Complications during Hemodialysis

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Introduction

Hemodialysis is the most successful and most commonly used form of organ replacement therapy. Its success and worldwide use attest to its safety. Advances in dialysis technology (both in machinery and disposable parts) contribute significantly to the safety of this therapeutic modality. Awareness of the potential complications of the procedure should facilitate preventive and remedial interventions. While many of the acute complications of hemodialysis are not immediately life threatening, they do add to the morbidity of dialysis patients and to the overall cost of the therapy.

Cardiovascular Complications

Hypotension

Clinical Features

Intradialytic hypotension (IDH) is one of the most common complications observed during hemodialysis. Cross-sectional studies suggest that it occurs in about a third of patients. Prospective longitudinal studies placed the incidence closer to 15% of all treatments [1]. Its occurrence is closely correlated with other symptoms such as cramps, nausea and vomiting. Predisposing factors appear to be a low body mass (women in particular), advanced age and the presence of cardiovascular disease [1]. The incidence of symptomatic hypotensive episodes is particularly high in patients who have normal or low blood pressure at the initiation of dialysis and in patients who have large interdialytic weight gains [2]. The development of IDH does not seem to be influenced by the type of hemodialysis membrane used [3].

Some authors have distinguished between two types of IDH based on the temporal behavior of blood pressure [4]. In one type (gradual hypotension), blood pressure declines gradually during hemodialysis with eventual appearance of symptoms. The other type is more acute (sudden hypotension) characterized by an abrupt and sharp fall in blood pressure along with the appearance of symptoms. While some mechanistic differences have been proposed to distinguish between the 2 types [4], it is unclear at present whether these types tend to occur in distinct subsets of patients and whether separate predisposing factors can be identified.

Pathophysiology

To understand the pathogenesis, etiology, and management of IDH, a brief review of the

determinants of arterial blood pressure on dialysis follows. Mean arterial pressure (MAP) is determined by peripheral vascular resistance (PVR) and cardiac output. Cardiac output is a function of stroke volume (SV) and heart rate, and SV in turns depends upon plasma volume (PV) and myocardial contractility. During ultrafiltration and/or dialysis, reduction of PV will result in hypotension if compensatory changes in myocardial contractility, heart rate, or PVR do not occur. During conventional dialysis, the reduction in plasma osmolality (P_{osm}) favors fluid shifts from the extracellular fluid compartment (ECF) to the intracellular fluid compartment (ICF), exacerbating the volume depleting effects of dialysis. The reduction in PV with both ultrafiltration and hemodialysis also leads to an increase in plasma oncotic pressure and a decrease in capillary hydrostatic pressure. Both of these forces mobilize fluid from extravascular spaces. The degree to which PV decreases thus depends not only on the rate of ultrafiltration and ICF shifts, but also on the plasma refilling rate from intracellular and interstitial fluid (ISF) compartments.

Volume-dependent Factors

While fluid removal during hemodialysis occurs from the intravascular space, refilling from interstitial fluid is effective enough that by the end of a typical dialysis treatment there is a greater reduction in interstitial fluid volume than in plasma volume. Vascular refilling depends on the rate and degree of ultrafiltration by hemodialysis as well as on other patient-related factors such as body size, fluid status, regional blood flow distribution, plasma osmolality and plasma protein concentration [5]. Refilling takes place during ultrafiltration and continues after cessation of fluid removal. Salt and water alterations (under condition of ultrafiltration with normal-sodium or high-sodium dialysate) are restricted mostly to the ECF component of the total body water [6]. In the ECF, it is principally the ISF that buffers salt and water depletion. The ISF is therefore, the buffer zone which maintains the proper balance and relationship between vascular capacity and volume. In end-stage renal disease (ESRD), interstitial colloid osmotic pressure is reduced and transcapillary colloid osmotic gradient is raised, conditions that would favor refilling [7]. After hemodialysis, interstitial colloid osmotic pressure tends to rise indicating fluid loss, but the transcapillary gradient remains in favor of refilling [7].

The dependence of refilling on interstitial hydration would imply that overhydration is associated with better refilling. Moreover, as ultrafiltration proceeds and the interstitial volume gradually contracts, one would expect a progressive drop in refilling rate over the course of a hemodialysis session. This formulation is consonant with the observation that IDH occurs usually during the latter half of a hemodialysis run.

Maneuvers that are aimed at enhancing vascular refilling would be expected to have a salutary effect on the occurrence of vascular instability during dialysis. Sodium modeling [6, 8, 9] has been shown to be effective in this regard. Improved hemodynamic stability utilizing sodium bicarbonate dialysis may be due, in part, to a greater plasma refilling and a better preservation of plasma volume. Underestimation of postdialytic dry weight will cause interstitial dehydration and consequently a low refill capacity. Maintenance of intravascular fill such as with red blood cell transfusions in anemic subjects reduces the short-term frequency of hypotensive episodes [10].

The latter half of dialysis does not always correspond to the maximal reduction in

plasma volume. In many patients, there is usually no sharp fall in blood volume nor any change in the plasma refilling rate at or before the time that IDH takes place [11]. This observation suggests that IDH is caused by a sudden breakdown of the blood pressure support mechanism compensating for a contracted blood volume.

Vascular Tone-related Factors

During hemofiltration and sequential ultrafiltration, the patient's ability for vasoconstrictive counterregulation is better maintained than during conventional hemodialysis [12]. Hemodynamic studies have repeatedly shown that while significant reduction of cardiac output, SV, pulmonary artery pressure and PV are observed during hemodialysis, only a minimal elevation in PVR is observed [12].

Inappropriate peripheral venodilatation has been proposed as an important contributor to the development of IDH [13 – 15]. Bradley et al. [14] found that while vascular resistance in the forearm rose during dialysis with acetate and with bicarbonate (more so with the latter), the venous bed of the forearm dilated. Maeda et al. [13] in a hemodynamic study found a sharp drop in cardiac output during IDH, along with concomitant sudden drops in the mean pulmonary arterial pressure and in the mean right atrial pressure. These changes have been attributed to a reduction in venous return [15]. Since there was no recognizable alteration in blood volume with the sharp fall in blood pressure, this curtailment in venous return is believed to be caused by a relocation of circulating blood, possibly associated with a sudden decrease in venous tone [13].

Converse et al. [16] likened the development of sudden hypotension during hemodialysis to that encountered in hemorrhage-induced hypovolemia. The latter can trigger a sudden fall in sympathetic activity resulting in bradycardia and vasodilatation. A similar type of vasodepressor reaction developing during dialysis would exacerbate the volume-dependent decline in blood pressure. Furthermore, Converse et al. compared the hemodynamic and sympathetic nerve activity (using intraneural microelectrodes for measurement) responses during hemodialysis in patients with and in those without a history of IDH. While progressive rises in vascular resistance and sympathetic activity were observed in the hypotension-resistant patients, in the hypotension-prone patients, however, the precipitous fall in blood pressure was accompanied by reductions in sympathetic activity, PVR, and heart rate as well as symptoms of vasodepressor syncope. These findings indicate that in some hemodialysis patients, hemodialysis-induced hypotension is not caused by a chronic uremic impairment in arterial or cardiopulmonary baroreflexes but rather by an acute, paradoxical withdrawal of sympathetic vasoconstrictor drive. Such a withdrawal often engenders a vasodepressor syncope [16].

Autonomic Neuropathy

Abnormalities of autonomic function have been observed in patients with chronic renal failure (CRF) both before and after initiation of maintenance dialytic therapy. The cold pressor test, response to sudden loud noise and mental arithmetic maneuvers were normal in non-dialyzed patients with CRF suggesting an intact efferent sympathetic pathway [17]. Expiration/inspiration ratio, lying/standing ratio, Valsalva ratio and the baroreceptor sensitivity slope were significantly abnormal in nondialyzed patients. These results indicate a defective parasympathetic pathway and a depressed baroreceptor sensitivity [17]. The heart rate response to

standing and the baroreceptor sensitivity are significantly lower in patients who develop IDH [17]. Similarly, Hebert et al. [18] found that day/night blood pressure variations were significantly reduced in patients with CRF when compared with a control population. Hemodialysis patients had a 'square wave' response to the Valsalva maneuver. In this group of patients, the IDH was not due to left ventricular dysfunction, but to a failure of the baroreceptor response to volume depletion during hemodialysis. Lilley et al. [19] have suggested that IDH may result from a lesion in the baroreceptors, cardiopulmonary receptors, or visceral afferent nerves.

Role of Dialysate

IDH is more common during acetate dialysis compared to bicarbonate dialysis, particularly in elderly subjects [20]. This phenomenon has been attributed to a slower metabolism of acetate as reflected in lower post-dialysis plasma bicarbonate concentrations [20]. Hyperacetatemia results in a decrease in preload, a finding compatible with the venodilatatory effect of acetate [21]. Indeed, Bradley et al. [14] have shown that the rate of fall of blood pressure was significantly greater during dialysis using acetate compared with that using bicarbonate. In addition, acetate dialysis led to a smaller rise in PVR and a greater venodilatation.

Prevention

A variety of therapeutic measures have been used to prevent and treat IDH (Table 1). Generally, ultrafiltration rates in excess of 0.3 mL/kg/min (1.2 L/hr in a 70 kg patient) should be avoided.

Patient Factors

As at least one type of dialysis hypotension is dependent on the volume of fluid removed, it is important that the patients should strive to gain as little weight as possible between dialysis treatments. It is doubtful that this limitation in weight gain can be accomplished with restrictions of fluid intake as almost all patients present with a normal pre-dialysis serum sodium value on the day of dialysis. The underlying mechanism, therefore, appears to be related to the development of thirst as a result of sodium intake. Consequently, in order to curtail weight gain, sodium intake must be restricted. Patient education is a very time-consuming process and the return on inadequate effort is often regrettably meager. Most dialysis patients gain about 1 kg of weight daily. This must mean that the patient's sodium intake is close to 9 g of sodium chloride (154 mmol), a value approximating a normal intake in most of the developed world. Nevertheless, limiting sodium intake is the key to a successful treatment. The limitation on weight gain, however, should not lead to reduction in food intake or compromise adequate nutrition. Meticulous blood sugar control in diabetics is mandatory to avoid excessive thirst. Some patients have abnormal thirst and present with hyponatremia. Angiotensin converting enzyme (ACE) inhibitors are useful antidipsogenic agents. Patients should also be told not to eat shortly before dialysis if they are prone to hypotension to avoid the contribution of postprandial blood pressure drop [22]. It is also prudent to withhold short-acting blood pressure medications shortly before dialysis.

Dialysis Procedure

A longer dialysis session which curbs the amount of ultrafiltration per time unit may be beneficial. The use of linear or modeled ul-

Table 1. Strategies for Prevention and Management of Intradialytic Hypotension

I. Prevention

1. Patient Factors
   - Avoid excessive interdialytic weight gain (< 5% of body weight)
   - Frequent assessment of dry weight
   - Low sodium diet
   - Meticulous diabetes control
   - Avoid antihypertensive drugs prior to dialysis
   - No food on, or just prior to, dialysis
   - Reduce intake of narcotic analgesics and sedative hypnotics
   - Improve nutritional status and hypoalbuminemia if present
   - Increase hematocrit to ≥ 33% (target 33 – 36%)
   - Evaluate for silent pericardial effusion
   - Administer prophylactic oxygen, especially in elderly with cardiac and/or respiratory disease and predialysis P_aO_2 < 80 mmHg
   - Ameliorate risk factors for LVH

2. Dialysis Procedure
   - Avoid ultrafiltration rates > 1.2 L/hr (0.3 mL/kg/minute) [slower, longer dialysis]
   - Use dialysis machines with ultrafiltration controls
   - High dialysate sodium (140 – 145 mEq/L)
   - Sodium ramping programs
   - Bicarbonate dialysis (especially with high blood flow)
   - Higher dialysate calcium (3.5 mEq/L)
   - Lower dialysate temperature (34 – 35°C)
   - Sequential ultrafiltration/dialysis (occasionally necessary when high UF rates are required)

3. Pharmacologic
   - Hyperoncotic albumin (20 – 25%)
   - Midodrine (ProAmitine)
     - 2.5 – 5.0 mg 30 – 45 minutes prior to dialysis. Alternately, 2.5 md bid on dialysis days, 1.25 mg bid on non-dialysis days
   - Others: mannitol, L-DOPA, L-carnitine

II. Acute Treatment

Volume	[200 mL boluses of isotonic saline, hypertonic saline (10 mL 23%), Mannitol (50 mL 20%), Dextran 70 (100 – 500 mL 6%)]
Vasoconstrictors:	Phenylephrine, metaramine, norepinephrine, midodrine, dopamine

trafiltration using volume controllers may be of help; so may sodium modeling (Figure 1) with a higher sodium dialysate level during the early part of dialysis [23]. Sequencing dialysis with separation of ultrafiltration and hemodialysis is not uniformly successful and the logistic burden may preclude its applicability.

Dialysate Cooling

The greater cardiovascular stability encountered during isolated ultrafiltration has been related to the cooling of blood in the extracorporeal circuit by as much as 2° C [24, 25]. This observation lends support to the suggestion that lowering blood temperature

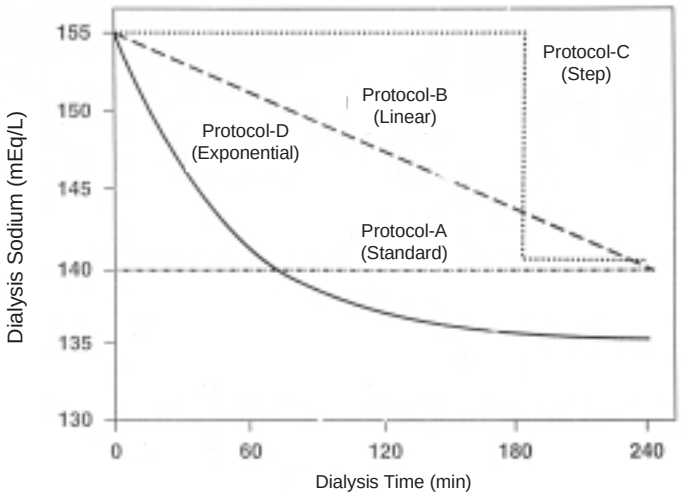

Figure 1. Graphic presentation of the 4 dialysate sodium delivery protocols: Protocol A, standard dialysis (sodium of 140 mEq/L); Protocol B, linear ramping (initial dialysate sodium of 155 mEq/L, continuous decline to 140 mEq/L by the end of dialysis); Protocol C, stepwise ramping (dialysate sodium of 155 mEq/L for the first 3 hours and 140 mEq/L for the last hour of dialysis); and Protocol D, exponential program (a smooth curve reduction of dialysate sodium from the entered percent maximum of 155 mEq/L to 135 mEq/L baseline level 2 hours before the end of dialysis). Program D result in a geometric mean dialysate sodium of 143 mEq/L, a value higher than the 140 mEq/L of standard dialysis.

during hemodialysis may afford a similar advantage [24]. Lowering dialysate temperature from 37° to 35°C significantly reduces the incidence of IDH [24, 25]. While the decline in incidence has been reported to be dramatic in short-term studies [24], the overall reduction in incidence in prospective long-term studies has been modest [25, 26]. Moreover, the possibility of having a placebo effect has also been raised [25]. Greater elevations in PVR and higher post-dialysis catecholamine levels suggest that dialysate cooling may enhance vasoconstrictor mechanisms. In one study, dialysate cooling brought about a greater incidence of cramps [26].

