Complications of Haemodialysis

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Clinical Scenario

You are called to assess an unwell 67-year-old male with End Stage Kidney Disease (ESKD) secondary to hypertensive nephropathy on the haemodialysis unit. On initial assessment, he is dialysing via a native left brachiocephalic arteriovenous fistula: he is conscious, with a GCS of 15/15, but is pale, clammy and cool to touch. He has a blood pressure of 80/60 mmHg and a pulse of 115 beats per minute. His oxygen saturations are 98% on air. His blood glucose is 7 mmol/L; he has no concurrent chest pain, and his ECG shows a sinus tachycardia, with voltage criteria for left ventricular hypertrophy.

How would you manage this patient acutely, and what further information would help establish the cause of his presentation?

Introduction

Worldwide, haemodialysis (HD) is the commonest form of kidney replacement therapy (KRT), and can be associated with various complications related to uremia, vascular access, fluid and electrolyte management, as well as increased potential for bleeding due to use of anticoagulation. Progressive loss of kidney function leads to a uraemic state, associated with accumulation of fluid, acid-base disorders, multi-organ dysfunction, and retention of various solutes. Haemodialysis can be used to correct several of these abnormalities, but can cause problems related to technique, frequency or other pathophysiological processes occurring. For instance, repeated needling of a fistula can lead to aneurysmal dilatation, rupture and severe bleeding requiring transfusion, hospitalisation or death. Similarly, anaemia may be worsened by repeated blood loss due to clotting of the dialysis line. Although most HD complications occur acutely (e.g. seizures, febrile episodes, etc), others are insidious and take to develop and diagnose (e.g. dialysis-related dementia). In this chapter, we present an overview of common complications associated with HD with available treatment

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options. Complications of continuous ambulatory peritoneal dialysis (CAPD) are discussed in a separate chapter.

Cardiovascular Complications of Haemodialysis

Intradialytic Hypotension

Definition of intradialytic Hypotension [1, 2]:
Intradialytic hypotension was defined by KDOQI in 2005 as a reduction in systolic blood pressure (SBP) ≥20 mmHg or a reduction in mean arterial pressure (MAP) by 10 mmHg with associated symptoms of cardiovascular (CV) compromise such as dizziness, nausea, vomiting, deep sighing or yawning [1]. More recently, KDIGO proposed in 2020 this be amended to "*Any symptomatic decrease in SBP or a nadir intradialytic BP <90 mmHg should prompt reassessment of BP and volume management* [2]"

Intradialytic hypotension is prevalent in between 15 and 50% of dialysis sessions, depending on the case definition criteria employed [2, 3]. Pathophysiologically, it is a maladaptive response to the acute and apparently fixed fluid (water) shifts that occur during a dialysis session i.e. a target ultrafiltration volume that has to be removed within a time constraint of usually 4 h. Normally in the setting of volume loss, cardiovascular and neurohormonal mechanisms are activated, including: increased heart rate and myocardial contractility, increased peripheral resistance and activation of the sympathetic nervous system and the renin angiotensin aldosterone system. These all promote plasma refilling, and thereby maintain intravascular volume and BP. With intradialytic hypotension however, certain procedure-related and/or patient-related factors lead to ineffectual responses with resulting hypotension (Fig. 18.1). Dialysis-related factors usually include dialysate composition (low sodium, low calcium), use of warm dialysate, acetate dialysate buffer, aggressive ultrafiltration, and low plasma osmolality. Large interdialytic weight gain, pre-dialysis use of antihypertensive medications, ingestion of meals during dialysis sessions (leading to significant splanchnic bed pooling of blood volume), hypoalbuminemia, pre-existing comorbidities (e.g. pericardial effusion, peripheral vascular disease, autonomic dysfunction in diabetic patients) are all examples of patient-related factors that are associated with intradialytic hypotension.

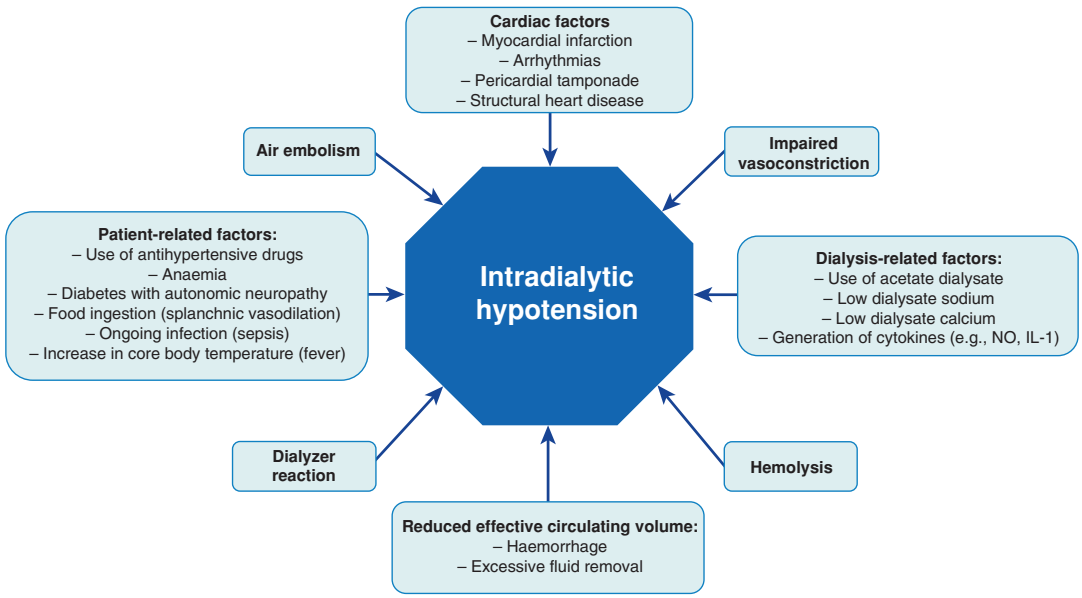

Fig. 18.1 Factors contributing to intradialytic hypotension.
NO Nitric oxide, *IL-1* Interleukin-1

The acute management of symptomatic intradialytic hypotension episodes is dictated by the severity of each episode and can entail postural adjustments to improve venous return (e.g. the Trendelenburg position), stopping ultrafiltration—with or without terminating the dialysis session altogether, and the administration of intravenous fluid and oxygen.

There are long term sequelae to repeated intradialytic hypotension. Hence, this should be minimised in HD patients, as it portends adverse morbidity and mortality outcomes. The consequences of repeated intradialytic hypotension includes repeated myocardial stunning with resultant myocardial fibrosis and cardiac hypertrophy [4, 5], endotoxin translocation due to gut ischaemia associated with chronic systemic inflammation [6, 7], and loss of residual kidney function due to repeated kidney parenchymal ischaemia (Fig. 18.2).

