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ACUTE COMPLICATIONS ASSOCIATED WITH HEMODIALYSIS

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INTRODUCTION

In the 27 years since maintenance hemodialysis was first introduced in Seattle, this treatment has been revolutionized. In 1960 maintenance hemodialysis for chronic renal failure was a 14-h experimental procedure, performed on a few highly selected patients by a team of physicians and other staff who were uncertain of the complications which might ensue, both during the dialysis and as a result of the prolongation of life by this new treatment. Now there are more than 300,000 patients treated by maintenance dialysis throughout the world, and almost all of them have their treatment supervised by nurses or by technicians. There are also thousands of patients who perform their own hemodialysis treatment at home.

Hemodialysis has proved to be a remarkably safe procedure, and the major complications occurring in association with it have been documented carefully. Despite development of more biocompatible membranes and newer techniques such as hemofiltration and hemodiafiltration, it seems unlikely that significant new acute complications of hemodialysis will be described in the future. Nevertheless, new complications association with long-term dialysis continue to be described. For example, the previous edition of this book included carpal tunnel syndrome as a recognized complication in dialysis patients, but its possible relationship

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to beta-2 microglobulin production and amyloidosis had not yet been recognized.

This chapter briefly reviews the major complications associated with hemodialysis and, in particular, those not dealt with at length elsewhere in this book. In general, it excludes complications occurring in the dialysis patient that do not relate directly to the procedure. The topics discussed are not an exhaustive list of all the complications that have been recorded as occurring or that relate to hemodialysis, but rather those considered most important or interesting. Similarly, when therapy is described, the emphasis is generally on treatment which is felt the most appropriate in the light of personal experience.

Dialysis patients may develop the same emergency and semi-emergency situations that can occur in any other type of patient, and treatment may be identical with that in the nondialysis patient or may be modified because of concurrent renal failure and dialysis treatment. In addition, certain complications are specific to the patient undergoing hemodialysis. For an exhaustive discussion of the risks and hazards associated with the dialysis equipment, the reader is referred to the report by Keshaviah and co-workers (1) and to Chapter 12.

SUDDEN DEATH IN HEMODIALYSIS PATIENTS

Death in hemodialysis patients is most commonly related to cardiovascular disease and its complications. Sudden death and death due to hemorrhage may occur at any time during hemodialysis itself or between dialyses (2). Deaths related to dialysis but occurring between dialyses are most comonly due to pericardial tamponade from pericardial effusion or result from suicide (3). Suicide may be by deliberate exsanguination or by electrolyte imbalance because of dietary indiscretion involving salt and water or potassium, as well as the more usual forms of suicide. The frequency of suicide in dialysis patients is greater than in the general population, but information is not available as to whether suicide is more common in dialysis patients than in patients with other life-threatening chronic diseases.

Sudden death occurring during hemodialysis is an unusual event (4). The usual causes, many of which are discussed below, include brain herniation; air embolism; acute hemorrhage which may also result from machine malfunction or disconnection; electrocution; cardiac arrhythmias, primarily related to potassium abnormalities; complications of subclavian intravenous catheter insertion; cardiac conduction defects; and other technical problems related to the dialysis procedure.

HYPOTENSION, DISEQUILIBRIUM, AND RELATED SYMPTOMS

The most frequently encountered problems in dialysis patients relate to hypotension occurring during dialysis, nonspecific symptoms during and after dialysis apparently unrelated to hypotension or disequilibrium, and the dialysis disequilibrium syndrome. The latter remains a potential problem in patients with acute renal failure and in patients first starting treatment by maintenance dialysis.

Hypotension

Episodes of hypotension occur in 20% to 30% of all hemodialyses (5, 6), and relate to various factors affecting cardiac output and systemic vascular resistance (7, 8). Cardiac output depends on myocardial contractility and filling volume, which in turn relates to vascular volume and heart rate, the increase of which may be limited in dialysis patients. Systemic vascular resistance is controlled through the autonomic nervous system and the presence of various vasoactive substances, and inability to increase vascular resistance is important in the development of dialysis hypotension. When not the result of a specific cause such as septicemia, arrhythmia, myocardial infarction, or another cardiac problem, hypotension in hemodialysis generally is secondary to acute reduction in blood volume due either to excessive ultrafiltration or to acute hemorrhage. Symptoms are similar, whatever the cause, and may include unexplained anxiety, nausea and pallor, possibly vomiting which may result in temporary relief, headache and cramps. On sitting up, the patient becomes dizzy, develops tachycardia, and may become unconscious.

Hypovolemia decreases cardiac refilling pressure and stroke volume which, with reduced or absent vasoconstriction, results in hypotension if cardiac output is not maintained by increasing the heart rate (8).

Hypotension associated with sodium and fluid depletion

Hypotension as a result of sodium and fluid depletion may occur at any time during or shortly after dialysis, and the time of onset may give a clue to the cause. Predialysis blood volume is less in patients who suffer from hypotensive episodes during hemodialysis (9), and this may be aggravated by previous vomiting, diarrhea, fever, or reduced dietary sodium intake. In such patients the predialysis weight is low. Many patients have mild symptoms of hypotension on connection to the dialyzer during their early dialyses, but generally this problem does not persist.

Hypotension occurring during the course of dialysis usually is due to excessive ultrafiltration which results in hypovolemia and a decrease in stroke volume (10). Excessive ultrafiltration may result from too short a dialysis with consequent rapid ultrafiltration, an incorrect estimate of the ultrafiltration rate required to remove accumulated fluid, or venous obstruction with consequent increased pressure in the dialyzer and excessive ultrafiltration. Hypotension during dialysis also may be an early indication of a pericardial effusion. Hypovolemia is particularly likely to occur with use of a lower dialysis fluid sodium concentration (11), and hypotension is less frequent when dialysate sodium is higher (12).

Occasionally, hypotension may occur shortly after dialy-

sis. The most likely cause is excessive ultrafiltration, symptoms appearing when the patient becomes active following the end of dialysis.

Other factors related to dialysis hypotension

Autonomic dysfunction also may play a significant role in toleration of hypovolemia during hemodialysis. Reduced baroceptor sensitivity has been demonstrated by abnormal responses to the Valsalva maneuver and the amyl nitrite test, and may relate to the existence of autonomic neuropathy in many dialysis patients (13). However, recent studies have shown that while cardiac efferent parasympathetic pathways may be affected, adrenergic responses are normal (14, 15).

Left ventricular function is also important, and dialysis patients generally have increased cardiac output related to anemia and the presence of an arteriovenous fistula. Abnormal left ventricular function in keeping with a uremic cardiomyopathy has been shown (16), and hemodynamic changes during dialysis correlate with predialysis left ventricular function (17).

Other factors which may be associated with hypotensive episodes during dialysis include the occurrence of myocardial infarction, pulmonary embolism, hemorrhage, sepsis, and the excessive use of antihypertensive medications.

The role of acetate and hypoxemia

With development of automated single-pass dialysis equipment in the 1960s, acetate became the standard anion in dialysate, replacing bicarbonate because of the need to prevent precipitation of calcium and magnesium (18). Acetate is readily metabolized in the body, resulting in the regeneration of bicarbonate from carbon dioxide (19).

More recently, with larger surface area dialyzers and more rapid dialysis, transport of acetate into blood can occur at a rate exceeding the capacity of the body to metabolize it, and this is associated with hypotension (20, 21). Acetate ion is a vasodilator (22), and during dialysis the drop in systemic vascular resistance correlates with the plasma acetate level (23). This effect is greatest at the start of dialysis when the blood acetate level increases rapidly (24). The usual effect of acetate on the heart is to increase heart rate and improve left ventricular function and cardiac output, thus tending to compensate for the drop in vascular resistance (25). A cardiodepressant effect of acetate on dialysis patients has been described (26), but a recent study failed to confirm a direct myocardial depressant effect (27).

Acetate metabolism also results in hypoxemia (28) and decreased carbon dioxide consumption (29), and there is also a loss of CO_2 through the dialyzer (30). Hypoxemia also may result from blood-membrane interaction, and this effect is greater with cellulosic membranes than with newer synthetic membranes (31). Activation of the complement cascade following exposure of blood to the cellophane membrane (32) causes white-cell aggregation in the pulmonary vascular bed. This results in transient leukopenia early in dialysis, associated with hypoxemia which correlates with the severity of the leukopenia (33). The incidence and severity of hypotensive and other symptoms during dialysis can be ameliorated by the administration of oxygen (34), but this does not affect the vasodilatory effects of acetate (35).

Dialysis hypotension and vasoactive substances

Decreasing dialysate flow rate and less efficient dialysis has been shown to reduce the incidence of hypotensive episodes during dialysis. This could be the result of slower intercompartmental fluid shifts, but also might relate to increased depletion of vasoactive substances such as epinephrine and norepinephrine which may be removed through the dialysis membrane (36). However, the concentration of epinephrine and norepinephrine in blood does not necessarily correlate with their concentration at the vessel walls, and hypotension more likely results from imparied vasoconstrictor response due to autonomic dysfunction (37). Use of cooled dialysate has also been shown to reduce the incidence of hypotension (38), perhaps because of increased norepinephrine release as a result of the cooling (39).