Modulated Dialysis

Determination of blood volume changes by continuous monitoring has allowed the development of blood volume controlled ultrafiltration. Such measures have resulted in a lower incidence of symptomatic IDH [27].

Membrane Type and PD

Large studies have found no effect of membrane type on blood pressure values during dialysis [3, 28, 29]. Should a patient have excessive hypotension, dialytic therapy should be switched to PD.

Pharmacological Manipulation

Hyperoncotic albumin 20 – 25% may prevent hypotension and allow more ultrafiltration to take place. If given, albumin should be infused rapidly during the first 15 – 30 minutes of dialysis to promote mobilization of any edematous fluid that may be present. The excessive fluid can then be removed by ul-

trafiltration. Nasal oxygen has also enabled some patients to maintain blood pressure; so have mannitol infusions. These infusions, however, cannot be given for more than 3 or 4 dialyses because of the problem of accumulation.

Miscellaneous Treatment

Elevating the legs or using compressive bandages may facilitate mobilization of the edema and allow more ultrafiltration to proceed with less blood pressure problems. Similarly, raising the hematocrit (HCT) by transfusions or by erythropoietin (rHu-EPO) therapy has curtailed the incidence of IDH in some patients. It is also important to provide patients with appropriate stimulation since simply the boredom of lying and waiting may worsen hypotensive episodes.

Acute Treatment

Volume Administration

The management of IDH has relied on volume expansion irrespective of the underlying mechanism in each particular patient. Volume expansion has frequently been done by infusions of normal saline, a practice that frustrates attempts to attain dry weight by increasing the fluid burden, thus necessitating greater ultrafiltration and further hypotension. As a consequence, a vicious cycle is created. The volume overload present in between dialysis sessions gives rise to hypertension that necessitates the use of antihypertensive agents. Such use aggravates the hypotension occurring during dialysis.

Hypertonic saline solutions safely and effectively treat IDH and may offer a better alternative. When a patient is given equal osmolal loads, the more concentrated solutions produced a greater increase in systolic blood pressure. The addition of an oncotic agent such as dextran may prolong the blood pressure response [30].

Dextrans are useful plasma expanders to employ in the management of hypotension. Recent autopsy and biopsy reports [31], however, have documented the intracellular deposition of dextrans in various tissues such as lymph nodes, the heart, adrenals, the bone marrow and others. A similar problem may be encountered with mannitol as the fate of this non-metabolizable alcohol is also unknown.

Vasoconstrictors

As at least some of the pathophysiology of dialysis hypotension appears to be due to vasodilatation, simply giving the patient vasoconstrictors such as metaramine, phenylepinephrine, norepinephrine, midodrine, amezinium, vasopressin or caffeine, has been associated with better maintenance of blood pressure [32, 33].

Midodrine, a selective peripherally-acting α-receptor agonist, has been studied extensively in the treatment of neurogenic orthostatic hypotension. It elevates blood pressure by both a constrictor effect on the arterioles and venous capacitance vessels as well as through an increase in cardiac output based on a decrease in venous pooling and augmented venous return. It has minimal cardiac and central nervous system (CNS) effects, by virtue of its α1-receptor specificity and its inability to cross the blood brain barrier.

Experience with midodrine in dialysis patient is limited and only 3 studies in patients with ESRD have been published [33 – 35]. In the small number of patients studied, midodrine therapy improved blood pressure stability and clinical symptomatology. Since the active metabolite (deglymidodrine) of midodrine is renally excreted, the dose should be

reduced in dialysis patients. A dose of 2.5 – 5.0 mg administered 30 – 45 minutes prior to dialysis, seems effective. Doses of 2.5 mg twice daily on dialysis days and 1.25 mg twice daily on non-dialysis days were also found effective.The most serious adverse reaction is supine hypertension, which has been reported in 8% of patients in one study, and may require discontinuation of therapy.

Arrhythmias

Arrhythmias are frequent occurrences in patients on hemodialysis with reported incidences varying from 30 – 48% of patients [36, 37]. These abnormalities can span from supraventricular to severe ventricular arrhythmias. There is an increased frequency of occurrence clustering around dialysis time [36, 38]. Identified predisposing factors include increased left ventricular mass, advanced age, pre-existing ischemic heart disease, potassium depletion, and the duration of ESRD. IDH, which may impair coronary perfusion, acute shifts in electrolytes (particularly potassium) conduction system calcifications, and digitalis therapy are other predisposing risk factors.

Left ventricular mass is increased in the majority of dialysis patients, both normotensive and hypertensive [37], and, as in patients with normal renal function, represents a major risk factor for ventricular arrhythmias. The wide electrolytic and volume changes taking place during dialysis may create a window of vulnerability leading to serious arrhythmic consequences. The presence of pericarditis is also associated with a heightened frequency of supraventricular arrhythmias [39]. The elevation of plasma calcium concentration during hemodialysis might induce either reentry-activity or triggered-activity types of arrhythmias during treatment. Use of dialysate with a lower calcium concentration reduces the incidence of arrhythmias in certain subjects [40].

A higher frequency of ventricular arrhythmias was encountered during acetate dialysis than during bicarbonate dialysis [38]. The quicker and more regular correction of acidosis with bicarbonate dialysis and the consequent difference in ionic flows between the intra-and extracellular spaces, could account for the seemingly less arrhythmogenic effect of bicarbonate dialysis [38].

Treatment of arrhythmias during hemodialysis is much the same as in non-dialysis situations except that in ESRD the altered pharmacokinetics and protein binding of drugs should be taken into account.

Hypertensive Emergencies

Sometimes during dialysis and ultrafiltration a paradoxical hypertensive response occurs. This hypertensive response to hemodialysis may be due to exaggerated vasoconstrictor responses to fluid removal. In some patients, we have observed a dramatic rise in plasma catecholamines in parallel with the increment in blood pressure, and an abrogation of the hypertensive response with phentolamine administration. Alternatively, activation of the renin-angiotensin system as a result of volume depletion may be contributory. However, since the paradoxical hypertension has been observed both in the absence of changes in sympathetic activity and in anephric subjects, the above mechanisms cannot be claimed to occur uniformly in all subjects with the condition. The occurrence of this hypertensive response to fluid removal does not appear to be related to the dialysate calcium level. Hypertensive patients are usually instructed to withhold their antihyperten-

sive medications on the day of dialysis to avoid IDH. The persistent elevation of blood pressure at the end of dialysis may represent a rebound of antihypertensive withdrawal which should respond promptly to resumption of medications. Under conditions when the physician considers that such delays may be injurious to the patient, immediate therapy is in order. The real need for institution of urgent antihypertensive therapy has to be clearly established particularly as a delayed hypotensive response to hemodialysis may be observed. The simple resumption of the patient's established antihypertensive regiment may be sufficient in the majority of cases.

Pericarditis with Pericardial Effusion

Pericarditis in ESRD patients can be categorized into 2 varieties, namely, uremic pericarditis and dialysis pericarditis [41]. Uremic pericarditis, a manifestation of renal failure, occurs in individuals who have never received dialytic therapy and often responds to intensive dialysis, e.g. daily 4-hour dialysis runs for 2 – 3 weeks. Dialysis pericarditis, on the other hand, occurs in patients who have already been treated with maintenance dialysis for a period of time. Although most authorities believe that dialysis pericarditis is a manifestation of inadequate dialytic therapy, this form of pericarditis may not readily respond to intensive dialysis (only about 40% of patients respond [45]). Because of this peculiar characteristic, it has been suggested that this form of pericarditis might be of viral origin [42].

Patients with pericarditis often present with precordial pain, hypotension, dyspnea, fever and rapid weight gain due to fluid overload. A pericardial friction rub may be heard. A large percentage of pericarditis patients may develop pericardial effusion. Patients with significant pericardial effusion tend to be intolerant of fluid removal by ultrafiltration, presumably because a high venous pressure is required to maintain adequate cardiac filling and cardiac output. When this high venous pressure is lowered by fluid removal during ultrafiltration, reductions in venous return, cardiac output and blood pressure are the consequences. Should fluid removal by ultrafiltration be excessive for the degree of pericardial effusion, cardiac tamponade characterized by tachycardia, hypotension and a rising venous pressure may result. Death from cardiac tamponade is not uncommon. Noteworthy is the fact that in many patients suffering from cardiac tamponade, a pulsus paradoxus may not be demonstrable [43].

Since patients with pericardial effusion are prone to develop hypotension during ultrafiltration, large volumes of saline are frequently administered intravenously to combat this untoward effect. As a consequence, an already substantial state of overhydration is often aggravated.

It should be noted that the amount of fluid necessary to produce tamponade may be as little as 250 mL when the fluid accumulates quickly, or over 2 L in slowly developing effusions when the pericardial sac has had the opportunity to stretch and adapt to the increasing volume of fluid. In addition, a pericardial effusion accumulating in a previously healthy distensible pericardial sac has less hemodynamic effect than that of an effusion developing in a previously diseased, non-compliant pericardial sac. Finally, certain dialysis patients have a small amount of fluid in their pericardial sacs. These small effusions have no clinical significance [44].

Diagnosis of pericardial effusion is based on a high index of suspicion and best confirmed by echocardiography. Once the diagnosis is established, further dialysis should be

performed with a heparin-free technique to minimize the risk of developing hemopericardium. Intensive dialysis should be carried out daily for 2 – 3 weeks, using a higher dialysate potassium value than normal (e.g. 3.5mmol or so instead of 2mmol if removal of potassium by the daily dialysis is excessive), and a lower dialysate buffer base level than usual (if metabolic alkalosis develop). Should dialysis-induced hypophosphatemia appear likely, dialysate can be enriched prophylactically with phosphate salts.

In order to avoid the risks associated with intensive dialysis, and since dialysis pericarditis with effusion responds less readily to intensive dialysis, prompt surgical drainage of moderately large (e.g. 250 mL) or very large effusions has been recommended [45]. With regard to surgical drainage, we prefer the subxiphoid pericardiotomy approach utilizing local anesthesia and a large-bore drainage tube with or without the topical instillation of non-absorbable steroids [46]. Should local drainage fail, pericardiectomy or pericardial fenestration is usually required.

Pulmonary Complications

Hypoxemia

Clinical Features

Patients maintained on intermittent hemodialysis harbor a continuously changing acid-base internal environment. In the interdialytic period, the progressive accumulation of non-volatile acids leads to a compensatory hyperventilation. During dialysis, retitration of the retained acids takes place along with a gain of alkali and an abatement of the hyperventilation, only to have the acidosis recur as the acid burden progressively rises postdialysis [47]. The intradialytic period is more complex and involves changes in both oxygen and carbon dioxide levels.

Hypoxemia of variable degrees and duration occurs in the intradialytic period. In some subjects it occurs early and is of short duration, while in others it may have a late onset and be prolonged [48]. The latter pattern has been associated with a heightened release of tissue plasminogen activator (TPA) [48]. The hypoxemia is especially pronounced in patients with preexisting pulmonary abnormalities in that it may persist postdialysis. Continuous measurements of oxygen saturation reveal a drop in saturation of 1 – 4% coinciding with the observed hypoxemia [49]. The hypoxemia is usually innocuous except when severe in patients with underlying respiratory decompensation, or in subjects with partially compensated ischemic heart disease who may experience anginal episodes necessitating oxygen supplementation for prevention. There is no relationship between dialysis-induced hypoxemia and hypotension [50].

Pathophysiology

Effects of Dialysate

Most studies agree that acetate dialysis is associated with a more severe hypoxemia than bicarbonate dialysis or isolated ultrafiltration [47]. The role of dialysate composition in the genesis of hypoxemia has been elegantly illustrated by the study of Francos et al. [51]. Patients were studied with both polyacrylonitrile (PAN) and cuprophan membranes containing different priming solutions. Despite leukopenia and complement activation, hy-

poxemia did not occur during membrane contact only. After 15 minutes of subsequent acetate dialysis, significant hypoxemia occurred with both membranes. Significantly less hypoxemia was noted during bicarbonate dialysis.

While there is general agreement that carbon dioxide unloading is a primary factor in the genesis of the hypoventilation and the associated hypoxemia, the mechanisms of carbon dioxide unloading remain a subject of debate. During acetate dialysis, a significant loss of carbon dioxide and bicarbonate takes place across the dialyzer. The resultant hypocapnia has been assumed to give rise to hypoventilation and subsequent hypoxemia [52]. Another possible cause for the hypocapnia has been advanced by Oh et al. [53]. These authors suggested that the loss of carbon dioxide was too small to alter significantly carbon dioxide balance and that greater carbon dioxide consumption occurs with metabolism of the acetate acquired during dialysis.

Hypoxemia has also been observed with bicarbonate dialysis, albeit of a much milder degree. In this setting, hypoxemia has been related to the degree of alkalization induced by a high-bicarbonate bath [54]. By raising the affinity of hemoglobin for oxygen, such alkalization would reduce tissue oxygen delivery and thereby magnify the clinical effects of dialysis-induced hypoxemia [55].

Effect of Membrane

If pulmonary leukosequestration plays a role in dialysis-induced hypoxemia, then membranes with differing complement-activating potentials and varying ability to induce neutropenia would be expected to cause disparate degrees of hypoxemia in proportion to their neutropenic effects. Under conditions of acetate dialysis, however, no differences in the degree of hypoxemia have been observed between membranes [52, 56, 57]. These observations may be explained by the different time course of pulmonary leukosequestration and hypoxemia. Ross et al. [58], using indium-radiolabelled leukocytes, found similar degrees of pulmonary leuko sequestration with both acetate and bicarbonate dialyses. However, hypoxemia developed later in the course of dialysis and was seen only with acetate dialysis.

Taken together, these observations suggest that the main mechanism of dialysis-induced hypoxemia is carbon dioxide unloading with minor contributions from other mechanisms, and that difference between membranes are not clinically significant.

