S.17.C.1 Neurological disorders in patients with acute renal failure

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Introduction

Patients with rapidly progressive uraemia often become confused, due to a combination of uraemia, electrolyte and acid-base disorders, sepsis, the accumulation of drugs and other organ failure. Some groups with pre-existing renal disease are more prone to neurological complications; cerebral venous thrombosis in patients with the nephrotic syndrome, CNS infection in renal transplant recipients, and subarachnoid haemorrhage in adult polycystic kidney disease. Similarly, the incidence of renal failure is increased in patients with bladder dysfunction; spina bifida and multiple sclerosis.

In the critically ill patient, and especially those with acute renal failure following neurosurgery and acute liver failure, haemodialysis treatment may itself lead to cerebral hypoxia and/or oedema. To help understand the mechanisms involved, this chapter starts with a short introduction to the basic physiology regulating cerebral blood flow and intracranial pressure, in normal subjects and those with acute renal failure.

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Cerebral blood flow and the pathogenesis of cerebral oedema

The normal cerebral blood flow averages 50–55 ml · 100 $g^{-1} \cdot min^{-1}$, with a range of approximately 40–67 ml · 100 $g^{-1} \cdot min^{-1}$. The cerebral blood flow of grey matter is three to four fold greater than that of white matter [1]. The cerebral capillaries are similar to nonfenestrated capillaries in muscle and other organs. However, there are tight junctions between these endothelial cells that, under normal circumstances, do not allow the passage of proteins and other solutes that are able to pass between endothelial cells in other capillary beds. As cerebral endothelial cells possess relatively few cytoplasmic vesicles, transcellular vesicular transport is thought to be reduced compared to other sites. In addition to the differences in cerebral blood flow through the cerebral grey and white matter, local cerebral blood flow can be regulated according to neuronal activity, such that an increase in PCO_2, hydrogen ions, adenosine, and lactate result in an increased local flow by causing arteriolar dilatation [2], as does a decrease in pH and PO_2 [3]. Conversely, a decrease in PCO_2 or increase in PO_2 and/or pH cause a reduction in local cerebral blood flow [2].

About 50% of the cerebrospinal fluid that fills the cerebral ventricles and subarachnoid space is produced in the choroid plexuses, and the remainder is formed locally around the cerebral vessels and along the ventricular walls. The composition of the cerebrospinal fluid depends upon filtration and diffusion from the blood, along with facilitated diffusion and active transport, much of it across the choroid plexus, and is essentially identical to cerebral extracellular fluid. The cerebral extracellular space occupies approximately 15% of the cerebral volume, but decreases following cerebral hypoxia, as a result of neuronal swelling, to 45% or less.

The cerebral capillaries are much more permeable at birth than in adulthood, and the blood brain barrier develops during the early years of life. The blood brain barrier probably functions to maintain the environmental homeostasis of the cerebral neurones. However, the blood brain barrier can break down following trauma, irradiation, infection or at the site of tumours, so allowing the formation of vasogenic cerebral oedema (Fig. 1).

The cerebral circulation is efficiently autoregulated at perfusion pressures between 40 and 180 mmHg (cerebral perfusion pressure (CPP) is the difference between the mean arterial blood pressure (MAP) measured at the level of the carotid syphon and the mean intracranial pressure (ICP)) [4]. The normal ICP

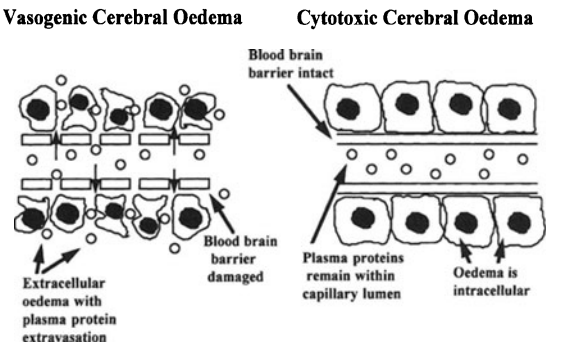

Figure 1. The blood brain barrier remains intact in the presence of cytotoxic cerebral oedema, but breaks down in cases of vasogenic cerebral oedema.

is <10 mmHg and is dependent upon cerebral arterial blood flow, cerebral metabolic rate, cerebral venous blood flow and capacitance, and also cerebrospinal fluid volume, but these same factors also regulate cerebrospinal fluid production and craniospinal buffering [5, 6]. As head upright posture increases both venous capacitance and craniospinal buffering mechanisms (CSF capacitance), ICP can be reduced by postural changes, before other changes, such as a reduction in CPP, leads to a decline in CSF production [5]. However, when such venous capacitance and craniospinal buffering mechanisms are maximally activated, in cases of sustained increased ICP, head elevation may no longer lead to a reduction in ICP. Indeed the decline in CPP coupled with a reduction in cardiac output can result in further cerebral ischaemia, with a further, resultant increase in ICP [5, 6].

