrapulmonary. On the other hand a negative Mantoux in no way rules out TB, in fact in severe or disseminated TB the Mantoux can be negative.

Please continue...

I will do a chest x-ray to look for obvious changes, such as consolidations, pleural effusions, cavitation and mediastinal lymphadenopathy. I will also get an ultrasound abdomen done, to look for organomegaly, gall bladder, lymph nodes, free fluid etc. A skull x-ray sinus view might be useful if I suspect sinusitis. I will arrange for an echocardiogram to look for any evidence of infective endocarditis, tumours like atrial myxoma, pericardial effusions, or any valve lesions. I will request HIV screening, VDRL and hepatitis serology in this patient. Considering the possibility of an autoimmune aetiology at this age, ANA should also be done. During the process of evaluation if there are any positive results, further investigations will be planned accordingly.

Can an echocardiogram reliably rule out endocarditis?

An echocardiogram is a useful test when the probability of endocarditis is moderate or high, but not when the probability is low. Transthoracic echo has only about 60% sensitivity in picking up vegetations; however if the valves are normal, this makes endocarditis less likely. Trans-oesophageal echocardiogram is much more sensitive at picking up vegetations, and also, if the valves are normal on trans-oesophageal echo, endocarditis can almost be ruled out.

Evaluation of this patient with the above investigations did not reveal any specific diagnosis except for mild normocytic normochromic anaemia with elevated ESR. What will you do next?

At this point, I would repeat his blood cultures in both aerobic and anaerobic media, including fungal cultures. A contrast enhanced CT chest abdomen and pelvis would be the next step, to look for septic foci, deep-seated abscesses, lymphadenopathy or malignancies. I would also go back and do a detailed clinical assessment again, looking for new symptoms or signs. I would consider doing a lumbar puncture for CSF examination if there is any headache.

It is extremely important to repeat your clinical assessment since there can be new clinical signs; for example cardiac murmurs in infective endocarditis may not be evident on presentation, but may appear later. Imaging with CT will be useful when no other clue is present. Colonoscopy maybe necessary, to look for bowel malignancy or inflammatory bowel disease, but in the absence of bowel symptoms there is no immediate indication for it.

You mentioned that he complained of myalgia - what could be the significance of this?

Yes, myalgia was one of his most prominent complaints. This raises the possibility of inflammatory disorders of muscle, such as polymyositis or dermatomyositis. A normal creatine kinase is unusual in these conditions, however I would consider arranging for muscle biopsy.

None of your investigations so far have given you any leads to diagnosis of his fever. What would you do next?

I will consider sending off serology for rare infections, such as brucellosis, toxoplasmosis etc, in consultation with the microbiologist. I would also screen for other autoimmune disorders, in particular vasculitic conditions.

If all the investigations including CT scan, echocardiogram and cultures have not given a diagnosis, invasive investigations would be the next step.

In that case, if the fever persists, I would consider invasive tests such as liver biopsy and bone marrow biopsy. In granulomatous conditions, lesions may be identified in the liver. Bone marrow biopsy is also useful in identifying infections, such as TB, other chronic infections such as leishmaniasis, brucellosis and melioidosis, and conditions like sarcoidosis and haematological malignancies. If the patient was elderly, I would consider temporal artery biopsy to look for giant cell arteritis - this is unlikely in this patient.

Bacterial culture from bone marrow is of great value in the diagnosis of typhoid, compared to blood culture, since bone marrow culture has sensitivity up to 90% whereas blood culture has sensitivity less than 50%.

If a bone marrow biopsy is planned, how will you prepare the patient for the procedure?

There are no absolute contraindications for bone marrow biopsy. Bleeding tendency is not an absolute contraindication. Bone marrow biopsy is contraindicated in severe bleeding disorders, such as haemophilia, disseminated intravascular coagulopathy. Generally, thrombocytopaenia is not a contraindication, although if the platelet count is very low, it should be corrected to over $20,000/\text{mm}^3$. There should not be any active infection at the of biopsy site. The usual sites are posterior iliac crest, anterior iliac crest and manubrium of sternum.

I will inform Mr JF that investigations done so far have not identified a cause for his ongoing fever. I will explain to him that the bone marrow can harbour infections as well as blood cancers, which can be picked up by taking a sample and analyzing. I will inform him who will perform the procedure, and how it will be done, the common side effects (pain at the site, bleeding and rarely infection) and contraindications (such as bleeding tendency). I will give him time to think about the information given, and if he agrees, take written consent. I will check the site for local skin infections. I will liaise with the haematology team for a suitable time for the test, and arrange the required instruments for the procedure. Both bone marrow aspiration and trephine would be required in this patient. Samples will be sent for bacterial culture, TB culture and PCR, and for cytology and examination of the trephine biopsy. If available I will also arrange for flow cytometry on the bone marrow aspirate.

What are the complications of bone marrow biopsy and post procedure care?

There is often some discomfort and pain but this responds to simple analgesics like paracetamol. There can be bleeding from the site, and rarely damage to adjacent structures such as soft tissue and branches of arteries, or infection which could be local or systemic.

What is meant by a 'dry tap' on bone marrow aspiration? What is its significance?

It means that no marrow spicules are obtained on the aspiration, although blood is present in the aspirate. Faulty technique, where the needle has not properly entered the marrow, is a possibility. But more often it is due to alterations in the marrow, such as marrow fibrosis in myeloproliferative disorders, or due to granulomatous or malignant infiltration of the marrow.

At the end of all the above investigations if you have been unable to arrive at a diagnosis will you consider a therapeutic trial for Mr JF?

Therapeutic trials could be with antibiotics, corticosteroids or anti-TB drugs. A trial of conventional antibiotic therapy to cover conditions like typhoid could be considered. In this patient, with no evidence for TB, I do not think a therapeutic trial of anti-TB drugs would be appropriate, at this stage, but it is something to consider if the fever persists. Patients with neutropenia would normally be given empiric antibiotic therapy.

I would take the decision to start therapeutic trials only in consultation with my seniors and with the input obtained from other specialists. Starting an inappropriate antibiotic or steroid trial can mask underlying illness, giving temporary relief of symptoms, but leading to further complications later on.

Diseases like adult onset Still's disease need a high degree of suspicion and could benefit from a trial of steroids. I will discuss with a rheumatologist and a microbiologist the merits of giving steroids. Raised serum ferritin may be seen in Still's disease.

If you have a patient with nosocomial FUO how will the focus of your diagnosis differ?

Nosocomial FUO is due to hospital-acquired infections from local pathogens. Therefore more emphasis should be placed on attempts to diagnose infection and its focus. Common causes of nosocomial infection include hospital acquired pneumonia, antibiotic associated *Clostridium difficile* infection, cannula and procedure site infections, urinary and other catheter related infections.

Thorough clinical examination, chest radiograph, cultures from possible sites, and repeated blood cultures are important. Other possible causes that I will consider are drug fevers, transfusion reactions, pulmonary embolism, deep vein thrombosis, and acalculous cholecystitis.

Case 14

Mrs SA, 36-year-old female was admitted from the medical clinic. She gave a history of multiple joint pains, with swelling and deformities, for 4 years. At the beginning, she had developed insidious onset progressively worsening pain in the small joints of the hands. With time, her wrist joints, elbows, knees and small joints of the feet were affected. Joint involvement was symmetrical, and there was stiffness on waking, which lasted about 2 hours. Initially she took treatment from an ayurvedic practitioner. The treatment seemed to work at the beginning, however she had periods of worsening intermittently. Over the last year she noticed that her hands were becoming deformed, and the pain was getting worse. She then saw her family doctor who referred her to the rheumatology clinic. She was started on several medications, although she did not know their names. One of the tablets prescribed was to be taken only once a week (this is likely to be methotrexate), and she was also given some small white tablets, initially 12 tablets a day in the morning, reduced over a few weeks to 4 a day (this is likely to be prednisolone).

She claims that her pain had subsided after starting these drugs, but as the number of tablets were reduced, the symptoms were reappearing. At the time of presentation, she had pain and swelling in the small joints of the hands and feet, elbows and

es, associated with morning stiffness. She had no pain in her shoulders, no neck or back pain, and no pain on opening her mouth. The pain and stiffness worsens with rest, and also with heavy work, and during colder weather. She also complained of fatigue for several months, which improved at times. She had no shortness of breath, wheeze, cough, haemoptysis, or chest pain. Her appetite had been poor earlier, but had improved after starting medications, and she had gained weight recently. Her bowel habits were normal, she had no abdominal pain, and no urinary symptoms. Her periods were regular and normal, and the last period was 3 weeks ago. She did not complain of dry eyes or dry mouth, red eyes, or changes in vision. She had not noticed any colour changes or pain in her fingers on exposure to cold.

She had never been admitted to hospital in the past, and had not undergone any surgeries. She did not have any food or drug allergies. There was no history of any other illnesses. There was no family history of similar illness. She is married, and has an 8-year-old son who is schooling. She is a housewife, and her husband owns a grocery. Their monthly income is adequate. Until her illness, she was able to do all housework unassisted, but this has become increasingly difficult over the past few months, and she had had to get help from her mother who lives close by. She lives in a single storey house with three bedrooms. She travels to hospital by bus or taxi. Though she is educated up to O-levels, her understanding and awareness of her health issues is poor, and based on mother's recommendation she tried native treatment. Her expectations are that her joint problem can be completely cured, and the deformities reversed.

Can you summarise your history before proceeding to the examination findings?

Mrs SA, a 36-year-old housewife, has chronic progressive symmetrical polyarthritis with morning stiffness, of 4 years duration. Her small

joints of hands, wrists, elbows, knees and small joints of feet are affected. She has had several exacerbations of her symptoms, and over the last year has noticed deformities in her hands. She had no other systemic features. She initially took native treatment, and is now being treated at the rheumatology clinic, most probably on methotrexate, a tapering regimen of prednisolone, and some other drugs. She appears to have had some adverse effects from steroid treatment. There are significant limitations in her functional status resulting from the illness.

What underlying diagnoses would you consider?

Given the history of symmetrical inflammatory type polyarthritis, with morning stiffness, rheumatoid arthritis would be my first diagnosis. Seronegative arthritis such as psoriatic arthritis, reactive arthritis and ankylosing spondylitis can also present with polyarthritis, but in these conditions spinal involvement is predominant, unlike in rheumatoid arthritis. Autoimmune conditions like SLE also can have a pattern of joint involvement which is similar to rheumatoid arthritis, but in SLE what is found is typically arthralgia with soft tissue involvement, and not a true synovitis. Primary generalised osteoarthritis and nodal osteoarthritis can also present with polyarthritis, usually in older patients.

Clinically, how will you differentiate the other conditions from rheumatoid arthritis?

In rheumatoid arthritis there is symmetrical polyarthritis with predominant involvement of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, with characteristic sparing of the distal interphalangeal joints. There is spindle shaped swelling of the fingers due to joint sinovitis of the proximal interphalangeal joints. Arthritis causes significant deformities such as ulnar deviation, volar subluxation, swan neck deformity, boutonnière deformity and Z-thumb deformity. Other features like subcutaneous nodules and eye involvement also occur in rheumatoid arthritis.

In nodal osteoarthritis there can be an inflammatory phase, with some degree of morning stiffness, but this is not long lasting, and also there is involvement of distal interphalangeal joints. After the inflammatory phase there are painless bony prominences called Heberden's node in the distal interphalangeal joints and Bouchard's nodes in the proximal interphalangeal joints. Functional impairment in the hands due to osteoarthritis is minimal, and there are no associated extra-articular manifestations. Also, nodal osteoarthritis generally has an onset after 50 years, in contrast to rheumatoid arthritis which appears in a younger age group.

In SLE both proximal and distal interphalangeal joints can be affected in a symmetrical manner. However, although there is joint pain, the joints clinically appear normal except for slight soft tissue swelling, and deformities generally do not occur. Furthermore, SLE is characterized by other systemic features, such as photosensitivity, oral ulcers, alopecia, and skin rash.

Psoriatic arthritis is mostly asymmetrical and mainly involves the DIP joints. There is diffuse swelling of the fingers causing a 'sausage' appearance. It maybe associated with nail changes and skin changes of psoriasis. A family history of psoriasis or arthritis may present. These features help to differentiate it from rheumatoid arthritis.

Nonetheless, seronegative spondyloarthritides can present in a manner very similar to rheumatoid arthritis.

Would you like to present your examination findings now?

Mrs SA was not dyspnoeic, and was comfortable lying on bed. Her height was 152 cm and weight was 59 kg. Though her BMI is $25.5\text{kg}/\text{m}^2$ her waist circumference was 89 cm. She was not pale, not icteric, had no cervical lymphadenopathy, no subcutaneous nodules or rashes, and no oedema. There were pink striae on the

abdomen. Cardiovascular examination was normal except for blood pressure of 150/90 mmHg. Pulse was 76/min regular with good volume. Respiratory system and abdomen were clinically normal. There were no focal neurological signs or evidence of peripheral neuropathy or proximal muscle weakness.

Her gait was normal, and she was able to stand in the normal straight posture. She had normal mouth opening with no tenderness over the temporo-mandibular joints. Neck movements were normal, and there were no deformities over the spine, and there was no restriction on bending, or with rotational movements of the back.

On examination of the hands, the skin was red over the wrists and fingers with warmth and swelling over metacarpophalangeal joints and wasting of small muscles of the hands bilaterally. There was ulnar deviation of fingers and volar subluxation of proximal phalanges on both hands. There were no swan neck, boutonnière or Z-thumb deformities. Nails appeared normal. There was tenderness over wrist, metacarpophalangeal, and proximal interphalangeal joints, but no tenderness over distal interphalangeal joints. There was mild subluxation of the MCP joints. There was no joint crepitus. Both wrist joints had almost normal range of movement but there was restriction in MCP joints of the left hand, particularly on flexion. The cylindrical grip of the hand was poor, with the left side more affected; pincer grip was intact and strong.

Rather than testing for individual movements, what matters most is to test for the functional ability of the hand. The two key grips are cylindrical grip (needed to hold onto things) and pincer grip (needed to pick up and hold small objects).

Except for slight tenderness over the elbow joints and knee joints examined

feet, but no evidence of plantar fasciitis. I could not palpate any rheumatoid nodules.

What is the most likely diagnosis of her joint condition, according to your history and examination?

With the symmetrical polyarthritis of the small joints causing typical deformities, the most probable diagnosis is rheumatoid arthritis.