Given the serious consequences, preventive strategies must be implemented in the HD patient who suffers repeated episodes of intradialytic hypotension: First line preventive measures, as outlined by the European best practices guidelines [8], include dietary sodium restriction, bicarbonate buffer use, a clinical reappraisal of patient's dry weight, adjusting dialysate temperature to 36.5 °C, avoiding meals during dialysis, and adjusting the doses and timing of administration of antihypertensive medication. In more refractory cases, Midodrine—a selective alpha-1 adrenoceptor agonist—may be used, and L-carnitine supplementation is also advocated. If all measures are unsuccessful, the patient may benefit from a change in dialysis modality.

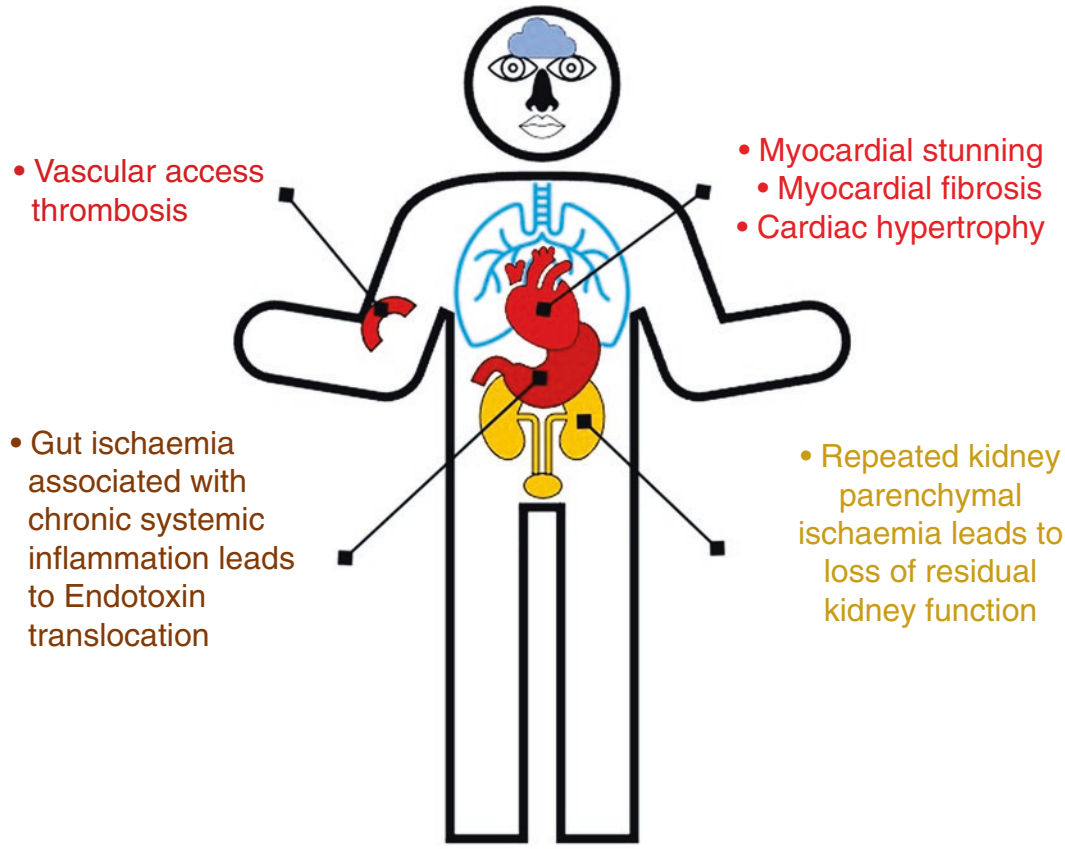

Fig. 18.2 **Consequences of Intradialytic Hypotension**

Intradialytic Hypertension

Definition of intradialytic Hypertension [2]:
Intradialytic hypertension has not hitherto been defined in international consensus guidelines, although KDIGO recently proposed in 2020 a definition of: "*An SBP rise >10 mmHg from pre- to post-dialysis in the hypertensive range in at least 4 of 6 consecutive dialysis treatments should prompt a more extensive evaluation of BP and volume management, including home and/or ABPM* [2]".

Whilst haemodialysis is physiologically more likely to lead to a fall in BP, in a subgroup of patients, a paradoxical increase in BP is recurrently observed during most treatment sessions. Intradialytic Hypertension has hitherto variously been classified as an increase in mean arterial pressure (MAP) of >15 mmHg during a treatment session or shortly after a session, or as hypertension occurring in the second or third hour of dialysis treatment following substantial ultrafiltration, and as a pre- to post-dialysis increase in SBP of 5–10 mmHg [9]. KDIGO's has recently issued a statement defining it as an SBP rise >10 mmHg from pre- to post-dialysis in the hypertensive range in at least 4 of 6 consecutive dialysis treatments should prompt a more extensive evaluation of BP and volume management, including home and/or ABPM [10]. Intradialytic hypertension occurs in 5–15% of HD patients [11] and is associated with poor short- and long-term cardiovascular outcomes [12–14]. Patients prone to developing intradialytic hypertension are characterized by non-modifiable factors such as increased age, male gender, and Caucasian race [15]. In addition, modality-related factors such as short dialysis duration, short dialysis vintage, and smaller interdialytic weight gain and hence low ultrafiltration volumes per treatment have also been noted to typify HD patients who develop recurrent intradialytic hypertension [15]. These patients' metabolic profile is characterized by lower Hb, creatinine, albumin, calcium and phosphate levels, and a lower total iron binding capacity [15].

The pathophysiologic mechanisms underlying intradialytic hypertension have not been fully elucidated, but a few associations have been identified and include a chronically expanded extracellular volume, osmolality shifts and endothelial cell dysfunction. Chronic extracellular volume overload has consistently been demonstrated in patients with intradialytic hypertension. Paradoxically, these patients weigh relatively less, have smaller interdialytic weight gains and have relatively lower pre-dialysis BP readings [12]. They however, have a higher post-dialysis extracellular water-to-total body water ratio (ECW/TBW) despite adequate ultrafiltration volumes. Ultrafiltration goals in HD are usually dictated by the acute ECW gain in the inter-dialytic period and not the overall ECW gain over time and as such, in intradialytic hypertension there is a persistence of extracellular space overload. This is the rationale for ultrafiltration probing as a management strategy in intradialytic hypertension (see below).

As previously discussed under intradialytic hypotension, serum osmolality changes due to solute shifts during dialysis usually cause a BP decline. However, in patients with recurrent intradialytic hypertension, the gradient of solute shift is not significant enough to cause BP reductions. This is because these patients tend to have lower pre-dialysis serum levels of osmotically active solutes such as creatinine, blood urea nitrogen, phosphate, albumin and a lower interdialytic weight gain relative to other HD patients [12]. The dialysate-to-plasma sodium gradient is also an important contributor to intradialytic osmolar shifts and intradialytic hypertension in predisposed patients. A higher dialysate-to-plasma sodium gradient results in less effective extracellular fluid (ECF) removal as a higher gradient favors both ECF and intracellular fluid removal rather than ECF removal alone [16, 17]. The absence of active therapeutic intradialysis BP control with antihypertensives occurring either as a result of withholding all BP lowering agents prior dialysis sessions, or their loss into the dialysate during dialysis sessions has additionally been identified as a contributing factor to the occurrence of recurrent intradialytic hypertension [18].