Musculoskeletal and Skin Complications

Muscle Cramps

Clinical Profile

Muscle cramps represent a vexing and persistent problem plaguing a significant number of patients maintained on hemodialysis. Such cramps develop repeatedly in about 25% of all hemodialysis patients [59]. While benign in its biological significance, the clinical and emotional toll of the condition can frustrate the most stoic of patients. Painful cramps, usually of the lower extremities, occur in the second half of a dialysis session and are sometimes preceded by hypotension. A delayed course is also observed and cramps can recur over several hours after the end of a dialysis run. Cramps are commonly observed in the setting of rapid ultrafiltration (even if all the

excess fluid has not yet been completely removed), or when a patient's volume status falls below the empirically determined dry weight.

Pathophysiology

There have been very few studies examining the mechanisms underlying the appearance of muscular cramps during or after hemodialysis. Since cramps take place in a setting of relative hypovolemia developing as a result of the discrepancy between the magnitude of the ultrafiltration and the vascular refilling rate, a role for volume contraction in their genesis has been entertained. This assertion is supported by the common observation that volume expansion with hypertonic solutions frequently brings relief. Electromyographic measurements in cramp-prone subjects during dialysis demonstrated a progressive rise in tonic activity during the second half of hemodialysis culminating in the paroxysm of the cramp [60].

Vasoconstrictor mechanisms activated by volume removal are plausible mediators of reduced muscle blood flow. The success of nifedipine in alleviating established cramps may be considered adjunctive evidence for a role of vasoconstrictor mechanisms [60]. Cramps, however, can continue to take place in hemodialysis patients treated with chronic calcium-channel blocker therapy. Piergies et al. [61] have shown that activation of the renin-angiotensin system has no role in the causation of skeletal muscle cramps during hemodialysis. The activation of the renin-angiotensin system was not unusually enhanced in patients with frequent cramps, nor did ACE inhibition reduce the frequency or severity of the cramps. In a follow-up study, the same investigators suggested that cramps were prone to develop during hemodialysis in patients whose sympathetic nervous system response to volume stress was partially intact since a greater ratio of tilt/recumbent norepinephrine levels was demonstrated in patients with frequent cramps than in those who cramped infrequently [62]. The role for a more marked sympathetic nervous system response to volume stress in patients who have cramps is supported by the observation that small doses of prazosin given at the beginning of a dialysis session significantly reduce the frequency of cramps when compared to administering a placebo [63]. The use of prazosin, however, was associated with an increase in the incidence of hypotension making the intervention not clinically useful.

Tissue hypoxia has been suggested as a cause for dialysis-induced cramps. Cramping, however, is not usually a feature of extremity ischemia and the relief of the pain with maneuvers that do not alter oxygen delivery, makes this hypothesis less likely. The observation that L-carnitine supplementation is associated with a reduced incidence of muscle cramps has led to the formulation of the hypothesis that uremic cramps may be due to carnitine deficiency [64]. The latter, however, causes myopathy rather than cramps, and when carnitine deficiency-related cramps develop, they usually take place during exercise and not at rest. It is clear from the above that while many of the conditions associated with cramps are known, a definitive pathophysiologic scheme relating cramping to one or several of such conditions, is at present lacking.

Management

Hypertonic Solutions

Hypertonic solutions of dextrose, mannitol, and saline are effective treatments for hemo-

dialysis-associated muscle cramps. The concern that post-dialysis retention of mannitol and saline may lead to increased thirst, interdialytic weight pain, and elevated blood pressure has not been validated. In a prospective, randomized, double blind crossover study the safety and efficacy of the three solutions have been found to be equivalent [65]. Cramps can be treated with 50 mL (126 mOsm) 50% dextrose water, 100 mL (138 mOsm) 25% mannitol, and 10 – 15 mL (126 mOsm) 23.5% saline. Saline solutions of lower concentrations can also be used. Mild postdialysis hyperglycemia and hypernatremia during administration of dextrose and saline, respectively, are the only significant laboratory abnormalities observed [65].

Drug Therapy

Both quinine (325 mg orally at bedtime) and vitamin E (400 IU orally at bedtime) are effective in reducing the incidence and severity of leg cramps in hemodialysis patients. The effect of these drugs is observed early (within 2 weeks of therapy) and has been found to be maintained in short-term studies (up to 2 months) [66]. The two drugs have similar efficacy, but it is not known whether their effects are additive or whether subjects unresponsive to one agent would respond to the other. Quinine reduces the excitability of the motor endplate to nerve stimulation and enhances the muscle refractory period. The drug is cleared primarily by the liver and toxicities, while serious, are very rare with the usually prescribed dosages [60]. Variability in response among patients may be related to the drug's variable bioavailability. There is anecdotal evidence that administration of chloroquine phosphate (a drug effective in alleviating ordinary cramps) may reduce the frequency of cramps during hemodialysis [67], the side effects of the drug need to be considered before chronic use.

L-Carnitine Supplementation

Several studies have suggested that correction of the carnitine deficiency of uremia may have a salutary effect on the musculoskeletal symptoms associated with hemodialysis. A double-blind, placebo-controlled, and randomized study in a large sample of long-term hemodialysis patients, showed a decrease in the incidence in intradialytic cramps with L-carnitine supplementation given intravenously at the end of a dialysis session. This improvement was observed in association with a reduction in the incidence in intradialytic hypotension, which frequently accompanies cramping, and improvement in muscle mass and several biochemical parameters [64].

Modulated Dialysis

The frequent association of hypotensive episode and the development of cramps has encouraged the examination of the effects of maneuvers aimed at alleviating hypotension on the incidence of cramps. Sodium modeling and blood volume-controlled ultrafiltration have reduced the incidence of hypotension and cramps in parallel [27].

Acute Allergic Reactions

Clinical Features

Allergic reactions occurring immediately after the initiation of dialysis using new dialyzers (also known as the 'first-use syndrome') consist of a constellation of many of the following symptoms: burning retrosternal

pain, burning sensation along the arteriovenous fistula, sensation of diffuse heat, cold perspiration, urticaria, pruritus, periorbital and facial edema, flushing, laryngeal stridor, bronchial hypersecretion, bronchospasm, dyspnea, hypotension, bradycardia, and loss of consciousness. Death can occur [68].

Pathophysiology

Sterilant-related

Acute allergic reactions occurring when new dialyzers were used, were claimed to be due to cuprophan, but subsequently were linked to the sterilant ethylene oxide. Such reactions were more common with the use of hollow-fiber dialyzers than with the use of parallel plate and coil dialyzers [69].

Ethylene oxide (ETO) has been clearly implicated in the causation of a majority of cases of acute anaphylactic reactions to new dialyzers [70, 71]. The higher incidence of the first-use syndrome in the case of hollow-fiber dialyzers is believed to be related to the universal presence of the polyurethane potting material which functions as a reservoir for ETO. Removal of ETO from dialyzers is directly related to the volume of rinse, the temperature of the rinsing solution, and the duration of storage of the dialyzers prior to use. Priming solutions that have remained within the blood compartment of a dialyzer for a substantial length of time should be discarded and not be given to the patient. This is because ETO can diffuse from the potting material into the priming solution to reach an inordinately high level.

Specific ETO-related IgE antibodies are found in patients with hypersensitivity reactions to the sterilant [70, 71, 73, 74]. IgG antibodies, in contrast, are demonstrated in many hemodialysis patients who have never suffered from any hypersensitivity reactions. The presence of these antibodies denotes mere exposure [72]. Both cutaneous testing and enzyme-linked immunosorbent assay (ELISA) testing for assessing reactivity to ETO-human serum albumin can be carried out in hemodialysis patients with anaphylactic reactions. Cutaneous testing, while clinically simpler, offers no real advantage as the sensitivity, specificity, and negative predictive values of the 2 methods are similar [74].

In the majority of patients with anaphylaxis to dialysis, ETO has been identified as the etiologic agent. However, in a significant minority of patients sustaining such reactions, the responsible agent remains unidentified. Complement activation has been proposed as a mechanisms in some of the subjects with no identifiable antigen(s). No correlations between the time of onset of symptoms (if any symptoms were present) and the degree of complement activation were detected, however, among patients suffering from severe, moderate, or no hypersensitivity reactions [71], suggesting that complement activation plays no role in these reactions. Moreover, as mentioned above, hollow-fiber, parallel-plate and coil dialyzers of comparable surface areas activate complement to a similar extent [75]. If the complement activation were responsible for the dialyzer reactions, why should only hollow-fiber dialyzers be associated with a high incidence of the ‘first-use syndrome’? Anaphylaxis to formaldehyde during reuse has been reported [76]. In a few unique cases, allergic reactions continued to occur irrespective of modifications in dialyzer choice, in sterilization methods and in prophylactic measures [77]. Symptoms reminiscent of the first-use reactions have also been encountered during reuse. However, it has been suggested that the development of such reactions is not related to the type of disinfectant product the

reprocessing method (manual or automated), or the type of dialysate (bicarbonate, acetate, or both) [78]. Finally, anaphylactoid reactions have also been reported in patients who were dialyzed with reused dialyzers and receiving ACE inhibitors at the same time [79].

Membrane-related

Recently, however, acute allergic reactions have been reported when AN69 (a type of polyacrylonitrile membrane) dialyzers were used in patients taking ACE inhibitors [80, 81]. There is convincing evidence that this reaction is related to an early and vigorous production of bradykinin induced by the contact of blood (via the contact pathway) with the negatively-charged AN69 membrane. In the setting of using the AN69 membrane along with an ACE inhibitor, bradykinin accumulates in the blood because ACE inhibitors block the action of the enzyme kininase II which is responsible for the destruction of bradykinin.

Pruritus

Clinical Features

The incidence of pruritus is high in dialysis patients. At present, at least 50% of patients maintained on dialysis suffer from itching [82, 85]. The prevalence of pruritus seems to rise with the duration of dialysis. This finding has led to the postulate that either the dialytic procedure contributes to the development of itching, or, the longer survival made possible by dialysis and the failure of dialysis to correct the uremic state fully, combine to allow pruritogenic mechanisms to become more manifest.

Continuous monitoring studies [83] in hemodialysis patients suffering from pruritus reveal that itching peaks at night, occurs relatively more often during dialysis treatment and the least often on the day following dialysis. These observations are consistent with the notion that the condition is improved by dialysis, suggesting that the accumulation of pruritogenic substances is of major importance in the pathogenesis of uremic pruritus. Contrary to this postulate, there have been reports [84] of pruritus occurring mostly during or soon after hemodialysis in some 25% of patients, and becoming more severe during dialysis in an additional 40% of subjects. This disparity in clinical behavior highlights an underlying heterogeneity in the clinical manifestations and in the pathophysiology of the disorder.

Pathophysiology

Although subjected to intense study, the mechanism(s) underlying pruritus in subjects treated with renal replacement therapy continues to elude a unifying formulation. Several mechanisms have been proposed that may be responsible, singly or in combination, for the development of this condition. It is clear, however, from the variance in the literature that a great deal of individual variations may be present and that a search for major contributory factors should be individualized. While uremic subjects are not immune to the myriad of conditions that induce pruritus in the general population, the following discussion is restricted to the pathophysiology of the itching that is peculiar to the uremic state.

Dryness or xerosis has been investigated as a possible cause of uremic pruritus. In xerosis, the stratum corneum epidermidis becomes devoid of water. Being very dry, the most super-

ficial layer functions like a foreign body. Scratching removes this superficial layer and relieves itching. Evidence for and against this mechanism has been advanced [82].

The observation that severe pruritus disappeared 2 – 7 days after subtotal parathyroidectomy in maintenance hemodialysis patients, suggested that either parathyroid hormone (PTH) or derangements in calcium or phosphate metabolism may be responsible for the pruritus [85]. Several lines of evidence favor a role for PTH in the genesis of pruritus in uremia. Patients with pruritus have significantly higher serum concentrations of PTH than those without [83]. Moreover, reduction of PTH values by control of hyperphosphatemia or by charcoal hemoperfusion brings about a reduction in pruritus. It is noteworthy that not all uremic patients with secondary hyperparathyroidism, even when severe enough to warrant subtotal parathyroidectomy, suffer from pruritus. These observations have led to the contention that additional factors may be operative in uremic pruritus.

Histamine has been implicated to play a major role in the pathogenesis of uremic pruritus. Plasma histamine values are higher in patients with CRF compared to those in controls [86]. Since histamine and its metabolites are normally excreted in the urine, the higher concentrations of histamine may be a consequence of its retention in renal failure. Furthermore, plasma histamine values were, in a few studies, shown to be significantly higher in hemodialysis patients with pruritus than in those without [86].

As mast cells and monocytes are known to be the main source of histamine production, several studies have investigated the relationship of these cells to pruritus in uremia. In some studies, the number of mast cells was found to be raised in patients undergoing maintenance hemodialysis [87]; and, in addition, patients with pruritus were discovered to have, in their skin, many, diffusely scattered and degranulated mast cells. Consequently the high plasma level of histamine might be a result of degranulation of the mast cells and the basophils. In contrast, Mettang et al. [88] found no relationship between the level of plasma histamine, the number of skin mast cells and the extent of pruritus in uremic patients. Moreover, Cohen et al. [89] showed that the number of mast cells was the same in itching dialysis patients and in controls who happened to be living-related kidney donors. Francos et al. [90] demonstrated that ketotifen, a mast cell stabilizer, was effective in reducing itching without causing any significant change in histamine level, histaminase activity or skin histamine content. Such an observation suggests that mast cell activation, separate from histamine release, may contribute to the pruritus in uremia. It is clear from this survey of possible etiologies that a unitary etiology or mechanism for the pruritus of uremia is not discernible. It is very likely that different factors may be operative in different subjects and while some common elements may be evident, individualization of evaluation needs to be observed.

Management

Since pruritus appears to be multifactorial in its pathogenesis, several modalities of treatment have been suggested. In some patients, dialysis is enough to relieve the itching; in others, however, pruritus starts during dialysis or is even exacerbated by dialysis. Some have suggested that pruritus may be alleviated by an improvement in the dialysis prescription as judged by urea kinetic modeling. Subtotal parathyroidectomy has been found to be successful in patients with secondary hyperpa-

rathyroidism who suffered from pruritus. However, this treatment is not effective in all cases, and not all uremic patients with secondary hyperparathyroidism suffer from pruritus either.

Sun exposure is known to relieve the pruritus associated with several unrelated dermatoses and sunburn doses of ultraviolet light from artificial sources are effective in treating uremic pruritus. In an extensive literature search focusing on the most effective treatment for uremic pruritus, Tan et al. [91] found that ultraviolet B (UVB) phototherapy is the treatment of choice in moderate to severe uremic pruritus. The response occurs more rapidly in patients treated 2 – 3 times weekly than in those treated once weekly. Recurrences can come about, but usually respond to new UVB treatments. Being rare and mild, side effects mainly consist of localized sunburn. The mechanism of action of UVB is unclear. Since many patients with generalized pruritus respond to half body phototherapy, it has been suggested that UVB can inactivate a circulating pruritogenic substance or induce the formation of an antipruritic substance that relieves the pruritus. UVB irradiation might inhibit mast cell granule release or might relieve pruritus by damaging the cutaneous nerves.