Other dialyzer-related effects on blood pressure

Hypotension and a syndrome resembling anaphylaxis may occur at the onset of dialysis in some patients (40), particularly with the first use of a cuprophan dialyzer (41). Symptoms disappear when dialysis is discontinued without return of blood to the patient, but may recur with use of the same membrane. These reactions may be related to either bacterial endotoxins (42) or hypersensitivity to ethylene oxide used in sterilization of the dialyzer (43). This hypersensitivity may be associated with eosinophilia and elevated plasma IgG levels (44).

While full blown anaphylaxis is rare, on occasion this may be fatal (45). More frequently, hypotension and related symptoms develop during the first 30 min of dialysis with a new dialyzer, usually in association with use of a cuprophan membrane. This 'first-use syndrome' may be related to complement activation and is much less frequent with other synthetic membranes (46). Dialyzer reuse more or less removes the complement-activating potential of the membrane (47), and this provides a rationale for multiple reuse of dialyzers in patients with symptoms occurring early during dialysis. The association of first-use syndrome with complement activation also suggests that the complement-activating potential of a dialysis membrane is a useful index of its biocompatability (48).

Prevention and treatment

Prevention of hypotension during hemodialysis requires accurate assessment of the patient's dry weight, monitoring of dietary sodium intake, knowledge of whether the patient is taking antihypertensive medications, and consideration of the type of dialyzer and the dialysate composition.

Increasing the dialysis fluid sodium concentration from

126 to 140 mmol/l reduces the number of hypotensive episodes (12), and at least one study has shown that raising the dialysate sodium level higher than 137 mmol/l does not produce further improvement (49). The higher dialysate sodium concentration induces tachycardia which compensates for hypovolemia (50), reduces the blood pressure drop resulting when the carotid sinus is stimulated (51), and produces a lesser increase in the plasma level of prostaglandin E_2 than does use of hypotonic dialysis fluid (52). However, use of such dialysate may increase weight gain between dialyses and so require increased ultrafiltration during dialysis. Sequential ultrafiltration has also been used to reduce the incidence of hypotensive episodes.

The use of dialysis fluid containing bicarbonate rather than acetate also reduces the severity of side effects, even with the use of high sodium dialysis fluid (53), but does not significantly reduce the frequency of hypotensive episodes (45). The long-term use of bicarbonate dialysis solution eventually increases predialysis plasma bicarbonate concentration (55). This suggests better correction of metabolic acidosis (56). It also results in better control of serum phosphate levels (57).

The treatment of hypotension occurring during dialysis includes lying the patient flat, and reducing negative dialysate compartment pressure to zero to prevent further ultrafiltration. Other possible causes of hypotension, particularly cardiac complications, pericardial effusion, or septicemia, must be excluded. With mild symptoms, intake of a salty food such as soup or potato chips may be all that is required. If hypotension persists or becomes more severe, an appropriate volume of a saline must be administered via the venous blood line. The volume and rate of infusion must be based on the response of symptoms and blood pressure (58).

Disequilibrium symdrome

Clinical manifestations

Dialysis disequilibrium syndrome is now seen most commonly during hemodialysis of severely uremic patients with acute renal failure and occasionally in patients with chronic renal failure who are commencing maintenance hemodialysis, particularly when using large-surface-area or high-flux dialyzers and shorter dialysis times.

Mild disequilibrium may present only as restlessness and headache during dialysis, sometimes associated with nausea, vomiting, blurring of vision, and muscle twitching. Blood pressure may be raised, and there may be disorientation and tremor. Seizures occur in more severe cases and occasionally may be accompanied by cardiac arrhythmias (59). Both grand mal and petit mal seizures may occur, but focal signs are more often associated with preexisting neurologic disease (60). With current dialysis techniques, seizures, coma and death are uncommon occurrences.

Pathogenesis

Cerebral edema is regarded as the major cause of disequilibrium because of the consistent occurrence of an associated elevated cerebrospinal fluid (CSF) pressure and also the finding of cerebral edema in patients dying with this syndrome. During hemodialysis the urea concentration and osmolality in the CSF fall more slowly than in blood, and a concomitant rise in CSF pressure occurs, the so-called reverse urea shift (61,62). After rapid hemodialysis in uremic dogs, the urea concentration is only marginally higher in the brain than in plasma (63). Consequently, the rate of urea clearance from the brain more or less parallels that from plasma, and there is a delay in clearance of urea from CSF during dialysis. This is associated with a paradoxical acidosis in the CSF and a fall in CSF pH during dialysis, despite correction of systemic metabolic acidosis and rise in arterial pH (59). The alteration in CSF pH may impair mentation, and the intracellular acidosis in the brain can increase intracellular osmolality by altering osmotic activity of intracellular cations, resulting in brain edema.

The paradoxical CSF acidosis during correction of metabolic acidosis depends on more rapid diffusion of carbon dioxide than bicarbonate across the blood-brain barrier, so that during hemodialysis CSF pCO_2 is rapidly corrected, while bicarbonate concentration remains low. However, in maintenance dialysis arterial pCO_2 does not increase at the end of dialysis or shortly thereafter (64); and in rapidly hemodialyzed patients, no difference is found in pCO_2 or bicarbonate concentration in plasma or lumbar CSF, whether disequilibrium occurs or not (65).

Hypoglycemia (66) and hyponatremia (67) have also been suggested as causes for disequilibrium, but there is little evidence that hypoglycemia plays any significant role in this, although the mild hyponatremia associated with use of dialysate of low sodium concentration may play a minor role.

Brain edema causing disequilibrium also may result from generation of idiogenic osmoles in the brain during dialysis (68,69). This theory is based on experiments in uremic dogs showing a significant osmotic gradient between brain and blood during dialysis not due to changes in concentrations of sodium, potassium, chloride, calcium, magnesium, or urea in the brain. The nature of these idiogenic osmoles remains unclear, but their genesis may relate to changes in intracellular binding of sodium and potassium caused by their replacement by ammonium ions resulting from the equilibrium between glutamine and glutamic acid. Thus, an increase in glutamic acid concentration in the brain could cause a fall in intracellular pH, loss of hydrogen ion into the CSF, and a fall of CSF pH and rise in brain osmolality due to accumulation of acid osmoles.

Diagnosis

The characteristic electroencephalogram (EEG) findings of disequilibrium are an increase of slow wave activity with increased spike wave activity and bursts of delta waves, and with loss of normal alpha rhythm (68). However, more recently it has been shown that the EEG is normal and disequilibrium does not occur with the use of bicarbonate dialysate (70, 71). The CSF pressure is normal in the un-

complicated nondialyzed uremic patient, but generally rises during dialysis whether disequilibrium occurs or not. This does not necessarily indicate brain edema, but could be due to an increase in CSF volume or cerebral blood flow. However, autopsies of patients who died during dialysis have shown brain swelling, often with tentorial herniation; and early studies of brain density using computerized tomographic (CT) scanning and densitometric analysis showed that brain density falls significantly during and after hemodialysis. These changes are in keeping with a postdialysis gain in cerebral water, and were particularly marked in the region of the basal ganglia (72). More recent studies in stable hemodialysis patients have shown no postdialysis EEG deterioration or change in brain density and ventricular size (73).

The differential diagnosis of disequilibrium includes a number of conditions discussed elsewhere. These include hypotension, nonspecific malaise associated with rapid dialysis, subdural hematoma, cerebrovascular accident ,the uremic syndrome, hypertensive encephalopathy, dialysis dementia, cardiac arrhythmias, hyponatremia, hypernatremia, hypoglycemia, copper intoxication, and other conditions.

Prevention and treatment

Prevention of disequilibrium was originally achieved by adding osmotically active solute to the dialysate. This prevents the fall in plasma osmolality resulting from urea removal by passage of osmotically active solute from dialysate to plasma, so reducing the brain-plasma osmolality gradient. Solutes used have included urea (74), dextrose (75), fructose (61), mannitol (76), sodium chloride (77), and glycerol (78), but results generally have not been impressive. Because disequilibrium occurs most commonly during rapid hemodialysis, the simplest preventive measure is to slow the rate of biochemical change by shorter and more frequent dialyses, with or without reduction in blood flow. This approach is useful in patients with acute renal failure and in the initial phase of maintenance dialysis, particularly in patients with severe overhydration, severe metabolic acidosis, or very high BUN levels. Alternatively, peritoneal dialysis with resulting slower biochemical changes may be effective, although disequilibrium has also been described with this technique.

While shorter, more frequent hemodialysis is preferable, anticonvulsant drugs may be used in both the prevention and treatment of disequilibrium, although they have no effect on cerebral edema. In extremely uremic patients first starting dialysis, phenytoin may be useful in prevention as a loading dose of 1,000 mg (4 mmol) at least one day before commencing dialysis, followed by a maintenance dose of 300 to 400 mg daily until the patient is stable and uremia is controlled. Phenytoin is of little value during seizure activity as, although it enters the brain rapidly, the brain level also declines very rapidly unless there is continued administration. Intravenous diazepam (Valium) produces high brain levels within minutes and is one of the most effective agents for suppression of acute seizure activity. The effect of intravenous injection lasts 30 to 60 min, and respiratory depression is less than with barbiturates (79). Short-acting barbiturates, such as thiopental or pentobarbital, also are effective within minutes, but are more dangerous because of the greater respiratory depression.