You didn't mention anything about her eyes. What would you look for?

In rheumatoid arthritis, patients can have scleritis, episcleritis and karatoconjunctivitis sicca. To recognize them I'll check for red eyes. In scleritis visual acuity can be reduced. Therefore testing for visual acuity is important. Steroids can predispose to glaucoma and cataract. I would do a quick fundoscopic examination looking for the red reflex (if absent, will suggest cataract) and for the appearance of the optic cup. If there is any suspicion of eye involvement I would refer her to the ophthalmologist.

Also, since her blood pressure is high I will look for hypertensive changes on the retina.

You mentioned that the respiratory system was normal. What relevant things did you look for?

Rheumatoid arthritis can cause pulmonary involvement. There are several pulmonary manifestations: pleurisy, pleural effusions, fibrosing alveolitis, lung nodules, and Caplan's syndrome. I looked for evidence of pleural effusions (pleural rub and dullness to percussion) and basal fine crackles which can occur in fibrosing alveolitis.

The commonest lung manifestation of rheumatoid arthritis is pleural disease, resulting in pleural effusion. Another component is interstitial lung disease, which leads to progressive pulmonary

fibrosis. This has a better prognosis than idiopathic pulmonary fibrosis. Another asymptomatic finding is intrapulmonary and pleural nodules that can cavitate. A rare but interesting pulmonary manifestation occurs in patients with rheumatoid arthritis with exposure to silica. This is called Caplan's syndrome where they develop large cavitating pulmonary nodules.

What are the problems you identified in Mrs SA?

Her medical problems are,

- bilateral symmetrical small joint arthritis with deformities suggestive of rheumatoid arthritis
- central obesity, possibly due to drug-induced Cushing syndrome
- high blood pressure

Her psychosocial problems are,

- poor awareness of the illness
- disability resulting from the illness, with limitation of activities of daily living

What activities of daily living are you interested in? Did you use any scoring systems to assess her disability in relation to activities of daily living?

I asked about bladder and bowel continence, ability to use a toilet and shower, ability to groom and dress herself, independence in transferring, mobility and climbing chairs, and feeding.

In my patient I did not use any particular scoring systems but assessed these subjectively.

Activities of Daily living (ADL) refer to basic self-care activities that an individual has to perform, and they are used as a measure of one's functional status, particularly when afflicted by a condition like stroke, arthritis, dementia, and in the elderly. There are many scales

developed to measure these activities, such as Barthel index, Katz ADL scale and Bristol activities of daily living scale. However in your long case, with limited time, you will generally not be expected to apply such a scale, although you should be able to discuss about ADL in depth.

Have you heard of something called instrumental activities of daily living?

Yes. They are activities that are not essential for individual self-care, but important for the person to function independently in the community. They include basic housework, preparing meals, washing and ironing clothes, managing finances, handling transportation, using a telephone, shopping, and taking medicines.

You mentioned that she is obese. On what basis did you say so?

I diagnosed central obesity in her based on the fact that waist circumference was 89cm. Waist circumference in women >88cm is a strong predictor of obesity related health issues. In this patient the BMI is above the normal range, with increased waist circumference, indicating increased central fat deposition and central obesity.

What is the significance of obesity and high blood pressure in this patient?

In a woman of this age, both these manifestations could be a result of steroid treatment. Tailing off the steroids will improve these. On the other hand, rheumatoid arthritis, which is a chronic inflammatory condition, is a risk factor for cardiovascular disease. The presence of other risk factors like obesity and hypertension will further increase the risk of cardiovascular disease.

The most common cause of death in rheumatoid arthritis is cardiovascular disease.

What investigations would you do in this patient?

I will start with basic investigations including full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), which will provide supportive evidence of an inflammatory arthritis. In the full blood count, anaemia may be seen.

What are the causes for anaemia in rheumatoid arthritis?

There are several mechanisms for anaemia in rheumatoid arthritis. Because it is a chronic inflammatory condition, normocytic normochromic anaemia of chronic disorder may be seen. However iron deficiency can occur as a result of occult gastrointestinal bleeding due to long term NSAID use. Certain drugs used may cause bone marrow suppression. Sometimes there can be associated autoimmune haemolytic anaemia.

Please continue...

The platelet count can be elevated in active disease. In some patients there can be neutropenia and hypersplenism, and this is known as Felty's syndrome.

ESR and CRP are usually elevated in rheumatoid arthritis, and correlate with the disease activity. I will do the rheumatoid factor as a serological test to diagnose rheumatoid arthritis. A high positive titre will strongly suggest rheumatoid arthritis.

I will also perform hand x-rays to establish the diagnosis of rheumatoid arthritis. In rheumatoid arthritis, there are many changes which can be seen, such as soft tissue swelling, loss of joint space, subchondral erosions and periarticular erosions in early disease. In more advanced cases, bone destruction may be seen. Changes are predominant in wrist joints, MCP and PIP joints. Ultrasound scan of the joints will give more information than plain x-ray.

How useful is rheumatoid factor in diagnosing rheumatoid arthritis?

It has sensitivity of about 70-80% and can have false positive results as well. Therefore we can't entirely depend on rheumatoid factor for the diagnosis. However the rheumatoid factor titre correlates with disease severity.

With sensitivity of 70-80% you can miss many patients if you rely on rheumatoid factor alone for diagnosis. On the other hand it has low specificity. It can have false positive results in conditions like Sjogren's disease, SLE, systemic sclerosis and in <2% of normal population. It can also be positive in chronic infections like chronic hepatitis and infective endocarditis. However, positivity signifies more severe disease.

Do you know of any other serological markers in this condition?

Anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies) are useful in diagnosis of the disease especially because it has greater specificity (90-95%), although sensitivity is slightly less than rheumatoid factor in early stages of the disease. However it can be positive in some patients in whom rheumatoid factor is negative. Patients with positive anti-CCP antibodies in the early stages of disease are at increased risk of progressive joint damage.

She has had the disease for around 4 years. What is the impact on her long-term outcome?

Joint destruction begins very early in the course of illness. Therefore delay in initiation of drugs to prevent the progression of the disease can lead to permanent joint damage and disability. In this case she has already got some deformities, which are irreversible. However even at this stage, DMARDs are likely to be of benefit in preventing further damage.



What are the objectives of treatment?

The main objectives are to treat her symptoms like pain and stiffness, slow disease progression and damage to joints, and identify and treat extra-articular complications. Improving her functional status, minimize side effects from long-term medications and management of cardiovascular risk factors are also important goals.

What is the place for steroids in this context?

Since disease-modifying drugs take time to take effect, steroid are used as bridging therapy until these drugs act. Steroids rapidly control symptoms. Short courses of steroids are also used to treat acute disease flares. In some patients, as in Mrs SA, regular low dose therapy is used when there is inadequate response to other drugs. For symptomatic relief local steroid injections are sometimes given into acutely inflamed joints.

Steroids are also known to reduce disease progression to some degree, although they are not used primarily for this purpose given their adverse effects.

What factors increase the risk of osteoporosis in patients with rheumatoid arthritis?

The main factor is the long-term use of corticosteroids. Generally, prednisolone 5mg daily for three months or more is associated with a risk of osteoporosis. Other factor that increases risk is RA itself, because it is a systemic inflammatory state with elevated IL-1 and TNF- α levels, which will stimulate osteoclast activity. Factors like poor appetite and Sjogren's syndrome contribute to osteoporosis by impairing calcium intake. Reduced mobility also increases the risk.

Are there any measures you can do to prevent osteoporotic fractures in Mrs SA?

Prevention of osteoporosis and care to prevent falls important. One measure is to maintain the steroids at the lowest possible dose for the shortest possible period, to minimize steroid induced osteoporosis. Regular exercises are also useful, preferably with the input of a physiotherapist, to maintain joint mobility and stability. Regular monitoring of bone density by DEXA scanning is necessary, so that treatment can be initiated when indicated. Calcium and vitamin D supplementation are also helpful. Bisphosphonates are given if osteoporosis is present or the risk is high. When long term steroids are used, there is a place for concurrent prophylactic bisphosphonates.

What drugs are used to prevent the progression of disease?

These drugs are called disease modifying anti-rheumatic drugs (DMARDs). There are non-biologic and biologic DMARDs. Non-biologic drugs include methotrexate, sulphasalazine, leflunamide and hydroxychloroquine. Biologic DMARDs are anti-TNF agents like infliximab and adalimumab, the IL-1 receptor antagonist anakinra, and the CD-20 antibody rituximab to deplete B cells.

She is on methotrexate. What are its side effects, and what precautions will you take when treating her with methotrexate?

The common side effects are nausea, vomiting and diarrhoea. Patients can also develop mucositis, oral ulcers and hair loss. Serious side effects are hepatotoxicity, renal impairment, neutropenia, thrombocytopenia and pulmonary fibrosis.

I will tell Mrs SA about the common side effects and serious side effects. I will ask her to stop methotrexate and come to hospital if she develops oral ulcers, cough or shortness of breath. Also I will do baseline full blood count, liver enzymes and serum creatinine, and monitor these during treatment. If the baseline

creatinine is more than 2mg/dL I will choose alternative drugs. If there is elevation of liver enzymes or neutropenia, methotrexate should be stopped. I will also do a chest x-ray before starting methotrexate, and will start only if there is no evidence of pulmonary fibrosis. If Mrs SA develops symptoms of lung fibrosis I will do lung functions tests and look for evidence of restrictive lung disease, or arrange for her to have a HRCT to confirm the clinical suspicion.

Folic acid is given weekly to prevent toxicity, particularly mucosal and gastrointestinal side effects. Methotrexate is contraindicated in pregnancy. So I will advise her on effective contraceptive methods and the need to stop the drug before planning pregnancy.

If she does not respond to methotrexate what will you do?

Combinations of DMARDs in high doses can be given, and these have proven efficacy over using methotrexate alone. We can combine methotrexate with sulphasalazine and hydroxychloroquine or leflunamide. These are very specialized drugs and are used by rheumatologists. If she is still not responding we should consider adding a biologic DMARD.

The rheumatologist has decided to start her on infliximab. What special things should you consider before giving this drug?

Infliximab will increase the risk of infection, and therefore it should not be given to patients with active infection. Reactivation of latent tuberculosis is another important problem. The patient should be screened for tuberculosis clinically and by Mantoux test and chest X-ray. If any suspicion of TB is present, a course of anti-TB treatment could be considered prior to giving infliximab.

Can the kidney be affected in rheumatoid arthritis?

Yes, there are many reasons for renal involvement in rheumatoid arthritis. Long term use of NSAIDs and DMARDs can cause renal damage. Gold, penicillamine and cyclosporine can cause glomerulonephritis. Secondary amyloidosis can occur in rheumatoid arthritis, and this can cause kidney damage. Very rarely a primary focal glomerulonephritis can occur in rheumatoid arthritis.

This patient comes and complains you about epigastric burning sensation and pain after meals. What are your concerns?

Dyspeptic symptoms could be due to many reasons including gastritis, peptic ulcer disease, gallstones and even gastric carcinoma. In this patient in particular, steroids and NSAIDs increase the risk of gastric erosions and peptic ulcer disease. An upper GI endoscopy is indicated.

After treating with proton pump inhibitors and tailing off steroids she continued to be symptomatic, and an upper gastrointestinal endoscopy was arranged for her. Is there any particular precaution you have to take prior to the procedure?

In some patients with rheumatoid arthritis, atlanto-axial subluxation can happen. Antero-posterior subluxation is unstable, and can cause cervical cord compression. Procedures like intubation and gastrointestinal endoscopy need manipulation of the neck, and there is a high risk of subluxation if the joint is not stable. Therefore lateral neck x-ray extension and flexion views should be done prior to the procedure, and the procedure should be undertaken by an experienced team aware of the potential problems.

Case 15

Mr GL is a 27-year-old tailor with haemophilia. He presented with pain and swelling of the left knee of one week's duration. His symptoms developed spontaneously, and were of acute onset. Since then he had had constant pain even at rest, worsening with movement. He could move his knee, but not to the full range of movement. The swelling gradually worsened over the first two days, and then began to get better. Two days later he developed fever. This was a low grade fever (although he had not measured his temperature), with no chills or rigors. He was admitted on second day of the illness, and was treated with factor VIII and antibiotics, with slight improvement. He had no other bleeding manifestations during this period.

He was diagnosed to have haemophilia at the age of 18 months, and since then had had recurrent episodes of haemarthrosis involving the right ankle joint, both knee joints and the small joints of the hand, as well as thigh and calf bleeds. He usually experienced an episode of haemarthrosis once or twice a month, but none of the episodes have been this severe. He had never had episodes of severe headache, loss of consciousness, fits, or episodes of severe abdominal pain. Bleeds were usually treated with cryoprecipitate and factor VIII. He had been initially followed up at the children's hospital, and later on in an adult

medical unit of a teaching hospital. He had a good understanding of the disease, and was able to recognize bleeding episodes. He was compliant with follow up, although sometimes there were delays in admission because he lived 20 miles away from the teaching hospital. Factor VIII is unavailable at his local hospital, and since he is aware of the benefits of treatment with factor VIII over blood products, he would normally wait until he can come over to the teaching hospital for treatment. His joint involvement has of late begun to affect his work as a tailor. He has been advised to avoid vigorous activities and contact sports. He is well aware of his illness and its chronic nature. He had been fully immunized against hepatitis B, and gave no history of jaundice.

He had never undergone any surgery. He had not developed any significant reactions to any drugs or blood products. Both his maternal uncle and cousin had haemophilia. He lives with his wife and mother, and is the breadwinner of the family. He married recently. His father had died 5 years ago following snakebite, and his sister is married with a son and a daughter. He has a reasonable income.

On examination he was afebrile and in pain. He was not pale or icteric. There were no deformities in the left knee joint, which was swollen, tender and warm. The range was reduced both with passive and active movement. There was no joint crepitus. There was a valgus deformity of the right knee joint and a fixed flexion deformity of the proximal inter-phalangeal joint of the right middle finger. The other joints were normal with no evidence of arthritis or deformity. There was no muscle wasting in any of the limbs.

His pulse rate was 82/bpm and blood pressure was 110/70. Cardiovascular system, respiratory system, nervous system, and abdomen were normal.

Would you like to summarize the history and examination?