Several drugs have been used in the treatment of uremic pruritus, but all have met with varying degrees of success and of failure. Topical emollients are hydrophilic compounds that hydrate the skin and form an occlusive film that reduces evaporation. These medications are helpful in alleviating pruritus caused by dryness of the stratum corneum epidermidis. Although histamine is a major itch mediator, use of antihistamines is not consistently successful.

It is likely that pruritus will continue to plague patients and their physicians, and unless more definitive and practical therapeutic regimens are discovered, the management of this condition will remain problematic.

Hemolysis

A mild degree of hemolysis manifested by the presence of detectable free hemoglobin in blood is commonly observed during dialysis. This finding, however, is of minimal clinical significance and can be attributed to a variety of factors including mechanical trauma to the red blood cells and possibly complement activation [92]. Inherent changes in the red blood cells of uremic subjects which are thought to contribute to the mild chronic hemolysis observed in uremia, may predispose to this hemolysis. These inherent changes include increased red blood cell rigidity and fragility, and reduced deformability secondary to oxidative damage [93].

Clinically significant hemolysis is observed with technical problems related to the dialysis procedure itself. Kinked blood lines, contamination of dialysis fluid with hydrogen peroxide because of inadequate rinsing of the water treatment system after disinfection, residual formaldehyde in reused dialyzers, and accidental hypochlorite infusion, have all been reported to be associated with serious life-threatening hemolysis. Clinically, the affected patients complain of malaise, nausea, headache and severe abdominal pain. Death due to hyperkalemia may also occur.

Bleeding during Dialysis

The bleeding tendency of uremia is considered to represent an acquired defect in primary hemostasis. The most common clinical mani-

festations of uremic bleeding are the least severe, and include ecchymoses, purpura, epistaxis, gingival bleeding, and bleeding from venipuncture sites. Major hemorrhages, from gastrointestinal, retroperitoneal, pericardial, or intracranial sites, seldom develop spontaneously and frequently reflect underlying pathology.

Pathophysiology

A multiplicity of defects may underlie this bleeding diathesis. A precise pathogenetic framework continues to be elusive. While defects in blood coagulation factors, alterations of the fibrinolytic system, and vascular abnormalities have been considered to be contributory, platelet dysfunction has been the most consistently described hemostatic abnormality in patients with ESRD [94]. Uremic platelets exhibit reduced adhesion to vascular subendothelium and impaired aggregation response to various stimuli such as ADP, epinephrine, collagen, and thrombin. Abnormal platelet aggregation improves after hemodialysis. Altered interaction of adhesive macromolecules such as fibrinogen and von Willebrand factor (vWf), with platelet membrane glycoproteins have been suggested to contribute to the aggregation and adhesion defects.

Uremia results in a defect in platelet adhesion to subendothelial structures, thus contributing to the increased bleeding tendency. Fibrinogen receptor function of platelets from chronic renal failure patients is impaired. Hemodialysis improves fibrinogen binding indicating removal of a uremic inhibitor by dialysis treatment. The defect is reproduced in normal platelets when they are incubated in predialysis uremic plasma, but not with postdialysis plasma. CRF patients treated with recombinant human erythropoietin (rHu-EPO) for correction of anemia show amelioration of platelet dysfunction [94].

Management

Treatment of uremic platelet dysfunction and uremic bleeding is summarized in Table 2.

Dialysis

Both peritoneal dialysis and hemodialysis can lead to correction, often only partial, of the uremic hemostatic defect. Moreover, adequacy of dialysis has been suggested to be an important factor in the improvement in bleeding tendency. Platelet fibrinogen receptor function is ameliorated after dialysis, the amelioration likely to be due to the removal of a dialyzable toxic product that accumulates in uremia [94]. Thus, adequate dialysis treatments may improve platelet aggregation and lower bleeding tendency by removing substances that interfere with fibrinogen-platelet binding and, therefore, platelet aggregation. Removal of toxic products may also improve platelet adhesion to the subendothelium. The often partial character of the response to dialysis implies that patients with high bleeding risk may require further pharmacological therapy.

Recombinant Human Erythropoietin (rHu-Epo)

The hemostatic defect of uremia improves after treatment with rHu-EPO, which transiently raises platelet counts, shortens skin bleeding time, and improves platelet aggregation. Moreover, platelets from patients receiving rHu-EPO therapy appear to be more activated during hemodialysis; such activation could pose problems in terms of dialyzer clotting and arteriovenous fistula thrombosis.

Table 2. Treatment of Uremic Platelet Dysfunction

1.	RBC transfusions Recombinant erythropoietin	Keep HCT > 30% (33 – 36%)
2.	DDAVP[a]	0.3 µgm/kg LV over 15 – 30 mins (in 50 mL saline)
3.	Cryoprecipitate[b]	10 units IV q 12 – 24 hours
4.	Conjugated estrogens[c]	0.6 mg/kg IV daily for 5 days

[a]Useful for acute bleeding before surgery; releases FVIII/vWF from vascular endothelium; onset of action < 1 hour, duration 4 – 8 hours; tachyphylaxis may develop after 1 – 2 doses.
[b]Useful for acute bleeding; risk of viral hepatitis and AIDS; rich in FVIII/vWF and fibrinogen; onset of action 1 – 4 hours, duration 24 – 36 hours.
[c]Not useful for acute bleeding; onset of action in 6 hours with progressive shortening of bleeding time over next 5 – 7 days; duration of action of about 2 weeks; mechanism of action unknown.

rHu-EPO treatment augments the number of GPllb-llla molecules found on the platelet plasma membrane [94]. Administration of rHu-EPO to uremic patients might, therefore, have an impact on thrombopoiesis in addition to erythropoiesis. Consequently, uremic patients with a high frequency of bleeding complications may benefit from appropriate rHu-EPO therapy.

Cryoprecipitate

Cryoprecipitate shortens or normalizes bleeding time in patients with renal failure. The peak effect appears several hours after infusion and persists for 12 – 24 hours. Factor VIII/von Willebrand factor complex (FVIII/vWf) has been shown to play an important role in the pathophysiology of uremic bleeding and it is this component of cryoprecipitate that is postulated to give rise to improved platelet functions in uremia. The delayed onset of action, the short duration of effect, and the risk of contracting infections may limit its application.

Desmopressin (DDAVP)

The importance of FVIII/vWf for uremic platelet dysfunction is substantiated by the fact that 1-deamino-8-D arginine vasopressin (DDAVP) which causes the release of autologous, preformed FVIII/vWf from endothelial storage sites, is effective in the treatment of the bleeding tendency present in patients with acute or chronic renal failure. Bleeding time is improved or normalized one hour after the infusion while the effect of the infusion lasts approximately 4 – 6 hours. The treatment is very well tolerated and has been said to prevent bleeding complications when given prophylactically. Von Willebrand activities rise after DDAVP therapy in the responders but not in the non responders.

Estrogen

Estrogen therapy appears to be effective in improving the bleeding tendency in uremia, although the mechanism of action is unclear. Between 2 – 5 days after beginning estrogen therapy, bleeding time improves or normal-

izes in patients with CRF. After discontinuation of the therapy, the bleeding time remains normal for 3 – 10 days. Although the duration of action compared to that of cryoprecipitate or of DDAVP is longer, the absolute magnitude of the effect on bleeding time may be less.

Seizures on Hemodialysis

The incidence of seizures in patients with ESRD is markedly increased compared to that found in the general population [95, 96]. A number of factors contribute to this increased risk (Table 3) including the neurologic effects of uremia, altered drug kinetics leading to toxicity, the effects of underlying diseases, and metabolic and hemodynamic alterations related to uremia. Dialysis-associated seizures can occur during hemodialysis or following its termination. Hypotension is a frequent cause of seizures and should be avoided and treated accordingly.

Table 3. Etiology of Dialysis-associated Seizures

- Uremic encephalopathy
- Dialysis disequilibrium syndrome
- Hypertensive encephalopathy
- Intracranial hemorrhage
  - Subdural hematoma
  - Intracerebral hemorrhage
  - Ruptured aneurysm (AV malformation in ADPKD)
- Aluminum-related encephalopathy
- Dialysance of anticonvulsant drugs
- Anoxia/ischemia
  - Hypotension
  - Cardiac arrhythmia
  - Anaphylaxis
- Drugs (e.g. penicillins)
- Alcohol or drug withdrawal
- Encephalitis/meningitis
- Vasculitis
- Primary or metastatic intracranial neoplasms
- Idiopathic epilepsy
- Metabolic disorders: hyponatremia, hypernatremia, hypoosmolality, hyperosmolality, hypocalcemia, hypoglycemia, hypomagnesmia, acid-base disturbances
- Air embolism

Uremia

The seizure activity associated with uremia or dialysis tends to be generalized and rarely focal [97]. Presence of focal seizure activity often indicates localized neurologic disease and should prompt an evaluation for presence of intracranial hemorrhage, tumor, localized infection, or other conditions. However, focal seizures may occur with a variety of metabolic disorders (e.g. hypoosmolality or hyperosmolality, hypoglycemia) and hypertensive encephalopathy in dialysis patients, in the absence of discernible lesions.

It is important to distinguish true seizures from metabolic or toxic myoclonus. The generalized convulsive movements of major motor seizures (grand mal) involve large proximal muscle groups, are usually rhythmic, bilaterally symmetric, and associated with loss of consciousness and post-ictal confusion. In contrast, uremic myoclonus is typically a multifocal, nonpatterned twitching of the muscle groups of the face and extremities with no loss of consciousness.

Recombinant Human Erythropoietin (rHu-EPO)

RHu-EPO, commonly used for treatment of renal anemia, has been reported by some to increase the incidence of seizures. These seizures are usually associated with rHu-EPO

induced new onset hypertension or exacerbation of preexisting hypertension. The risk of seizure is greatest during the first few months of therapy, when the drug dosage is usually highest, the rise in erythrocyte mass is greatest, and platelet count is increased. It should be noted, however, that most studies have failed to demonstrate a consistent relationship between changes in blood pressure and the rate of increase in the hematocrit during rHu-EPO therapy. These observations, along with demonstration of increased isolated vascular smooth muscle tone in the presence of erythropoietin in vitro, have lead to speculation that erythropoietin may have a direct effect on vascular resistance and cerebral blood flow [98, 99].

The risk of seizures during rHu-EPO therapy can probably be minimized by dosing the drug in a manner as to produce a slow, gradual rise in hematocrit. In addition, meticulous monitoring of blood pressure and prompt initiation of adjustment of antihypertensive therapy, when indicated, is essential [100]. It should be noted that several recent large series have failed to show a significant association between rHu-EPO therapy and seizure disorders [98].

Aluminum Encephalopathy

Aluminum toxicity (dialysis dementia, dialysis encephalopathy) may occur with the use of aluminum-contaminated dialysate or extended use of aluminum-containing phosphate binders [101]. Routine treatment of water supplies to maintain the dialysate aluminum concentration <10 µg/L has largely eliminated dialysate as a source of aluminum. Moreover, widespread use of calcium-containing phosphate binders has reduced long-term aluminum accumulation. Patients with aluminum toxicity typically exhibit dementia, speech disturbances, apraxia, myoclonus, facial dystonia, and sometimes seizures. In addition, other manifestations of aluminum toxicity including erythropoietin-resistant microcytic anemia, hypoplastic bone disease, hypercalcemia, and depressed PTH levels may be present [101]. Although blood aluminum concentration is usually greater than 50 µg/L in symptomatic cases, aluminum concentration does not always correlate with clinical symptoms [102].

Management

Dialysis should be stopped. Patency of airway and avoidance of aspiration are of immediate concern in the management of seizures occuring during dialysis. Hypotension should be checked, and if present, treated promptly. Blood lines should be checked for air embolism. Supplemental oxygen administration should be considered, especially in patients with underlying cardiac or pulmonary dysfunction. In patients with chronic obstructive lung disease, high concentrations of oxygen (> 24%) should be avoided to prevent hypercarbia. Blood should be sent immediately for glucose, calcium and electrolyte determinations. If hypoglycemia is suspected, dextrose 50% should be administered. If seizures persist after correction of hemodynamic and metabolic abnormalities, specific anticonvulsant therapy should be considered. Intravenous diazepam (5 – 10 mg) can be given every 5 minutes to a maximal dose of 30 mg to terminate the seizure. Phenytoin can then be given at a loading dose of 10 – 15 mg/kg by a slow IV infusion (not to exceed 50 mg/min) and with constant ECG monitoring.

When using antiepileptic drugs, knowledge of their altered pharmacokinetics in ESRD and their dialysance is essential. Phenytoin is normally 90% protein bound with a volume

of distribution (V_d) of 0.6 L/kg and a half-life ($t^{1/2}$) of 18 hours [103]. In ESRD, protein binding is decreased, V_d is increased, and its half life decreases to 8 hours. Normal therapeutic range of *total* drug is 10 – 20 mg/mL. Normally, the unbound fraction is 0.1 of total; hence the *free* (unbound fraction) drug level associated with optimal treatment is 1 – 2 µg/mL. In uremia, the unbound protein fraction can increase to 0.3 total. Consequently, in uremia a total drug concentration of 5 – 10 µg/mL is considered therapeutic and this level will lead to a therapeutic unbound fraction of 1 – 2 µg/mL. Drugs known to displace phenytoin from plasma protein binding sites include valproic acid, non-steroidal antiinflammatory agents (NSAIDs), and salicylic acid. Finally, phenytoin follows first-order kinetics. Increases in dosing should be small, and sufficient time should be allowed to achieve a new steady state. The altered protein binding and shortened half-life of phenytoin necessitates an additional adjustment in dosage schedule in uremia, namely to give phenytoin in divided dosage (TID schedule).

Prevention

To lessen the risk of seizure activity on dialysis, particularly in predisposed patients, the following measures should be observed:

- if a patient is known to be on anticonvulsant drugs, give an additional dose postdialysis if the drug is dialyzable. Anticonvulsant drugs that are not dialyzable include diphenylhydantoin and carbamazepine. Valproic acid may be partly dialyzable. Dialyzable drugs that need supplemental dose post dialysis include phenobarbital, ethosuximide, trimethadione, and paraldehyde.
- In severely hypocalcemic patients, especially in the presence of severe metabolic acidosis, consider calcium treatment even before dialysis;
- anticipate and avoid conditions associated with dialysis disequilibrium syndrome (see below); and
- drugs that may have untoward CNS effects in uremia should have careful dose adjustment. These include penicillins, cephalosporins, nitrofurantoin, isoniazide, meperidine, morphine, cimetidine, phenothiazines, haloperidol, barbiturates, benzodiazepines, antihistamines, hypoglycemic agents, methyldopa, β-adrenergic antagonists, cyproheptadine, anticoagulants, and neuromuscular blocking agents.