COMPLICATIONS ASSOCIATED WITH BIOCHEMICAL CHANGES

Incorrect proportioning in the preparation of dialysis solution may occur as a result of both technical and human errors, the most important consequences being the development of acute hyponatremia or hypernatremia, depending upon the error. Both of these conditions may result in confusion, lethargy, muscle weakness, myoclonus, seizures, coma, and death (80).

Hyponatremia

Hyponatremia occurs when plasma is allowed to equilibrate with hypotonic dialysis fluid. With batch-mix dialysis equipment, hyponatremia and hypoosmolality can occur at the start of dialysis or following a bath change as a result of failure to add concentrate, failure to test dialysate prior to use, or use of the wrong quantity of concentrate or water. In proportioning systems, failure to connect to the concentrate container and to note or set the conductivity limits or both (and failure to follow the checklist for initiation of dialysis) will produce hyponatremia at the start of dialysis. Hyponatremia can also occur during the course of dialysis with a proportioning system if the concentrate container runs dry and the conductivity limits have not been set appropriately (see also remarks on monitoring of conductivity in Chapter 12).

Acute hypoosmolality causes the abrupt onset of hemolysis (81) with transient marked hyperkalemia which, assuming the patient survives the acute episode, rapidly subsides as potassium distributes throughout the body compartments. In addition, any residual renal function may be jeopardized if acute renal failure develops. At the same time as acute hemolysis occurs, the massive infusion of water from the hypotonic dialysate results in hypervolemia, hemodilution of all plasma constituents, acute water intoxication, and cerebral edema (82).

Symptoms include pain in the vein receiving the hypotonic hemolyzed blood from the dialyzer, anxiety, restlessness and headache. Pulse rate decreases initially, then increases, and the patient develops precordial pain, cold and clammy skin, and distended neck veins, the latter associated with myocardial dysfunction. Severe lumbar pain and abdominal cramps also may occur, perhaps due to ischemia.

Treatment consists of clamping the blood lines; the hemolyzed blood must not be returned from the dialyzer to the patient. When clinically indicated, 100% oxygen should be administered and the patient placed on a cardiac monitor with a defibrillator available. In the event of seizures, intravenous diazepam should be given. Blood should be ob-

tained for baseline hematocrit, plasma hemoglobin, serum electrolytes, crossmatching, and serum enzyme levels. At the same time, a further batch of dialysate should be prepared, or in the case of a proportioning system, this could remain in bypass with appropriate concentrate until the dialysate composition is up to normal levels. Dialysis then should be restarted without delay, using a new dialyzer. Once dialysis has recommenced, a high transmembrane pressure is necessary to remove water excess, and it may be necessary to infuse saline, colloid, or blood to maintain blood pressure. Following dialysis, the hematocrit, serum hemoglobin and electrolyte concentrations should be remeasured, and the patient hospitalized for 24 to 48 h for serial enzyme studies and observation for possible myocardial damage.

Prevention of acute hyponatremia and hypoosmolality depends on meticulous attention to detail in preparing for dialysis. The final step before connecting dialyzer and patient should be checking of the dialysate in a batch system, or checking the conductivity meter and its setting with a proportioning system.

Hypernatremia

Hypernatremia and hyperosmolality due to use of inappropriate dialysate (83) may occur inadvertently with a batch-mix system if the wrong concentrate or wrong volume of concentrate or water is used and no check of the dialysate is made prior to dialysis. It may also occur when water and concentrate are incompletely mixed. With a proportioning system, this problem can only occur if the conductivity meter malfunctions or the alarm points are not set appropriately and the proportioning system is maladjusted; if the water treatment equipment malfunctions (84); or in a hydraulically driven proportioning system, if the concentrate source is elevated, so providing a head of pressure to the system.

The effects of hypernatremia include transfer of water from the intracellular to the extracellular space, causing intracellular water depletion and hyperosmolality. Depending upon the rapidity of the shifts of sodium and water, the extracellular volume may be increased or decreased; in any event, the extracellular fluid is hyperosmolar and cell volume is contracted. Symptoms include headache, nausea and vomiting, profound thirst, convulsions, coma, and death (80, 82).

Hyperkalemia

Serious hyperkalemia is an uncommon problem in patients on maintenance dialysis except in those who are markedly underdialyzed or following significant dietary indiscretion. In patients using single-needle dialysis, hyperkalemia may develop if recirculation occurs. This can be recognized by a disparity between the urea concentration of blood from the dialyzer and that from a peripheral vessel. The concentration of potassium in dialysate, usually between 1.0 and 3.0 mmol/l, results in net removal of potassium during dialysis. Potassium-free dialysis solution can be used, but usually causes subnormal postdialysis plasma potassium levels which may contribute to postdialysis fatigue. Consequently, most patients are dialyzed with a dialysis fluid potassium concentration of at least 1.0 mmol/l.

Nevertheless, hyperkalemia may develop in association with hemolysis, as described elsewhere in this chapter. Hyperkalemia has also occurred in association with severe hyperglycemia in diabetic dialysis patients. This was ascribed to passive transfer of potassium from the intracellular space as a result of hyperosmolality of the extracellular fluid because of the severe hyperglycemia; insulin deficiency also may have played a role. Thus, in dialyzed diabetic patients, adequate blood glucose control is essential.

For patients receiving digitalis and related drugs, and particularly patients with left ventricular hypertrophy, rapid lowering of the serum potassium level during dialysis is a well-recognized cause of cardiac arrhythmias (85). Consequently, it is usual to dialyze such patients with a dialysis fluid potassium concentration of between 2.0 and 3.5 mmol/l, depending on the patient's serum potassium level. Ventricular extrasystoles, sinus tachycardia, atrial fibrillation, and other arrhythmias may occur and can cause sudden death. Electrocardiographic monitoring should be used if problems are anticipated during dialysis of a digitalized patient. The occurrence of potentially lethal hyperkalemia in patients on relatively small maintenance doses of digoxin has been described (86).

Hypokalemia

Hypokalemia is not generally severe in patients with chronic renal failure, but may result from prolonged potassium loss secondary to nausea, vomiting, diarrhea, nasogastric suction, or diuretic therapy. Hypokalemia during dialysis usually is not a significant problem, but sometimes may be life-threatening when associated with marked predialysis acidosis. In these circumstances, dialysis with rapid correction of the acidosis results in a major transcompartmental shift of potassium at a rate exceeding the capacity for transfer of potassium across the dialysis membrane; as a result, severe hypokalemia may develop (87). Patients likely to suffer from this problem have a history suggestive of potassium loss and a low or low-normal predialysis serum potassium level together with a low serum bicarbonate level and severe acidosis. Use of a high potassium dialysate should be considered in such patients, and serum potassium levels should be monitored during dialysis.

Hypercalcemia and hypermagnesemia

In the early days of hemodialysis, dialysis fluid was prepared using untreated tap water. However, it became obvious that in locations where the water contained high concentrations of calcium or magnesium, and particularly when these levels fluctuated appreciably, water for dialysis solution required treatment prior to use. All water used for dialysis fluid preparation must be treated by deionization, reverse osmo-

sis, or a combination of these processes (1, 88) in order to control the levels of divalent cations and also to remove aluminium, fluoride, and other trace minerals that may be present. In some areas the mineral content of the water is so high that considerable water treatment is necessary (see Chapter 12).

The 'hard water syndrome' is an acute syndrome occurring during dialysis, precipitated by hypercalcemia and hypermagnesemia, and associated with failure of the water treatment process (89). Nausea and vomiting occur after the first hour of dialysis, and may persist throughout the treatment. Hypertension accompanies the vomiting, even if there is significant weight loss due to ultrafiltration during dialysis, and the rise in systolic pressure is greater than that of the diastolic pressure. This increase in blood pressure is attributed to the acute hypercalcemia, which may also cause acute pancreatitis (90). Lethargy, muscular weakness, headache, and an acute central nervous syndrome similar to dialysis dementia and associated with disorientation, dysarthria, seizures, myoclonic jerks, hallucinations, irritability, confusion, memory and judgment defects, and bizarre behavior have been described (91). If there is hypermagnesemia, burning sensations in the skin also may occur.

If the hard water syndrome develops, dialysis should be stopped and restarted as soon as possible using appropriately treated water for dialysis fluid preparation. Prevention depends upon regular maintenance and servicing of water treatment equipment.

Hypercalcemia in hemodialysis patients is a well recognized manifestation of secondary hyperparathyroidism. It has also been described in association with hyperthyroidism (92), as a manifestation of vitamin A toxicity due to excessive use of multivitamin preparations containing this vitamin (93), and in patients with tuberculosis, resulting from extrarenal production of calcitriol (94).

Hypermagnesemia may occur in dialysis patients, but is unlikely to be sufficient to cause symptoms unless the patient is taking magnesium containing phosphate binders (95). Although not an acute problem, use of a dialysate magnesium concentration of 0.5 mmol/l (1.0 mEq/l or a 1.2 mg/dl) induces slight hypermagnesemia and an elevated bone magnesium content. It has also been shown that a rise in plasma magnesium concentration in dialysis patients reduces circulating plasma parathyroid hormone levels (96).