Mr GL, a 27-year-old man with haemophilia, presenting with a painful swollen left knee joint with reduced movements, and low grade fever for one week. He was treated with factor VIII but with little improvement. He had had similar episodes once or twice a month, which were treated with factor VIII and cryoprecipitate, but those episodes were less severe. He had no other bleeding manifestations. He is married, works as a tailor, and his work has been affected by physical disability resulting from repeated joint haemarthroses. His understanding of the illness is good, and he has adapted to his chronic illness and physical disability.

He has evidence of acute left knee arthritis with some restriction of movements and deformities in the right knee joint and PIP joint of right middle finger. He was systemically well.

What are the problems that you identified in your patient?

His acute problem is pain and swelling of the left knee joint with poor response to usual treatment, with fever.

His main long term medical problem is haemophilia, with recurrent haemarthroses and some joint deformities. He has been fortunate not to have other major bleeding manifestations. He has had multiple transfusions with cryoprecipitate and needs factor VIII transfusions 1-2 times a month. He has functional disability due to recurrent haemoarthritis, which, along with recurrent hospital admissions, have affected his work.

In relation to the acute problem what are the possibilities?

This presentation could be due to haemarthrosis, but I would also consider septic arthritis as my most important differential diagnosis. Other causes of monoarthritis should also be kept in mind, such as gonococcal arthritis, mycobacterial arthritis, reactive arthritis, and crystal arthropathies like gout and pseudogout, but given the history these are clearly less likely.

What is the typical clinical presentation of haemarthrosis?

Haemarthrosis typically presents with acute onset painful swelling of the joint. The patient usually keeps the joint flexed, allowing no movement. There is warmth and tender swelling of the joint. There may or may not be a history of trauma to the joint, and there can be low grade fever. The swelling gradually settles when blood is absorbed over a few days.

In haemophilia, the commonest joint to be affected is the knee joint. The other joints that get commonly affected are ankles, elbows, shoulders and hips. However small joints of hands and feet can also be affected. With recurrent episodes, there can be some degree of chronic arthritis with swelling, deformities, restricted movements and subluxation.

If this patient's presentation is suggestive of haemarthrosis, why do you consider septic arthritis?

There are a few features which are cause for concern. This episode is more severe than any other episodes, and he has developed fever. He has not responded to routine therapy. Septic arthritis has serious consequences, and I am keen to rule it out completely.

The other important point is that haemophilic arthropathy itself is considered to be a predisposing factor for septic arthritis. It is difficult to differentiate the two conditions by clinical examination alone.

Since you suspect septic arthritis in this patient what will you do?

After correction of his coagulopathy, I will arrange for joint fluid aspiration. Fluid should be sent for full analysis, gram stain smear, and culture with antibiotic sensitivity. I will do a full blood count to look for neutrophil leukocytosis, which will favour septic arthritis, although mild elevation of the neutrophil count can be seen in haemarthrosis also. ESR and CRP may also

suggest infection if raised. I will take blood culture and start on intravenous antibiotics. X-ray of the joint could be done- they are generally normal, or may show some chronic changes resulting from haemarthrosis, however they may demonstrate evidence of osteomyelitis. I would consider referring the patient to the orthopaedic surgeon to consider arthroscopy.

How do you classify haemophilia A based on severity?

Clinical severity depends on the degree of factor VIII deficiency. The amount of residual activity of factor VIII as a percentage of normal activity is used to indicate the severity. In severe disease this is less than 1%. In moderate disease it is 2-5%, and in mild disease it is 6-30%. In severe disease recurrent spontaneous bleeding occurs. In moderately severe disease, occasional spontaneous bleeding and bleeding after minor trauma takes place. In mild disease bleeding occurs only after significant trauma or surgery.

What are the other bleeding manifestations seen in haemophilia?

The commonest bleeding manifestations are haemarthroses and muscle haematomas. Other spontaneous bleeding manifestations are gastrointestinal bleeding, haematuria, intracranial haemorrhages, intraperitoneal bleeding and bleeding into the oropharyngeal spaces. Serious bleeding can also occur after trauma or during surgery.

How do you manage a patient with haemophilia presenting with haemarthrosis?

This includes supportive management with analgesics, preferably paracetamol and opioids, rest, and temporary immobilization of the joint in extension. NSAIDs are not used, as they increase bleeding. For definitive management factor VIII is used to correct coagulopathy. If factor VIII is not available, cryoprecipitate can be used - this is what is available in Mr GL's local hospital.

Calculation of factor VIII dose is beyond the scope of a usual long case discussion. If you can remember it, it will impress the

examiner, and the likelihood is that if you start to describe the dose calculation, the examiner will stop you and move on! The dose of factor VIII and IX are expressed in units and the units needed to be infused to patient at a time is based on the target factor percentage, per kg will result in a 2% rise in factor level. One unit

$$\text{Factor VIII dose (IU)} = (\text{Target level} - \text{baseline level}) \times \text{body weight (kg)} \times 0.5$$

Target factor percentage depends on the clinical condition. In spontaneous bleeding like haemarthrosis or muscle haematoma the target is 30-50%. In major surgery, post-traumatic bleeding and life threatening bleeding, 100% is the target, and levels should be maintained above 50% when acute bleeding has stopped.

Another treatment option that can be used in patients with mild haemophilia to increase the factor VIII level is parenteral or nasal administration of DDAVP (desmopressin). By acting on endothelial cells this will cause a rise in circulating factor VIII levels, but this is not effective in patients with severe disease. Oral or intravenous antifibrinolytic therapy with tranexamic acid can be used as an adjuvant to factor replacement. Because of its short half-life, tranexamic acid needs to be given in repeated doses for 5-7 days per episode of bleeding.

What are the complications of bleeding into musculoskeletal system?

There are acute as well as long-term complications. Haemarthrosis can temporarily hinder joint function. Muscle haematomas in extremities can cause entrapment neuropathy due to local pressure and compartment syndrome.

Recurrent episodes of haemarthrosis result in synovial thickening and synovitis. This leads to progressive joint damage and deformity. There can be large encapsulated haematomas in muscle and fascial planes and large bones like the pelvis. With subperiosteal bleeding there can be bone destruction and new

bone formation, causing progressive cystic swelling. This is called a pseudotumour.

What is the inheritance of haemophilia?

Both haemophilia A and B are X-linked recessive disorders. It is therefore almost always seen in males, while females are carriers.

Can you briefly describe the haemostatic derangement which occurs in haemophilia?

In response to vascular injury there are three components which are activated to stop bleeding. There is a vascular response (vasoconstriction), a platelet response, and activation of the coagulation cascade. To make a clot a meshwork of fibrin is required. This is achieved by converting fibrinogen to fibrin, which is done by thrombin. Thrombin is formed from prothrombin and this conversion is done via two different pathways, the intrinsic and extrinsic pathways. Multiple clotting factors are involved in this cascade. In the extrinsic pathway, after tissue trauma, tissue factor is released. It converts factor X to activated factor X with the help of activated factor VII. Activated factor X combines with activated factor V and calcium and platelet phospholipids which converts prothrombin to thrombin. In the intrinsic pathway, following exposure of blood to collagen, there is a cascade of activation of factors XII, XI and IX, in sequence. Activated factor IX together with activated factor VIII and platelet phospholipids activates factor X. This converts prothrombin to thrombin. In haemophilia A factor VIII is deficient causing problems in the intrinsic pathway and clot formation.

We have been talking about haemophilia A all the time. What is haemophilia B?

Haemophilia B, known as Christmas disease, is another inherited coagulation disorder, which occurs due to factor IX deficiency. It also has an X linked recessive inheritance and has similar clinical

features, although it is less common and generally milder compared to haemophilia A.

Why is it called Christmas disease?

The first patient described was named Stephen Christmas. Also, the first report was published in the Christmas edition of the British Medical Journal in 1952.

What is the other common inherited coagulation disorder that is inherited with autosomal inheritance?

The commonest inherited bleeding disorder is Von Willibrand Disease. It is inherited by autosomal inheritance. There are several types, some transmitted dominantly and some recessively.

Von Willibrand Factor has two major functions. One is to facilitate platelet adhesion to the vessel wall and the other is binding to factor VIII and protecting it from being destroyed in circulation. There are several subtypes of VWD and clinical features are more related to platelet dysfunction.

What are the main laboratory findings you see in a patient with haemophilia A?

Activated partial thromboplastin time (APTT) is prolonged. Platelet count is normal. Prothrombin time and bleeding time are also normal. Prolonged APTT is corrected by a 50:50 mix of normal and test plasma. Factor VIII assay will be reduced.

When you are replacing factor VIII how frequently do you do it? What is the rationale behind this practice?
Factor VIII is injected twice daily to maintain therapeutic levels, because its half life is 12 hours.

You have noticed that this patient has not responded to factor VIII therapy. What could be the most likely reason for becoming unresponsive to factor VIII therapy?

This could be due to the formation of antibodies (inhibitors) to factor VIII.

This is a serious complication in haemophilia A. It is commonly seen in children. It is detected either by routine surveillance for inhibitors, or when patients do not respond to therapeutic doses of factor replacement. Unlike in usual haemophilia patients these patients' APTT is not corrected by mixing studies, because inhibitors neutralize factor VIII from normal plasma. When there is a patient with inhibitors there are two goals of management. One is to control episodes of bleeding. This is done by giving high doses of recombinant factor VIII in patients with low level of inhibitors, and by administering prothrombin complex concentrates or activated Factor VII in patients with high level of inhibitors. The second goal is to eradicate inhibitors, which is done by immunosuppression and a method called immune tolerance induction. These are advanced details and will not normally come up in a final MB discussion.

What do you know about the life expectancy and prognosis of these patients at present, compared to past?

Decades ago their life expectancy was reduced compared to normal population. But with the availability of clotting factors, survival to adult life improved considerably. Prior to the establishment of screening for viruses in blood and blood products, most patients developed hepatitis C as well as hepatitis B and HIV. Now, with the availability of strict screening patients are protected from blood borne infections. Therefore people with haemophilia can now have an almost normal lifespan.

Despite this, patients do develop disability and deformities due to recurrent joint involvement. Current guidelines recommend prophylactic factor VIII treatment to be administered three times

Case 15

a week in patients with severe haemophilia A, to maintain factor levels >1%. By this strategy, patients can reach adult life without significant arthropathy.

This patient and his family have been given genetic counseling from the clinic earlier. His wife is of the view that their children will be unaffected. Do you agree?

Not quite. Their sons won't be affected because Mr GL will pass his Y chromosome to the son and not his defective X chromosome. But he will pass the defective X chromosome to all his daughters. They will be carriers of haemophilia. It is thought that about 50% of factor level is enough to avoid significant bleeding. But due to random inactivation of X chromosome, which is called lyonization, this level can vary from patient to patient. Thus his daughters can be at risk of bleeding following major trauma and surgery if their factor levels are in the low side.

Case 16

Mrs JJ, 63-year-old woman with a history of hypertension, presented with sudden onset inability to speak four weeks ago. She had been well until 2 weeks prior to the onset of speech difficulty, when she developed fever, loss of appetite and malaise, for which she consulted a specialist, who had treated her with oral antibiotics. She was relaxing at home when she found that she was unable to speak. She had not noticed any limb weakness or numbness, double vision, loss of vision, imbalance, facial droop, headache, loss of consciousness or fits. She presented 2 hours after the onset of symptoms to the hospital, and her speech showed little improvement over the next few days. She also complained of altered bowel habits on and off, with several episodes of loose stools; there was no bleeding.

She was evaluated extensively during her hospital stay with brain imaging, blood and urine investigations and imaging methods, including transoesophageal echocardiogram (TOE). She also had undergone a minor surgical procedure, which is likely to be temporal artery biopsy. She was started on speech therapy soon after admission and has had some improvement in speech within 2-3 weeks. Following the TOE she was told that she has an infection in the heart, and she was started on a course of intravenous antibiotics. She was told that the antibiotics would have to be given for at least 6 weeks. Her ESR and CRP were checked several times, and according to her knowledge both were

high initially, and the CRP has become normal now although her ESR is still high. During treatment her blood was checked almost daily, and she was told that her kidneys were affected, and she was advised to monitor intake and output; her urine output had been over a litre per day. Her constitutional symptoms had improved during hospital stay. She did not have any chest pain, shortness of breath, urinary symptoms or joint pain. She had not had any dental procedures, childhood cardiac problems, cardiac surgeries, or preceding hospital stay with IV drug administration. She had not undergone any surgeries, and had no known drug or food allergies. She is a widow, and a mother of two children who are employed. She has good family support, but is concerned about her prolonged hospital stay, and long term outcome.

On examination she looked well, was pale, with no peripheral oedema. There were no peripheral stigmata of infective endocarditis. Blood pressure was 140/60mmHg with a pulse rate of 68/min, regular with good pulse volume. The pulse was not collapsing. JVP was not elevated. All peripheral pulses were present, and no carotid bruits were heard. The cardiac apex was felt normally in the left 5th intercostal space, mid-clavicular line. First and second heart sounds were normal, with a grade 3 early diastolic murmur in the aortic area, which was suggestive of aortic regurgitation. Respiratory examination and abdomen were normal, no focal neurological signs, mild slurring of speech and normal optic fundus.

Can you provide a summary of the important points in the history and examination?

Mrs JJ is a 63-year-old woman with hypertension, who presented with aphasia, suggestive of a stroke. She was subsequently diagnosed and treated for infective endocarditis with intravenous antibiotics. Her constitutional symptoms and aphasia have resolved with treatment. She appears to have had altered bowel habits over past

few weeks, and renal impairment which developed during hospital stay. Her history does not reveal any significant predisposing factor for infective endocarditis. She is pale, with a grade 3 AR with no residual neurological signs, and is haemodynamically stable.

Can you list out the problems that you have identified in this patient?

- Aortic regurgitation with infective endocarditis
- Stroke, probably due to septic embolization
- Acute kidney injury (AKI), either secondary to IE or due to nephrotoxic drugs, or long standing hypertension, or a combination of these
- Hypertension
- Altered bowel habits
- Psychological impact due to her illness and prolonged hospital stay

What could her altered bowel habits be due to?

One possibility is that it is antibiotic induced. Many antibiotics cause antibiotic diarrhoea. *Clostridium difficile colitis* is less likely, as I would expect her to be much more ill. The other possibility is an underlying bowel malignancy, or even inflammatory bowel disease.

I would further explore her past history, to find out whether these bowel symptoms were present earlier. I will ask her to maintain a bowel chart with stool consistency, frequency and presence of blood, mucus or malaena. She needs a digital examination of the rectum, and flexible sigmoidoscopy, stools for *C. difficile* toxin and GDH enzyme, stool culture and examination for ova, cysts and parasites.