Many conditions, including malignant hypertension, head trauma, intracranial tumours, abscesses, haemorrhage, metabolic and infective encephalopathies, and even fever may results in an increase in ICP [7]. When ICP is increased to more than 33 mmHg for a short period of time, this result in local cerebral arteriolar vasoconstriction, and a reduction in cerebral blood flow, as the volume of blood, spinal fluid and brain in the cranium at any one time must be relatively constant (Monro–Kellie doctrine) [1]. The resultant ischaemia stimulates the vasomotor centre and the systemic blood pressure increases to maintain the CPP. In addition, stimulation of the cardioinhibitory centre produces bradycardia and respiration is slowed. This response to maintain the CPP is known as the Cushing reflex. Cerebral autoregulation is normally sustained over a wide gradient of 40–180 mmHg, but can be compromised at the extremes during cardiorespiratory

arrests and malignant hypertension [8], with resultant cerebral hypoxic damage. Elderly patients with atherosclerotic blood vessels may require a greater CPP to maintain adequate cerebral neuronal oxygen delivery.

However, if the increase in ICP is sustained and the increase in cerebral perfusion inadequate, then cerebral hypoxia may occur. This may be localised, or more generalised if the cerebral blood flow is less than the threshold for cerebral autoregulation. The reduction in effective oxygen delivery at the neuronal level will disrupt oxidative phosphorylation [8]. Neurones switch to the less efficient anaerobic metabolism, with a consequent reduction in ATP biosynthesis, so impairing normal Na^+/K^+ pump function, leading to intracellular Na^+ accumulation and extracellular K^+ accumulation [9]. Other high energy phosphates, such as phosphocreatinine, are also depleted, and inorganic phosphate and lactate accumulate, causing tissue acidosis [8]. The osmotic gradient created within the cerebral neurones by the increased concentrations of sodium, lactic acid and the breakdown of intracellular proteins due to intracellular acidosis, facilitates the rapid influx of water to neurones and glia. This cytotoxic oedema is initiated within minutes of the onset of cerebral ischaemia, and can produce an increase in brain tissue water of 3–5% [8] (Fig. 1). If the hypoxia is prolonged, then there will be subsequent endothelial injury resulting in a loss of the integrity of the blood-brain barrier, thereby allowing the extravasation of plasma proteins from the intravascular compartment as well as an accumulation of extravascular water. The time course of this vasogenic cerebral oedema occurs some hours later than that of cytotoxic oedema [8] (Fig. 1). The severity of vasogenic oedema depends upon a variety of factors, including the degree of reperfusion and the extent of collateral blood flow to the ischaemic area [8, 9]. Reperfusion of the occluded cerebrovascular bed can markedly exacerbate cerebral oedema by increasing both the rate and amount of fluid exudation into the surrounding cerebral tissue [10]. Thus, in the critically ill patient, although the CPP may be sustained >40 mmHg, localised areas of cerebral hypoxia may develop, with consequent cytotoxic or vasogenic cerebral oedema and local disruption of the blood brain barrier. Under these circumstances, a CPP of 60 mmHg or greater may be required to prevent the development of such focal areas of cerebral hypoxia [11], as studies on brain metabolism have shown that the management of a patient based on the maintenance of an adequate CPP does not, necessarily, prevent cerebral hypoxia [12].

Cerebral blood flow in acute renal failure

Early studies on global cerebral blood flow in patients and animals with uraemia, have shown that cerebral blood flow may be increased, normal, or reduced [13]. In part, an increase in total cerebral blood flow may be consequent upon anaemia or systemic acidosis [14], as in patients with chronic renal failure, the correction of anaemia with erythropoietin results in a reduction in cardiac output and total cerebral blood flow. Abnormalities in the distribution of the blood supply at the neuronal level, resulting in a reduction in neuronal oxygen delivery and consumption, have been demonstrated clinically and experimentally [15]. Although acute renal failure is not associated *per se* with the development of cerebral oedema, patients and animals with renal failure have been shown to have abnormalities of the blood brain barrier, and are predisposed to develop both cytotoxic and vasomotor cerebral oedema [15]. This is supported by more recent studies in patients with acute renal failure, in the setting of sepsis and/or multiorgan failure, which have shown not only a reduction in total cerebral blood flow, but also a reduction in cerebral oxygen uptake [16], thus implying a degree of cerebral hypoxia.