Conversely, studies with magnesium-free dialysate and dialysis fluid containing only 0.25 mmol/l (0.5 mEq/l or 0.6 mg/dl) of magnesium have shown this may stimulate parathyroid hormone production, so increasing 1,25-dihydroxycholecalciferol production, intestinal calcium absorption, and bone mineralization (97). Hypomagnesemia may also cause arrhythmias in dialysis patients, especially in those receiving digitalis (98).

Miscellaneous dialysis fluid-related problems

Acute copper intoxication and hemolysis secondary to leaching of copper from copper tubing in a dialysis fluid supply system in association with a fall in pH following deionizer exhaustion has been reported (99). Chronic copper poisoning can also occur when dialysis solution is made from untreated water supplied through copper pipes (101, 101).

Intoxication with other metals such as zinc (102, 103), lead (104), and nickel (105) may occur, and other trace elements such as fluoride may accumulate in dialysis patients. These problems are discussed in detail in Chapter 49. Hemolysis associated with nitrates (106) and with chloramines (107) in the water used for dialysate has also been reported.

Dialysis fluid concentrate errors can cause serious acid-base abnormalities (108). It is possible to dialyze using acid concentrate in place of acetate, and the proportioning equipment can dilute this to the appropriate conductivity, resulting in severe metabolic acidosis. Similarly, the wrong acid and bicarbonate concentration can be used in the wrong equipment. Consequently, it is important to take considerable care in preparation for dialysis.

FEVER AND ENDOTOXEMIA

Infections and pyrogen reactions

Febrile reactions during dialysis usually are associated with endotoxemia causing a 'pyrogen' reaction. Less commonly they are due to infection, and rarely they result from failure of temperature control of the dialysis equipment.

Fever due to infection is most likely to occur at the start of dialysis or shortly after its end, while fever and chills developing during the course of dialysis are much more apt to be due to a pyrogen reaction in association with endotoxemia (109, 110).

Fever at the start of dialysis usually is due to contaminated equipment, and may be more likely to occur with a dialyzer which has been stored and reused if procedures are not followed carefully (see also Chapter 18). In the event of fever developing at the start of dialysis, treatment should be stopped, appropriate measures taken for investigation and treatment of infection, and dialysis restarted using fresh equipment.

Fever developing within an hour or so of the termination of dialysis suggests infection has occurred during the coming-off procedure. The risks of contamination and air embolism are reasons to prefer saline rinsing rather than air rinsing to return blood from the dialyzer at the end of dialysis. The patient should be investigated and treated for possible infection.

Fever developing during the course of dialysis generally is due to a pyrogen reaction secondary to endotoxemia. Usually the fever is associated with chills and nausea, and sometimes hypotension. The severity of the episode varies from very mild to very severe, but in general responds promptly to treatment with antipyretics. Circulating endotoxins or endotoxin-like activity have been shown in blood taken from patients during febrile episodes, and endotoxin has been demonstrated in dialysate (109) and in hollow fiber dialyzers (111). Endotoxin may be introduced from the dialysate, and

high titers of antibodies against bacterial endotoxins have been found in dialysis patients (112). Although theoretically the pore size of cellulosic membranes is too small to allow passage of a molecule the size of endotoxin, small isolated defects could permit passage of sufficient endotoxin to cause a pyrogen reaction. With increasing use of more porous membranes, it is essential to insure sterility and nonpyrogenicity of the dialysate (113). Pyrogen reactions occurring with hollow fiber dialyzers containing a cellulosic membrane may be associated with endotoxins in the linters remaining in the dialyzer following manufacture, while in contrast, extracts of cuprammonium-derived hollow fibers do not show Limulus amebocyte lysate reactivity (111).

Treatment of a pyrogen reaction occurring during dialysis is with antipyretic agents. The possibility of infection should always be considered (114), but most febrile reactions occurring during dialysis are associated with contamination by pyrogens.

Prevention of pyrogen reactions requires effective cleaning and disinfection of dialysis equipment, as microbial contamination of the water used for dialysis is frequent (115). This may be particularly important for home dialysis patients, an appreciable number of whom have been found to use inadequately cleaned equipment (116). With high-efficiency dialysis using more porous synthetic membranes, it becomes essential to use effective water treatment to insure nonpyrogenicity of the dialysate (113). In addition, liquid bicarbonate concentrate can support rapid bacterial growth and endotoxin production and so should not be stored for prolonged periods of time, and bacteriological monitoring should be carried out before use and at least weekly. If concentrate is prepared from powder, this should be done immediately prior to dialysis, and all containers should be rinsed and disinfected daily (117). Pyrogen reactions have also been reported with use of a heparinized saline solution which was contaminated (118). Despite repeated patient concerns, dialyzer reuse generally has not been associated with an increase in the incidence of pyrogen reactions (119).

Overheated dialysate

Failure of the thermostat in the dialysate temperature monitoring system may result in overheating of the dialysate. This can cause immediate severe hemolysis and lethal hyperkalemia, or, if less severe, milder hemolysis may develop gradually. Thermostat failure causes a gradual rise in dialysate temperature, noted by the conscious patient as an increasing sensation of warmth. If undetected, heat-induced red cell damage may occur (120); but if the patient is not obtunded, overheating will be detected before the temperature rise is extreme.

If the dialysate temperature rises above 51° C, immediate and massive hemolysis can occur and may result in death from acute hyperkalemia (121). If the dialysate overheats to temperatures between 47° C and 51° C, the onset of hemolysis may be delayed for up to 48 h (122.123).

Prevention of this rare complication requires setting the high-temperature monitor on the dialysis equipment to alarm so as to prevent temperatures in excess of 42° C.

In the event of a dialysate temperature rise to 51° C, dialysis must be stopped immediately, and the blood in the system should not be returned to the patient. The patient should be monitored closely for development of hyperkalemia, transfused if necessary, and have a further dialysis with fresh equipment as soon as possible.

AIR EMBOLISM

Air embolism is an ever-present risk during hemodialysis because of the combination of a blood pump and the extended extracorporeal blood circuit (124). The frequency of significant air embolism during hemodialysis is uncertain, and cases generally go unreported. Nevertheless, with present-day equipment, the frequency is likely to be small.

Causes

Many causes of air embolism have been recognized (1). Air leakage may occur into the portion of the extracorporeal blood circuit which is under subatmospheric pressure, i.e. the prepump segment during fistula dialysis. Leakage can occur around the fistula needle or needle hub, as a result of arterial disconnection, through the heparin syringe at the connection to the tubing, between barrel and plunger, or through a crack in the barrel wall, at the arterial monitor line connection, in the arterial monitor, at a defective arterial drip chamber, through a split pump segment, or through a vented intravenous bottle. Air also can pass in large quantities from dialysate to blood in the dialyzer. Refrigerated dialysate, as once used, could contain a large amount of dissolved air likely to come out of solution when the dialysate was warmed by blood in the dialyzer. This may still be seen when water used to prepare the dialysis fluid is very cold, so allowing more air to be dissolved than the deaerating capacity of the equipment. A similar problem may be seen if the deaerater is defective. Air embolism is also a possible complication with the use of subclavian vein access (125). Finally, air embolism may occur as a result of an error in the procedure for returning blood to the patient at the end of dialysis.

Signs and symptoms of air embolism

Death is said to have occurred with as little as 5 ml of air, although this must be extremely uncommon and would require very selective placement of the air. The amount of air necessary to produce symptoms depends on several factors. For example, more air can be tolerated as microbubbles infused at a slow rate, thus allowing time for the air to dissolve in the blood. Arterial introduction of air can cause death by occlusion of a major cerebral or coronary artery. During hemodialysis, air usually enters the body through the venous end of the extracorporeal blood circuit, although air can be infused into an artery during a cannulation procedure.

The signs and symptoms of air embolism depend in large part upon position. If the patient is sitting or the head is elevated, air entering an arm vein will travel through the axillary and subclavian veins, then in retrograde fashion up the jugular vein to the cerebral venous system where it obstructs the venules in the brain, resulting in cell damage. Death may ensue if a critical area of the brain is affected. Classically, the patient is said to cry out in alarm because of the sound of air rushing through the venous system to the brain, then, depending on the volume of air infused, convulse, lose consciousness, and possibly die.

When the patient is lying flat, air passes to the right atrium and right ventricle where it forms a foam, so interfering with the pumping ability of the heart. Especially if the patient is lying on his right side, air may pass through the pulmonary arteries to block the pulmonary capillary bed and cause acute pulmonary hypertension. Some air may pass through the lungs to the left ventricle and systemic circulation, resulting in arterial embolization and possibly cardiac arrhythmias and neurological defects. In these circumstances, the patient develops acute dyspnea, cough, and tightness in the chest, gasps for breath, becomes agitated and cyanosed, and may lapse into unconsciousness. Depending on the volume of air, respiratory arrest may occur. Upon examination, pulse and blood pressure may be unobtainable, and auscultation may reveal a churning sound caused by foaming of blood within the heart.

If the patient is in the Trendelenburg position because of hypotension at the time that air embolism occurs, air will pass to the lower extremities and cause patchy cyanosis associated with partial blockage of the circulation. If infusion of air is stopped in time and the patient is kept in position so that the air remains trapped in the leg veins, there may be no serious sequelae.