In a patient with multiple inter-related problems, it is useful to identify all the medical, psychological and social problems, and

present them in an organized manner. Often, at undergraduate level, the focus will be on the main clinical problem, but be prepared to address all problems you have identified.

Do you see any relationship between stroke and infective endocarditis in this patient?

In IE, there will be vegetations on the heart valves, and these can break off, causing septic embolisation of any organ. The stroke could be a result of embolism. However, there is also the possibility of a septic embolus causing a mycotic aneurysm in the brain, and also cerebral abscess.

About 20-30% patients with IE develop strokes due to emboli, and in about half of the cases strokes may precede the diagnosis of IE.

What are the classifications that you have heard of for infective endocarditis?

IE can be classified according to the temporal evolution, type of valve involved, organisms involved and the risk factors.

According to temporal evolution it is classified as either acute or subacute IE. It also can be classified based on the fact whether native valves or prosthetic valves are involved. Mrs JJ had subacute IE of her native aortic valve.

What are the common symptoms and signs of infective endocarditis?

Clinical features of IE vary between acute and subacute disease. In acute disease, there is an abrupt onset of symptoms such as high spiking fever, and features of congestive cardiac failure may be evident. In contrast, patients with subacute illness may have an insidious onset with constitutional symptoms like fever, fatigue, malaise, anorexia, due to systemic involvement. Other features

of IE are due to cardiac involvement, embolic phenomena and immunological phenomena.

Cardiac involvement can give rise to shortness of breath, palpitations, and new or changing murmurs.

Embolic phenomena manifest as strokes, splenic and hepatic micro-abscesses, painless hematuria due to renal infarcts, and digital gangrene.

Immune mediated phenomena are due to deposition of immune complexes in tissues. They include Osler's nodes (painful lesions in the pulp of the fingers), Roth spots (vasculitic fundal lesions), backache due to immune complex deposition in the disc space, joint symptoms due to synovitis, features of glomerulonephritis and renal impairment.

There are multiple causes for heart failure in IE. It is commonly due to valvular dysfunction, though immune mediated myocarditis and intracardiac fistulae are also possible causes. Extension of infection can also affect the conduction system of the heart, resulting in heart block.

What are the common organisms responsible for infective endocarditis? Do the organisms differ based on the source of infection?

Streptococcal viridans is the commonest cause for IE, and their portal of entry is the oral cavity. Poor dental hygiene is known to be a risk factor, and they usually affect damaged valves. *Streptococcus bovis* (*Streptococcus galolyticus*) is known to cause IE in relation to gastrointestinal polyps and intestinal tumours. Following genitourinary procedures, enterococci can cause IE. IV drug abusers can get infection due to *Staphylococcus aureus* – usually right sided endocarditis on normal valves, resulting in acute IE. Prosthetic valve infection can be due to *Staphylococcus aureus* or Coagulase negative staphylococci. There are numerous other organisms such as HACEK organisms, *Coxiella* and fungi.

You mentioned that she has not had any dental procedures or blood transfusions. How do you think she got endocarditis? An identifiable source is not always present. However, the presence of specific organisms on blood culture will raise suspicion of a particular source. I would keep in mind her bowel symptoms, and if an unusual organism such as *S. bovis* is found, she will need a colonoscopy.

Her full blood count showed mild neutrophil leucocytosis, with haemoglobin of 10.2g/dL and MCV of 76. Platelet count was 423,000/mm³. Can you comment on this?

Neutrophil leucocytosis is likely to be due to chronic infective process. She has anaemia with a low MCV suggestive of the presence of microcytes. I would like to confirm the red cell morphology with a blood picture, since sub-acute infective endocarditis is usually associated with normocytic red cells. I will arrange for iron studies and folic acid and vitamin B12 level for Mrs JJ. Iron deficiency anaemia with a high platelet count in 63-year-old woman who is on a normal diet is most likely due to occult blood loss. In this case, bowel malignancy could be the cause. Chronic blood loss and chronic inflammatory processes like IE both could cause increased platelet production.

Do you know of any criteria used in the diagnosis of infective endocarditis?

Duke's criteria are used in the diagnosis of IE. It consists of two major criteria and five minor criteria.

Major criteria are positive blood culture (the number of cultures varies depending on the type of organism yielded), and echocardiographic evidence of endocardial involvement.

Minor criteria are the presence of predisposing factors, fever, vascular phenomena, immunological phenomena, or blood culture positivity not fulfilling major criteria.

What are the indications for transthoracic echo (TTE) and transoesophageal echo (TEE)?

Echocardiography has become the mainstay in diagnosis and evaluation of IE. The choice of TTE or TEE is based on the clinical scenario. TTE has lower sensitivity than TEE, especially when the vegetations are small, on prosthetic valves, in right heart lesions, and in patients with COPD or morbid obesity. Also TEE is better in detecting intracardiac complications compared to TTE. In the initial assessment TTE is used in most patients because it is non-invasive, and because of availability and convenience. However if it is suspected that TTE doesn't provide a good quality echocardiographic window, or in patients with high risk of IE and its complications, TEE might be performed directly. Once TTE is performed and if it is negative, TEE has to be performed if there is still a high clinical suspicion. If TTE is positive TEE might help in identifying complications, when suspected. For follow up purposes, TTE is performed when a complication is suspected and to monitor vegetation size.

What are the special steps you will follow in taking blood culture in a patient suspected of IE?

In Mrs JJ I will take a minimum of three blood cultures before starting antibiotics. These will be taken from three different venepuncture sites over a time period depending on the severity of the illness. If Mrs JJ was acutely ill, the 3 cultures should be done over a short duration at least an hour apart. In IE the bacteraemia is continuous, therefore it is not essential to take cultures at the time of fever spikes. The bacteraemia is low grade, and we would need to take 10-20 ml of blood at a time, from different sites, to increase the yield on culture.

Can you briefly outline the antibiotic management of infective endocarditis?

Antibiotic therapy is different based on the severity of the infection, causative organism and other host factors. IV antibiotics must be given, usually in combination, for 4-6 weeks. It is possible to wait 1-3 days until the preliminary results of the blood culture and investigations are available in a patient like Mrs JJ who was not acutely ill. If she was acutely ill empirical antibiotic therapy should be started based on clinical suspicion after the blood cultures were taken. If native valve endocarditis is suspected and the decision is to start on empiric antibiotics, the most commonly used combination is a beta-lactam agent like penicillin, in combination with an aminoglycoside. This combination is highly effective against streptococcal and enterococcal endocarditis, but is not adequate for staphylococcal endocarditis. For Mrs JJ I will start IV benzylpenicillin or ceftriaxone, with IV gentamicin, and review with culture results. In penicillin allergy IV vancomycin is used.

Why is it necessary to give antibiotics intravenously, in combinations, for so long?

Vegetations in IE are avascular and include a fibrin-platelet thrombus. It is difficult to eradicate bacteria from this because of the high organism concentration, deep positioning inside the vegetation, interference from fibrin and white cells, and the metabolically inactive state of the organisms. Therefore high concentrations of antibiotics must be achieved, that can reach the organisms through passive diffusion. The IV route achieves this with a predictable bioavailability. A prolonged course is given to kill all bacteria in the vegetations. Combination therapy is used because of the synergistic effects of antibiotics.

Mrs JJ was told that she has had renal impairment. Can you explain the possible mechanisms for the development of AKI?

Mrs JJ's AKI could be due to IE, or the antibiotic treatment she received. Long standing hypertension might be a contributory factor, and other factors such as dehydration may contribute.

IE can cause renal impairment due to immune mediated glomerular nephritis. Gentamicin, which is nephrotoxic, is commonly used in combination treatment for at least for 2 weeks. Gentamicin causes AKI due to tubular cell necrosis in the proximal renal tubules. Ideally, gentamicin levels should be measured regularly. It is recommended that serum levels are measured after 3-4 doses and then every three days or after any dose changes. More frequent monitoring should be done in patients with renal impairment. Proper hydration of the patient, monitoring of renal function regularly, and dose adjustments will reduce the risk of renal impairment due to gentamicin. Other potentially nephrotoxic drugs should be avoided, such as diuretics and ACE inhibitors or angiotensin receptor blockers.

What are the indications for surgery in patients with infective endocarditis?

The two broad indications for surgery are poor response to medical therapy, and the development of significant valve leaks. Patients with IE will usually become afebrile after 3-5 days after treatment. Blood cultures need to be repeated after 5-7 days, and serially, to identify non-responders. Surgery may also be considered for IE due to organisms such as fungi and brucella, where good antimicrobial therapy is lacking. If there is persistent bacteraemia in spite of adequate antibiotic therapy, surgery may be considered.

Clear guidelines are available for surgical intervention. The commonest indication is heart failure due to valve dysfunction, severe AR or MR, or para-valvular infection with abscess or fistulae formation.

What can cause a recurrence of fever in a patient who initially responded to antibiotics for IE?

Recurrence of fever could be due to a complication of IE, due to the treatment, or due to an unrelated hospital acquired infection. Complications which can cause persistent fever include paravalvular abscesses, and extracardiac abscesses due to septic embolisation. Antibiotics can give rise to drug fever, antibiotic related colitis (although uncommon with penicillin and gentamicin). Hospital acquired infections include cannula site infections, catheter related UTI if the patient is catheterized for some reason, and hospital acquired pneumonia.

What do you know about antibiotic prophylaxis in IE?

In the past, there used to be a low threshold for giving antibiotic prophylaxis for endocarditis. This has now changed however, because evidence doesn't strongly support the use of antibiotic prophylaxis after common procedures. Currently, antibiotic prophylaxis is given mainly to patients at highest risk of adverse outcome after IE— prosthetic valves, history of endocarditis, and congenital heart disease.

The concept of antibiotic prophylaxis for IE is outdated because evidence does not support this practice. According to the 2008 NICE guidelines, prophylaxis is not indicated in patients undergoing dental, upper and lower respiratory tract, genitourinary or lower gastrointestinal tract procedures. It is recommended good oral health and hygiene is maintained in everyday life than during moderate risk procedures.

Currently prophylaxis antimicrobials are limited to patients with cardiac conditions with the highest risk of adverse outcome from IE (prosthetic valves, history of endocarditis and congenital heart disease) who are undergoing procedures that may result in transient bacteremia. These include having dental procedures with manipulation of gingiva, peri-apical region of the teeth or

perforation of the oral mucosa, procedures of the respiratory system involving incision or biopsy of respiratory mucosa, procedures involving infected skin or muscular skeletal system, or patients with on going GI or GU infections.

The prophylactic antibiotic dose normally needs to be given 30-60 minutes before the procedure. For oral, dental, skin, musculoskeletal and upper respiratory tract procedures oral amoxicillin 2 g as single dose is recommended.

When unable to take orally, ampicillin 2g IV or IM. If allergic to penicillin, oral cephalexin 2 g or in severe allergy clarithromycin/ azithromycin 500mg. When unable to give orally ceftriaxone IV or IM 1g, in severe penicillin allergy, clindamycin 600mg IV or IM.

Case 17

Mr DL, a 32-year-old previously healthy male, presented with fever for 1 week that resolved 5 days ago. He also noticed dark urine. He had been well until around 10 days ago, when he developed on and off low grade fever. He had had no chills or rigors. He also had severe loss of appetite since the onset of fever, which was now improving gradually. There was associated malaise, headache, bodyaches and nausea, but no vomiting. These symptoms were severe initially and had improved. He noticed that his urine was becoming dark during the last 5-6 days. Since yesterday his family members had noted that his eyes had become yellowish. He did not have altered bowel habits, or any abnormality in his stools, but he had noticed slight upper abdominal discomfort. His stools were normal in colour. He had no urinary symptoms other than the colour change, and had a good urine output. He also complained of mild itching. He did not complain of any chest pain, shortness of breath, cough, sputum, any sleep disturbance, skin rashes or bleeding manifestations. He had taken medicine from his general practitioner four days after the onset of his illness, but the details were not available. He felt better with the treatment but came to hospital after the yellow discoloration of his eyes was noticed.

He had not had any previous illnesses, similar episodes in the past, or surgeries. He is not allergic to any drugs or food. He cannot recall of any similar illnesses among his close relatives

or friends. He usually has all his meals from home prepared by his wife. He had recently eaten some sandwiches and drunken water from an eatery near his workplace. Apart from this, he always drinks boiled and cooled water or bottled water. He had never had any blood transfusions, and denies high risk sexual exposures. He smokes 5-6 cigarettes per day, and drinks less than half a bottle of spirits about once a week. He mentioned that he had developed distaste for cigarettes over the past few days. He had never used any other recreational drugs. He is married, and has two children who are 2 and 4 years old. He is a welder, and his wife is a housewife.

On examination he was comfortable and looked well. He was afebrile, and icteric but not pale. There was no cervical lymphadenopathy, peripheral stigmata of chronic liver disease, flapping tremors or oedema. His pulse rate was 80/min, blood pressure 120/70mmHg. Cardiovascular and respiratory systems were clinically normal. Abdominal examination revealed a tender 2cm firm hepatomegaly, with regular margins and smooth surface. He had no splenomegaly or other lumps, and no free fluid or bruits. He was well alert and oriented with normal neurological examination.

Can you summarize your history and examination?

My patient is a 32-year-old previously healthy welder who presented with fever, constitutional symptoms, severe anorexia, mild itching, and upper abdominal discomfort, followed by jaundice, over a period of one week. He has a history of consuming unsafe food and water, and occasional alcohol use, but had no history of exposure to blood or blood products or drugs, or unsafe sexual exposure. He is feeling better now. He was icteric and afebrile. There was tender 2cm hepatomegaly, and the rest of the examination was normal.

Would you like to give a provisional diagnosis or differential diagnoses?

I think he has acute viral hepatitis, probably hepatitis A.

Your diagnosis should be as comprehensive as possible. The most likely diagnosis in this setting is acute viral hepatitis, and since he is improving and has a history of consumption of potentially contaminated food and water, it is reasonable to think that this is hepatitis A.

If you are asked to mention a possible differential diagnoses what would it be?

This clinical picture correlates well with acute hepatitis. The causes that I would consider are viral hepatitis, drug induced hepatitis, alcoholic hepatitis and autoimmune hepatitis. Viral hepatitis includes hepatitis A, B, C, E as well as infection by viruses like EBV and CMV. Other rare causes include haemachromatosis and Wilson's disease, but the acute onset and absence of other symptoms make these unlikely.