Intradialysis BP levels may become severely elevated necessitating the use of immediate

release or short acting BP lowering agents to lower the BP. The long-term management of intradialytic hypertension involves a downward review of dry weight over time i.e. dry-weight probing, reducing dialysate sodium to reduce the dialysate-plasma gradient, and the use of antihypertensives prior to commencing dialysis sessions. Dry weight probing addresses the chronic ECW excess state in these patients while a less steep or flat dialysate-plasma sodium gradient ensures that ultrafiltration effectively addresses the ECV compartment alone. Withholding antihypertensives prior to dialysis sessions should not be a broad approach applied to all dialysis patients. In patients with recurrent intradialytic hypertension, non-dialyzable antihypertensives (e.g. Amlodipine) can be administered [19]. While the choice of antihypertensives is driven by factors such as comorbid states and underlying CV risk factors, ACEis/ARBs and β-blockers are particularly beneficial.

Cardiac Arrhythmias, Sudden Cardiac Arrest, and Sudden Cardiac Death

Cardiovascular disease remains an important cause of mortality in kidney failure patients with sudden cardiac death (SCD) accounting for 78% of CV causes of death [20]. SCD has been defined as "an unexpected death due to cardiac causes in a person with known or unknown cardiac disease, within 1 h of symptom onset (witnessed SCD) or within 24 h of the last proof of life (unwitnessed SCD) [20, 21]". Included in this definition is a distinct subgroup of patients in whom sudden cardiac arrest (SCA) in dialysis is the cause of SCD. The risk for arrhythmias and SCA is higher among HD patients relative to CAPD patients in the first 2 years of dialysis initiation but this risk equalizes thereafter [16]. Forty percent of deaths among dialysis patients are attributable to arrhythmias and SCA with the reported event rates of occurrence ranging between 4.5–7.0 per 100,000 HD sessions [22–24]. Prognosis following intradialysis SCA is dismal with 7.8% dying intradialysis following unsuccessful resuscitative attempts while only 40% remain alive 2 days post event [23].

SCA represents an interplay between a triggering event for a fatal arrhythmia and a predisposing/underlying CV disease. CKD and kidney failure are associated with myocardial structural changes, such as left ventricular hypertrophy (LVH), coronary vascular calcification, and myocardial fibrosis, which in turn disrupt the architecture of cardiac electrical pathways resulting in arrhythmogenic zones and conduction delays in fibrotic areas [25]. Fluxes in electrolyte levels especially with regards to dialysate potassium and calcium (low levels of both predispose to prolonged QT interval and QT dispersion on ECG), intracorporeal fluid compartment volume fluctuations, and myocardial stunning, constitute identified triggers [26, 27]. A relationship exists between dialysis timing and the occurrence of SCD. HD patients are most at risk after a long interdialytic interval (>2 days), with the risk being highest in the last 12 h of the interdialytic period, during or after the first dialysis session of the week and within 6 h after a dialysis session [28–31]. Both tachy- and bradyarrhythmias are known to occur in the dialysis population. While tachyarrhythmias have been widely held to be the commoner cause of SCA, more recent data suggests that bradyarrhythmias account more for fatal intradialysis arrests. Tachyarrhythmias include atrial fibrillation, supraventricular tachycardia, and non-sustained ventricular tachycardia [32].

Management strategies are directed towards the prevention of arrhythmias and encompass avoiding rapid electrolyte shifts during dialysis sessions, more frequent dialysis session scheduling to avoid long interdialytic intervals, the use of cardioprotective agents such as ACEi/ARB which are known to have a beneficial effect on modifying myocardial hypertrophy and fibrosis, and β-blockers with pleiotropic benefits beyond BP control including inhibitory effect on the sympathetic system, promoting of heart rate variability, and improving baroreceptor sensitivity. The use of cardiac devices such as implantable defibrillators has also been advocated. Other causes of SCD in dialysis patients other than fatal arrhythmias identified from autopsy series include acute myocardial infarction and dissecting aortic aneurysms [33].

Dialysis Pericarditis

Dialysis pericarditis refers to pericarditis occurring 8 weeks after the initiation of dialysis [34]. The exact incidence and prevalence of dialysis pericarditis is unknown as most data usually do not make the distinction between uremic and dialysis pericarditis. While uremic and dialysis-related pericarditis share a similar etiologic factor of the accumulation of uremic toxins, dialysis-related pericarditis is perpetuated by inefficient solute clearance during dialysis (not achieving kt/V), infrequent scheduling, and suboptimal dialysis flow rates [34, 35]. It must be borne in mind that pericarditis from other etiologies such as Dressler's syndrome, connective tissue disorders like systemic lupus erythematosus, infections or malignancies can also account for pericarditis in the dialysis patient. For diagnostic purposes, atypical electrocardiographic (ECG) findings are more commonly observed [36]. An associated infection should be suspected in the patient with dialysis pericarditis who has the representative ECG tracings of widespread ST elevation or PR segment depression seen in pericarditis unrelated to kidney failure. Inflammatory markers and white cell counts are also elevated [37, 38].

The characteristic chest pain of pericarditis is infrequently observed in these patients. More frequently, intradialysis hypotension and clinical features of heart failure from complicating pericardial effusion are the clinical manifestations in this patient group [34–36]. Non-specific constitutional symptoms of malaise, chills and fever, cough, and dyspnea have also been observed. Treatment approaches involve improving solute clearance by augmenting dialysis parameters—improving blood flow, increasing dialysis duration, and/or increasing frequency. Trial data [39, 40] demonstrates no benefit of non-steroidal anti-inflammatory drug (NSAID) use while data is poor for the efficacy of steroids or colchicine. Surgical treatment—needle pericardiocentesis, pericardiotomy with continuous drainage, partial or complete pericardiectomy—may be necessary in dialysis pericarditis with recurrent pericardial effusions [38].

Dialysis Access Ischemia Steal Syndrome

Dialysis access ischemic steal syndrome (DAISS) is an access-related complication seen in 1–8% of HD patients with arteriovenous (AV) dialysis accesses [41]. While most AV access demonstrates evidence of distal arterial steal, not all patients will develop the ischemic symptoms that typify this complication. It occurs as a result of decreased distal arterial blood flow beyond the point of an AV anastomosis; blood diversion through the anastomosis accounts for the distal "steal" of blood supply while resultant distal hypoperfusion and ischemia rather than the steal alone accounts for symptoms. Risk factors for DAISS include a proximally placed AV access i.e. brachial artery access points, diabetes mellitus, peripheral vascular disease, age > 60 years, and female gender [41]. Clinical manifestations include cold hands, pain in the hands during dialysis (could also occur off dialysis), tingling and numbness in the hands, sensory and motor deficits, and skin changes such as ischemic fingertip ulcers and dry gangrene of the digits in chronic cases [42]. In addition to typical history and examination findings, a doppler ultrasonography to assess access flow and establish improved digital pressures with compression at the AV anastomotic site strongly suggest the presence of significant steal [42]. An arteriography is critical to making a diagnosis of steal and associated distal hypoperfusion and helps to guide the best treatment approach. The available treatment modalities are varied depending on the severity of symptoms and the pathophysiologic vascular hemodynamic processes at play and range from observation of symptoms to ligation of the AV access in extreme situations [42, 43].