Treatment

When air embolism is detected, the venous blood lines must be clamped *immediately,* before any other action is taken. The patient should be positioned with chest and head down, turned on the left side. If the patient is dialyzing on a bed, they should be pulled off, leaving hips and legs on the bed. The bed can then be put in the Trendelenburg position and the patient slid back on to it, remaining on his left side throughout. If air embolism occurs while dialyzing in a chair, the patient can be pulled off so that the left shoulder is on the floor and the hips are still elevated. The patient should remain in this position in the ambulance en route to the hospital. This position traps air at the apex of the right ventricle, away from the pulmonary valve, so that the right ventricle acts as a bubble trap. Blood can continue to flow to the pulmonary arteries and lungs through the more dependent portion of the right ventricle.

If the patient is conscious, 100% oxygen by mask should be given. If unconscious, an airway or endotracheal tube should be placed and assisted respiration using 100% oxygen started.

If the patient is in cardiopulmonary distress and examination reveals foam in the right heart, percutaneous aspiration of foam may be necessary using an intracardiac needle and large syringe. Cardiac massage should not be commenced until foam has been removed from the right ventricle, so as to avoid passage of air into the pulmonary bed and left heart, so compounding the problem with arterial embolization. The use of 100% oxygen helps to supply oxygen to those parts of the lungs still being adequately perfused, and also increases the gas pressure gradient for nitrogen from bubbles to blood, so increasing diffusion. Other measures include intravenous adminstration of corticosteroids to reduce cerebral edema, and infusion of heparin and low molecular weight dextran to increase microcirculation (124). If available, consideration should be given to putting the patient in a compression chamber so as to drive the embolized air into solution. The patient can then go through decompression at a rate which will allow air to be expired through the lungs without coming out of solution (126).

Prevention of air embolism

Because air embolism is a life-threatening complication of hemodialysis, and treatment is difficult, often with poor results, prevention is of paramount importance. All intravenous fluids administered into the extracorporeal blood circuit should come only from collapsible plastic bags, as these can withstand pressures of at least 150 mmHg without withdrawing air. This is particularly important if fluid is administered into the subatmospheric pressure area of the prepump segment of the blood circuit. Preferably, intravenous fluids should be administered through the venous drip chamber as rapidly as possible, with the blood pump turned off, and this also avoids puncturing the arterial drip chamber or blood line sleeve. Care should always be taken whenever intravenous fluid is being administered during dialysis.

Heparin should be infused into the extracorporeal blood circuit at a point beyond the blood pump, i.e. against a positive pressure gradient. All needle-blood line connections must be tight, as must all arterial or prepump monitor line connections. An infusion sleeve on the prepump segment should not be used unless absolutely necessary. An air detector with a blood line clamp must be used on the venous blood line. Photocell air detectors may not detect very fine microbubbles unless the detector sensitivity is set so as to give frequent false alarms, and clot on the wall of the drip chamber may mask the photocell, so permitting the bubble trap to empty undetected. Conductance type air detectors are preferable and depend on change in capacitance across the drip chamber when it empties to actuate a blood line clamp (see also Chapter 12).

Perhaps the greatest risk of air embolism occurs if an air rinse is used to empty the dialyzer of blood at the end of dialysis. While air, or air and saline rinsing is said to be the most effective means to empty the extracorporeal circuit, the potential risk is such that saline rinsing should generally be used. In the event air is used, the proper procedure must be followed scrupulously. Both patient and attendant should have hemostats placed across the venous blood line

so that either can clamp the tubing at the end of the rinse, and the complete attention of both must be focused on the procedure. If the dialyzer is being emptied using air pumped through the blood pump, the attendant must keep one hand on the blood pump switch at all times. If blood is being returned using a hand-squeezed pump, enough pressure must be used to keep blood flowing freely into the venous drip chamber. If possible, the air detector and line clamp on the venous line should remain in the 'active' mode during the rinse procedure.

HEMORRHAGE

An increased incidence of spontaneous bleeding episodes occurs in hemodialysis patients. These include gastrointestinal bleeding, subdural hematoma, uremic hemopericardium, retroperitoneal hematoma, hemorrhagic pleural effusion, spontaneous bleeding into the anterior chamber of the eye, subcapsular hematoma of the liver, and bleeding into the skin and other sites. Such bleeding is related to several factors, including heparinization during dialysis, ongoing anticoagulant therapy, and the functional platelet abnormalities of uremia (127, 128). Platelet-membrane interactions cause platelet adhesion on the dialyzer membrane, formation of platelet factor 4, beta-thromboglobulin and thromboxane (129, 130), defects in platelet aggregation (131), and thrombocytopenia (132, 133). These interactions may be dependent on the characteristics of the dialysis membrane (134). The abnormalities in platelet function and prostacyclin activity are not always corrected by dialysis (135, 136). Thus the dialysis patient is always at some risk of bleeding. Petechial hemorrhages, blood blisters in the skin, and bruising around fistula punctures are common, and usually have no significance except as a reminder of the potential risk of bleeding. The possibility of internal bleeding always must be considered in any instance of unexplained hypotension during or after dialysis.

Gastrointestinal bleeding

The causes of gastrointestinal bleeding in maintenance hemodialysis patients generally are similar to those in nonuremic patients, including peptic ulceration, aspirin ingestion, hiatal hernia, and colon ulcers (137). In general, serum gastrin levels are higher than normal in dialysis patients, and some, particularly the elderly, have associated gastric hyposecretion; these patients have the highest incidence of gastrointestinal hemorrhage. Chronic gastritis is also relatively common in chronic renal failure patients, and may be responsible for much of the morbidity from gastrointestinal complications during hemodialysis (138). Gastrointestinal bleeding is an indication for the use of regional heparinization, low-dose or no heparin during dialysis (139) or peritoneal dialysis. Otherwise, the treatment of gastrointestinal bleeding in dialysis patients is straightforward, apart from the need to coordinate surgery with the dialysis schedule.

Subdural hematoma

Subdural hematoma occurs in up to 3% of hemodialysis patients (140, 141), and should be suspected in any patient with headache or neurologic symptoms resembling disequilibrium but which are not readily explained by this or other causes. Contributory factors include head trauma, anticoagulation, excessive ultrafiltration, hypertension, and the increased cerebrospinal fluid pressure and brain swelling which may occur during dialysis. Frequent episodes of access-site infection or cannula clotting are said to be common in such patients.

The symptoms and signs of subdudral hematoma may be nonspecific and are often confused with disequilibrium. However, the latter is unusual with maintenance dialysis except in new patients. The symptoms of disequilibrium usually do not fluctuate as much as those of subdural hematoma, and although headache is common with disequilibrium, it usually disappears shortly after dialysis. A diagnosis of subdural hematoma should always be considered when a previously stable dialysis patient presents with unexplained symptoms suggestive of disequilibrium. Headaches usually are severe, persisting through subsequent dialyses, and there may be focal or multifocal neurologic signs which may fluctuate. Neurologic signs are usually of little value in localizing the site of the intracranial bleeding.

Lumbar puncture and electroencephalography are of little help in diagnosis, as abnormalities of both can occur with disequilibrium, and radioisotope scanning produces an appreciable percentage of false negative results. The most useful investigations include cerebral arteriography (142), echoencephalography, and computerized tomography of the brain.

When subdural hematoma is a serious possibility, it may be preferable to use peritoneal dialysis until the diagnosis is confirmed or rejected (143). Treatment is by surgical exploration and removal of clot, but the results are disappointing, with a reported patient survival of less than 50% (144, 145). This is comparable to the results of treatment of acute subdural hematoma in nonuremic patients, where mortality is approximately 75% (146).

Uremic hemopericardium

Pericarditis is not uncommon in dialysis patients, and may occur early in the course of treatment or at any time after the patient becomes stabilized on dialysis (147). While the former is commonly uremic in origin, pericarditis in a stable dialysis patient is more likely to be associated with cytomegalic or other virus infection, and has also been described in patients receiving minoxidil for refractory hypertension (148). Pericardial effusion appears to be more common in patients on hemodialysis than in those treated by peritoneal dialysis (149). Pericarditis without effusion is an indication for more frequent dialysis, preferably with regional heparinization or low-dose heparin, or for peritoneal dialysis to avoid the use of anticoagulants.

An obvious pericardial effusion may develop in a small number of patients and may be associated with bleeding into the pericardial sac. While relatively uncommon, this is important to diagnose because of the potential risk of tamponade, which may escape early recognition. Such patients often give a history of preceding upper respiratory infection, and have symptoms of chest pain, respiratory distress, hypotension, and evidence of fluid overload. This is usually associated with fever and symptoms suggestive of a mild upper respiratory or gastrointestinal viral infection. In patients developing signs and symptoms suggestive of pericardial effusion, the diagnosis should be confirmed by X ray, sonography, isotope scanning, or other means. Initial treatment, particularly for smaller effusions, should be repeated pericardiocentesis with installation of a nonabsorbable steriod into the pericardial sac (150). If this fails, pericardectomy or pericardial fenestration usually is required (151). An enlarging effusion despite repeated pericardiocentesis requires prompt surgical drainage before hypotension or tamponade occur.