Why can't this be haemolytic jaundice?

He is not pale, and has dark urine. This makes haemolytic jaundice unlikely.

What about obstructive jaundice?

Again, the history is more suggestive of acute viral hepatitis. However, I agree that this should be a clinical differential diagnosis.

You mentioned about autoimmune hepatitis. Can it present like this?

Yes, it can also present as an acute hepatitis. But more commonly it has an insidious onset. It is more common in women, and is often associated with other features of autoimmune disease.

In about 25% of patients, autoimmune hepatitis can initially present as an acute hepatitis and even resemble typical acute viral hepatitis. More commonly it runs a chronic course, similar in presentation to chronic viral hepatitis. It can present later with features of chronic liver disease too. It is commoner in females, and is associated with features like polyarthritis, skin rash, kidney or lung involvement.

So coming back to your diagnosis, why did you consider acute viral hepatitis due to hepatitis A as the most likely diagnosis?

In this patient the history and examination gives the typical presentation of acute viral hepatitis, with preceding prodromal symptoms, followed by an icteric phase. The classical presentation in viral hepatitis is with an initial phase of fever, severe loss of appetite with distaste for food (and even cigarettes), nausea, vomiting, upper abdominal pain – during this stage the patient feels ill. With the onset of jaundice, there is recovery from the constitutional symptoms and the appetite improves. This patient gives a history of unsafe food and water consumption. He has no history of exposure to hepatotoxic substances, like paracetamol overdose, any other drugs, or anaesthetic agents. He drinks below the safe limit. As I mentioned earlier, autoimmune hepatitis comes lower down in the list, followed by inherited liver disease. Out of the viral hepatitis types, hepatitis A is the commonest and he has obvious risk factors for hepatitis A, whereas I could not find any risk factors for blood borne hepatitis.

Why don't you consider acute cholangitis in this patient?

Acute cholangitis characteristically presents with right upper abdominal pain, high fever spikes and features of obstructive jaundice. He had low-grade fever with no chill or rigors. He doesn't have significant abdominal pain. So despite the fact he had fever and jaundice, I did not consider cholangitis or cholecystitis in this patient.

Can you remember the physiology of bilirubin metabolism? Bilirubin is produced from the breakdown of haemoglobin that takes place in reticuloendothelial system. Haemoglobin is broken into haem and globin chains. This haem group is further cleaved to release the porphyrin ring and iron. The porphyrin ring is catabolized to biliverdin and then to bilirubin. This product is water insoluble and is carried to hepatocytes bound to albumin. Once it enters the hepatocyte it is conjugated with glucuronic acid to produce bilirubin monoglucuronide and diglucuronide. Conjugated bilirubin is water soluble. This conjugated bilirubin is secreted into bile canaliculi and released into the duodenum. From there it passes through the gut and is converted again to unconjugated bilirubin by gut bacteria, and then to urobilinogen. Urobilinogen can be absorbed back into the bloodstream or pass along the gut (where it is called stercobilinogen) and passed with the stools. That which is absorbed into the blood can be excreted in urine, as urobilinogen. Urobilinogen (stercobilinogen) is colourless, but is converted to urobilin (stercobilin), which is brown in colour, on exposure to air.

It's all very confusing, this business of conjugated bilirubin and unconjugated bilirubin. Could you clarify its clinical relevance?

Unconjugated bilirubin (indirect bilirubin) is bilirubin bound to albumin. It is not water soluble. If the levels are raised, there will be jaundice, as it can enter tissues. But it will not enter the urine. Therefore the urine will not be dark, and there will be no bile in the urine. Raised unconjugated bilirubin with normal conjugated bilirubin levels occur most commonly in haemolysis. Conjugated bilirubin is water soluble, and can be excreted in the urine if levels are high, resulting in bilirubinuria.

How do you classify the causes of jaundice?

Causes of jaundice can be classified as direct (conjugated hyperbilirubinemia) and indirect (unconjugated) hyperbilirubinemia based on the type of bilirubin in the serum. Normally, most of the bilirubin in blood is unconjugated. If the direct bilirubin fraction in blood is >20% it is called direct hyperbilirubinemia. The other method of classification is based on site of involvement as pre-hepatic, hepatocellular and post-hepatic jaundice.

Pre hepatic jaundice is mainly seen in haemolytic anemia, ineffective erythropoiesis, with certain drugs like isoniazid, and in conditions like Crigler-Najjar syndrome and Gilbert syndrome where there is an enzymatic defect in conjugation. Hepatocellular jaundice occurs in conditions where there is hepatocellular damage: hepatitis, cirrhosis, haemachromatosis, Wilson's disease. Post hepatic jaundice is also called obstructive jaundice. Causes might be related to intrahepatic obstruction as in cases of cirrhosis or hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis, or extra-hepatic obstruction such as cholangiocarcinoma, pancreatic head tumors, bile duct stones, biliary strictures and chronic pancreatitis.

What is the pathophysiology behind jaundice in hepatitis?

In hepatitis there is jaundice due to hepatocellular damage. Reduced conjugation results in a rise in unconjugated bilirubin, while damage to hepatocytes results in increased levels of conjugated bilirubin in the blood. Swelling of the hepatocytes results in obstruction to the biliary canalicular, resulting in a degree of cholestatic jaundice. In some patients, this cholestatic phase can be prolonged.

How will you investigate this patient?

My investigations will be directed towards establishing the diagnosis and severity of hepatitis, and looking for the etiology and complications of the disease. In view of establishing the diagnosis of hepatitis, serum ALT, AST and alkaline phosphatase should be

done. I expect ALT and AST to be very high while ALP maybe normal or elevated in acute hepatitis. Serum bilirubin will be high with direct fraction more than 20%. I will also check his serum albumin levels though I don't expect it to be low in this patient. But if it is low I will think of a chronic underlying process. I will also do a full blood count, which is likely to show mild neutropenia with lymphocytosis. As a routine, I will also check his renal function.

To look for the etiology of the disease I will do anti-HAV (anti-hepatitis A virus) IgM, HBsAg (hepatitis B surface antigen) and anti-HCV (antibody for hepatitis C virus). Based on my provisional diagnosis I will do anti-HAV IgM to establish the diagnosis of hepatitis A infection. However there is a possibility of co-infection with hepatitis B or C, which should not be missed. Therefore even if the first is positive I will do the other two. If all the above are negative I will have to think of other possible causes and arrange investigations like autoantibody screening for autoimmune hepatitis, and also look for hereditary causes.

To look for complications I will check prothrombin time- if it is elevated it indicates severe hepatocellular damage, and poorer prognosis.

Why do you want to check anti- HAV IgM rather than IgG?

IgG can be elevated due to past infection whereas IgM indicates acute infection. Particularly in developing countries, many adults have anti-HAV IgG positivity, even if they can't recall previous episodes of hepatitis.

If you suspect hepatitis B infection, and HBsAg is negative, what investigations will you do?

I will check anti-HB core IgM.

In acute hepatitis B infection sometimes HBsAg may be undetectable due to low titre. In such cases you can check anti-HBc IgM; in the ideal setup both should be done, but this adds to cost. Another

value of this marker is when you get an asymptomatic patient with HBsAg positivity. If anti-HBc IgM is positive it indicates recent acute infection, whereas if it is negative it is most likely due to chronic carrier state.

Can you briefly discuss the serological and virological markers in hepatitis B acute infection and chronic infection?

There are several viral antigens relevant clinically in hepatitis B infection. One is HBsAg, which is one of the earliest markers to be elevated in acute infection even before clinical features and elevation of liver enzymes appear. With clinical resolution this disappears a few weeks after recovery from jaundice. The decline in antigen levels is associated with the development of anti-hepatitis B surface antigen (anti-HBs) which will persist lifelong. However if the antigen persists beyond 6 months, this indicates chronic infection. In these patients anti-HBs antibody is not detected.

Another antigen is HBcAg. This is intracellular and not found freely in circulation, and is not detected in serological assays. However anti-HBc IgM is useful in diagnosing acute infection, although if total anti-HBc is elevated it might be due to elevated IgG fraction from old infection.

Hepatitis Be antigen (HBeAg) is seen in acute infection, becoming detectable after surface antigen and declining before the HBsAg. Together with this anti-Hepatitis Be (anti-HBe) is detectable in serum. In chronic infection initially the antigen may be high, and then it will gradually decline with appearance of antibody. In chronic infection, positive HBe antigen indicates viral replication, and therefore it is a marker of infectivity.

Another marker of viral replication is hepatitis B viral DNA (HBV DNA). This can also be used as sensitive marker of replication and is also positive in hepatitis due to mutant forms, where the HBsAg will be negative.

Your patient's anti-HAV IgM was positive, confirming your diagnosis. What possible complications you would look for? Most of the patients recover without any complications. But some will have a cholestatic phase, which will have a prolonged course. These patients also usually recover spontaneously.

The most serious complication is fulminant hepatitis due to massive hepatic necrosis. Fortunately this is not common and occurs more often in patients who are elderly and who have underlying chronic hepatitis or liver disease. Patients with fulminant hepatitis develop features of hepatic encephalopathy and can go into coma. The prothrombin time is prolonged and they can have spontaneous bleeding. Bilirubin levels rise further and liver enzyme levels can go down with shrinkage of liver due to loss of hepatocytes. They can have hypoglycemia with severe liver failure. Death occurs most commonly due to cerebral oedema and herniation. Other causes of death are sepsis, gastrointestinal bleeding and renal failure.

What are the sequelae of hepatitis B infection?

Most patients with hepatitis B will have complete recovery. Fulminant hepatic failure is one complication in the acute setting, which is not common.

There are some patients who will not clear HBsAg in 6 months. Some will clear slowly with time, though a small subset will continue to carry the viral antigens. These patients might be either asymptomatic carriers or patients with chronic hepatitis. Patients with chronic hepatitis can develop cirrhosis or even hepatocellular carcinoma. There can be extrahepatic manifestations such as serum sickness like illness, and glomerulonephritis.

Chronic hepatitis B can present without a preceding episode of acute hepatitis though in some it can follow acute hepatitis B, and some patients will have acute exacerbations of chronic hepatitis B.

What is the acute management of this patient?

Management is mainly supportive since this is a self-limiting condition. Until he feels well, the patient should be advised bed rest. Dietary restrictions are no longer recommended. Symptomatic treatment for fever, vomiting and pruritus is given if necessary. I will make sure not to prescribe hepatotoxic drugs for him. The other important thing is to watch for complications and manage accordingly.

Anti-viral medications and steroids are not recommended in acute hepatitis A. All patients do not need admission. If the patient is well systemically and there is no evidence of liver failure, the patient can be managed as outpatient provided there is good family support and easy access to health care.

Will you take any steps to prevent spread of this infection in the ward?

Infectivity is high mainly during incubation period, which is two weeks before the onset of symptoms, and during the prodromal period. When patient becomes icteric viral shedding in the faeces is reduced. Therefore strict isolation is not necessary. However adherence to basic hygienic measures including hand washing with soap and water before meals and after using the toilet, and universal precautions like washing hands between patients and before doing any procedures, disposal of soiled bed linen and following hospital policy by all health care staff should be emphasized at all times. I will educate the patient and his family on hygienic measures to prevent spread to his family and other patients.

On discharge his wife asks whether their children can get hepatitis A, and asks how to prevent it.

I will first explain that the disease spreads by consumption of food or water that is contaminated with the virus (faeco-oral transmission). The disease is more likely to be transmitted before

symptoms start, and he is less likely to be infectious now. There is a possibility that the children can get the disease, and if so they would show symptoms in the coming days or weeks. I will ask her to look out for symptoms like low grade fever, poor appetite, and importantly I will educate her on prevention of transmission in water, washing raw food very well, and hand washing before eating and feeding children, preparing food, and after going to toilet. Food should not be left open for flies to land or plates left for cockroaches to walk on.

Don't forget the place of active and passive immunization in hepatitis A. Passive immunization is where you do post exposure prophylaxis with immunoglobulin soon after the exposure of close contacts to prevent the illness. This does not give long lasting immunity but protects one from acute infection. Though this is not routinely practiced you should be able to provide these options to the family. The other type is active immunization where you administer inactivated hepatitis A virus containing vaccine. This will not provide immediate protection, and is too late for this episode for this family, but will provide longer lasting immunity.

How will you protect yourself as a healthcare worker from hepatitis B infection?

Hepatitis B is a highly infectious disease. Universal precautions should be practiced. All patients need to be considered as potential asymptomatic carriers. All healthcare workers should have antibody screening, and if their antibody titres are inadequate, should be vaccinated against hepatitis B. The vaccine provides active immunization with recombinant hepatitis B vaccine, which is given as three doses. If a healthcare worker is infected, they should be placed on restricted duty to prevent transmission to patients and colleagues, and referred for expert care.

Universal precautions include good hand hygiene, personal protective equipment (PPE) for healthcare workers which include barriers to protect skin, airway, mucus membrane and clothing from infectious agents. These include gloves, isolation gowns that cover the arms and the front of the body from neck to mid-thigh or below, face protectors like masks. People doing procedures like indirect laryngoscopy should protect their airway and mucus membrane with goggles and not touch their face with contaminated gloves. Safe work place practice to prevent needle stick injury and other sharps-related injury should be in place and followed.

Once you are vaccinated with Hepatitis B vaccine how do you confirm that you are protected from hepatitis B?

Anti-HBs antibody levels are checked about 9 months following the injections.

Case 18

Mrs SS, a 26-year-old woman diagnosed to have systemic lupus erythematosus (SLE), presented with generalized body swelling and chest pain of two weeks duration.

She developed progressively worsening bilateral painless lower limb oedema associated with facial puffiness and upper limb swelling. The facial puffiness was more marked in the morning. She had not noticed any abdominal distension. She also noticed reduced urine output for the same duration, without frothy urine, haematuria or dysuria. Over the last two weeks she had been getting intermittent episodes of tightening-type retrosternal chest pain which is worse on lying down and relieved by sitting up. The pain did not radiate, and was not associated with nausea, vomiting, dizziness, sweating or shortness of breath. It was not related to breathing or meals but was aggravated by movements. She also complained of fatigue and malaise over the last one month, with associated shortness of breath on mild exertion, but not at rest. She did not have orthopnoea, palpitations or paroxysmal nocturnal dyspnoea. She did not give a history of fever, cough or sputum.