Dialysis Accidents

Erroneous Temperatures

Dialysate temperature, normally set at 37° C, is regulated by a thermostat, a component of the dialysate temperature monitoring system. Malfunctions of the thermostat or of the other components of the monitoring system can result in abnormal dialysate temperatures. Although a cool dialysate (e.g. 34.5° C) has been used to promote vasoconstriction to maintain an adequate blood pressure during dialysis, too low a temperature can bring about shivering and increased secretion of catecholamines.

High dialysate temperatures lead to cutaneous vasodilatation, sweating, and a sensation of warmth. For the conscious patient, overheating is often detected before a dangerous elevation in body temperature makes its appearance. If dialysate temperature is allowed to rise to 55° C or higher, massive hemolysis with resultant hyperkalemia [104] and death can take place. Delayed hemolysis has been

observed with intermediate temperatures. This delay is related to splenic trapping and peripheral destruction of the damaged erythrocytes.

Treatment for hemolysis requires the immediate cessation of dialysis, the discard of blood present in the extracorporeal circuit and the transfusion of blood in case anemia is severe. Hyperkalemia should be treated by the usual means, not the least of which is another dialysis treatment using functional equipment and potassium-poor or potassium-free dialysate.

Air Embolism

Air embolism is one of the dreaded complications of hemodialysis and the extracorporeal system is designed with redundant safeguards to avoid its occurrence. It is important, however, to maintain vigilance as human and technical failures are always possible. It can occur either as a result of the manipulation of the extracorporeal circuit, or as a complication of a temporary vascular access placement procedure. Venous air embolism, however, remains an infrequent complication. The cardiovascular, pulmonary, and central nervous systems may all be affected, with severity ranging from absence of symptoms to immediate cardiovascular collapse. Symptoms and signs attributable to air embolism can take place with small volumes of air entering the patient's circulation. While it is difficult to quantitate the amount of air in clinical settings, experimental studies suggest that the introduction of 1 mL/kg may be fatal.

The manifestations of air embolism depend on the posture of the patient and the flow of air obeys the law of gravity. In the sitting position, air will flow along the venous system to reach the central circulation and then will backflow into the cerebral venous system. The patient will transiently be aware of the sound of the air in his vessels and then will lose consciousness and develop seizures. In recumbent patients, air will reach the right atrium and the right ventricle, with the developing air-blood foam occluding the right ventricular outflow tract and the pulmonary vascular bed. Chest pain and shortness of breath appear, followed by cardiovascular collapse.

Venous air embolism can occur during the insertion, the disconnection or the removal of a central venous catheter [105]. Air embolization through a residual track after removal of a central venous catheter, particularly after long-term catheterization or repeated use of the same puncture site, is an elusive mechanism that while rare, can be recognized only if searched for carefully.

Venous air embolism induces rapid hemodynamic changes, most notably a sharp increase in central venous pressure. In addition to the obstructive element, pulmonary vasoconstriction modulated by the action of the platelet activating factor, also takes place. Pulmonary edema can set in. Entry of air into the pulmonary arterial tree causes physical obstruction of the microvasculature and leads to permeability changes, release of mediators, and injury to lung tissues. In addition to its hemodynamic consequences, air in the circulating blood activates complement in a dose-dependent fashion [106].

Air in blood vessels can be visualized by real time ultrasonography and air volume, estimated by a doppler [107]. Therapeutic interventions include mechanical measures, such as positioning, withdrawal of air from the right atrium, and means aimed at reducing bubble size. Speed in therapy is essential. The blood lines should be clamped and the patient rapidly positioned in the Trendelenburg position with the left side down. This posture reduces the movement of air to the brain and traps the air bubbles in the right ventricle. This

air trapping minimizes foaming which ordinarily takes place also mainly in the right ventricle. In this position, air may even migrate to the periphery; such air migration can be detected by the development of patchy cyanosis over the lower extremities. While migration of the air may affect distal sites, it is clearly less catastrophic than having air in the central circulation or in the cerebral vessels.

Hyperbaric oxygen therapy holds some promise in accomplishing reduction of air bubble size [108]. Even after a prolonged delay, patients with cerebral air embolism may still benefit from hyperbaric oxygen therapy. Even normobaric oxygen may be useful, particularly if mechanical ventilation is employed. Experimental studies suggest that the removal rate of air from cerebral vessels is dramatically enhanced by mechanical ventilation at partial pressure of oxygen (F_iO_2) of 1.0 [108]. The prompt application of mechanical ventilation with an F_iO_2 of 1.0 is recommended when air embolism is suspected particularly in centers where facilities for administering hyperbaric oxygen therapy are not available.

While prevention and early diagnosis represent the cornerstones of management, definitive therapy of a massive air embolus may require aspiration of the air through an appropriately located multi-orifice catheter. Throughout management, the patient should be moved as little as possible.

Dialyzer Rupture or Clotting

Dialyzer rupture is a rare event in hemodialysis. It is usually detected by an alarm which is triggered by the presence of very low concentrations of blood in the dialysate. A variety of factors predisposes to this complication; such factors include faulty construction, high venous pressures secondary to clotting or kinking of blood lines, and improper priming. While most ruptures result in the loss of only a small amount of blood and may seal spontaneously, the potential for massive blood loss requires that immediate remedial measures be taken. Septicemia is also a risk. The blood lines should be clamped, the patient disconnected from the extracorporeal circuit and the latter completely changed. Moreover, the dialysate circuit and the blood leak detector will need to be cleaned.

Dialyzer clotting is a more common event and is usually due to inadequate heparinization. This, however, cannot be the sole cause as hemodialysis without anticoagulation is readily performed with either intermittent or continuous saline rinsing. Additional factors include a high venous pressure, a low blood flow, a large amount of air in the drip chambers or in the dialyzer headers because of poor attention to proper rinsing procedures prior to starting dialysis. Furthermore, rapid connection of the patient to the extracorporeal circuit immediately after heparin administration without allowing for systemic anticoagulation to begin taking effect may be contributory.

Dialysis Disequilibrium

Clinical Features

This dialysis-induced syndrome consists of a constellation of manifestations including mental confusion or agitation, nausea, vomiting, headache, drowsiness, lassitude, confusion, muscle twitching, delirium, seizures and coma. In severe cases, there is an rise in blood pressure, pulse rate and respiratory rate. Occasionally, death can occur [109, 110]. In addition, characteristic electroencephalographic (EEG) abnormalities in the form of

high-voltage rhythmic delta waves are commonly encountered.

The syndrome is more likely to develop when the initial plasma urea level is markedly elevated and correction of the azotemia is rapid. Therefore, the syndrome is encountered mostly in the early stages of dialysis therapy when plasma urea level often is highest, but may recur even after many months of dialysis should the patient raise his protein intake. The syndrome is frequently seen toward the end of a dialysis session and usually transient, lasting for 24 hours after the termination of dialysis. A predisposing factor for the development of the syndrome is a preexisting neurologic disorder [109].

Pathophysiology

The exact pathogenetic mechanism for the dialysis disequilibrium syndrome is not fully understood at present. What is known for certain is that there is evidence of cerebral swelling. There are several theories concerning the pathogenesis of the dialysis disequilibrium syndrome, the most popular being the 'reverse urea effect' theory. In this theory, the intracellular water gain is believed to be a result of a dialysis-induced lowering of the plasma urea level in the presence of a lesser fall in intracellular urea concentration [109, 110]. This urea gradient implies the slower passage of urea out of brain tissue and the consequent transfer of water from the blood to the brain. Furthermore, the suppression of dialysis-induced EEG abnormalities by the use of a urea-enriched dialysate adds weight to the 'reverse urea effect' contention. In a similar vein, clinical manifestations associated with the dialysis disequilibrium syndrome can be ameliorated by maintaining plasma osmolality with the use of a high-sodium dialysate [111]. Recently, the concept of the 'reverse urea effect' has received additional support from the finding of an elevation in brain water and a rise in the brain-to-plasma urea ratio in azotemic rats subjected to acute hemodialysis treatments [112].

Management

The syndrome is rarely seen when a moderately elevated plasma urea nitrogen level (e.g. 29mmol (80 mg/dL)) is lowered by conventional or high-efficiency dialysis (e.g. to 15mmol (40 mg/dL)). Moreover, it is best to initiate dialysis long before azotemia becomes extreme and with current recommendations for initiation of dialysis at residual renal function levels of 10 – 15 mL/min of GFR, the syndrome should become a rarity. In the event that dialysis is required in a patient with an extremely raised plasma urea nitrogen value, an inefficient dialysis treatment can be delivered by shortening the duration of a dialysis run to 25 – 40% of the normal, by lowering dialyzer blood or dialysate flow rates, or by using a less efficient dialyzer. If no untoward effects appear, the efficacy of the subsequent daily dialysis treatments can be lengthened in a step-wise manner over the next several days until regular dialysis treatments can be safely delivered.

Prophylactic administration of osmotic agents such as glucose, mannitol, urea and sodium chloride either IV or via the dialysate route, with the aim of reducing the incidence of the dialysis disequilibrium syndrome has been recommended [111]. However, since modern dialysis machines can raise dialysate sodium levels readily, use of a high sodium dialysate may be the most convenient approach. Once the dysequilibrium syndrome sets in, treatment will be symptomatic. Seizures can be treated with intravenous diazepam, with effects lasting 30 – 60 minutes.

When compared to barbiturates, diazepam causes less respiratory depression. Short-acting barbiturates can also be given but are more dangerous since they can cause more respiratory depression. It should be noted that even though diazepam and some related drugs are metabolized by the liver, great care should be exercised in their use since many renal failure patients cannot tolerate the dosages ordinarily recommended for patients with normal liver and renal functions.

Electrolyte Abnormalities

Metabolic Alkalosis

Metabolic alkalosis as a consequence of intensive dialysis (e.g. daily dialysis) using a dialysate with a high level of buffer base (e.g. 40mmol), is rarely described. What is more often encountered, however, is metabolic alkalosis developing as a complication of hemodialysis employing sodium citrate as a means of regional anticoagulation [113]. The infused citrate is converted into bicarbonate by the body. In some regional anticoagulation regimens, citrate concentrations of 7mmol have been found in afferent blood, resulting in severe metabolic alkalosis. Prevention requires employing as small an amount of citrate as possible. Should reduction in citrate administration be impossible, the level of buffer base in the dialysate can be curtailed. Severe metabolic alkalosis can be treated, if desired, by hemodialysis using a low buffer-base and high chloride dialysate.

Metabolic Acidosis

Metabolic acidosis can develop if the delivery of buffer base to the dialysate in the form of sodium acetate or sodium bicarbonate is defective [114, 115]. For instance, the single 'acetate concentrate' meant for dilution with water to form an acetate-based dialysate can be accidentally replaced by the 'acid concentrate' component of a two-component, bicarbonate-based dialysate generating system. This can occur in units that continue to practice both types of buffer delivery. This 'acid concentrate' contains sodium, potassium, calcium, magnesium, chloride, glucose and acetic acid. Since this concentrate is devoid of buffer base, its use would bring about metabolic acidosis as a result of the removal of bicarbonate from the blood by dialysis. Another way for metabolic acidosis to set in during dialysis involves the faulty delivery of a buffer base-containing concentrate. For example, the tube responsible for the siphoning off of a 'bicarbonate concentrate' can be damaged [115]. A third way for metabolic acidosis to develop centers on the presence, in the dialysate, of too much water in relation to the available buffer base (an example of dilution acidosis). Treatment of the acidosis comprises the administration of sodium bicarbonate, or of a properly performed acetate- or bicarbonate-based dialysis session using appropriate and functional equipment.

Hyponatremia

Inadvertent use of a markedly hyponatric dialysate during dialysis can occur if conductivity limits of the dialysis machine are not adjusted appropriately such that abnormal proportioning among concentrate(s) and product water are left undetected. Use of such hyponatric dialysates can bring about hyponatremia as a result of the removal of sodium from, and the introduction of water into, the body. The resultant plasma hypoosmolality causes water to enter the intracellular space

leading to water intoxication, cerebral edema and hemolysis. Clinical manifestations include abdominal pain, diarrhea, leg cramps, hypertension, Kussmaul breathing, apprehension, coma, and other neurological disturbances. Hyperkalemia can occur because of the hypoosmolality-induced hemolysis while metabolic acidosis can take place because of dilution of plasma bicarbonate by dialysate water and loss of plasma bicarbonate into the dialysate. Treatment consists of cessation of the current dialysis run, initiation of another dialysis treatment using sound equipment and proper dialysate. Since the onset of the hyponatremia is abrupt, rapid correction of the hyponatremia with hypertonic saline infusion, is justified in order to reduce the degree of cerebral edema [116]. However, serum sodium level should not be brought back to a level higher than 120 – 125mmol or so initially. Blood transfusion should be given if the anemia is severe. Prevention of dialysis-associated hyponatremia depends on meticulous attention to details in the preparation of dialysate and the frequent monitoring of dialysate conductivity value.

Hypernatremia

Dialysate sodium concentrations can be abnormally raised as a consequence of technical failures in water or concentrate pumps or if the conductivity sensors are defective. The hypernatremia can abstract water into the extracellular space from the intracellular compartment causing cellular (including cerebral) dehydration. In those situations in which a hypernatric dialysate is used, extracellular fluid volume may not be elevated because water is also being lost to the dialysate. CNS manifestations such as headache, disorientation, seizures, spasticity and coma are frequently encountered. Other symptoms include nausea, vomiting, hot flushes, weakness, and profound thirst. Death can result.

Treatment consists of discontinuation of the current dialysis session, drinking of water, IV administration of 5% glucose water, and dialysis with a dialysate containing appropriate levels of sodium. The rate of fall of plasma sodium permitted should be guided by the general guidelines for the treatment of acute hypernatremia.

Hypokalemia

Renal failure patients who are dialyzed against a very low-potassium or a potassium-free dialysate can develop hypokalemia and intracellular potassium depletion due to loss of potassium into the dialysate [117]. This complication can take place even in the patient with predialysis hyperkalemia. Patients who are hypokalemic are at risk of developing cardiac arrhythmias, including premature ventricular contractions (PVC) and ventricular fibrillation. In addition, hypotension, fatigue, muscular weakness and paralysis can occur.

Acute lowering of serum potassium engenders a high ratio between intracellular and extracellular fluid potassium concentration, resulting in a more negative resting membrane potential and, hence, a hyperpolarization block. Coronary artery disease, hypertensive cardiovascular disease, digitalis therapy, hypercalcemia, hypomagnesemia and metabolic alkalosis predispose to this hypokalemia-induced cardiac arrhythmia. Patients entering dialysis with a history suggestive of prolonged potassium loss, marked metabolic acidosis, moderate hypokalemia or normokalemia are especially vulnerable to this complication.