Retroperitoneal hematoma

Spontaneous retroperitoneal hemorrhage with a resultant hematoma is an uncommon complication of hemodialysis, occurring in less than 1% of patients (152). Diagnosis may be difficult in the absence of a history of trauma. There may be massive bleeding into the retroperitoneal space requiring transfusion of a large volume of blood, or the onset may be more insidious. Predisposing factors include minor trauma and anticoagulation, although spontaneous retroperitoneal bleeding is a rare complication in nonuremic patients receiving anticoagulants. An iatrogenic retroperitoneal hematoma can result afrom perforation of the iliac vein during insertion of a catheter via the femoral vein by the Seldinger technique.

Retroperitoneal bleeding presents with abdominal and flank or back pain, frequently associated with a distended abdomen and hypoactive or absent bowel sounds. An abdominal mass may be palpable. X-ray of the abdomen may show a soft tissue density and absence of the psoas shadow, and a barium contrast meal may show a nonspecific ileitis. Fever can occur after significant bleeding without evidence of simultaneous infection. Bleeding around the pancreas can cause pancreatic injury and an increase in the serum levels of pancreatic enzymes. Neuropathy due to retroperitoneal bleeding and hemorrhage around the femoral nerve has also been described. Selective renal angiography may be helpful in diagnosing perirenal hemorrhage (153), and sonography is also useful.

Treatment is usually conservative, with replacement of blood loss and hemodialysis using minimal or no heparin or peritoneal dialysis. Anticoagulant therapy should be stopped and the patient kept at rest. Surgical exploration usually is unnecessary. Spontaneous retroperitoneal bleeding should be considered in any hemodialysis patient with unexplained acute abdominal distress and a falling hematocrit without obvious external blood loss.

Hemorrhagic pleural effusion

Pleuritis is a complication of uremia (154), and hemorrhagic pleural effusion occasionally occurs in dialysis patients (155), probably related to anticoagulation in a patient with a fibrinous pleuritis. Treatment includes hemodialysis with low dose or no heparin, peritoneal dialysis, pleurocentesis, and use of a nonabsorbable steroid as in the treatment of pericarditis. The possible development of pulmonary constriction must be borne in mind in the patient who has had recurrent hemorrhagic pleuritis. A hemorrhagic pleural effusion should always suggest the need to exclude the possibility of coexisting cancer or tuberculosis.

Subcapsular liver hematoma

Spontaneous subcapsular liver hematoma may occur in dialysis patients and should be considered if such a patient presents with right upper quadrant pain, a rising alkaline phosphatase level, and falling hematocrit, without evidenced of external blood loss (156, 157). Radioisotope scanning can provide supporting evidence. Management depends upon the extent and location of the liver injury and may require evacuation or partial hepatectomy.

Epidural spinal hematoma

Epidural spinal hematoma occurs occasionally in dialysis patients, presumably as a result of anticoagulation. Symptoms of cord compression develop, with rapid onset of bilateral leg weakness and sensory loss, resulting in paraparesis and paraplegia. The development of spinal cord signs in a dialysis patient is an indication for urgent treatment, as permanent paraplegia may result unless there is early surgical evacuation of the compressing hematoma.

Hemorrhages into the skin

Petechial hemorrhages and an increased frequency of blood blisters and bruising around fistula punctures are not uncommon in dialysis patients. Typical subungual splinter hemorrhages, identical with those of bacterial endocarditis, also may occur (158).

MISCELLANEOUS PROBLEMS ASSOCIATED WITH DIALYSIS

Restlessness and insomnia are frequent symptoms in patients with severe uremia, particularly in the months immediately prior to starting dialysis. Usually these symptoms are relieved within a few weeks of starting treatment.

When these symptoms develop in a stable patient on maintenance hemodialysis, causes such as anxiety are most likely, but the possibility of inadequate dialysis should always be considered. Consequently, predialysis blood chemistry should be reviewed in any dialysis patient developing insomnia and restlessness. Treatment is symptomatic. In a

home hemodialysis patient suffering from insomnia, medication should be avoided in the period shortly before dialysis.

Restless legs

The restless leg syndrome is an irresistable compulsion to move the legs, occurring particularly when the patient is at rest, and often worse at night. It may be associated with paresthesiae, pruritus, and dull aches in the legs. It occurs in 40% of patients with chronic renal failure (159) and may be an early manifestation of neuropathy. The pathogenesis is obscure, and no abnormalities of nerves or muscles have been shown (160). Restlessness causes insomnia and may also be associated with nocturnal myoclonus. The syndrome causes embarrassment and can affect job performance, yet patients may not volunteer information on this problem except on direct questioning. Relief may occur with institution of dialysis or with the use of mild tranquilizers (161) or Levodopa (162).

Hypoglycemia due to beta-blocking agents

Beta adrenergic-blocking agents are used in the treatment of the hypertension of chronic renal failure, for treatment of persistent hypertension in dialysis patients, and for control of angina and arrhythmias. Severe acute hypoglycemia with beta-blocking agents was first described in association with the use of glucose-free dialysate in a single-pass system for patients who had fasted for more than 18 h (163). Episodes of profound hypoglycemia have been reported in nondiabetic dialysis patients receiving propranolol for hypertension and who were not fasting (164). The effect of beta-blocking drugs on glucose metabolism is complex, and may result in either hypoglycemia or hyperglycemia (165). Hypoglycemia is presumably the result of the effects on hepatic glycogenolysis, glucagon release, and lipolysis (166), and other possible contributory factors include poor nutritional intake with decreased glycogen stores and other causes of liver dysfunction. Hypoglycemia has also been reported in dialysis patients undergoing hyperalimentation with solutions of high dextrose content, presumably due to rapid passage of glucose from blood to dialysate (167).

Symptoms and signs of hypoglycemia include a sharp rise of blood pressure, presumably due to release of catecholamines, vomiting, and unconsciousness occurring early in dialysis. Hypoglycemia should be ruled out whenever such symptoms develop in any dialysis patient receiving beta-blocking agents.

Because beta-blocking agents are in common use, many dialysis patients, especially with those with diabetes, liver dysfunction, or poor nutrition, may have transient episodes of hypoglycemia without autonomic symptoms because these are prevented by the beta blocker. Since use of a glucose-free dialysate may contribute to development of hypoglycemia, glucose-containing dialysate should always be used for patients receiving beta blockers. Alternatively, frequent blood sugar determinations may be made on maintenance hemodialysis patients taking beta blockers.

Dermatological abnormalities associated with hemodialysis

Xerosis, pruritus, skin infections, and disorders of pigmentation occur in patients with chronic renal failure and in dialysis patients (168–170). Among the other dermatological problems reported in such patients are lesions resembling erythema multiforme, bullous dermatosis, and porphyria cutanea tarda. Bullous dermatosis is characterized by the occurrence of moderately painful bullae on the dorsa of the hands and feet, unassociated with trauma (171, 172). The cause is unknown, and the condition is not related to medication, although there is a suggestion sunlight may be a causative factor.

Porphyria cutanea tarda

Porphyria cutanea tarda has been reported in dialysis patients (173, 174), presumably due to insufficient removal of porphyrins by dialysis. This results in high levels of plasma porphyrins and severe, potentially mutilating skin lesions. Iron overload may be a precipitating factor (175), as this catalyzes production of activated oxygen species which can cause oxidative damage to the erythrocytes (176). Treatment is very difficult because chloroquine is ineffective (175), and venesection is not usually practical because of anemia. A recent case report described dramatic improvement in one patient during treatment with deferoxamine for iron overload (177).

Pruritus

Pruritus frequently complicates end-stage renal disease, occurring in 50% to 75% of patients (178), and a survey found that 37% of hemodialysis patients had bothersome itching, and an additional 41% had experienced this in the past (179). In two thirds of the patients who had experienced pruritus, discomfort was most severe or only occurred during or soon after dialysis. Local topical emollients and orally administered antipruritic agents were relatively ineffective, providing relief in only about 18% of patients. While somewhat less of a problem with adequate dialysis, pruritus remains a distressing problem for many patients.

The etiology of pruritus remains unclear, although various changes have been found in the skin of dialysis patients. Dermal mast cells are increased, and pruritus might result from release of histamine as a result of extracorporeal circulation (178), and ketotifen, a putative mast cell stabilizer, has been shown to relieve itching (180). Biopsies have shown elevated skin contents of calcium, magnesium and phosphorus in patients with pruritus; and following successful treatment with ultraviolet B (UVB), the skin phosphorus level was reduced to values comparable with nonpruritic uremic patients, suggesting increased divalent ion content precipitating microdeposits of calcium or magnesium phosphate in the skin may be responsible for pruritus (181). Microangiopathy has also been described in skin from ure-

mic and dialysis patients, changes which regressed following transplantation (182), and pruritus associated with hypercalcemia and secondary hyperparathyroidism shows a dramatic response to subtotal parathyroidectomy (183).

In a double-blind study, 100 mg (427 mmol) of lidocaine intravenously relieved pruritus completely in some patients and had a marked effect in others (184). Unfortunately, relief lasted only for one day following infusion, pruritus always recurring by the next day. Blood levels of lidocaine achieved were no greater than those used in treating cardiac arrhythmias; and if the drug was given at a rate no greater than 7 mg (13 mmol/min), no adverse effects were noted other than occasional episodes of hypotension. In patients with chronic renal failure, lidocaine has a normal plasma half-life, suggesting that persistence of relief into the day after administration is due either to a metabolite normally excreted by the kidney being active as an antipruritic agent, or lidocaine is acting in a kinetic compartment from which the drug has a very slow rate of egress.