She did not complain of any bleeding manifestations, and has normal regular menstruation. Her bowel habits were normal. Her appetite had been reduced over the last few weeks, but she had not noticed a significant change in weight recently. She did not complain of any joint pains, swelling or stiffness, or any skin rash,

recently. She did not complain of headache, seizures, reduced consciousness or poor concentration.

She was diagnosed to have SLE four years ago, when she presented with excessive hair loss and multiple large and small joint pains. She did not have skin rashes or photosensitivity at the time. She also had shortness of breath and generalized body swelling with frothy urine. She was found to be anaemic and hypertensive. She was initially started on prednisolone, which was tailed off later on. She was also started on hydroxychloroquine and nifedipine. One year after the initial diagnosis she had had another episode with similar symptoms following what appeared to be a respiratory tract infection. During that episode she had also had an episode of jerky movements of the limbs, with loss of consciousness, and was told that she had a seizure. She was not started on anti-epileptics. During that admission she also had a blood transfusion and a renal biopsy. After that, she was started on captopril and admitted to hospital for monthly cyclophosphamide injections, following which she was started on mycophenolate mofetil. In between she was given prednisolone for long periods of time. She had another similar episode one year ago, and was restarted on prednisolone, which was tailed off and stopped one month ago. During the last admission she had been started on alendronate tablets weekly. She had experienced weight gain and increased appetite with prednisolone. She has not experienced any problems with alendronate or other drugs. During the last one year she had feeling well until the start of the recent complaints.

She had never undergone any surgeries. She is allergic to pineapple and tomatoes, but has no known drug allergies. She does not have any family history of similar illnesses, diabetes mellitus, hypertension or renal disease.

She was educated up to the GCE O- levels, and worked as a typist in a private office. She had to resign from her job after onset of joint symptoms. She got married one year ago, and lives

with her husband and his family. Her husband is supportive and is aware of the risks of pregnancy and the need for contraception. He is an accountant with adequate monthly income. Both the patient and family were well educated about the illness and she had been compliant with follow up and medicine. She is being followed up at the rheumatology clinic, with monthly visits. After admission, her medications were changed, and her chest pain has disappeared.

You have presented quite a long history because of the multiple problems she has. Shall we summarize and identify her problems?

Mrs SS is a 26-year-old housewife with SLE diagnosed 4 years ago. Her history indicates that she had arthritis, renal involvement, anaemia, and a seizure, with a few renal flare ups particularly when steroids were tailed off or when she developed chest infections.

This time she was admitted with generalized body swelling, reduced urine output, retrosternal tightening chest pain for two weeks with no fever, cough or sputum. She also complains of shortness of breath on mild exertion, fatigue and malaise. She is a housewife and has a supportive husband and a family.

The acute problems I identified in my patient are:

- Generalized body swelling, reduced urine output for 2 weeks, in a patient with SLE who was treated for renal involvement with prednisolone and mycophenolate mofetil after renal biopsy
- Chest pain and shortness of breath on exertion for two weeks
- Her long standing medical problems are:
- SLE with renal involvement, anaemia, arthritis
- History of seizures for which the cause is not clear, but probably cerebral lupus

- Side effects due to steroids, and disease flares on tailing off steroids

Although she has good family support, her day to day activities are restricted and she has lost her job due to illness. She needs to travel long distances for follow up and for other medical problems. She is 26 years of age, married for one year, and has hopes of starting a family and leading a normal life.

You have touched several important aspects in social history. We would like to know more about the impact of her illness on her life, as well as her response to illness.

In between exacerbations she can do her normal household work like cooking, washing clothes and cleaning the house. Her husband prefers her being at home without going for a job. But when she gets disease flares she is unable to engage in the usual household tasks. She used to go marketing, though it was stopped recently because of fatigue and shortness of breath. Losing her job and losing the ability to do shopping has socially isolated her and she feels more dependent on her in-laws. Though medicine is provided from hospital there is significant expenditure for transport and investigations.

Despite all this she attends the clinic regularly and takes medicine regularly. Transport is not always easy, as she lives 25 miles away from hospital, but she prefers attending the rheumatology clinic rather than the local hospital. As such, there are sometimes delays in reaching the hospital. She usually travels to hospital by bus, although when she is ill she comes in a taxi.

She seems to be coping with the illness well at the moment with good support. She is aware of the chronic progressive nature of her illness. Her husband is caring, and has a good knowledge about her illness and medical needs. She is worried about her future, her need to be on long term medication, and potential problems related to pregnancy.

Her parents live close to her home and her mother stays with her when she is admitted to hospital.

Did you ask her about the method of contraception?
They are using a contraceptive method but I am not sure what the method is.

What is its importance?

At present she should not get pregnant. Mycophenolate is teratogenic, and she is having active disease. She needs a very effective method of contraception. Oral contraceptive pills are known to be associated with increased risk of disease flare and increased risk of venous thromboembolic disease, and are unsuitable. Considering the fact that she is nulliparous and the risks of hormonal contraceptives, barrier contraceptives would be best.

Shall we go through your examination findings?

She weighed 48 kg and was 155 cm in height. She looked ill, but is not dyspnoeic. She had diffuse alopecia. She was afebrile, pale, anicteric, and had oral ulcers, malar rash and facial puffiness. She had no lymphadenopathy, vasculitic rash or evidence of active arthritis or joint deformity. There was a buffalo hump and striae on the skin over her abdomen and thighs, and bilateral pitting oedema upto mid thigh.

Her pulse was regular, 80/min with good volume. BP was 140/90mmHg, JVP was not elevated, apex was not shifted and there were no thrills or palpable heart sounds. First and second heart sounds were normal with no added sounds.

Respiratory examination was normal except for a respiratory rate of 20/min, and the abdominal examination was also normal. She was fully conscious, well oriented, and did not have any focal neurological signs.

What are the possible causes for her oedema and chest pain?

Out of the many causes of generalized oedema, I will first consider a renal pathology in view of her SLE, past history of renal disease and reduced urine output. At the same time I will also look for a cardiac pathology since she also had shortness of breath and chest pain. The other possibility is severe anaemia.

Renal conditions to be considered would include either proteinuria or renal impairment.

Chest pain could be due to a cardiac cause like pericarditis or ischaemic heart disease. Her history is not suggestive of ischaemic heart disease. However considering the fact that she had shortness of breath and oedema I would exclude heart failure which can be a result of ischemic heart disease. Severe retrosternal chest pain worsening on lying down and movements relieved by sitting forward is more suggestive of acute pericarditis. A similar chest pain can occur due to pleurisy. I will also consider pulmonary embolism.

Considering all these I feel she has a disease flare with renal involvement and possible serositis.

What are the examination findings expected in pericarditis?

The commonest finding is a pericardial friction rub. If there is a significant pericardial effusion the friction rub will not be heard and heart sounds will become softer. The patient can develop cardiac tamponade due to a large pericardial effusion, and this will present with the classical signs of raised JVP, pulsus paradoxus and even cardiogenic shock.

Did you detect any of these in this patient?

No. However pericarditis without a large pericardial effusion will not produce any signs of cardiac tamponade. Even a pericardial friction rub is not always heard in pericarditis, although it is found in about 85% of the patients.

If you think this is a flare of SLE what investigations can be done to show increased disease activity?

Increased disease activity is indicated by the presence of high ESR, increased ds-DNA titre and reduced C3 and C4 complement levels. But these are not always seen in all patients. The CRP is generally normal in SLE, unless there is concomitant infection.

These investigations are used as overall markers of disease activity. But you should not forget other organ specific investigations. For example patients with a renal flare will have increased urinary protein excretion, granular and red cell urinary casts, and elevated serum creatinine. Patients will have anaemia, leucopenia or thrombocytopenia. Liver transaminases also can increase with disease activity.

What are the investigations that you would be doing at this point?

Considering her acute presentation I will check her serum creatinine and electrolytes to see whether there is any renal impairment, and any associated electrolyte abnormalities. I will do urinalysis to see whether there are casts, protein or cells. A urine protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR) should be done to assess the protein leak. I will check her full blood count to see the degree of anaemia and to look for white cell and platelet counts; low blood counts are also suggestive of increased disease activity. If anaemia has significantly worsened from her previous state I will send blood for reticulocyte count, blood picture, and Coomb's test to look for autoimmune haemolytic anaemia.

An ECG should be done to look for features of pericarditis, like saddle shaped ST elevations or T wave inversions. The ECG will also be useful to identify ischaemic changes. If there are any ischaemic changes I will do a troponin test to look for acute coronary syndrome causing atypical chest pain. Chest radiograph and echocardiogram should also be arranged in order to look for evidence of pericarditis and heart failure.

She has a history of seizures. What are the possible causes in her case?

Seizures could be related to SLE or unrelated. The most important SLE related cause is cerebral lupus, which is a serious manifestation of SLE. Patients with SLE are also at higher risk of arterial and venous thrombotic events due to the presence of antiphospholipid antibodies, and also increased atherosclerosis. As a result they can have cerebral venous thrombosis or ischaemic infarctions, which can present with seizures.

Other possibilities include metabolic causes such as uraemia or electrolyte abnormalities as a result of renal disease or drugs. Certain drugs, e.g., mycophenolate mofetil and hydroxychloroquine can rarely cause seizures.

A rarer possibility is encephalitis, meningoencephalitis or even cerebral abscess, as a complication of immunosuppression.

What is the rationale to perform a renal biopsy on her?

All patients with suspected SLE are screened for protein, cells and casts in urine. In her case these investigations probably showed abnormalities suggesting the possibility of lupus nephritis. Lupus nephritis one of the serious manifestations of SLE, and its management depends on the histological type of the disease. Therefore before starting immunosuppressive therapy for lupus nephritis she needs evaluation of her renal histology.

What are the diagnostic criteria of SLE you have elicited from your history and examination?

She has oral ulcers, which are detected on examination, not noticed by the patient since they are painless. This is one criterion. She gives a history of multiple small joint arthritis, which is another criterion. According to the history she probably has lupus nephritis. There are some more criteria, which can't be definitively decided solely on clinical findings. Although there is suspicion of pericarditis I have

to confirm it with further investigations. She also has had seizures but whether it is due to cerebral lupus or any other underlying cause is not clear from her history. She is anaemic, but whether it is anaemia of chronic disease which is the most common form in SLE, or haemolytic anaemia has to be differentiated. If it is haemolytic anaemia it also adds to the list of criteria.

The diagnosis of SLE is made using the American College of Rhematologists criteria. Generally, an undergraduate student will not be expected to remember all of these.

What are the immunological investigations that will be done to aid the diagnosis of SLE?

Serum antinuclear antibodies (ANA) is the most sensitive marker of SLE. But its specificity is low. Double stranded DNA (dsDNA) is a highly specific marker, although it lacks sensitivity. Another highly specific antibody is anti-Sm antibody, which is useful in patients with negative ANA.

These are the most important antibodies used in diagnosis of SLE. There are various other antibodies which are seen in overlap syndromes. Antiphospholipid antibodies are present in some patients with SLE, and these patients are at increased risk of arterial and venous thrombosis and recurrent miscarriages. They include anticardiolipin antibodies, anti β_2 glycoprotein-1 antibodies, and the lupus anticoagulant. Anti-Ro and anti-La antibodies are tested in patients planning to have pregnancy because their presence is associated with a risk of neonatal lupus. Antihistone antibodies are commonly positive in drug induced lupus. Complement levels are low in SLE.

She was given hydroxychloroquine. What side effects should be watched for?

Renal and liver functions should be checked prior to starting treatment. Retinopathy occurs rarely when used for some time, and having a baseline eye assessment and regular monitoring for

visual symptoms and visual acuity should be done. If there is any suspicion the patient should be referred to an ophthalmologist.

Why do you think she was started on alendronate?

It is a bisphosphonate, used in treatment and prevention of osteoporosis. From my history I could not find evidence to suggest that osteoporosis had been confirmed in her. Therefore she may have been given alendronate to prevent osteoporosis, because of the prolonged use of corticosteroids.

Patients taking prolonged causes of corticosteroids, including those who take intermittent but frequent doses, are at increased risk of osteoporosis because the cumulative dose increases the risk of osteoporosis. It is important to assess her bone mineral density with DEXA scan, as fracture risk assessment tools using calculators such as FRAX and QFracture can not be used in Mrs SS who is only 26 years of age. Methods to minimize the risk of osteoporotic fractures include using the lowest possible doses of corticosteroids for the shortest possible time, prescribing calcium and vitamin D supplementation, and preventing falls. Bisphosphonates should not be used in pregnancy, Breast feeding, or if the eGFR<35ml/m². The drugs carry a risk of atypical femoral fracture when used for more than 5 years.

As the house officer what advice would you give a patient being started on alendronate?

I will tell Mrs SS that alendronate will reduce her risk of having fractures if she were to have a fall. I will explain to her how to take the drug, particularly whether to take daily or weekly. In general it is given once weekly. I will tell her about the common side effects such as oesophageal reactions, altered bowel habits and musculoskeletal pain. I will tell her that oesophageal reactions can be prevented by taking the tablet on an empty stomach, with a tall glass of water, while sitting or standing, and not to lie down for about 30-45 minutes. She should not eat for 30-45 minutes after

swallowing the tablet. I will advise the patient to stop medicine and seek medical advice if she develops any features of oesophageal reactions such as dysphagia, new or worsening heartburn, or retrosternal pain. A very rare complication is osteonecrosis of the jaw, and I will advise her to maintain good oral hygiene, and to see a dentist if she develops any dental or oral symptoms.

What are the side effects of long-term use of corticosteroids?

Steroid use causes side effects related to almost every system. Endocrine effects include Cushing syndrome with obesity, hypertension, striae, bruising, and menstrual irregularities. They can develop secondary diabetes mellitus. Adrenal suppression can occur with prolonged use, which can result in Addisonian crisis if steroid are abruptly stopped. Musculoskeletal effects include osteoporosis, proximal myopathy, tendon damage and avascular necrosis of bones. Gastrointestinal effects include gastritis, peptic ulcer disease and pancreatitis. Effects on the central nervous system include depression, psychosis, aggravation of schizophrenia, epilepsy and raised intracranial pressure. Ophthalmic effects are cataract, glaucoma, and thinning of the cornea and sclera. Due to suppression of the immune and inflammatory response there is high risk of infection and also atypical presentations of infection. Reactivation of dormant infection such as varicella and tuberculosis can occur. Poor tissue healing and increased thromboembolic risks are other side effects.