Intensive dialysis in an average dialysis patient without severe metabolic acidosis can

bring about a metabolic alkalosis with resultant hypokalemia even if a normal potassium dialysate is used. In such patients, the dialysate buffer base level should be lowered appropriately. Proper attention to dialysate potassium levels will prevent many of these complications.

In patients prone to have dialysis-associated cardiac arrhythmias, special precautions are necessary. Raising dialysate potassium reduces the frequency of arrhythmias in those patients who suffered from arrhythmias while being dialyzed with low potassium dialysate. This reduction, however, results in higher predialysis serum potassium value of the succeeding dialysis treatment.

Hyperkalemia

Hyperkalemia occurs commonly in dialysis patients with dietary indiscretion. Dialysis-induced hyperkalemia occurs with hemolysis. Intradialytic hemolysis has been reported following accidental exposure to overheated or hypotonic dialysate, chloramine, formaldehyde, nitrate, copper, and sodium hypochlorite. Another rare cause for the development of hyperkalemia is dialysis with fluoride-contaminated dialysate [118]. Iatrogenic hyperkalemia could occur if a dialysate with an inordinately high potassium level were inadvertently used.

Hypophosphatemia

Hyperphosphatemia is almost a universal finding in ESRD patients because of the intermittent nature of phosphate removal during hemodialysis. Dialysis-induced hypophosphatemia develops under unusual situations such as:

- intensive (e.g. daily) dialysis for patients suffering from dialysis pericarditis;
- thrice weekly regular dialysis treatments in patients with poor dietary intake either because of intercurrent illness or failure to thrive. Dialysis-induced hypophosphatemia can also be seen in patients with normal renal function who are dialyzed because of intoxications with poisons such as lithium. Therapy of such intoxications often focuses on prolonged and repeated dialysis treatments. Hypophosphatemia may develop in these patients because of the removal, by dialysis, of phosphorus from their bodies whose phosphorus contents are not elevated to start with on account of the presence of normal renal function.

Hypophosphatemia causes dysfunction of erythrocytes, leukocytes, platelets, the CNS, skeletal and cardiac muscles as well as the skeleton. However, hypophosphatemic manifestations are usually mild unless serum phosphorus level falls below 0.33mmol (1.0 mg/dL). Treatment of hypophosphatemia centers on the ingestion of phosphorus-rich food (such as skim milk) and of phosphorus salts (such as sodium or potassium phosphate), and, in severe cases, the IV administration of sodium or potassium phosphate. Dialysis-related hypophosphatemia can be prevented by the use of a phosphorus-enriched dialysate.

Hypercalcemia and Hypermagnesemia

Dialysis against a conventional 1.32mmol calcium dialysate can raise plasma calcium concentrations of dialysis patients from a predialysis value of 2.28mmol to a post-dialysis

level of 2.45mmol [119]. This dialysis-induced hypercalcemia is partly due to an increase in plasma protein concentrations brought about by the loss of a protein-free fluid from plasma as a result of ultrafiltration. The rise in plasma protein level is accompanied by a corresponding increase in the protein-bound fraction of plasma calcium [120]. In addition, the small intradialytic gain of calcium by the body from the dialysate also contributes to the hypercalcemia. Dialysis-induced hypercalcemia is transient in nature and does not lead to symptoms. No treatment is required.

In the recent past when aluminum-containing phosphate binders were used, a dialysate calcium level of 1.75mmol was the standard dialysate calcium concentration used in most dialysis centers. With the replacement of aluminum hydroxide by calcium salts (such as calcium acetate or carbonate) as phosphorus-binders and the widespread use of calcitriol and related compounds to combat renal osteodystrophy, hypercalcemia is not uncommonly encountered if a dialysate calcium level of 1.75mmol is used [121]. Because of the above reasons, dialysate calcium level is nowadays often lowered to 1.0 – 1.25mmol to discourage the development of hypercalcemia.

Treatment for this type of hypercalcemia consists of ingesting calcium-containing phosphorus binders only during meals so that the calcium administered will combine with the phosphorus present in food to form insoluble calcium phosphates. In addition, vitamin D therapy should be discontinued. Aluminum toxicity, if present, should be promptly treated. A dialysate containing an appropriately low level of calcium should be employed. If the use of a low dialysate calcium is unsuccessful, alternate methods are available. Pamidronate, a drug that reduces osteoclast-induced resorption of bone and curtails transformation of osteoclast precursors into mature osteoclasts, has been used successfully to control the present variety of hypercalcemia [122].

In many parts of the world, water intended for consumption often has very high concentrations of calcium and magnesium [123]. Specifically, the levels of calcium and magnesium in such water have been found to reach values as high as 2.0 and 0.95mmol respectively [123]. Should the means of purification of such water (e.g. water softener or deionizer) for the purpose of dialysis be faulty, a patient could be exposed to inordinately elevated dialysate levels of the divalent cations, resulting in what is known as the “hard-water syndrome”.

Patients suffering from the “hard-water syndrome” often complain of nausea, vomiting, general malaise, somnolence, weakness, sweating, warm skin sensation, abdominal pain, tachycardia, hypertension or hypotension. In addition, neurological manifestations in the form of headaches, dysarthria, seizures and myoclonic jerks are common. Mental abnormalities such as hallucinations, confusion, memory loss and judgment defects can occur.

Treatment for hypercalcemia or hypermagnesemia as a consequence of the inadvertent use of high-calcium and/or high-magnesium dialysate centers on the use of a dialysate containing appropriate amounts of the divalent cations.

Contamination of Dialysate Water

Fluoride

Dialysis patients are particularly susceptible to fluoride intoxication due to their repeated exposures to the large volumes of water in the course of dialysis (120 L per

dialysis session; 19,000 L per year of maintenance hemodialysis) and to their lack of the usual renal route of fluoride excretion. Since fluoride has a molecular weight of only 19 daltons, it is readily transferable into the blood from the dialysate. Although municipal water generally contains in the realm of 53 micromolar fluoride, product water used for preparing dialysate should have a fluoride level less than 11 μM (i.e. < 0.2 parts per million (ppm)) [124]. In general, properly reverse osmosis-treated and deionized water can more than meet this requirement. Faulty reverse osmosis and deionization systems can result in contamination of product water by fluoride [124]. Continued use of the exhausted resins to treat municipal water causes low-affinity anions, such as fluoride, already bound to the resins, to be displaced into the effluent by higher-affinity anions, such as nitrate, sulfate, and chloride. As a consequence, a patient can be exposed to a dialysate fluoride level as high as 1,000 μM [118]. Finally, a rare cause for a high level of fluoride in dialysate is the accidental gross contamination of municipal water with fluoride-containing compounds while reverse osmosis and de-ionization equipment is not being utilized [125].

The toxicity of fluoride is related to its ability to oxidize other chemicals and to combine with organic compounds, resulting in a direct interference with various cellular metabolic processes. In addition, fluoride, being the most electronegative element, can readily bring down the serum levels of calcium and magnesium because of its tight binding with these cations.

Because a period of fluoride accumulation is necessary to incite patient responses, the onset of clinical manifestations can be anticipated to take place late into, or soon after dialysis [118]. Many patients in the same dialysis unit (if they share the same source of product water) are likely to demonstrate similar signs and symptoms at approximately the same time [118]. Early symptoms include nausea, vomiting, pruritus, burning or feverish feeling, headache, syncope, back or abdominal pain, diarrhea, chest pressure or pain, cardiac irritability and bradycardia. Later on, binding of blood calcium by fluoride can bring about generalized muscle twitching, tetany, petechiae and bleeding from vascular access puncture sites. Still later, respiratory failure, hypotension, seizure, coma, cardiac arrest, and death can occur [125]. Treatment of acute fluoride poisoning entails the immediate cessation of the current dialysis; intravenous administration of calcium salts, sodium bicarbonate, glucose and insulin (for the therapy of hyperkalemia, acidosis and hypocalcemia if these abnormalities are present); and prompt dialysis using a bicarbonate-based, zero to normal potassium and fluoride-undetectable dialysate. Multiple or prolonged dialysis treatments may be required to remove adequate amounts of fluoride from the body. Should hemodialysis using fluoride-undetectable dialysate be unavailable, peritoneal dialysis should be instituted. Prevention of fluoride toxicity involves the meticulous purification of product water, frequent measurement of the fluoride concentration in product water and the ensuring of proper functioning of the reverse osmosis and the de-ionization systems.

Methemoglobinemia

When the ferrous ion that is attached to the heme of hemoglobin is oxidized to the ferric form by an oxidizing agent, a derivative of hemoglobin known as methemoglobin, is produced. Methemoglobin is without function because its heme molecule cannot bind oxygen. Dialysis-associated methemoglobinemia

can occur as a result of exposure to oxidizing agents such as:

Nitrate

Patients who are dialyzed with nitrate-rich well water can develop methemoglobinemia [126]. Wells that are poorly constructed or poorly located may have a high level of nitrates in their water due to seepage of wastes. Prevention of the present methemoglobinemia depends on the removal of nitrites from product water by means of a de-ionizer. When the methemoglobinemia is mild, no treatment is necessary since the methemoglobin will be spontaneously reduced to hemoglobin by the body over 2 – 3 days. For severely affected patients, l – 2 mg/kg of a 1% solution of methylene blue in saline is administered IV over 10 minutes. A second dose can be repeated in an hour if needed.

Chloramine

Chlorine is often used as a disinfectant for municipal water supplies. However, chloramines, compounds composed of chlorine and ammonia, are increasingly considered to be environmentally safer alternatives to chlorine for disinfecting water supplies [127]. This is because chloramines are less volatile and have a less objectionable smell and taste than chlorine. Furthermore, unlike chlorine chloramines do not react with naturally occurring organic compounds to form chloroform. For the purpose of dialysis, municipal water treated with chloramines is ordinarily purged of these disinfectants by passage through charcoal filters (also known as carbon filters) containing granular activated carbon particles [128].

In case the delivery of municipal water to a charcoal filter is excessive in relation to the capacity of the filter to remove chloramines, that particular filter can become prematurely exhausted and allow chloramines to enter and contaminate the product water. Drought conditions require the use of larger amounts of chloramines because drought-induced stagnation of water encourages bacterial and fungal growth. The greater quantity of chloramines added may tax the capacity of existing filters to remove these disinfectants.

According to Association for the Advancement of Medical Instrumentation (AAMI) standards, product water geared for dialysis should not have a chloramine level higher than 0.1 mg/L (0.1 ppm) [129]. High blood levels of chloramines can oxidize the hemoglobin in the blood to form methemoglobin and Heinz bodies, the latter being intracellular precipitates of denatured hemoglobin. Red cells exposed to chloramines are very susceptible to hemolysis and a hemolytic anemia is readily encountered.

The hemolytic anemia due to exposure to chloramines can be severe enough to warrant blood transfusion. Prevention consists of routing municipal water through appropriate charcoal filters [129], with the realization that chloramines are not removed by reverse osmosis. The American Food and Drug Administration (FDA) recommends that 2 charcoal filters be used in series for a water treatment system. A systemic plan for replacing the filters as they become exhausted should be established. Exhausted charcoal filters should be replaced with fresh ones, and should not be rejuvenated by backwashing. Although backwashing may loosen the packed carbon particles and restore surface area, it does not remove previously aggregated material from the charcoal and, therefore, does not regenerate the filter [127]. In order to ensure the absence of chloramines, product water should be tested for the chemicals at least once per patient shift to ensure patient safety [129].

Addition of vitamin C, a reducing agent, to a dialysate at a concentration of 17 – 34 mg/L

has also been found to be effective in converting dialysate chloramines to the relatively innocuous ammonium chloride, whether the batch method or the proportioning method of producing dialysate is used [130]. It should be emphasized that patients who are dialyzed with vitamin C-enriched dialysate should not take oral vitamin C supplements. This approach of enriching dialysate with vitamin C will only result in serum levels approximating those seen in maintenance dialysis patients taking standard oral vitamin supplements. Some centers employ both charcoal filters and vitamin C enrichment at the same time.

Miscellaneous Complications

Febrile Episodes and Endotoxin

Pyrogenic episodes associated directly with hemodialysis treatments are infrequent [131] and their presence should always elicit a search for underlying bacterial infections [132]. Occasionally, clustering of febrile episodes, particularly after any mechanical work on the water supply system, raises the possibility of contamination. Bicarbonate dialysate concentrates can support bacterial growth with endotoxin production. Endotoxins or bacteria may cross or interact at the membranes of high-flux dialyzers, triggering the release of endogenous pyrogens (e.g. certain cytokines) by peripheral blood mononuclear cells to cause pyrogenic reactions. Pyrogenic reactions occur at a rate of 0.7 reaction per 1,000 hemodialysis treatments [133]. This incidence is not different between conventional, and high-flux or high-efficiency modalities of dialysis [133].

Pyrogenic reactions occurring in clusters are more frequently reported in centers that reuse conventional dialyzer membranes compared to centers that do not [134 – 136]. Use of dialyzers with detachable components such as headers has been associated with an increased incidence of infections (e.g. 'header sepsis') with a variety of organisms including Xanthomonas, and other slow-growing organisms, a problem that can be solved with proper disinfections of the O rings and other components of the header [137, 138]. Improper preparation of the disinfectant has also been associated with clusters of infection with Pseudomonas species [139]. Nontuberculous mycobacteria are ubiquitous in municipal water and outbreaks of infection with these organisms during reuse have been reported. Because of the organisms' greater germicide resistance compared to that of most other naturally occurring water bacteria, attention to the quality and concentration of disinfectants is mandatory.

The minimal dose of endotoxin necessary to induce fever in man (5 ng/kg; 1 ng corresponds to 10 endotoxin units) can be readily achieved in some contaminated dialysates. Levels > 100 EU/mL have been found in up to 10% of German dialysis units surveyed [140].

Endotoxin transfer may contribute to cytokine induction. While the clinical significance of the latter phenomenon remains unknown, the use of ultrapure water has been reported to result in a reduction in the prevalence of the carpal tunnel syndrome [141]. In examining for endotoxemia in dialysis patients, care should be taken to use the proper test. The limulus amebocyte lysate-reactive material (LAL-RM) is cellulose-derived and cross-reacts with LAL via factor G. Using the conventional chromogenic limulus test, all patients treated with regenerated cellulose dialyzers will show elevated values. In this setting, a specific endotoxin assay with factor G-free LAL should be used.