Administration of the nonabsorbable anion-exchange resin, cholestyramine, has also met with some success in the treatment of uremic pruritus, 5 g twice daily in juice producing partial relief in most patients in a randomized, four-week, double-blind study (185). Cholestyramine has the ability to bind organic acids, which may be a clue to a chemical cause for pruritus. It also relieves the itching of obstructive jaundice, possibly by binding bile acids, and reduces the itching of polycythemia vera. However, another study failed to show relief of uremic pruritus by cholestyramine (186), and this drug may induce or aggravate metabolic acidosis (187) and is very difficult to present in a palatable form.

Relief of uremic pruritus with oral charcoal, 6 g daily, has been reported in an eight-week double-blind cross-over study (188). Charcoal is presumed to act as a sorbent of numerous organic and inorganic compounds. Heparin infusion has also been described as relieving pruritus (189), as has reduction of the dialysate magnesium concentration to 2.0 mmol/l (0.48 mg/dl) and consequent lowering of the predialysis serum magnesium concentration (190). Modified acupuncture technique using electrical needle stimulation has also been shown to provide relief in a controlled but not blinded study (191).

In 1977 relief of uremic pruritus with the use of phototherapy was reported (192), and sunburn-spectrum ultraviolet (UVB) phototherapy using slightly below-minimum erythemal doses of ultraviolet B radiation has been shown to be beneficial (193). When patients were treated by applying UVB phototherapy to one-half of the body and placebo phototherapy to the other half, there was generalized improvement of itching without localization of benefit to the treated side, suggesting a systemic effect of UVB phototherapy. Remissions of up to several months were obtained, and a more rapid response occurred with more intensive schedules of treatment and with a second course of phototherapy (194). Possible explanations for the response to UVB phototherapy include inactivation of circulating substance(s) present in uremia and responsible for pruritus, a photoproduct with a long half-life may relieve pruritus without directly affecting the cause, or an effect of the reduction of skin phosphorus to levels comparable to those in nonpruritic uremic patients and healthy volunteers (181). Ultraviolet A (UVA) light also was reported to relieve pruritus in dialysis patients (195), but a placebo-controlled trial failed to confirm this (196).

As is usual in medicine, the wide range of measures available to treat uremic pruritus suggests that none is universally effective, and that a better understanding of the cause of itching is required. Meanwhile, general measures should not be neglected, including the use of antihistamines, tranquilizers, and sedatives (197), and the wearing of light clothing and few bedclothes. Tepid baths or showers may help the patient who has difficulty in sleeping due to itching, and may give sufficient though temporary relief to allow sleep. Cooling of the skin can be achieved by application of a lotion such as calamine, but local anesthetic or antihistamine creams should be avoided bacause of the risk of allergic contact sensitization.

Muscle cramps

Painful muscle cramps are common in nondialyzed and dialyzed uremic patients, both during and between dialyses, particularly in the elderly. While not life-threatening, cramps may interfere seriously with patient well-being and rehabilitation.

Cramps occur in more than 20% of hemodialysis patients (198) and appear to relate to acute contraction of plasma and extracellular volumes due to rapid fluid removal or hypoosmolality. They tend to occur late during dialysis, more frequently in the legs, typically last about 10 min, taking 3 min to develop and 7 min to dissipate fully, and more frequent in patients who manifest a high degree of anxiety (199). In patients who develop muscle cramps, tonic electromyogram (EMG) activity increases during the latter part of dialysis, and this appears to be a useful predictor of the onset of cramps during dialysis (200).

Quinine sulfate has been used empirically for relief of cramps for many years. Its effectiveness has been confirmed by a double-blind study which showed that 320 mg (1.0 mmol) of quinine sulfate prior to each dialysis was effective in reducing both the frequency and severity of cramps, without hematologic, auditory, or visual side effects (201).

Relief or reduction in the frequency of cramps also has been described with use of a higher dialysis fluid sodium concentration (140 mmol/l) (12), administration of sodium chloride by mouth (202), or with a bolus intravenous injection of hypertonic dextrose or hypertonic saline. Injection of 20 ml of hypertonic (17.5%) (3 mmol/l) saline (203), a solution that must be appropriately labeled to avoid inadvertent use, reduces the effect of ultrafiltration in normalizing the patient's extracellular volume, and consequently hypertonic dextrose may be preferable. Double-blind studies have shown significant relief without complications using hypertonic (50%) dextrose injected intravenously (204, 205). This results in an acute rise of the plasma glucose level

which returns to normal within one hour. A double-blind study comparing hypertonic saline, hypertonic dextrose, and 5% dextrose showed no difference between hypertonic dextrose and hypertonic saline, although both were superior to 5% dextrose (206).

The frequency of muscle cramps during dialysis is also related to the dialysis technique, is influenced by the dialysate sodium concentration, and is less frequent with bicarbonate dialysis (207) and with sequential ultrafiltration (208). More recently, development of such techniques as hemofiltration (209) and automatic ultrafiltration control has also reduced the frequency of muscle cramps during treatment.

Priapism

Priapism has been reported to occur at some time in as many as 2.5% of male hemodialysis patients between the ages of 14 and 42 (210, 211). However, a recent multicenter survey in the United States found the considerably lower occurrence rate of only 1 in 196 patients. This difference might relate to the duration of dialysis and associated heparinization which was 6 to 8 h in the 1970's, but at the time of the more recent study was only 3.5 to 5.5 h (212). In most cases, priapism develops during or within a few hours after dialysis, suggesting a cause-and-effect relationship. It is not generally related to sexual activity, and patients may be sleeping when awakened by a painful erection. Erections are known to occur during rapid-eye-movement sleep, irrespective of dream content, and this may be a precipitating factor.

Most incidents of priapism develop while heparinized on hemodialysis, do not occur with peritoneal dialysis, and are not associated with generalized clotting problems or long-term anticoagulation. Priapism is known to occur in patients heparinized following myocardial infarction, pulmonary embolism, and thrombophlebitis (213), and heparin may increase blood viscosity by causing precipitation of fibrin degradation products, enhance thrombin generation, and cause abnormal spontaneous platelet aggregation. A relatively high hematocrit and hypovolemia as a result of ultrafiltration increase blood viscosity and may be precipitating factors, and heparinized blood clots more readily in the presence of acidosis. Androgen therapy has also been thought important in the genesis of priapism in some patients (214), and androgens should be discontinued in male patients with hematocrits greater than 25 so as to avoid an increased frequency of erections. The future availability of recombinant human erythropoietin should eliminate the need for androgens in dialysis patients.

The prognosis for return of sexual function after priapism is very poor in dialysis patients, despite venous bypass surgery. Following such surgery, only a small number of patients retain the capacity to sustain erection. Other treatments used have included spinal anesthesia and a variety of drugs such as phenothiazines, atropine, and Ancrod. The development of safe and effective penile prostheses have made these the most effective treatment for impotence following priapism.

Membrane biocomptability

Transient and marked leukopenia during the first 30 min of hemodialysis, recognized for many years (215), is associated with transient sequestration of neutrophils in the dialyzer and in the pulmonary capillary bed and the release of free radicals (216). The intitiating mechanism is activation of complement through contact of blood with the dialysis membrane, and this is responsible for increased margination and sequestration of neutrophils in the pulmonary capillaries (217). Trapping of microaggregates of leukocytes leads to hypoxia, and free radicals may also play a role in this (216). White cell studies and pulmonary function tests in patients before, during, and after hemodialysis have shown significant leukopenia and a fall in CO diffusing capacity within 15 min of the start of hemodialysis, and development of hypoxia within 30 min. The white cell count returns to baseline within 1 h, but pO_2 and CO diffusing capacity remain low throughout dialysis, and the level of these is directly related to the initial fall in white cell count (218). This persistence of hypoxia, together with the fact that hypoxia can also occur with dialyzers that do not cause leukopenia (218) has led to considerable investigation of the biocompatibility of various membranes in recent years.

Blood-membrane interactions include complement activation, activation of the coagulation and kallikrein pathways (219), prostaglandin activation (220), activation of monocytes leading to the release of interleukin-1 (221), platelet interactions (133), and absorption of various substances on the membranes (222).

Anaphylactic reactions

An anaphylactic reaction occurring at the start of dialysis is a rare but serious complication of hemodialysis, occurring in 4 of every 100,000 dialyses(45). This appears to be the result of hypersensitivity to ethylene oxide used in sterilizing the dialyzer (223), and antibodies to ethylene oxide have been found in some dialysis patients. The incidence of such antibodies is higher with hemodialysis than in peritoneal dialysis patients (224), and the incidence of hypersensitivity reactions is lower in patients using dialyzers not sterilized with ethylene oxide. The potting compound in the dialyzer may trap ethylene oxide and release this into the circulation at the start of dialysis (225), where it combines with proteins to form a hapten which binds to basophils and mast cells with release of histamine and other vasoactive compounds. This causes acute bronchoconstriction, vasodilatation, and the symptoms of anaphylaxis.