Practice Point 1: Cardiovascular Complications of Haemodialysis

Complication	Causes	Management
Intradialytic hypotension	See Fig. 18.1	Acutely: – rendelenburg, stop ultrafiltration, fluid bolus. – Consider underlying cause (see Fig. 18.1) – Dietary sodium restriction – Bicarbonate buffer – Review patient's dry weight – Adjust dialysate temperature to 36.5 – Avoid meals during dialysis, adjust timing of anti-hypertensives. – Consider midodrine or L-carnitine supplementation
Intradialytic hypertension	– Chronically expanded extracellular volume – Lower pre-dialysis levels of osmotically active solutes – Lower intra-dialytic weight gain – Inadequate BP control prior to dialysis – Loss of anti-hypertensives into dialysate	– Review dry weight – Consider reduction in dialysate sodium – Review and optimise medications – Consider use of non-dialyzable antihypertensives, e.g. amlodipine.
Cardiac arrhythmias	Both tachy- and bradyarrhythmias – Underlying cardiovascular disease with resultant myocardial structural abnormalities – Fluxes in electrolyte levels – Intracorporeal fluid compartment volume fluctuations	Prevention is key – Avoidance of rapid electrolyte shifts – Avoiding long interdialytic intervals – Use and up-titration of cardioprotective drugs
Dialysis pericarditis	Overlap between uraemic/dialysis-related pericarditis – inefficient solute clearance – suboptimal dialysis flow rates Consider other aetiologies for instance connective tissue disease	– Improvement of solute clearance – Augmentation of dialysis parameters – Consider steroids, colchicine (though a paucity of evidence)
Dialysis ischaemia steal syndrome (DAISS)	Risk factors include: – Proximally placed AV access – Diabetes, peripheral vascular disease, age >60 years, females.	Severe ischaemia warrants invasive treatment. Options depend on individual anatomy and pathology but include: – Angioplasty to inflow arterial stenosis – Precision banding – Ligation

Neurological Complications of Haemodialysis

Seizures

Hemodialysis-related seizure (HRS) is a common complication frequently observed in the younger age dialysis population. It has been reported in 7–50% of children with kidney failure [44, 45]. Young age, a medical history of seizures, dyselectrolytemias such as hypocalcemia and hypomagnesemia, as well as metabolic factors (e.g. hypoglycemia) and sustained acid-base abnormalities are known risk factors (Fig. 18.3). Rapid clearance of anti-convulsant drugs during dialysis (in patients known with epilepsy), or use

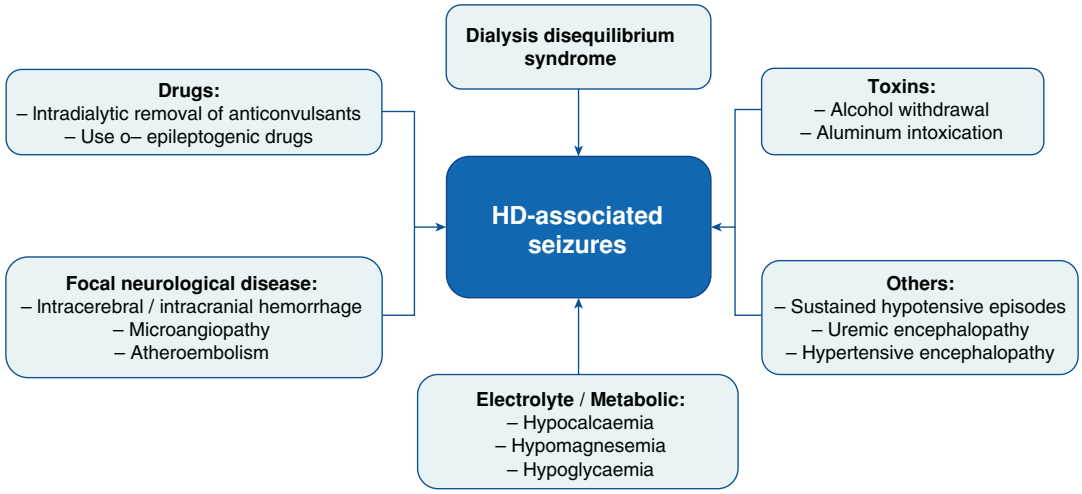

Fig. 18.3 Factors implicated in haemodialysis-associated seizures

of epileptogenic drugs (e.g. theophylline) can be triggers of a seizure disorder during dialysis. In addition, HD-related processes such as a relatively rapid clearance of solutes such as urea can lead to an osmotic gradient between the brain and the plasma, leading to dialysis disequilibrium syndrome (DDS): brain edema that manifests as neurological symptoms such as headache, nausea, vomiting, muscle cramps, tremors, disturbed consciousness, and convulsions. Other HD-related processes including the use of acetate buffer, heparinization-related intracerebral hemorrhage, and erythropoietin administration have also been associated with HRS [45, 46]. Generalized tonic-clonic seizures are more commonly observed than non-convulsive seizures [45]. There is a dearth of clinical trial efficacy data regarding the efficacy of antiepileptic drugs in the prevention and management of HRS. Diazepam, a benzodiazepine that is non-dialyzable has been reported to prevent the recurrence of HRS [44].

Headache

Dialysis-related headache (DRH) is a common neurologic complication of HD and is described by the International Headache society as a secondary form of headache occurring during, and as a result of HD, with no particular pathognomonic characteristics, and which spontaneously resolves within 72 h of the termination of the dialysis session [47]. Diagnostic criteria help to distinguish DRH from other headache phenomena that may be observed in HD patients [47]:

Diagnostic criteria for dialysis-related headaches (DRH) [47]

1. Patient is on HD
2. Two of the following to demonstrate HD causality:
   (a) Headache occurring during an HD session
   (b) Each headache episode worsening during the dialysis session and/or each headache episode resolving within 72 hours of HD completion,
3. Three headache episodes meeting the specifics above
4. Headaches no longer occurring after renal transplantation and cessation of HD altogether

A previous diagnosis of primary headache appears to be a risk factor for DRH. Pathophysiologic mechanisms have been attributed to changes in levels of solutes such as sodium, magnesium, and urea as well as intradialytic changes in blood pressure and volume status [48, 49]. No clinical trial data is available to guide prophylactic and therapeutic approaches to DRH management. There are case reports [50, 51] describing the prophylactic role of chlorpromazine, ACE-i [51], magnesium oxide and

nortriptyline, while paracetamol and the ergot alkaloids (ergotamine, dihydroergotamine) have also been shown to have therapeutic benefits [50]. The risk of AV fistula closure with alkaloid derivatives necessitates caution in its application for the treatment of DRH.