Cortical cerebral electrical activity, as assessed by EEG recordings in uraemic subjects, has similarly been reported to range from a normal pattern of activity, to minor abnormalities, through to markedly abnormal patterns with predominant slow wave activity [17, 18]. In patients with acute renal failure, those with predominant δ and θ wave activity are usually those with greater severity of illness [18]. More recently, multimodality evoked potentials have been advocated as part of the neurological assessment of patients with metabolic coma and following intracranial trauma [19]. By using a flash stimulus, visual evoked potentials can be recorded in unconscious patients, and more subtle abnormalities in cerebral function can be detected than by simple EEG recordings alone [20]. Patients with acute renal failure have been shown to have increased latencies for the later peaks. These abnormalities can be present in patients with normal ICP and CPP, and are thought to be due to local cerebral neuronal ischaemia [20].

Renal failure patients at risk of cerebral oedema/hypoxia

As the blood-brain barrier is not present at birth, neonates and young babies are potentially a risk group for developing cerebral oedema/hypoxia. In adult patients, the blood brain barrier can be disrupted

following neurosurgery and in association with metabolic derangements. Acute renal failure may occur in patients requiring neurosurgery, usually in the setting of multiple trauma and/or sepsis. In patients with known chronic renal failure, who require neurosurgical intervention for a variety of conditions including cerebral tumours and intracranial/subdural haemorrhage, there may be disruption of blood brain homeostasis. As for patients with metabolic coma, those with acute hepatic failure and diabetic coma are prone to develop cerebral oedema/hypoxia due to abnormalities of the blood brain barrier, coupled with a mismatch in cerebral blood flow and oxygen delivery, resulting in cerebral neuronal hypoxia [11].

In the intensive care setting, patients often have evidence of more than one organ failure, and the combination of renal failure with pulmonary failure and/or cardiac failure, will result in a reduction in cerebral oxygen delivery (Table 1), for example, patients with pancreatitis may develop an inflammatory pneumonitis, due the activation of kinins, elastase and of the cytokines from activated neutrophils and macrophages, and become confused [21]. As part of the sepsis syndrome, the reduction in systemic vascular resistance leads to a reduction of systemic tissue perfusion pressure, and this may be mirrored in the cerebral circulation. Cerebral blood flow has been shown to be reduced in these patients [16], and the combination of reduced cerebral oxygen delivery coupled with reduced cerebral oxygen uptake, leads to cerebral neuronal hypoxia [3], which may be localised or generalised, resulting in mild confusion through to coma [16]. These effects will be exacerbated in those patients with a reduced CPP, either due to reduced MAP or sustained increased ICP [1]. The maintenance of CPP alone does not necessarily prevent localised cerebral hypoxia [12], thus patients with pre-existing cardiac, pulmonary, and cerebrovascular disease, such as the elderly, are more prone to develop cerebral dysfunction during an episode of acute renal failure. In addition, some infections predispose to cerebral oedema/hypoxia by directly or indirectly causing cerebral endothelial damage, resulting in localised areas of hypoxia. These include severe cerebral malaria, leptospirosis, and haemolytic uraemic syndrome secondary to *E. coli* serotype O157 [22]. Occasionally, patients with underlying vasculitis, particularly systemic lupus erythematosus (SLE), present with severe cerebral involvement and renal failure (Table 2).

Table 1. Cardiac and pulmonary conditions resulting in reduced cerebral oxygen delivery.

Cardiac causes	ischaemic heart disease
	valvular heart disease
	myocarditis
	tamponade
Pulmonary causes	pneumonia
	ARDS
	pulmonary oedema
	pneumothorax
	pneumonitis
	pulmonary haemorrhage
	pulmonary emboli
	pulmonary vasculitis