Dialysis-Associated Catabolism

Hemodialysis is considered to be a catabolic event, increasing urea generation rate during dialysis and leading to a negative nitrogen balance. A major contributory factor to this event is the loss of amino acids during dialysis ranging between 6 – 13 g per dialysis session. This loss in amino acids via the dialysate leads to a decline in arterial amino acid concentrations and a concomitant rise in efflux of amino acids from tissue, mainly skeletal muscle. This phenomenon does not appear to be related to the presence or absence of glucose in the dialysate (or conversely the gain or loss of glucose) [142]. This effect appears to be dialyzer membrane-dependent, being greater with high-flux membranes, and still greater with the reuse of such membranes. Reuse of high-flux dialyzer membranes also appears to augment albumin losses during dialysis. After the 20th reuse, the loss of albumin can reach 10 g per session [143].

References

[1] *Orofino L, Marcen R, Quereda C, Villafruela J, Sabater J, Matesanz R, Pascual J, Ortuno J* 1990 Epidemiology of symptomatic hypotension in hemodialysis: is cool dialysate beneficial for all patients? Am J Nephrol *10:* 177

[2] *Jost CM, Agarwal R, Khair, Grayburn PA, Victor RG, Heririch WL* 1993 Effects of cooler temperature dialysate on hemodynamic stability in 'problem' dialysis patients. Kidney Int *44:* 606

[3] *Anonymous* 1991 Acute intradialytic well-being: results of a clinical trial comparing polysulfone with cuprophan. Bergamo Collaborative dialysis Study Group. Kidney Int *40:* 714

[4] *Shinzato T, Nakai S, Odani H, Nakane K, Takai 1, Maeda K* 1992 Relationship between dialysis induced hypotension and adenosine released by ischemic tissue. ASAIO J *38:* 286

[5] *Schneditz D, Roob J, Oswald M, Pogglitsch H, Moser M, Kenner T, Binswager U* 1992 Nature and rate of vascular refilling during hemodialysis and ultrafiltration. Kidney Int *42:* 1425

[6] *Van SJ, Bauer J, Carey J* 1982 The effect of dialysate sodium concentration on body fluid compartment volume, plasma renin activity and plasma aldosterone concentration in chronic hemodialysis patients. Am J Kidney Dis *2:* 58

[7] *Fauchald P* 1986 Transcapillary colloid osmotic gradient and body fluid volumes in renal failure. Kidney Int *29:* 895

[8] *Fleming SJ, Wilkinson JS, Greenwood RN, Aldridge C, Baker LR, Cattell WR* 1987 Effect of dialysate composition on intercompartmental fluid shift. Kidney Int *32:* 267

[9] *Po CL, Afolabi M, Raja RM* 1993 The role of sequential ultrafiltration and varying dialysate sodium on vascular stability during hemodialysis. ASAIO J *39:* 798

[10] *Sherman RA, Torres F, Cody RP* 1988 The effect of red cell transfusion on hemodialysis-related hypotension. Am J Kidney Dis *11:* 33

[11] *Maeda K, Morita H, Shinzato T, Vega BV, Kobayakawa H, Ishihara T, Inagaki H, Igarashi I, Kitano T* 1988 Role of hypovolemia in dialysis-induced hypotension. Artif Organs *12:* 116

[12] *Hampl H, Paeprer H, Unger V, Kessel MW* 1979 Hemodynamics during hemodialysis, sequential ultrafiltration and hemofiltration. J Dial *3:* 51

[13] *Maeda K, Fujita Y, Shinzato T, Morita H, Kobayakawa H, Takai I* 1989 Mechanism of dialysis-induced hypotension. Trans Am Soc Artif Intern Organs *35:* 245

[14] *Bradley JR, Evans DB, Gore SM, Cowley AJ* 1988 Is dialysis hypotension caused by an abnormality of venous tone? [published erratum appears in Br Med J (Clin Res Ed) 297:330, 1988 J. Br Med J *296:* 1634

[15] *Kooman JP, Gladziwa U, Bocker G, van BL, van HJ, Leunissen KM* 1992 Role of the venous system in hemodynamics during ultrafiltration and bicarbonate dialysis. Kidney Int *42:* 718

[16] *Converse RJ, Jacobsen TN, Jost CM, Toto RD, Graybum PA, Obregon TM, Fouad-Tarazi F, Victor RG* 1992 Paradoxical withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. J Clin Invest *90:* 1657

[17] *Agarwal A, Anand IS, Sakhuja V, Chugh KS* 1991 Effect of dialysis and renal transplantation on autonomic dysfunction in chronic renal failure. Kidney Int *40:* 489

[18] *Heber ME, Lahiri A, Thompson D, Raftery EB* 1989 Baroreceptor, not left ventricular, dysfunc-

tion is the cause of hemodialysis hypotension. Clin Nephrol *32:* 79

[19] *Lilley JJ, Golden J, Stone RA* 1976 Adrenergic regulation of blood pressure in chronic renal failure. J Clin Invest *57:* 1190

[20] *Hakim RM, Pontzer MA, Tilton D, Lazarus JM, Gottlieb MN* 1985 Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. Kidney Int *28:* 535

[21] *Daugirdas JT* 1991 Dialysis hypotension: a hemodynamic analysis. Kidney Int *39:* 233

[22] *Barakat MM, Nawab ZM, Yu AW, Lau AH, Ing TS, Daugirdas JT* 1993 Hemodynamic effects of intradialytic food ingestion and the effects of caffeine. Am Soc Nephrol *3:* 1813

[23] *Movilli E, Camerini C, Viola BF, Bossini N, Strada A, Maiorca R* 1997 Blood volume changes during three different profiles of dialysate sodium variation with similar intradialytic sodium balances in chronic hemodialyzed patients. Am J Kidney Dis *30:* 58-63

[24] *Sherman RA, Rubin MP, Cody RP, Eisinger RP* 1985 Amelioration of hemodialysis-associated hypotension by the use of cool dialysate. Am J Kidney Dis *5:* 124

[25] *Kerr PG, van Babel C, Dawborn JK* 1989 Assessment of the symptomatic benefit of cool dialysate. Nephron *52:* 166

[26] *Marcen R, Quereda C, Orofino L et al* 1988 Hemodialysis with low-temperature dialysate: a long-term experience. Nephron *49:* 29

[27] *Stiller S, Wirtz D, Waterbar F, Gladziwa U, Dakshinamurty KV, Mann H* 1991 Less symptomatic hypotension using blood volume controlled ultrafiltration. Trans Am Soc Artif Intern Organs *37:* 138

[28] *Branger B, Deschodt G, Oules R, Balducchi JP, Granolleras C, Aisabadani B, Fourcade J, Shaldon S* 1988 Biocompatible membranes and hemodynamic tolerance to hemodialysis. Kidney Int *24:* S196

[29] *Collins DM, Lambert MB, Tannenbaum JS, Oliverio M, Schwab SJ* 1993 Tolerance of hemodialysis: a randomized prospective trial of high-flux versus conventional high-efficiency hemodialysis. Am Soc Nephrol *4:* 148

[30] *Gong R, Lindberg J, Abrams J, Whitaker WR, Wade CE, Gouge S* 1993 Comparison of hypertonic saline solutions and dextran in dialysis-induced hypotension. Am Soc Nephrol *3:* 1808

[31] *Bergonzi G, Paties C, Vassallo G, Zangrandi A, Poisetti PG, Ballochi S, Fontana F, Scarpioni L* 1990 Dextran deposits in tissues of patients undergoing haemodialysis. Nephrol Dial Transplant *5:* 54

[32] *Warren SE, Olshan A, Beck CHJ* 1980 Use of phenylephrine HCI for treatment of refractory dialysis-aggravated hypotension. Nephrol Dial Transplant *9:* 492

[33] *Flynn JJ, Mitchell MC, Caruso FS, McElligott MA* 1996 Midodrine treatment for patients with hemodialysis hypotension. Clin Nephrol *45:* 261-267

[34] *Fang JT, Juang CC* 1996 Midodrine hydrochloride in patients on hemodialysis with chronic hypotension. Renal Failure *18:* 253-260

[35] *Perazella MA* 1997 Midodrine: a new therapy for intradialytic hypotension. Seminars in Dialysis *10:* 245-247

[36] *Ebel H, Saure B, Laage C, Dittmar A, Keucher M, Stellwaag M, Lange H* 1990 Influence of computer-modulated profile haemodialysis on cardiac arrhythmias. Nephrol Dial Transplant *1:* 165

[37] *Saragoca MA, Canziani ME, Cassiolato JL, Gil MA, Andrade JL, Draibe SA, Martinez EE* 1991 Left ventricular hypertrophy a risk factor for arrhythmias in hemodialysis patients. J Cardiol Pharma *17 (Suppl 2):* S136

[38] *Fantuzzi S, Caico S, Amatruda O, Cervini P, Abu-Turky H, Baratelli L, Donati D, Gastaldi L* 1991 Hemo-dialysis-associated cardiac arrhythmias: a lower risk with bicarbonate? Nephron *58:* 196

[39] *Rostand SG, Rutsky EA* 1990 Pericarditis in end-stage renal disease. (Review) Cardiol Clin *8:* 701

[40] *Nishimura M, Nakanishi T, Yasui A, Tsuji Y, Kunishige H, Hirabayashi M, Takahashi H, Yoshimura M* 1992 Serum calcium increases the incidence of arrhythmias during acetate hemodialysis. Am J Kidney Dis *19:* 149

[41] *Renfrew R, Buselmeier TJ, Kjellstrand CM* 1980 Pericarditis and renal failure. Ann Rev Med *31:* 345

[42] *Osanloo E, Salhoub RJ, Cioffi RF, Parker RH* 1979 Viral pericarditis in patients receiving hemodialysis. Arch Intern Med *139:* 301

[43] *Watson AJJ, Finn MMR, Keaugh JAB* 1981 Cardiac tamponade without demonstrable pulsus paradoxus in hemodialysis patients. Irish J Med Sci *150:* 78

[44] *Horton JD, Gelfand Mc, Sherber HS* 1977 Natural history of asymptomatic pericardial effusions in patients on maintenance hemodialysis. Proc Dial Transplant Forum *7:* 76

[45] *Leehey DJ, Daugirdas JT, Ing TS* 1983 Early drainage of pericardial effusion in patients with dialysis pericarditis. Arch Intern Med *143:* 1673

[46] *Daugirdas JT, Leehey DK, Popli S, McCray GM, Gandhi VC, Pifarre R, Ing TS* 1986 Subxiphoid pericardiotomy for hemodialysis-associated pericardial effusion. Arch Intern Med *146:* 1113

[47] *De Broe M, DeBacker W* 1989 Pathophysiology of hemodialysis-associated hypoxemia. (Review) Adv Nephrol Necker Hosp *18:* L297

[48] *Ozdemir O, Arik N, Ozcebe O, Arinsoy T, Sungur C, Dundar S, Turgan C, Yasauul U, Caglar S, Kiragli S* 1992 Evidence for the role of dialysis hypoxemia in the pathogenesis of hemodialysis-induced rise in tissue-type plasminogen activator. Thromb Res *67:* 697

[49] *Gilli Y, Binswanger U* 1990 Continuous pulse-oxymetry during haemodialysis. Nephron *44:* 368

[50] *Fujiwara Y, Hagihara B, Yamauchi A, Shirai D* 1985 Hypoxemia and hemodialysis-induced symptomatic hypotension. Clin Nephrol *24:* 9

[51] *Francos GC, Besarab A, Burke F, Peters J, Tahamont MV, Gee MH, Flynn JT, Gzesh D* 1985 Dialysis-induced hypoxemia: membrane dependent and membrane independent causes. Am J Kidney Dis *5:* 191

[52] *Kishimoto T, Tanaka H, Maekawa M, Ivanovich P, Levin N, Bergstrom J, Klinkmann H* 1993 Dialysis-induced hypoxaemia. Nephrol Dial Transplant *2:* 25

[53] *Oh MS, Uribarri J, Del Monte ML, Heneghan WF, Kee CS, Friedman EA, Carroll H* 1985 A mechanism of hypoxemia during hemodialysis. Consumption of C02 in metabolism of acetate. Am J Nephrol *5:* 366

[54] *Ganss R, Aarseth BP, Nordby G* 1992 Prevention of hemodialysis associated hypoxemia by use of low-concentration bicarbonate dialysate. ASAIO J *38:* 820

[55] *Soliani F, Davoli V, Franco V, Lindner G, Lusanti T, Parisoli A, Brini M, Borgatti PP* 1990 Intradialytic changes of the oxyhaemoglobin dissociation curve during acetate and bicarbonate haemodialysis. Possible interactions with haemodialysis-associated hypoxaemia. Nephrol Dial Transplant *1:* 119

[56] *Igarashi H, Kioi S, Gejyo F, Arakawa M* 1985 Physiologic approach to dialysis-induced hypoxemia. Effects of dialyzer material and dialysate composition. Nephron *41:* 62

[57] *Wiegmann TB, MacDougall ML, Diederich DA* 1988 Dialysis, leukopenia, hypoxemia, and anaphylatoxin formation: effect of membrane, bath, and citrate anticoagulation. Am J Kidney Dis *11:* 418

[58] *Ross EA, Tashkin D, Chenoweth D, Webber MM, Nissenson AR* 1987 Pulmonary leukosequestration without hypoxemia during hemodialysis. Int J Artif Organic *10:* 367

[59] *Chou CT, Wasserstein A, Schumacher HJ, Fernandez P* 1985 Musculoskeletal manifestations in hemodialysis patients. J Rheumatol *12:* 1149

[60] *McGee SR* 1990 Muscle cramps. Arch Intern Med *150:* 511

[61] *Piergies AA, Atkinson AJ, Hubler GL, Del GF* 1990 Activation of renin-angiotensin system does not cause skeletal muscle cramps during hemodialysis. Int Journal Clin Pharmacol Ther Toxicol *28:* 405

[62] *Kaplan B, Wang T. Rammohan M, Del GF, Molteni A, Atkinson AJ* 1992 Response to head-up tilt in cramping and noncramping hemodialysis patients. Int J Clin Pharmacol Ther Toxicol *30:* 1731

[63] *Sidhom O, Odeh Y, Krumlovsky F, Budris WA, Wamg Z, Pospisil PA, Atkinson AJ Jr* 1994 Low-dose prazosin in patients with muscle cramps during hemodialysis. Clin Pharmacol Ther *56:* 445

[64] *Ahmad S, Robertson HT, Golper TA et al* 1990 Multicenter trial of L-carnitine in maintenance hemodialysis patients. II. Clinical and biochemical effects. Kidney Int *38:* 912

[65] *Canzanello VJ, Hylander RB, Sands RE, Morgan TM, Jordan J, Burkart JM* 1991 Comparison of 50% dextrose water, 25% mannitol, and 23.5% saline for the treatment of hemo-dialysis-associated muscle cramps. Trans Am Soc Artif Intern Organs *37:* 649

[66] *Roca AO, Jarjoura D, Blend D, Cugino A, Rutecki GW, Nuchikat PS, Whittier FC* 1992 Dialysis leg cramps. Efficacy of quinine versus vitamin E. ASAIO J *38:* 481