Dialysis Dementia

Dialysis dementia is prevalent in about 4% of the HD population [52], and is associated with an increased risk of dialysis withdrawal and death. With the highly restricted use of aluminum-containing phosphate binders and improved water treatment systems that safeguard against aluminum contamination of dialysates, dialysis dementia in HD patients is now rarely observed [53]. It is a subacute, progressive, and fatal dementia occurring due to aluminum deposition in the cerebral cortex. More recently, risk factors for dialysis-related dementia include the poor clearance of middle-molecules with neurotoxin activity; the preservation of residual renal function in HD patients which ensures to an extent the excretion of middle molecules has been associated with reduced odds of dialysis dementia [52]. The chronic oxidative stress and inflammatory states induced by HD have also been implicated. Risk factors for dementia in the general population (increased age, race, low educational status, comorbidities such as cerebrovascular disease and diabetes) are also observed in patients with dialysis dementia. The management of aluminum-related dementia includes aluminum chelation with deferoxamine, improved water treatment methods, and substituting aluminum-containing phosphate binders with non-aluminum alternatives (calcium- or non-calcium-based binders) [54]. The clinical efficacy of medications for dementia in the general population have not been defined in the dialysis population, but hold promise.

Dialysis-Related Muscle Cramps

Muscle cramps are a frequent muscular complication in HD and typically present, usually towards the end of a dialysis session and may result in the premature termination of a session of dialysis. Cramps have been reported in up to 86% of HD patients [55]. Short-term painful discomfort to the patient and long-term inadequacy of dialysis sessions are consequences of muscle cramps that should be avoided. Muscle cramps usually occur in the lower extremities but can also manifest in the arm, hand, and abdominal muscles. The exact causes of cramps during dialysis are unknown but the temporal occurrence towards the end of a treatment session lend credence to the role of changes in ECV and solute/osmolarity shifts in promoting the abnormal muscular energy utilization and cramp triggering. Muscle cramps are observed in up to 74% of intradialytic hypotensive episodes [56]. It is believed that volume contraction from high ultrafiltration rates account for this. Preventive and treatment approaches thus involve limiting interdialytic weight gain (which limits dialysis sessions UF goals) and sequential/controlled ultrafiltration, respectively. Hyponatremia has also been implicated as a predisposing factor to muscle cramping by its role in influencing serum osmolarity and influencing water shifts across the various human volume compartments. Magnesium plays a critical role in skeletal metabolism influencing neuromuscular excitability. It also plays a regulatory role in sodium, potassium, and calcium ion channels transport. Hypomagnesemia among HD patients contributes to the occurrence of dialysis-related cramps. Magnesium is freely diffusible across the dialysis membrane and increasing dialysate magnesium concentrations cause an increase in serum magnesium thus promoting neuromuscular excitability stability. The use of magnesium-based phosphate binders can also be employed to improve serum magnesium levels in the HD population [57]. Broad non-specific treatment approaches employed include carnitine, and vitamins C and E supplementation [58, 59]. The use of benzodiazepines has also been documented [60].

Practice Point 2: Neurological Complications of Haemodialysis

Complication	Causes	Management
Seizures	See Fig. 18.2	Acutely: – stop dialysis, check glucose and bloods, rule out hypoglycaemia, manage as per local emergency protocols. Identify and treat underlying causes. Consider antiepileptics in conjunction with a neurologist—no specific evidence to guide choice of agent.
Dialysis related headache	Proposed mechanisms include: – changes in solute levels – intradialytic blood pressure and volume changes	– Rule out other potential causes of headache – Analgesia No specific clinical trial data to support prophylactic or therapeutic measures.
Dialysis Dementia	– Chronic oxidative stress and inflammatory state associated with haemodialysis – Metabolic and uremic factors – Underlying cardiovascular risk factors – Aluminium intoxication (now rarely seen)	– Investigate and treat as per non-CKD patients. – Chelators for treatment of aluminium toxicity
Dialysis related muscle cramps	– Changes in extracellular volume – Solute/osmolarity shifts. – Hypomagnesemia	Focussed on prevention: – Avoid excessive interdialytic weight gain – Avoid eating during haemodialysis – Consider increasing dialysate magnesium concentration and/or use of magnesium containing phosphate binders Stretching/warm compresses may help relieve symptoms

Haematologic Complications of Haemodialysis

Intra-Dialytic Haemolysis

This is an uncommon but important complication of HD because of the significant risk of morbidity and mortality [61]. Fig. 18.4 summarizes the possible aetiology of intradialytic haemolysis. Factors that increase mechanical or shear stress on the red blood cells include defective blood lines causing kinking in the lines, dialysis techniques that increase turbulence of flow like using a single needle technique, and when relatively high blood flow rates occur in the presence of small cannula size [10]. Contaminants, including chemicals used for water disinfection like chloramine, formaldehyde, chlorine are common causes of intradialytic haemolysis [62, 63]. Metals including Copper, zinc and aluminium and nitrates have also been implicated [64]. Overheated dialysate (usually above 47 °C). If the patient's osmolality falls below 250 mOsm/kg, either because of error in mixing dialysate (hypo-osmolar dialysate) or use of plasma expanders, intravascular haemolysis may occur [65, 66]. A host of patient factors predispose to intravascular haemolysis—malignant hypertension, autoimmune conditions like Systemic lupus erythematosus and thrombotic thrombocytopenic purpura, sickle cell anaemia, G6PD deficiency and hypersplenism. Medications that may induce haemolysis in dialysis patients include aspirin, sulphonamides, nitrofurantoin, quinidine and hydralazine [61, 67].

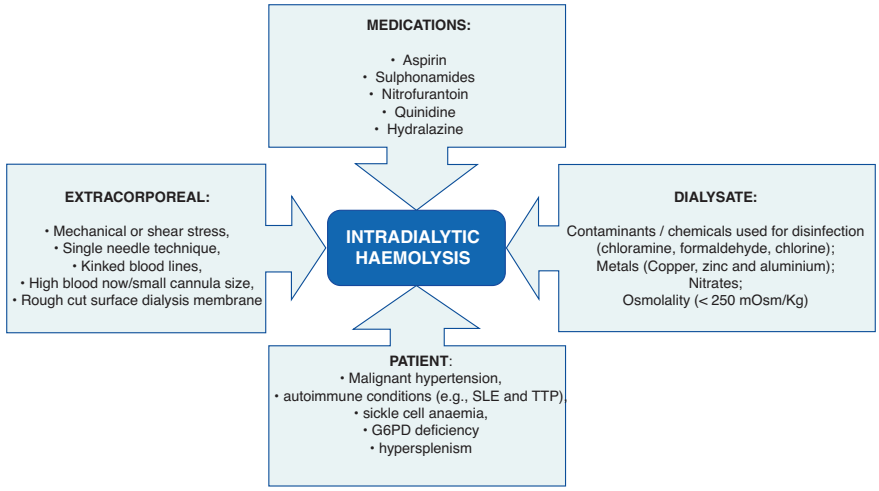

Fig. 18.4 Proposed aetiological factors for the development of intradialytic haemolysis