She was initially treated with hydroxychloroquine and prednisolone. Later she was started on cyclophosphamide and mycophenolate mofetil (MMF). How do you explain this?

In SLE with features like rash, arthritis and fatigue without life threatening or organ threatening problems, a conservative approach with symptomatic treatment is the accepted method. Pain is treated with simple analgesics and NSAIDs. Skin lesions are treated with sunscreen and local applications. For these symptoms

hydroxychloroquine is effective and is given as first line. Low dose steroids are also sometimes used. When patients have more severe disease, which is indicated by presence of lupus nephritis, CNS involvement, blood dyscrasias or severe pericarditis, they need to be managed with more aggressive immunosuppression. This includes high dose oral steroids and intravenous steroids, and other immunosuppressives like mycophenolate mofetil, cyclophosphamide, azathioprine and methotrexate.

Therefore in this patient either the diagnosis of lupus nephritis or cerebral lupus following seizures or both might have prompted the treating team to initiate these drugs.

What do you know about lupus nephritis?

There are six histological types of lupus nephritis, identified by biopsy. Generally, patients with class III or IV (diffuse or focal proliferative nephritis), and patients with severe class V nephritis (membranous nephritis) are treated with aggressive immunosuppression. This is because these types are associated with deterioration to renal failure. The other types do not need treatment straight away. However the type can change over time, and if the clinical presentation changes a repeat biopsy is necessary to decide whether it has changed to a worse type.

For a female with SLE when it is considered safe to have a pregnancy?

When patient is stable, free of exacerbations for six months, preferably not on immunosuppressants other than low dose steroids, pregnancy can be considered.

What are the problems you anticipate when a patient with SLE becomes pregnant?

There are problems that can affect the foetus as well as the patient. There is higher chance of miscarriage, particularly in patients with antiphospholipid antibodies or lupus nephritis. There can be

foetal defects due to drugs used to treat the mother. Attempts are made to control disease with the lowest possible dose of steroids. Steroids also can produce adverse effects on foetus such as low birth weight and CNS problems. Some patients with SLE have anti-Ro and anti-La antibodies, which can cross the placenta and cause neonatal lupus, which presents with rash and congenital heart block. Breastfeeding has to be decided on weighing the risk versus benefit when patient is on drugs that can be passed through breast milk. It is not common to have disease flare during pregnancy, but there is higher risk of disease flare post partum. Long term problems include difficulties in caring for the child when mother is having a chronic disease, which can have frequent flare ups.

Case 19

Mr SZ, a 25-year-old previously healthy male presented to hospital four days ago with fever for 3 days. He developed acute onset intermittent high fever, associated with chills and rigors. When he measured his temperature at the clinic it was 41 °C. The fever settled one day after admission to hospital, on day 4 of the illness. He also had body aches including muscle and joint pains, headache, loss of appetite, nausea and vomiting from day one. Vomiting was mainly following meals and there was no blood in his vomitus. There was mild upper abdominal pain from the second day. He did not have cough, shortness of breath, chest pain, urinary symptoms, skin rash, yellow discolouration of eyes, or altered bowel habits. There was no photophobia, seizures, or altered level of consciousness. He had noticed reduced urine output on the third day of illness, but this resolved after admission. There was no gum bleeding, haematuria, or any other bleeding manifestations.

His colleague at work recently had had dengue fever. He has not travelled to any other parts of the country recently, and has never gone abroad. On the first day of the illness he had taken medicine from his family doctor, but was not aware of the names of the medications. He was advised to come back in two days if fever persists; however since he didn't feel much improvement he got admitted to hospital directly on the third day. After admission he had had several blood investigations. He was told that he has dengue fever, and asked to have bed rest, measure his urine output, and drink fluids as advised. He was also given intravenous fluids.

He was closely monitored in the hospital. Fever settled one day after admission, but he continued to feel ill, with poor appetite and malaise. Since yesterday (day 7) he has felt much better, and his appetite had improved. He is awaiting discharge.

He had never had any significant illnesses before, and had not undergone any surgeries. There are no known drug or food allergies. He smokes 2-3 cigarettes per day and occasionally consumes alcohol. He works as a clerk in a private sector office. He stays in an apartment, which he shares with two other friends. There are many mosquitoes both at his work place and at the apartment. At night he uses a mosquito net. The surrounding environment is crowded and there is a garbage dump nearby. He had no history of contact with muddy water.

On examination he weighs 66 kg and is 174cm tall. At the time I saw him, he looked well, and was afebrile, not flushed. He was not dyspnoeic, pale or icteric. There was no cervical lymphadenopathy. His throat was not inflamed. There was no visible skin rash or leg oedema. His pulse rate was 56/min, regular with good volume. Blood pressure was 110/70 mmHg. Heart sounds were normal and there were no added sounds. There was dullness to percussion in the right lower zone of the lung with reduced breath sounds. The trachea was not deviated. Abdominal examination did not reveal any tender areas, lumps, hepatosplenomegaly or free fluid. There were no focal neurological signs.

As the house officer in the ward what would you consider in your differential diagnoses when he came on day three without any investigation reports?

He presented with acute fever, headache, bodyaches, nausea and vomiting. There are no definite localizing signs of any system. So I would consider dengue as my first differential diagnosis since it is common, he has been exposed to mosquito bites, and his

colleague had had dengue recently. Any other undifferentiated viral fever could also present with similar symptoms. I would consider leptospirosis as well in him, considering that it is common. I would also keep meningitis in mind since he had fever with severe headache, however in the absence of photophobia, skin rashes and features of meningism it is less likely. Typhoid fever is also a possibility with fever, headache and non-specific symptoms.

Does he give a history of exposure to muddy water in paddy fields for you to suspect leptospirosis?

He does not, but definite traditional exposure is not an essential requirement for the diagnosis of leptospirosis.

There have been many patients with leptospirosis who have not had traditional exposure such as working in paddy fields, bathing in unclean water, recreational exposure to water, etc. Unplanned urbanization has created many water collections, which can get contaminated with rat urine.

The full blood count done on admission showed the following: haemoglobin 14.6g/dL, WBC 3500×10^6 with 34% neutrophil, platelet count $110000/\text{mm}^3$, and haematocrit 46%. What is your impression?

In the presence of leucopenia and thrombocytopenia my first differential diagnosis of dengue is further strengthened. Mild leucopenia and thrombocytopenia can occur, however, with any viral infection. Neutropenia is seen in typhoid fever as well. But considering the overall picture I will not consider typhoid as very likely. In leptospirosis and meningitis a neutrophil leucocytosis is commonly noticed.

What are the other investigations that you will perform?

In order to confirm the diagnosis, I will do the dengue NS1 antigen test, since he presented on third day of illness.

NS-1 can be positive upto the 3rd day of illness, although its highest sensitivity is on day 1. After 5 days, it is more appropriate to do dengue IgM and IgG antibodies.

I will perform serum creatinine and serum electrolytes as baseline and serum AST and ALT since they can rise in dengue fever. I will also perform an ECG since cardiac involvement can occur in dengue either due to myocarditis or metabolic derangements. If available I will do a CRP test, which I will expect to be low in dengue. If it is high, then I would consider bacterial infection, and obtain a baseline blood culture, UFR, and urine for culture.

How does testing for dengue antibody help in diagnosing dengue and differentiating primary and secondary infection?

In primary dengue there is seroconversion of IgM with levels appearing from day five and reaching the peak levels in two weeks. Then gradually they disappear. IgG level rises late and will persist for a long time. In secondary dengue both IgM and IgG levels rise rapidly and the predominant antibody type even in the acute phase is IgG. Therefore in acute primary infection, IgM titre will be high. In secondary infection both IgM and IgG will be high.

The diagnostic value of this is controversial however, and it is not clearly known whether those with evidence of previous infection are more likely to have complications.

Can you tell whether he has got simple dengue fever or dengue haemorrhagic fever (DHF)?

Clinically, he appears to have a pleural effusion, which suggests that plasma leakage occurred. Therefore it is likely that he had dengue haemorrhagic fever. Plasma leakage is the characteristic feature in dengue haemorrhagic fever compared to dengue fever.

You might have learnt about several phases of dengue fever. Currently, according to your assessment what phase he is in? He is in the recovery phase. He feels better, has bradycardia, and his appetite is improving.

In a patient with dengue fever, one of the most important and early features of recovery is regaining the appetite. The patient will also say that he feels better. Other features of recovery are the appearance of a convalescence rash, pruritus, stabilization of cardiovascular parameters, bradycardia, increased urine output, and rising white cell count and platelet count. Resolution of fever is not an indicator of entry into recovery phase, in fact the point of resolution of fever is the turning point where patients either recover or go into the critical phase.

What particular problems do you anticipate during the recovery phase?

If the patient was given too much fluid during critical phase, which has leaked out, it can come back into the intravascular compartment. This can result in pulmonary oedema lead to respiratory distress. This is uncommon now, since the guidelines are very clear about how much fluid should be given.

What is the most likely cause for his reduced urine output on admission?

He has had reduced urine output during the febrile phase. Therefore the most likely cause is dehydration due to increased fluid loss from sweating and vomiting and reduced intake with poor appetite. This has improved soon after admission, further supporting this explanation.

This is an important concept you have been clear about. In early dengue or for that matter in any febrile illness dehydration happens due to the causes given above, leading to reduced urine output and features of hypovolaemia. Later on in the course of

dengue haemorrhagic fever, shock and reduced urine output can occur due to plasma leakage. This happens only after patient enters the critical phase.

How do you monitor him during the critical phase?

During the critical phase I will closely monitor with three times daily ward rounds. I will assess subjective and objective parameters. I will assess the presence or absence of fever, appetite, general well being, and any bleeding manifestations, from the history. I will also ask for vomiting, abdominal pain or postural dizziness. The patient will be started on critical phase monitoring chart where pulse rate, blood pressure, respiratory rate, capillary refilling time, and the condition of the peripheries will be checked hourly. Input and output will be checked three hourly. The haematocrit will also be done three hourly and full blood count will be done at frequent intervals. This monitoring will be more intensified if there is any abnormality in the parameters or if patient goes into shock.

How will you recognize early that he is entering the critical phase?

Things like resolving fever with dropping platelets and rising white cells might be surrogate markers of entry into critical phase. It is thought that the point at which the white cell counts drop and start to recover marks the onset of the critical phase. The appearance of pleural effusions and ascites are indicators of leakage. The presence of these signs indicates entry into critical phase. Due to plasma leakage there will be a rise in haematocrit, and a 20% rise from baseline is considered significant.

By the time clinically detectable ascites and pleural effusions have appeared, a substantial amount of leakage has happened. Therefore for early detection of leakage, the current recommendation is to do a focused ultrasound scan, which will show early pleural effusion and ascites. Without waiting for a 20% rise in HCT,

progressive rise in HCT is good enough to suspect entry into critical phase.

How do you manage fluids during critical phase in this patient?

Most likely this patient has entered the critical phase while in the hospital. The critical phase usually lasts for about 48 hours. Therefore I would calculate fluid quota for the estimated 48 hours of critical phase. Total requirement would be calculated for 50kg, which is 4600ml for 48 hours when both maintenance and 5% deficit is taken together. It will be initially given at a lower rate, anticipating the possible need to give more fluids if the patient develops shock. I will guide my fluid therapy on clinical grounds, and based on urine output. If there is diarrhoea and vomiting the quota of fluids may have to be increased. The fluid rate will be titrated to maintain a urine output $>0.5\text{mg/kg/hour}$.

Fluid will be given preferably orally, if the patient can drink. Fluids containing solutes are preferable to water. Intravenous fluids, Hartmanns or normal saline, are given if the oral intake is inadequate. If there is shock, intravenous fluid will be given as boluses.

What is your target minimum urine output for an hour?

Since he is 66kg my target is 33ml/hour (0.5ml/kg/hr)

This is wrong. You have to calculate your target urine output for the same weight that you calculated your fluid quota. Thus the target is 25ml/hour.

During the night you are informed by the nurse that his pulse rate has increased from 84/min to 96/min with blood pressure change from 110/80 to 110/94 over last two hours. What are your concerns? What will you do?

His pulse pressure has narrowed, and pulse rate has risen, although there is no tachycardia. He is in compensated shock. It could be

either due to leakage or bleeding. I will attend to him quickly, with the aim of preventing him from developing decompensated shock. I will assess the patient symptomatically and ask whether he has any new complaints, and whether there was any bleeding or malaena. I will check whether he had passed enough urine and examine for pallor, recheck the blood pressure, look for peripheries including capillary refill time, to see whether there is any evidence of decompensated shock. I will take blood for HCT and start him on IV normal saline 500ml over 1 hour as a bolus. I will also consider giving him supplemental oxygen. Further management will depend on his response and HCT.

The haematocrit has risen to 52%. What will you do next?

At the end of normal saline I will assess his status. If his pulse pressure has increased above 25mmHg I will reduce the hourly intake gradually, while monitoring urine output, HCT and vital parameters. If this is not achieved I will start the second bolus of normal saline 500ml after collecting blood for HCT.

Even after your second fluid bolus his pulse pressure was not corrected. What will be your next step?

Then I would start dextran-40, 500ml bolus after checking the HCT. If HCT has dropped markedly, or even remained the same, there could be concealed bleeding, in which case he might need red cell transfusion.

Will you take any special precautions before starting him on Dextran-40?

Yes. Dextran can interfere with the cross matching of blood. Therefore I will take blood for cross matching before giving dextran.

If the patient is not improving despite all these measures what are the possibilities?

It might be due to metabolic acidosis or hyocalcaemia producing

a negative effect on the heart. Other electrolyte abnormalities also can cause a similar problem. If there is concealed bleeding shock will not respond to crystalloid and colloid fluid replacement alone. Hypoglycaemia is also a possible factor.

This is remembered as ABCS for convenience. A- Acidosis, B- Bleeding, C- Hypocalcaemia and other electrolyte abnormalities, S- Sugar.

Other than monitoring and fluid management what are the other aspects of his management?

Symptomatic treatment is one important aspect. He would normally be given paracetamol and an anti-emetic to relieve his symptoms. I would also consider a drug like famotidine or omeprazole to reduce the risk of upper gastrointestinal bleeding. Bed rest is important.