First-use syndrome

Much more common than an anaphylactic reaction is the first-use syndrome which occurs shortly after starting dialysis with a new dialyzer, and results in acute discomfort, with pruritus, back pain, hypotension, and hypoxia. This occurs on first use of a dialyzer with a cuprophane or other cellulosic membrane, but does not occur with synthetic membranes

such as polyacrylonitrile. Symptoms decrease or disappear with reuse of cellulosic dialyzers. The syndrome is due to activation of the complement pathway by the membrane, and patients who are more likely to suffer from the first-use syndrome activate complement more vigorously and more quickly than other patients (48).

Usually these reactions are mild and self-limiting, although they may require the use of analgesics, antihistamines, or epinephrine (226). Adequate rinsing of new dialyzers with saline should eliminate this problem.

Postdialysis syndrome

Many patients experience feelings of fatigue and lack of energy immediately following dialysis, and it has been suggested that interleukin-1, synthesized by activated monocytes, may account for these symptoms. This remains to be proven.

Dialyzer reuse and morbidity

Chest and back pain occur with dialysis from time to time, and a double-blind crossover study has shown this is particularly associated with the use of a new dialyzer with a cuprophane membrane (227). A decreased frequency of symptoms has been shown with reused dialyzers and with dialyzers with polyacrylonitrile membranes (228, 229). Despite frequently expressed patient concerns about the safety of dialyzer reuse, there seem to be theoretical reasons for this to be beneficial, and patients using reused dialyzers have fewer dialysis-related days of hospitalization than do patients who do not reuse (230). A recent 5-year study in 4,000 patients of the variables associated with mortality found dialyzer reuse to be associated with a lower death rate (231).

Joint and tendon abnormalities associated with hemodialysis

Hemodialysis patients have long been known to be prone to acute episodes of arthritis or periarthritis, and the appearance of soft tissue calcification in periarticular tissues. More recently, the carpal tunnel syndrome and periarticular pains, particularly around the shoulder and hip girdles in patients on dialysis for many years, have been shown to be associated with beta-2 microglobulin production and the deposition of amyloid in bones, joints, tendons and periarticular structures. These problems are discussed further in Chapter 31.

Spontaneous tendon rupture

Spontaneous tendon rupture in dialysis patients usually affects the quadriceps and the hand. The cause is unclear. Chronic acidosis may lead to degeneration of tendons with changes in their tensile characteristics (232), but pathologic changes at the tendo-osseous junction associated with secondary hyperparathyroidism may be more important (233). The latter view is supported by the association of quadriceps tendon rupture with X-ray evidence of hyperparathyroidism (234). Tendon rupture occurs after years on dialysis, and in young patients. Finger tendon ruptures usually are ignored by the patient because they are not significantly disabling. Quadriceps tendon rupture is treated by immobilization, physiotherapy, and frequently by parathyroidectomy.

Uremic bursitis

In uremic patients, bursitis with or without effusion, is a manifestation of uremic polyserositis. Most commonly, this presents as an olecranon bursal effusion resulting from trauma, and associated with increased pressure in bursal vessels related to an arteriovenous fistula, together with the anticoagulant effect of heparin. In one report, as many as 6% of hemodialysis patients developed bursitis (235), and all had an arteriovenous fistula and used a cushion under their elbow for support. Bursitis usually occurred over the olecranon on the side of the vascular access, although effusions involving the trochanteric and Achilles bursae also occurred. Treatment consists of aspiration and injection of nonabsorbable steroids. Although aspiration usually is sterile, septic bursitis may also occur.

Septic arthritis

Septic arthritis is a much more common complication in dialysis patients than in the general population (236). Because joint pain is not uncommon in dialysis patients, the possibility of septic arthritis always should be borne in mind. The most common causative organism is a *Staphylococcus,* and the same microorganism is often cultured simultaneously from joint, blood, and/or arteriovenous fistula, suggesting hematogenous spread. Unlike nonuremic septic arthritis, in addition to the usual joints such as knee, elbow, hip and shoulder, other joints involved in dialysis patients include the sternoclavicular, sacroiliac, and acromioclavicular joint, and the arthritis is more frequently multiarticular. Early diagnosis is mandatory in order to minimize the risk of disabling joint disease. Unfortunately, the diagnosis is not always easy because other types of acute arthritis are frequent in dialysis patients, but acute attacks of pseudogout are not usually associated with other systemic complaints. Consequently, septic arthritis should always be considered when a dialysis patient develops arthritis, expecially if associated with fever or infection elsewhere, and an infectious cause must always be excluded by joint aspiration. Once septic arthritis is identified, prompt and early treatment is essential to prevent crippling joint damage.

Tuberculous arthritis

Extrapulmonary tuberculosis is more common in dialysis patients than in the general population (237) and has recently been reported as one cause of acute arthritis in dialysis patients (238). Because of its resemblance to acute septic arthritis, joint aspiration and synovial fluid culture should be considered in any dialysis patient presenting with monoarthritis.

Hearing loss

Hearing loss associated with dialysis may involve both vestibular and cochlear mechanisms and may be due to bleeding in the inner ear space as a consequence of heparinization or result from cellular injury in the hair cells of the cochlea as a result of edema (239). However, the frequent use of ototoxic drugs in dialysis patients making hearing loss difficult to evaluate, and there are contradictory reports as to whether or not most patients with chronic renal failure show evidence of hearing loss on audiometric examination (240, 241).

Visual loss

Occasionally, dialysis patients develop acute visual loss (uremic amaurosis) which can occur rapidly over minutes to hours. Loss of vision is complete, and pupillary reactions and fundoscopic examination are normal. Recovery usually occurs within 2 weeks (242).

Anterior ischemic optic neuropathy resulting in a sudden painless loss of vision has recently been reported in association with hemodialysis-associated hypotension. Presentation is with sudden painless loss of vision during an episode of hypotension on dialysis (243).

Hepatic friction rub

A hepatic friction rub is an auscultatory finding most commonly associated with malignant neoplasm of the liver, but also described in two hemodialysis patients (244). Presumably, such a rub is the equivalent of a uremic pericardial or pleural friction rub, and theoretically should disappear with increased dialysis, although this did not occur.

Mesenteric ischemia

Acute mesenteric ischemia occurs in dialysis patients, generally in association with severe episodes of hypotension and hypovolemia during dialysis. This may or may not result in bowel infarction. Characteristically, there is leukocytosis, and occult blood can be demonstrated in the stools. The diagnosis is suggested by the development of nonspecific abdominal symptoms and leukocytosis following hypotension during dialysis (245).

Bowel infarction

Nonocclusive bowel infarction has been described as a complication occurring in dialysis patients after a large weight loss secondary to vomiting, diarrhea, or ultrafiltration. Frequent and severe hypotension during dialysis occurred more commonly in patients who developed this problem. Death occurred in 9 of 12 patients (246).

Recurrent abdominal pain associated with digoxin

Severe recurrent central abdominal pain, brought on by exertion, occurring shortly after dialysis and especially after ultrafiltration, has been described in an elderly male dialysis patient (247). This was thought to be due to intestinal angina resulting from intestinal ischemia from reduced cardiac output or local vasoconstriction following intravascular volume depletion. Symptoms were relieved by discontinuing digoxin, probably because it is a mesenteric vasoconstrictor. This syndrome may occur in dialysis patients with calcified aortas who undergo rapid ultrafiltration and are taking digoxin. It should be considered as a possible cause of obscure abdominal pain in such patients.

Cecal necrosis

Necrosis of the cecum may be associated with reduced blood flow. Spontaneous perforation of the left side of the colon and cecum has been reported in dialysis patients and those with uremia and was considered secondary to distention from constipation. However, it has been suggested the cecum is more susceptible to ischemia than the remainder of the colon, and maximal distention develops at this point which, in association with impaired blood flow resulting from hypotension, may cause necrosis. A diagnosis of cecal necrosis and perforation should be considered in any dialysis patient who develops acute abdominal symptoms. Early exploration may be necessary (248).

Leachables

Because dialyzer tubing sets are made from plastic, there is always the likelihood of leaching polyvinyl chloride or plasticizer such as di-(2-ethylhexyl) phthalate (DEHP) into the blood (249). The latter probably is not very toxic, although it may affect various enzyme systems (250), but de-esterification produces the biologically active compounds mono-(2-ethylhexyl) phthalate and phthalic acid (251). Polyvinyl chloride has been associated with recurrent episodes of cutaneous necrotizing dermatitis in a dialysis patient (252), probably resulting from an immunologic process. The association between these and other chemicals leached from plastics and the occurrence of such effects as eosinophilia and itching during dialysis has not been clearly established, but substantial exposure does occur in dialysis patients (251). The occasional occurrence of immediate reactions resembling IgE-mediated anaphylaxis in dialysis patients has also been recorded and related to development of antibodies to phthalic anhydride, diphenylmethane diisocyanate (253), and other isocyanates derived from potting compounds (254).

COMMENT

Acute complications occurring during hemodialysis range from the trivial and merely transient to the catastrophic and fatal. Nevertheless, the great majority of dialyses are uneventful, and each year more than 30 million hemodialyses are performed around the world, many of these in patients'

homes. Because most dialyses are uneventful, it is important that nursing and technical staff, as well as patients, learn of the acute complications of hemodialysis, their recognition, and the appropriate responses. Patient well-being, whether dialyzing in a center or at home, demands confidence in the treatment and its safety. This can only come from the example of staff who are themselves familiar with the acute complications of hemodialysis and are experienced in their management.

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