SLE **Systemic lupus erythematosus,** *TTP* **Thrombotic thrombocytopenic purpura,** *G6PD* **Glucose-6-phosphate dehydrogenase**

The symptoms are non-specific. Chronic intradialysis haemolysis is usually asymptomatic, presenting as chronic anaemia with fatigue or erythropoietin resistance. Acute intradialysis haemolysis presents with nausea, vomiting, abdominal pain, diarrhoea, increasing dyspnoea and hypertension, headache, dark urine and possibly death. Inspection of the extracorporeal circuit may reveal a cherry red (less opaque) colour which may be associated with a pink tinged dialysate fluid if haemolysis is massive. Another indicator is a reduction in both arterial and venous circuits suggesting a kink in the bloodline. Important investigations include haptoglobin, LDH, Coomb's test, blood film, serum free haemoglobin and methaemalbumin.

Once acute haemolysis has been identified, it is important to stop dialysis immediately and not to return the blood in the extracorporeal circulation to prevent fatal arrythmias from hyperkalaemia. Some patients may require ICU care. Serum potassium levels should be monitored closely. Blood products should be given as indicated. The aetiology of the haemolysis should be investigated immediately and identified to prevent repeat episodes [68]. Prevention of this complication requires strict adherence to protocols for dialysis water safety by appropriately trained staff; avoidance of small needle/large flow rates and ensuring correct positioning of tubings in the dialysis machine pumps.

Haemorrhage

The need for extracorporeal anticoagulation during HD has introduced an increased likelihood for bleeding complications especially for individuals who are at increased risk. Major bleeding episodes occur in 1.7% to 3.7% of HD patients [69]. Bleeding can occur at any site—vascular access site [70], gastrointestinal, gall bladder, intracerebral, subdural, retroperitoneum, perinephric or even into the vitreous humor. Factors that increase risk of intradialysis haemorrhage include suboptimal control of BP, pre-existing gastrointestinal lesions, renal cystic disease, diabetic retinopathy, recent surgery or trauma, concomitant use of warfarin or aspirin and acute stroke [71]. The clinical presentation usually depends on the site of bleeding. Prevention or minimization of bleeding may be done by using dialysis modes that do not require use of systemic anticoagulation including using CAPD, heparin-free HD, regional anticoagulation with citrate, prostacyclin or mesilates. Regional heparin anticoagulation may also be employed.

Thrombocytopaenia and Other Platelet Function Abnormalities

Reduced platelet count is known to be a feature of CKD in both pre-dialysis CKD patients and those on maintenance HD. This is less pronounced for kidney failure patients on CAPD. For maintenance HD patients, thrombocytopaenia may occur from the effect of the dialyzer membrane on platelets or from an idiosyncratic reactions to heparin anticoagulation (heparin-induced thrombocytopaenia) [72]. In most cases, thrombocytopaenia from dialyzer membrane is subclinical. Platelet count is known to decrease in the first 1–2 h intradialysis, then returns to predialysis levels [72]. The degree of HD-associated thrombocytopaenia is dependent on the type of membrane and sterilization technique [73, 74]. Polysulfone membranes sterilized by electron beam appear to be most common culprit. Platelet factor-4 (PF4), β-thromboglobulin, LDH, CD62P and CD63 which measure platelet activation have been shown to be elevated during HD.

Hemodialysis associated heparin-induced thrombocytopaenia (HIT) has two types. Type I HIT occurs within 48 h of exposure to heparin, is non-immune and caused by heparin's direct effect on platelet activation. The platelet count returns to normal with continued heparin use. Type II HIT occurs in about 0.2% of individuals exposed to heparin [75]. It is potentially life threatening because of its prothrombotic effect. It has an autoimmune basis—antibodies to the heparin-PF4 complex. HIT II is usually diagnosed 5–14 days after heparin administration; platelet count reduces by at least 50% of pre-heparin administration level and the patient has thrombotic (not bleeding) sequelae [75]. Immunoassays to identify antibodies to heparin-PF4 complex is useful for making a definitive diagnosis. The mainstay of therapy is to discontinue heparin and all heparin-related products. Use direct thrombin inhibitors like lepirudin or indirect factor Xa inhibitors like fondaparinux or danaparoid. Others have used intravenous immunoglobulin for treatment.

Practice Point 3: Haematological Complications of Haemodialysis

Complication	Causes	Management
Intra-dialytic haemolysis	See Fig. 18.3	If acute haemolysis: – Stop dialysis immediately without returning blood in extracorporeal circulation – Monitor serum potassium closely – Liaise with haematology – Patient may require critical care support
Haemorrhage	– Suboptimal BP control – Underlying disease at risk of bleeding, e.g. gastrointestinal lesions, renal cystic disease, diabetic retinopathy – Recent surgery or trauma – Concomitant use of warfarin or aspirin	Consider measures to prevent or minimise bleeding risk – Heparin-free HD – Regional anticoagulation with citrate, prostacyclin or mesilates
Thrombocytopenia/ Platelet function abnormalities	– Platelet interaction with the dialyser membrane – Heparin-induced thrombocytopenia	– Most cases of thrombocytopenia are subclinical and transient. If HIT suspected: – use clinical prediction tool i.e. the 4Ts score +/− send HIT antigen assay. – Treatment involves: • Discontinuation of heparin • Non-heparin based anticoagulation e.g. argatroban.

Other Complications of Haemodialysis

Dialysis-Associated Pruritus

The prevalence of pruritus among adult HD patients has been estimated to be between 49–61% [76]. The aetiology and pathophysiology is unclear. Dialysis inadequacy, hyperparathyroidism, hypercalcemia and hypermagnesemia have been associated with dialysis-associated pruritus [77]. It may also be associated with dry skin or occur without it. Treatment include both topical and systemic agents. Moisturizers, mild topical steroids, 0.025% capsaicin cream, topical tacrolimus, parathyroidectomy, oral antihistamines, pregabalin, gabapentin, naltrexone have all been used with varying results [77]. A more recent medication is nalfurafine [78], which in combination with skin care, has been found to be effective.

Post-Dialysis Fatigue

This is a common complication of HD occurring in as much as 50% of adult HD patients. It is associated with high levels of tumour necrosis factor, rapid changes in BP during dialysis, high ultrafiltration levels, osmotic disequilibrium and psychologic factors like depression [79, 80]. It may be commoner in old age and those with heart disease. Treatment usually involves increasing the frequency of HD, use of low intensity exercises, treatment of depression, adjustment of dialysis prescription and adequate treatment of malnutrition, anaemia and heart failure.