In addition to cerebral damage, patients with acute renal failure may have peripheral nervous system damage, either as a pre-existing condition, or associated with the cause of the underlying acute renal failure (Table 3). Muscle weakness and nerve damage may occur during the treatment of multiple organ failure associated with sepsis. Motor nerve fibres are predominantly affected with a primary axonal degeneration [23]. Muscle biopsies predominantly show atrophy, affecting both type I and II fibres. In addition, scattered areas of necrosis are often present without evidence of vascular occlusion or inflammatory infiltrate [24]. This may be due to a combination of ischaemic damage during periods of relative hypotension, pressure necrosis, nutritional deficiencies associated with prolonged parenteral nutrition [25], reduced renal 1α hydroxylase activity with reduction in plasma 1,25 $(OH)_2D3$, and, in addition, some drugs may also cause a peripheral neuropathy when given to patients with renal failure. However, the most common finding is of a nonspecific, generalised polyneuropathy with widespread axonal degeneration. The precise cause of this critical illness, polyneuropathy, has yet to be elucidated, but electrophysiological studies have suggested a sepsis-related nerve failure caused by early impairment of axonal transport and transmembrane potential [26]. Continued sepsis may lead to further ischaemic/hypoxic damage, coupled with lack of movement/use. This is supported by both the skeletal muscle changes and necropsy findings of anterior horn cell chromatolysis, a centripetal response to axonal degeneration [24].

Patients with rapidly developing uraemia often display lethargy with loss of concentration, which can progress to an acute confusional state and eventually coma. Generalised cortical abnormalities are found on EEG recordings, with an increased proportion of both δ and θ slow wave activity [17, 18], similarly, multievoked potentials and flash visual responses also show delayed responses, with both prolongation of the later latencies and a reduction in amplitude [20].

Table 2. Central neurological disorders in acute renal failure.

Infections		
Bacterial	meningitis/encephalitis	Strep. pneumoniae
		N. meningitidis
		Staphylococcal toxic shock syndrome
		M. tuberculosis
		Typhoid
		Leptospira
		Rickettsiae
		Mycoplasma
	ventricular shunts	*S. eidermidis*
	cerebral abscess	*Streptococci*
		Staph.aureus
Protozoal	meningitis/encephalitis	Plasmodium malariae
Viral	meningitis/encephalitis	Herpes simplex
		Hanta viruses
		HIV-1
	(immunocompromised)	Cytomegalovirus
	Hepes varicella/zoster	
Metabolic	diabetes mellitus	keto-acidotic coma
		hyperosmolar coma
Vasculitic	meningitis/encephalitis	SLE
		microscopic polyangioitis
		Wegener's granulomatosis
		Kawasaki's syndrome
Hypertensive crisis	encephalopathy	Scleroderma
		malignant hypertension
		renal artery stenosis
Neoplastic	meningitis/encephalitis	Leukaemias
		Lymphomas
		hyperviscosity syndrome
Drugs	encephalopathy/coma	penicillins
		cephalosporins
		imipenem/meropenem
		opiate analgesics
		benzodiazepines
		barbiturates
		acyclovir/gancyclovir
		foscarnet
		cyclosporin A
		tacrolimus
Illegal drugs	coma/seizures	MDMA "ecstasy"
Other conditions	cerebrovascular accident (CVA)	cholesterol emboli
		fat embolus
		amniotic fluid embolus
	cerebral venous sinus thombosis +/− hypovolaemia	nephrotic syndrome
	encephalopathy/CVA	haemolytic uraemic syndrome
		thrombotic thrombocytopenic purpura
		disseminated intravascular coagulation
		post cardiac bypass surgery
		sickle cell disease
		cortical vein thrombosis
	bulbar paralysis	snake bite

Table 3. Peripheral nervous disease in acute renal failure.

Cord lesions	Trauma	
	Ischaemia	diabetes mellitus
		thrombotic thrombocytopenic purpura
		hyperviscosity syndrome
	Atheromatous	aortic anuerysm repair
		cholesterol emboli
	Viral	HIV-1
	Vasculitis	SLE
		microscopic polyangioitis
	Neoplastic	multiple myeloma
Peripheral nerve lesions	Trauma	
	Viral	HIV-1
	Inflammatory	Guillain-Barré
	Ischaemic	diabetes mellitus
	Intensive care neuromyopathy	
	Vasculitis	microscopic polyangiitis
		cryoglobulinaemia
		rheumatoid arthritis
	Neoplastic	myeloma
	Drug	nitrofurantoin
		metronidazole
		isoniazid
		amiodarone
		vincristine
	Snake bite	Elapidae
		Hydrophidae
	Others	sarcoid
		amyloid
	Toxic	lead