Preventive measures are important. In the first few days he can be a source of infection. Therefore the ward environment should be kept free of mosquitoes, and he should have a mosquito net. Notification of the disease soon after suspicion is another important aspect to prevent spread of the disease to community. I will also remember to advise him regarding keeping his environment clean to prevent mosquito breeding.

Do you think that the general practitioner did the right management by sending the patient home even without checking a full blood count?

Yes. This patient is an otherwise healthy young man who had simple acute febrile illness. All such patients should not be admitted and they need not have full blood count on day one. Most of the dengue patients will have normal counts on the first day. Unless there are special indications such as pregnancy or co-morbidities, a full blood count on day one is not required, and they need not be admitted. They can be reviewed in two days or earlier if necessary. But it is possible that the patient was not adequately advised about

warning signs, physical rest and the need for good hydration.

You mentioned that you would check on his liver transaminases. Why?

It is not unusual for his transaminases to be elevated. Sometimes significant elevation of transaminases can occur, giving rise to a hepatitis like picture.

Are there any long term sequelae?

Generally there are none. Patients can feel fatigued for some time, and should take plenty of rest.

Case 20

Mr RS, a 48-year-old farmer, was transferred to the teaching hospital one week ago from a base hospital. He had been well until two weeks ago, when he experienced high fever, and severe body aches. The fever was of acute onset, high, and associated with chills and rigors. He had severe frontal headache, anorexia, myalgia and arthralgia. His family initially noticed reddening of his eyes with fever and later after about 4 days his eyes had turned dark yellow. His urine was dark but there was no associated pale stools or pruritus.

He had not coughed up or vomited blood, and had not noticed blood in his urine. He had no other bleeding manifestations. There was no chest pain or cough. There was no sputum production or difficulty in breathing initially, but over the last 8 days he had developed progressively worsening dyspnoea which was now present at rest, with orthopnoea. He had not noticed any swelling of the body, but had noted a reduction in urine output about five days after the onset of fever. He had no other urinary symptoms, such as frequency, dysuria, or any abdominal pain, vomiting, altered bowel habits or skin rashes. There was no photophobia, and no seizures or altered level of consciousness.

He had been working in his paddy field daily until he fell ill. As a result he had many abrasions and cuts on his feet. He did not wear boots. He was not aware of any precautions that needed to

be taken to prevent rat fever. He has never travelled outside the country. According to his knowledge there were no others with similar illnesses amongst his family members or neighbors.

He was admitted to the local base hospital 10 days back. Prior to that he had used home remedies and paracetamol for fever. He stayed in his local hospital for three days, where he had several blood investigations and a provisional diagnosis of leptospirosis was made. One week ago he was transferred to the teaching hospital, because his kidneys were not properly functioning and he needed dialysis. He was dialysed on admission, the next day, and once, four days after admission. Currently he is feeling better and his urine output had improved. Fever settled about one week ago and he is regaining his appetite. The malaise and body aches persist, however.

He did not have any other previous illnesses, never had any surgeries. There was no known allergy to any drugs or food. He never smoked or took alcohol. He is married with two grown-up children who are married and living separately. He lives with his wife who is a housewife. His son lives close by. Mr RS owns a paddy field which he cultivates with the help of his wife. He does not use any personal protective equipment while working in the paddy field. He was educated up to grade 8. There is no regular monthly income, but money he earns from the crops is enough for their living.

On examination Mr RS was averagely built, lying comfortably in bed, and was not dyspnoeic at rest. He was afebrile, icteric, with conjunctival suffusion and haemorrhages. He was not pale, had no palpable lymphadenopathy, skin rashes, joint swelling, bleeding manifestations or oedema. There was a dialysis catheter for venous access on right side of the neck. His pulse rate was 76/min with blood pressure of 120/80mmHg, JVP was difficult to assess due to the line, and precordial examination was normal. Respiratory rate was 28/min, and he had fine basal crackles in his

lungs. There were no abnormalities in abdominal examination such as hepatosplenomegaly or free fluid.

Can you summarise your history and examination?

Mr RS, a 48-year-old farmer, transferred to the teaching hospital after an acute febrile illness with acute kidney injury. At the time of his transfer he was dyspnoeic at rest, and had reduced urine output. He has had 3 cycles of dialysis and is currently afebrile with icterus and conjunctival suffusion and haemorrhages.

If you saw Mr RS on third day of illness, what would be your differential diagnosis?

He presented with an acute febrile illness with constitutional symptoms, and no focus of infection. Bacterial or viral infection is likely, and considering his occupational history, leptospirosis would be at the top of my list. I would also consider other viral infections like dengue fever, simple viral fever and typhus in him. Malaria would have been in the differential diagnosis in the past, but is less likely now.

I would search for a focus of bacterial infection, such as community acquired pneumonia, cellulitis, UTI. Non-infectious causes are unlikely in this case.

This is a reasonable set of differential diagnoses with the given information. However you should also consider Hanta virus infection in this patient, given the clinical and epidemiological factors that leptospirosis and Hanta viral infection share. Hanta virus is also a zoonotic virus that is shed by rodents and transmitted by aerosolized excreta. Thus it is also commonly found in paddy farmers. There can be mild infections which are difficult to be differentiated from other acute febrile illnesses. However there are two severe forms which are hantavirus pulmonary syndrome and haemorrhagic fever with renal syndrome. These conditions can have a similar presentation to leptospirosis at the outset.

Mr RS was transferred without any investigation results. How will you proceed?

I will investigate to confirm the diagnosis of leptospirosis and to look for complications.

I will do a full blood count and CRP; in bacterial infections there will be neutrophil leukocytosis with high CRP. In leptospirosis white cell counts are more likely to be normal or slightly raised, with low platelets.

Urine full report will show red cells, some pus cells, protein, bile and casts in leptospirosis. If all these are present leptospirosis is very likely, but most of the time only one or few components will be positive.

I will ask for renal function and electrolytes, and I would expect them to be deranged in leptospirosis. Deranged renal function can also occur in typhus, hanta virus infection, and sometimes even in severe dengue. The serum potassium is of importance, because if he has hyperkalaemia in the setting of AKI, it is a medical emergency, needing urgent treatment.

His dyspnoea could be due to fluid overload, pulmonary involvement, heart failure due to viral myocarditis, or acidosis. I will do an ECG, a chest radiograph, and arterial blood gas analysis. A normal ECG makes cardiac causes unlikely. Pneumonia, fluid overload, or ARDS could be picked up on the x-ray. I will also do liver function tests, namely AST, ALT, ALP, bilirubin, albumin and prothrombin time.

I would also send off blood and urine for culture.

Classifying the answer will help you to reply in an organized manner and to cover important key areas. In this answer, investigations to diagnose the disease have been missed. It is necessary to send of blood for microscopic agglutination test (MAT) to confirm the diagnosis of leptospirosis. MAT is the most commonly used test for confirmation, although others are available. MAT

is done in the Leptospirosis Reference Laboratory of the Medical Research Institute, Colombo. IgM ELISA, PCR and rapid diagnostic tests are also available. Culture of the organism initially from blood and later from urine is possible but takes several weeks making it clinically less useful.

What is the aetiology of leptospirosis?

It is caused by the spirochaete *Leptospira*. There are many species but the most pathogenic is *Leptospira interrogans*.

How is it transmitted?

It is a zoonotic illness where man is an accidental host. The source of transmission is commonly from rodents, and also from other mammals (dogs, pigs). These animals excrete the organism in their urine. The route of entry is either the mucosal membranes like conjunctiva and oral mucosa, or abraded skin. Direct transmission can happen to veterinary workers or abattoirs when contact is made with infected urine, tissue or carcass. Indirect transmission happens when people get exposed to water contaminated with infected urine. This happens commonly during farming and recreation activities. It could also be transmitted following localized flooding in an area where there are pigs.

These are the common modes of transmission. However due to poorly planned urbanization, a significant proportion of infection happens in the urban setting where people get exposed to water contaminated with rat urine. Human to human transmission usually does not happen and therefore man is considered a dead end host. Recently there have been cases reported after whitewater rafting.

Do you know of a name given to severe leptospirosis with renal impairment and jaundice?

Weil's disease

What are the clinical expressions of leptospirosis other than Weil's disease?

It could be a subclinical infection or undifferentiated fever. Weil's disease is the most severe form.

Weil's disease usually has a monophasic course in contrast to the classically described text book leptospirosis which is biphasic. In this form the initial leptospiraemic phase (where the organism is seen in blood) is followed by an interval and a leptospiruric phase (where organisms are found in urine). This second phase is the immune phase.

What are the complications of leptospirosis?

Leptospirosis affects multiple systems and can cause various complications. The commonest is renal impairment. It can cause acute kidney injury, which might be oliguric or non-oliguric and commonly associated with hypokalaemia. Most of the time this is fully reversible. One dreaded complication is pulmonary haemorrhage. In pulmonary haemorrhage, the patient develops cough, haemoptysis and severe shortness of breath with desaturation. The mortality is high. Another important complication is myocarditis. This also can lead to cardiogenic shock and arrhythmias. Though jaundice and modest liver enzyme elevation is common, liver failure is rare. Rarely acute liver failure and hepatic encephalopathy can occur but this could be related to self-medication with high doses of paracetamol for fever. Other than pulmonary haemorrhage, bleeding manifestations such as gastrointestinal bleeding and cutaneous bleeding can occur due to coagulopathy and thrombocytopenia.

What are the main aspects in management?

Establishing the diagnosis and looking for complications are important aspects. If the diagnosis is confirmed, definitive therapy includes antibiotics, good hydration and monitoring for complications. Laboratory confirmation is

difficult to obtain, and we treat empirically where there is a high index of suspicion. Since he is having severe disease I will start him on intravenous benzyl penicillin or ceftriaxone. Supportive therapy includes symptomatic therapy such as paracetamol for fever and body aches and pains, and treating the complications. Mr RS had AKI and needed dialysis and support with managing fluid and electrolytes balance.

The other aspect is prevention and education about chemoprophylaxis to avoid future infection in him, his son and other farmers in the community. Leptospirosis is a notifiable disease and I would notify to ensure appropriate public health measures are taken.

What is the pathophysiology of renal impairment in leptospirosis?

Leptospirosis is thought to be due to a systemic vasculitis. Direct toxicity, together with immune mediated inflammatory changes and pre-renal elements contribute to the development of AKI. Acute tubular necrosis occurs as a result. Other mechanisms that can contribute are rhabdomyolysis and nephrotoxicity from certain antibiotics.

What antibiotics can be used for mild disease?

Tetracyclines are effective for mild disease, usually doxycycline.

What investigations are commonly used in clinical practice to ascertain the degree of renal impairment?

The commonest investigations are serum creatinine and blood urea. It is important to estimate the glomerular filtration rate. This will help monitor response to the underlying disease, response to treatment and recognize super-added treatable causes. Most definitions for acute kidney injury and chronic kidney disease use creatinine to calculate eGFR. Urea is less reliable.

Usually both urea and creatinine go up in tandem in renal failure. In what situations does urea rise disproportionately to serum creatinine?

Though both are filtered freely from the glomeruli, creatinine is minimally reabsorbed while urea reabsorption can vary. In pre-renal failure due to dehydration, urea is reabsorbed along with water and sodium. As a result urea rise is greater compared to the rise in creatinine. The other causes are gastrointestinal blood loss, hypercatabolic states, high dose steroid administration and in the elderly.

What are the indications for dialysis in acute kidney injury?

- Refractory pulmonary oedema
- Persistent hyperkalaemia ($K^+ > 7 \text{ mmol/L}$ despite medical management)
- Severe metabolic acidosis ($\text{pH} < 7.2$)
- Uraemic encephalopathy
- Uraemic pericarditis

One of the complications that occurs in leptospirosis is shock. If Mr RS developed shock as well how might have the management changed?

This could be purely due to sepsis or due to another cause like myocarditis. He will require inotropic support. Hypotension and shock can occur due to bleeding with coagulopathy or due to a complication like pulmonary haemorrhage. If any of these complications are present they need correcting. If acidosis is contributing to myocardial depression it has to be treated with intravenous sodium bicarbonate in the ICU with one to one nursing care and monitoring. Conventional haemodialysis in the presence of hypotension is not possible. So either we will have to

standard HD, or use an alternative method like haemofiltration or peritoneal dialysis.

What are the complications and problems associated with peritoneal dialysis?

There are minor complications like discomfort, prolonged bed rest during the procedure and bleeding. Catheter related infection, which could be mild and superficial like superficial soft tissue/ skin infection or severe like bacterial peritonitis and intra-abdominal abscess formation. Other catheter related complications are obstruction to flow, leakage of fluid, difficulty in insertion due to prior surgical intervention and accidental damage to intra-abdominal organs. Metabolic complications include hyperglycaemia due to dextrose in the dialysate. In general, peritoneal dialysis is not favoured now as haemodialysis is accessible in most settings.

Mr RS's renal function is recovering with increasing urine output. What immediate precautions would you take?

When patients with AKI due to acute tubular necrosis recover, they go into a polyuric phase, as the concentrating ability of the kidney is lost. At this point the intake has to be increased to match the output. Potassium excretion from the distal tubule can be high leading to hypokalaemia. I will look for clinical evidence of dehydration, carefully monitor his input and urine output, and replace fluids as appropriate, and also monitor serum electrolytes, especially potassium daily and if necessary twice a day.

What will you tell Mr RS about prophylaxis for leptospirosis?

I will inform Mr RS that the infection he had was leptospirosis, which he got through the skin lesions in the leg when he was working in his field. I will inform him that he should wear protective boots when in the field and wash his hands and feet well. In addition that he should take preventive treatment for it (doxycycline 200mg once a week). This should be taken to cover period of time when

he is at high risk of getting the infection or exposed to water contaminated with rodent urine. Also oral Doxycycline 200mg is recommended for single episodes of exposure like in recreational activities and during localized floods.

Is there anything that can be done to reduce the occupational hazards?

Yes. I will tell Mr RS that the organisms are dropped in to water by rats when they urinate and they get into humans through the damaged skin in the hands and feet, through the thin lining of the mouth and eyes. This infection can be avoided by using boots and gloves, and not using contaminated water to wash his mouth or face. I will also inform him about antibiotics and where to ask for these tablets. This alone will not be enough since he needs more practical guidance to initiate change in practice and culture. Thus I will advice him to talk to the MOH, public health inspector, medical officer at the rural hospital or the general practitioner. Notification of leptospirosis should be available to the public health officers who should contact him and the at-risk population.