Infections in Hemodialysis Patients

The common infections encountered as complications in HD include catheter-related blood stream infection (CRBSI), HIV and hepatitis B and C infection. Nosocomial transmission of hepatitis B and C still occurs in HD units despite significant reduction over the decades [81], the incidence of nosocomial HCV infection is about 1.2–2.9 per 100 patient-years [82]. HCV and HBV infections are associated with longer dialysis duration and frequency of blood transfusion [83]. Other factors include dialyzer reuse, internal contamination of HD monitors and more importantly, failure of dialysis staff to adhere to strict protocols as regards use of multi-dose medications. Hepatitis C virus (HCV) and HIV appear to be less infectious than HBV in HD units. Outbreaks of these blood-borne viruses can be avoided by strict adherence to infection control protocols in HD units.

The incidence of catheter-related bloodstream infection (CRBSI) is 2.5–6.6 per 1000 catheter-days with rates much higher in non-cuffed catheters than cuffed and tunnelled catheters. Most HD catheters are colonized within 24 h of placement [84]. Inoculation of bacteria is from the surrounding skin or the hands of healthcare works during manipulation. Bacterial biofilm which may occur within the lumen or externally is associated with persistent and metastatic infections. A delay in antibiotic treatment may increase the risk of metastatic infection which may lead to osteomyelitis, infective endocarditis, septic arthritis, spinal and psoas abscess [84]. Risk factors for CRBSI include location of insertion site (femoral catheters more likely to be infected than subclavian and jugular catheters); summer months have higher incidence of CRBSI incidents and the elderly may have lower incidence. New innovations like antimicrobial coated catheters, protective barriers, prophylactic intraluminal antimicrobial lock therapy and use of needleless connector devices [84]. The commonly cultured organisms in CRBSI include coagulase negative Staphylococcus species, Staphylococcus aureus and enterococcus species. Candida species infections also occur. Empirical treatment with vancomycin, a cephalosporin or carbapenem is usually appropriate. In many cases, removal of the catheter is necessary.

Priapism

This a rare complication of HD occurring 2–7 h after a treatment session and associated with

erythropoietin or androgen therapy [85]. Dialysis induced hypoxaemia and acidosis have also been suggested as risk factors. Priapism may resolve spontaneously or require the use of surgical intervention.

Hearing Loss

Hearing impairment affecting low, middle and high frequency sounds is not uncommon among adult HD patients. The stria vascularis and renal tubular cells have similar modes of active transport of fluids and electrolytes and may be responsible for the simultaneous affectations in medications that have ototoxic and nephrotoxic properties [86]. An inhibition of the Na^+-K^+ ATPase in the cochlea has also been implicated as a pathophysiologic pathway for sensorineural hearing loss in HD patients [86]. Some have suggested osmotic disequilibrium in the inner ear initiated or worsened by HD. Patients on HD will benefit from pure tone audiometry for monitoring of hearing function [87].

Acute visual loss following HD is an uncommon complication which could be caused by sudden hypotension or rapid ultrafiltration leading to a non-arteritic anterior ischaemic optic neuropathy [88]. The risk factors for visual loss caused by HD include diabetes mellitus, dyslipidaemia, smoking and hypertension. Immediate post-dialysis reduction in ocular perfusion pressure, choroidal and retinal thickness has been reported [89].

Practice Point 4: Other Complications of Haemodialysis

Complication	Causes	Management
Acute visual loss	• Causes include sudden hypotension or rapid ultrafiltration leading to a ischaemic optic neuropathy • Immediate post-dialysis reduction in ocular perfusion pressure, choroidal and retinal thickness has been reported	
Hearing loss	• Cochlear stria vascularis and renal tubular cells have similar modes of active transport of fluids and electrolytes • Suggested mechanisms include HD-induced: • Osmotic disequilibrium in the inner ear • Inhibition of the the Na^+-K^+ ATPase in the cochlea • Inadequate BP control prior to dialysis • Loss of anti-hypertensives into dialysate	
Priapism	• Rare complication, associated with erythropoietin or androgen therapy. • Dialysis induced hypoxaemia and acidosis suggested as risk factors.	• May resolve spontaneously • Surgical intervention
Post-dialysis fatigue	Associated with: • Rapid changes in BP during dialysis • High ultrafiltration levels • Osmotic disequilibrium Concomitant depression	• Increased frequency of HD • Adjust dialysis prescription • Treat depression • Optimise nutrition and treatment of co-morbidities such as anaemia and heart failure
Dialysis-associated pruritus	Multifactorial—following all implicated • Dialysis inadequacy • Hyperparathyroidism • Hypercalcaemia • Hypermagnesaemia	• Topical—Moisturisers, mild topical steroids, topical tacrolimus, • Oral—antihistamines, pregabalin, nalfurafine.

Conclusions

Returning to our patient: He has been a dialysis patient for several years. His blood pressure at the start of haemodialysis was 130/80 mmHg, which was usual for him after taking his antihypertensive medications each morning. He was afebrile, and had been otherwise well. He noted that he had been passing less urine recently, and that his interdialytic weight gains have over the last few weeks increased to around 4 kg, and he freely admits to having difficulty with fluid and salt restriction. At the point of review, he had completed 3 h of haemodialysis with an ultrafiltration of 3.5 L. You advise his nurse to administer a 250 mL bolus of 0.9% sodium chloride, following which his blood pressure improves to 110/80 mmHg, and he is able to successfully complete 4 h of dialysis without further ultrafiltration.

The likely cause of his intradialytic hypotension is multifactorial: whilst fluid restriction can be difficult, particularly for those new to dialysis, it is also an issue where patients with a significant native urine output become oligo-anuric on haemodialysis. Having excluded other contributory acutely reversible causes, in addition to better adherence to fluid restriction to limit interdialytic weight gains, the patient may be advised to reduce or omit their antihypertensive medication on dialysis days in order to facilitate ultrafiltration to euvolaemia.

Questions

1. A 43-year-old female who has been on maintenance hemodialysis for 11 months presented with unilateral leg swelling and was noticed to have fever, chills, flushing, worsening breathlessness and chest pain following a bolus of IV Unfractionated heparin injection. A doppler ultrasound scan of the limb was suggestive of a deep venous thrombosis. At presentation for the next hemodialysis session, she was noticed to have gangrene of three toes in her left lower limb. CBC was normal except for a platelet count of 81,200/mm^3. His platelet count was 223,400 two months ago. She had no splenomegaly and no abnormal bleeding. What is the best management option for this patient?
   A. Blood culture and commence empirical IV antibiotics
   B. Use low molecular weight heparin for treatment of DVT and continue hemodialysis using standard protocol
   C. Use dabigatran for treatment of DVT and continue hemodialysis using standard protocol
   D. Use warfarin for the treatment of DVT, discontinue all heparin products and use argatroban for hemodialysis.
   E. Give platelet concentrate infusion, IV antibiotics, low molecular weight heparin and continue hemodialysis using standard protocol.