[67] *Sever MS, Kocak N* 1990 Chloroquine phosphate reduces the frequency of muscle cramps during maintenance hemodialysis. (Letter) Nephron 56

[68] *Ing TS, Daugirdas JT, Popli S, Gandhi VC* 1983 First-use syndrome with cuprammonium cellulose dialyzers. Int J Artif Organs *6:* 235

[69] *Nicholls A* 1986 Ethylene oxide and anaphylaxis during haemodialysis. Br Med J *292:* 1221

[70] *Daugirdas JT, Ing TS* 1988 First-use reactions during hemodialysis: a definition of subtypes. Kidney Int *33 (Suppl 24):* 537

[71] *Lemke HD, Heidland A, Schaefer RM* 1990 Hypersensitivity reactions during haemodialysis: role of complement fragments and ethylene oxide antibodies. Nephrol Dial Transplant *5:* 264

[72] *Ing TS, Daugirdas JT* 1986 Extractable ethylene oxide from cuprammonium cellulose plate dialyzers. Trans Am Soc Artif Intern Organs *21:* 108

[73] *Lemke HD* 1987 Mediation of hypersensitivity reactions during hemodialysis by IgE antibodies against ethylene oxide. Artif Organs *11:* 104

[74] *Grammar LC, Roberts M, Wiggins CA, Fitzsimmons RR, Ivanovich PT, Roxe DM, Patterson R* 1991 A comparison of cutaneous testing and ELISA testing for assessing reactivity to ethylene

oxide-human serum albumin in hemodialysis patients with anaphylactic reactions. J Allergy Clin Immunol *87:* 674

[75] *Daugirdas JT, Potempa LD, Dinh N, Gandhi VC, Ivanovich PJ, Ing TS* 1987 Plate, coil, and hollow-fiber cuprammonium cellulose dialyzers: discrepancy between incidence of anaphylactic reactions and degree of complement activation. Artif Organs *11:* 140

[76] *Kessler M, Cao HT, Mariot A, Chanliau J* 1988 Hemodialysis associated complications due to sterilizing agents ethylene oxide and formaldehyde. Contrib Nephrol *62:* 13

[77] *Wenzel SK, Sharma AM, Keller F* 1990 Repeated dialysis anaphylaxia. Nephrol Dial Transplant *5:* 821

[78] *Update* 1991 Acute allergic reactions associated with reprocessed hemodialyzers-United States, 1989-90. MMWR *40:* 147, 153

[79] *Pegues DA, Consuelo M, Beck-Sague, Woollen SW, Greenspan B, Bums SM, Bland LA, Arduino MJ, Favero MS, Mackow RC, Jarvis WR* 1992 Anaphylactoid reactions associated with reuse of hollow fiber hemodialyzers and ACE inhibitors. Kidney Int *42:* 1232

[80] *Parnes EL, Shapiro WB* 1991 Anaphylactoid reactions in hemodialysis patients treated with the AN69 dialyzer. Kidney Int *40:* 1148

[81] *Schulman G, Hakim R, Arias R, Silverberg M, Kaplan AP, Arbeit L* 1993 Bradykinin generation by dialysis membranes: possible role in anaphylactic reaction. Am Soc Nephrol *3:* 1563

[82] *Balaskas EV, Chu M, Uldall RP, Gupta A, Oreopoulos DG* 1993 Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. Perit Dial Int *13:* S527

[83] *Stahle-Backdahl M* 1989 Uremic pruritus. Clinical and experimental studies. Acta Derm Venereol 145 Suppl 1

[84] *Gilchrest BA, Stern RS, Steinman TI, Brown RS, Arndt KA, Anderson WW* 1982 Clinical features of pruritus among patients undergoing maintenance hemodialysis. Arch Dermatol *118:* 154

[85] *Parfitt AM, Massry SG, Winfield AC, DePalma JR, Gordon A* 1971 Disordered calcium and phosphorus metabolism during maintenance hemodialysis. Correlation of clinical, roentgenographic and biochemical changes. Am J Med *51:* 319

[86] *Stockenhuber F, Kurz RW, Sertl K, Grimm G, Balcke P* 1990 Increased plasma histamine levels in uraemic pruritus. Clin Sci *79:* 477

[87] *Dimkovic N, Djukanovic L, Radmilovic A, Bojic P, Juloski T* 1992 Uremic pruritus and skin mast cells. Nephron *61:* 5

[88] *Mettang T, Fritz P, Weber J, Machleidt C, Hubel E, Kuhlmann U* 1990 Uremic pruritus in patients on hemodialysis or continuous ambulatory peritoneal dialysis (PD). The role of plasma histamine and skin mast cells. Clin Nephrol *34:* 136

[89] *Cohen EP, Russell TJ, Garancis JC* 1992 Mast cells and calcium in severe uremic itching. Am J Med Sci *303:* 360

[90] *Francos GC, Kauh YC, Gittlen SD, Schulman ES, Besarab A, Guyal S, Burke JF Jr* 1991 Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. Int J Dermatol *30:* 884

[91] *Tan JK, Haberman HF, Coldman AJ* 1991 Identifying effective treatments for uremic pruritus. J Am Acad Dermatol *25:* 811

[92] *Schaefer RM, Rauterberg EW, Deppisch RI Vienken J* 1990 Assembly of terminal SC5b-9 complement complexes: a new index of blood-membrane interaction. Miner Electrolyte Metab *16:* 73

[93] *Zachee P, Ferrant A, Daelemans R, Coolen L, Goosens W, Lins RL, Couttenye M, DeBroe ME, Boogaerts MA* 1993 Oxidative injury to erythrocytes, cell reigiity and splenic hemolysis in hemodialyzed patients before and during erythropoietin treatment. Nephron *65:* 288

[94] *Gawaz W, Dobos G, Mujais SK* 1994 Impaired function of platelet glycoprotein GP1lb/1lla in end stage renal disease. Am Soc Nephrol *5:* 36

[95] *Lockwood AH* 1989 Neurologic complications of renal disease. Neurol Clin *7:* 617-627

[96] *Swartz RD* 1986 Hemodialysis-associated seizures. In: Nissenson AR, Fine RN (eds.): Dialysis therapy. Hanley and Beifus, Philadelphia. pp 88-90

[97] *Mahoney CA, Arieff AI* 1982 Uremic encephalopathies: Clinical, biochemical, and experimental features. Am J Kidney Dis *11:* 324-336

[98] *Eschbach J, Abdulhade MH, Browne JK et al* 1989 Results of a phase III multi-center clinical trial with recombinant human erythropoietin in anemic patients with end-stage renal disease. Ann Int Med *111:* 992-1000

[99] *Raine AE* 1990 Seizures and hypertension events. Semin Nephrol 10 (2 suppl 1):40-50

[100] *Edmund ME, Walls J* 1991 Pathogenesis of seizures during recombinant erythropoietin therapy. Semin Dial *4:* 163-167

[101] *Coburn JW, Norris KC, Sherrard DJ et al* 1988 Toxic effects of aluminum in end-stage renal disease: Discussion of a case. Am J Kidney Dis *12:* 171-184

[102] *Ismail N, Hakim RM* 1992 A hemodialysis patient with hypercalcemia and microcytic anemia. In: Stone WJ (ed): Grand Rounds in Nephrology, Mosby Year Book, Inc., pp 185-201

[103] *Kalan B, Krumlovsky FA* 1992 Phenytoin in end-stage renal disease. Int J Artif Organs *15:* 69-70

[104] *Fortner R, Nowakowski A, Carter C, King L, Knepshield J* 1970 Death due to overheated dialysate during dialysis. Ann Intern Med *73:* 443

[105] Mennim P, Coyle CF, Taylor J 1992 Venous air embolism associated with removal of central venous catheter. Br Med J *305:* 171

[106] *Bergh K, Hjelde A, Iversen OJ, Brubakk AO* 1993 Variability over time of complement activation induced by air bubbles in human and rabbit sera. J Appl Physiol *74:* 1811

[107] *Bunegin L, Wahl D, Albin MS* 1994 Detection and volume estimation of embolic air in the middle cerebral artery using transcranial Doppler sonography. Stroke *25:* 595

[108] *Dunbar EM, Fox R, Watson B, Akrill P* 1990 Successful late treatment of venous air embolism with hyperbaric oxygen. Postgrad Med J *66:* 469

[109] *Peterson H de C, Swanson AG* 1964 Acute encephalopathy occurring during hemodialysis the reverse urea effect. Arch Intern Med *113:* 877

[110] *Kleeman CR* 1989 Metabolic coma. Kidney Int *36:* 1142

[111] *Port FK, Johnson WJ, Klass DW* 1973 Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. Kidney Int *3:* 327

[112] *Silver SM, DeSimone JA Jr, Smith DA, Sterns RH* 1992 Dialysis disequilibrium syndrome (DDS) in the rat: role of the 'reverse urea effect'. Kidney Int *42:* 161

[113] *Kelleher SP, Schulman G* 1987 Severe metabolic alkalosis complicating regional citrate hemodialysis. Am J Kidney Dis *9:* 235

[114] *Brueggemeyer CD, Ramirez G* 1987 Dialysate concentrate: a potential source for lethal complications. Nephron *46:* 397

[115] *Hartmann A, Reisaeter A, Holdaas H, Rolfsen B, Fauchald P* 1994 Accidental metabolic acidosis during hemodialysis. Artif Organs *18:* 214

[116] *Stern RH, Ocdol H, Schrier RW, Narins RG* 1994 Hyponatremia: pathophysiology, diagnosis, and therapy. In: Narins RG (ed.): Clinical Disorders of Fluid and Electrolyte Metabolism. 5th Ed, McGraw-Hill Inc. New York. p 585

[117] *Lazarus JM* 1980 Complications in hemodialysis: an overview. Kidney Int *18:* 783

[118] *Arnow PM, Bland LA, Garcia-Houchins S, Fridkin S, Fellner SK* 1994 An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. Ann Intern Med *131:* 339

[119] *Tamm HS, Nolph KD, Maher JF* 1971 Factors affecting plasma calcium concentration during hemodialysis. Arch Intern Med *128:* 769

[120] *Carney SL, Gillies AHB* 1988 Acute dialysis hypercalcemia and dialysis phosphate loss. Am J Kidney Dis *11:* 377

[121] *Argiles A, Kerr PG, Canaud B, Flavier JL, Mion C* 1993 Calcium kinetics and the long-term effects of lowering dialysate calcium concentration. Kidney Int *43:* 630

[122] *Davenport A, Goel S, Mackenzie JC* 1993 Treatment of hypercalcaemia with pamidronate in patients with end-stage renal failure. Scand J Urol Nephrol *27:* 447

[123] *Mulloy AL, Mulloy LL, Weinstein RS* 1992 Hypercalcemia due to hard water used for home dialysis. South Med J *85:* 1131

[124] *Keshaviah PR* 1989 Pretreatment and preparation of city worker for hemodialysis. In: Maher JF: Replacement of renal function by dialysis. 3rd Ed. Dordrecht, Kluwer Academic Publishers, p 189

[125] *Anderson R, Beard JH, Sorley D* 1980 Fluoride intoxication in a dialysis unit-Maryland. MMWR 29: 134

[126] *Carlson DJ, Shapiro Fl* 1970 Methemoglobinemia from well water nitrates: a complication of home dialysis. Ann Intern Med *73:* 757

[127] *Tipple MA, Shusterman N, Bland LA, McCarthy MA, Favero MS, Arduino MJ, Reid MH, Jarvis WR* 1991 Illness in hemodialysis patients after exposure to chloramine contaminated dialysate. Trans Am Soc Artif Organs *37:* 588

[128] *Meyer MA, Klein E* 1983 Granular activated carbon usage in chloramine removal from dialysis water. Artif Organs *7:* 484

[129] *FDA safety alert* 1988 Chloramine contamination of hemodialysis water supplies. Am J Kidney Dis *11:* 447

[130] *Ward DM, Minch K, Bahr TE* 1985 The use of ascorbic acid in water treatment for hemodialysis. Contemp Dial Nephrol *2:*33, and *3:* 35

[131] *Gaynes R, Friedman C, Maclaven C, Foley K, Swartz R* 1990 Hemodialysis-associated febrile episodes: surveillance before and after major alteration in the water treatment system. Int J Artif Organs *13:* 482

[132] *Goldman M, Vanherweghem JL* 1990 Bacterial infections in chronic hemodialysis patients: epidemiologic and pathophysiologic aspects. Adv Nephrol Necker Hosp *19:* 315

[133] *Gordon SM, Oettinger CW, Bland LA, Olivier JC, Ardvino WJ, Aquero SM, McAllister SK, Favero MS, Jarvis WR* 1992 Pyrogenic reactions in patients receiving conventional, high-efficiency, or

high-flux hemodialysis treatments with bicarbonate dialysate containing high concentrations of bacteria and endotoxin. Am Soc Nephrol *2:* 1436

[134] *Alter MJ, Favero MS, Miller JK, Moyer LA, Bland LA* 1989 National surveillance of dialysis-associated diseases in the United States, 2987. Trans Am Soc Artif Intern Organs *35:* 820

[135] *Alter MJ, Favero MS, Moyer LA, Miller JK, Bland LA* 1990 National surveillance of dialysis-associated diseases in the United States, 1988. Trans Am Soc Artif Intern Organs *36:* 107

[136] *Alter MJ, Favero MS, Moyer LA, Bland LA* 1991 National surveillance of dialysis-associated diseases in the United States, 1989. Trans Am Soc Artif Intern Organs *37:* 97

[137] *Flaherty JP, Garcia-Hutchins S, Chudy R, Arnow PM* 1993 An outbreak of gram-negative bacteremia traced to contaminated O-rings in reprocessed dialyzers. Ann Intern Med *119:* 1072

[138] *Roberts B, Alvarado N, Garcia, Solis Y, Lopez O, Dukes C* 1994 Header sepsis syndrome: waterborne Xanthomonas-induced fevers. Dial Transplant *23:* 464

[139] *Vanholder R, Vanhaecke E, Ringoir S* 1992 Pseudomonas septicemia due to deficient disinfectant mixing during reuse. Int J Artif Organs *15:* 19

[140] *Bambauer R, Schauer M, Vienken J* 1991 Contamination of dialysis water and dialysate. Blood Purif *9:* 32

[141] *Baz M, Durand C, Jaber K, Marzouk T, Berland Y* 1990 The impact of 12 years ultrapure dialysate use in hemodialysis related amyloidosis. Int J Artif Organs 13: 547

[142] *Gutierrez A, Bergstrom J. Alvesrand A* 1994 Hemodialysis associated protein catabolism with and without glucose in the dialysis fluid. Kidney Int *46:* 814

[143] *Ikizler TA, Flakoll PJ, Parker RA, Hakim RM* 1994 Amino acid and albumin losses during hemodialysis: Kidney Int *46:* 830