The correct answer is D.

This patient has developed heparin-induced thrombocytopenia (HIT). Paradoxically, they present with thrombotic phenomena instead of bleeding tendencies. Differential diagnoses include drug-induced thrombocytopenia from use of quinine, quinidine, chloroquine and sulfonamides; bacterial sepsis; TTP, ITP, disseminated intravascular coagulopathy and splenomegaly. We do not have any information regarding medication use except heparin. CBC would have shown neutrophilia if there is bacterial sepsis. The patient had no splenomegaly. Use of any heparin preparation will worsen the condition. Platelet concentrate is known to worsen thrombosis. Argatroban, bivalirudin, fondaparinux are non-heparin anticoagulants used in HIT.

2. Which of the following is **not** useful for the treatment of dialysis-associated pruritus?
   A. Naltrexone
   B. Skin moisturizers and low potency topical steroids
   C. Nalfurafine
   D. Propoxyphene
   E. Gabapentin

The correct answer is D.

Propoxyphene is a narcotic pain reliever which is not known to have any effect on pruritus. All others have been shown to have beneficial effect in individuals with pruritus.

3. A 56-year-old woman with end-stage renal disease secondary to diabetic nephropathy uses a cuffed, tunneled, right internal jugular catheter as vascular access for hemodialysis for 5 months. After the first 35 minutes of HD, she develops nausea and rigors and has a temperature of 38.3 °C. Her BP drops from 157/80 to 100/61 mmHg, and her heart rate is 113 beats per minute, regular. She had a similar experience during dialysis 3 days ago, but the temperature was 37.7 °C and she had transient rigors. Examination revealed mild erythema and tenderness of the exit site but no purulent discharge. No other patient having dialysis at the centre has similar occurrence. What is the most correct statement?
   A. Take a swab from the exit site and start empiric antibiotic
   B. The most likely cause of this intradialysis complication is bacterial contamination of dialysis water
   C. Commence IV antibiotic following local resistance pattern for Gram positive and negative bacteria after taking samples from the exit site, one from the catheter lumen (hub), and one from the bloodline.
   D. The most common causative organisms are Gram negative organisms
   E. Catheter removal is not essential if a fungal organism is cultured.

The correct answer is C.

This is most likely a catheter-related blood stream infection.

The identification of the offending organism and sensitivity pattern is critical in the establishment of correct treatment and prevention of metastatic infection and death. Taking a swab sample from the exit site only may not establish the offending organism(s) as catheter and bloodline samples are also important. Bacterial contamination of water would present with chills/rigors within one hour of treatment associated with fever one to two hours after treatment, hypotension and reducing hemoglobin levels. However, the latter will affect multiple dialysis patients in the same centre. Gram positive organisms like *Staph Aureus* are the commonest organisms implicated and having an established fungal catheter-related infection is an indication for removing the catheter.

4. A 60-year-old diabetic female with a current weight of 102 kg has recently commenced hemodialysis. Dry weight estimation by bioelectrical impedance analysis is 93 kg. She has been unable to complete her last 3 scheduled HD sessions due to intra-dialysis MAP drops up to 15 mmHg. The following are cardiovascular and neuroendocrine mechanisms that are expected to have occurred in this patient except
   A. Augmented myocardial contractility
   B. Increased peripheral resistance
   C. Activation of the parasympathetic nervous system
   D. Activation of the Renin-Angiotensin-Aldosterone system
   E. Increased heart rate

The correct answer: C.

Options A, B, D and E are all known compensatory, adaptive mechanisms that occur during hemodialysis to prevent blood pressure drops intradialysis.

5. One of the following can prevent the occurrence of intradialytic hypertension
   A. A steep dialysate-to-plasma sodium gradient favoring intracellular fluid shifts alone
   B. A moderate dialysate-to-plasma sodium gradient favoring net extracellular fluid shifts
   C. A moderate dialysate-to-plasma calcium gradient favoring total body water fluid loss
   D. A steep dialysate-to-plasma sodium gradient favoring total body water fluid loss
   E. A zero dialysate-to-plasma sodium gradient to prevent rebound hypervolemia

Correct answer: B.

As sodium plays a central role in determining serum osmolarity and thus intravascular volume, sodium shifts induced by dialysate-serum sodium gradients induce fluid

movement across the various fluid compartments, principally the intracellular and plasma/extracellular fluid compartments. It has been demonstrated by bioimpedance techniques that steeper sodium gradients of the dialysate relative to serum promotes intracellular fluid loss rather than plasma/extracellular fluid loss. With high gradients the extracellular fluid compartment remains expanded. It has thus been suggested that in the management of dialysis patients with intradialytic hypertension less steep dialysate-to-plasma sodium gradients be maintained and thus facilitate extracellular fluid loss.

6. A 54-year-old with end-stage renal disease from lupus nephritis who was transferred 10 weeks ago from peritoneal dialysis to hemodialysis following fungal peritonitis, has come into the HD unit with complaints of low-grade, continuous fever, malaise, and central chest pain. The pain is rather constant and is mildly improved by a change in posture to a seated position. There is no associated cough or dyspnea. A bedside 12-lead ECG done showed features of LVH and non-specific ST segment changes, while an echocardiogram revealed mild pericardial effusion. White blood cell count was 14,000cells/mm^3 while CRP was 62 mg/dL. B-D-Glucan assay was indeterminate. A highly likely diagnosis in this patient is:
   A. Uremic gastritis
   B. Tietze's disease
   C. Fungal pericarditis
   D. Lupus pericarditis
   E. Dialysis pericarditis

The correct answer: E.

Unlike pericarditis in non-uremic, non-dialysis patients, dialysis-related pericarditis usually presents without the classic ECG findings of diffuse PR segment depression and saddle-shaped ST segment elevation. The lack of associated epicardial inflammation in uremic and dialysis patients accounts for the absence of these typical ECG findings. Intensification dialysis schedule is known to improve associated pericardial effusions while anti-inflammatory agents such as steroids and NSAIDs have not been consistently shown to be helpful.

7. A 56-year-old woman with end-stage renal disease secondary to diabetic nephropathy uses a cuffed, tunneled, right internal jugular catheter as vascular access for hemodialysis for 5 months. After the first 35 minutes of HD, she develops nausea and rigors and has a temperature of 38.3 °C. Her BP drops from 157/80 to 100/61 mmHg, and her heart rate is 113 beats per minute, regular. She had a similar experience during dialysis 3 days ago, but the temperature was 37.7 °C and she had transient rigors. Examination revealed mild erythema and tenderness of the exit site but no purulent discharge. No other patient having dialysis at the centre has similar occurrence. What is the most likely cause of clinical scenario?
   A. Gram positive infection
   B. Gram negative infection
   C. Fungal infection
   D. Virus infection
   E. Parasite infection

The correct answer is C.

This is most likely a catheter-related blood stream infection and Gram positive organisms like *Staph Aureus* are the commonest organisms

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