Cerebral oxygen delivery in acute renal failure depends upon the underlying pathogenesis [16], however, additional regional reductions in oxygen delivery may occur due to atheromatous large vessel disease or small vessel damage. This may lead to localized areas of cerebral hypoxia, resulting in increased free radical oxygen production and increased lipid peroxidation induced damage. Animal experimental models of acute uraemia have shown that cerebral neuronal oxygen demand is reduced, but whether this is an adaptation to reduced oxygen delivery has not been established. Na^+/K^+ activated ATP-ase activity and total adenine nucleotides from whole brain extracts was found to be either normal or reduced [27]. This, coupled with increased ATP and creatinine phosphate and reduced adenosine mono-diphosphate and lactate, suggests that under experimental conditions, the cerebral neurones of acutely uraemic animals are unable to utilise ATP adequately, but can maintain normal cell energy charge and redox state. Cerebral glycolysis is reduced in acute uraemia, but this also occurs in other metabolic encephalopathies, and is exacerbated by coexistant metabolic acidosis. Investigation of cerebral electrolyte content in both animals and humans with acute renal failure, has shown that there were no differences in total brain content for K^+, water, and Mg^{2+}, whereas there was a small increase in Na^+ and almost a two-fold increase in Ca^{2+} [28]. This is supported by *in vitro* data which has shown that several important cell membrane and subcellular ion exchange pumps, Na^+/Ca^{2+}; Na^+/K^+ and Ca^{2+}-ATPase are down regulated in acute uraemia [29]. By interfering with intracellular calcium fluxes, then a number of key, second intracellular signalling systems will be affected. This may then lead to alteration in both the response to and the secretion of neurotransmitters.

Patients with chronic renal failure have well documented abnormalities of plasma and cerebrospinal fluid amino acids. These could potentially affect cerebral neuronal function, as found in hepatic encephalopathy and in inherited disorders of amino acid metabolism, by altering neurotransmitter production. In particular, glutamine concentrations are reduced, so

potentially resulting in reduced GABA (gamma aminobutyric acid) synthesis, whereas glycine is increased [30]. As GABA is a post-synaptic anti-excitatory neurotransmitter, and glycine a pre-synaptic excitatory transmitter, the net effect would be to potentially increase neuronal excitability, and therefore promote myoclonic jerks and even seizures [8]. In acute renal failure, although there are abnormalities in plasma and cerebrospinal fluid amino acid profiles, they are more heterogenous than those found in chronic renal failure, and depend upon both the underlying aetiology and the presence of sepsis [31].

After the liver, the kidney is the next most important organ involved in the metabolism of both endogenous and exogenous compounds, including drugs. Some drugs can accumulate and cause encephalopathy and even fitting (Table 2). Thus drug doses and administration schedules need to be adjusted for the degree of renal impairment. All sedatives accumulate, even propofol, as the metabolites, which have some activity, are renally excreted. For example, elderly patients sedated with midazolam may remain deeply unconscious for longer than a week following discontinuation of the infusion.

Acute uraemia may also affect peripheral nerve function, due to the accumulation of the waste products of protein catabolism [32]. In particular, the retention of 3-methylguanidine in chronic renal failure has been shown to interfere with the assembly of tubulin, the key structural protein building block, in peripheral nerves. Muscle weakness is a common feature in patients in acute renal failure, and is due to a combination of factors. Muscle biopsies have noted the presence of ischaemic damage, due to periods of relative hypotension, and reduced energy stores with glycogen depletion [33]. The reduction in plasma glutamine concentrations results in reduced carnitine synthesis, and, coupled with prolonged parenteral nutrition, may result in muscle carnitine deficiency [25]. In addition, 1,25 $(OH)_2D3$ synthesis is decreased in acute renal failure. Careful attention to maintaining an adequate tissue perfusion pressure, with early good quality enteral nutrition and replacement of vitamin D3 with alfacalcidol, may result in a reduction in the incidence of intensive care neuromyopathy and a shorter recuperative period following an ICU stay.

The effect of electrolyte disorders in acute renal failure

Acute electrolyte disorders are common in patients with acute renal failure, but few cause serious neurological manifestations. Hyponatraemia is usually asymptomatic unless severe and neurological problems arise most commonly as a consequence of rapid correction [34]. Hypernatraemia results in a confusional state when the plasma sodium exceeds 160 mmol/l. Disorders of potassium metabolism seldom give rise to neuronal difficulties except in profound hypokalaemia. Similarly, hypocalcaemia and hypomagnesaemia are not usually associated with tetany or seisures unless profound, or in association with encephalitis, or drug toxicity (cyclosporin A, tacrolimus, acyclovir).

Sodium

Hyponatraemia

Hyponatraemia may occur in acute renal failure if the patient has been treated with intravenous hypotonic fluids, or more commonly, in the setting of chronic liver disease. Acute severe hyponatraemia (<115 mmol/l) may present with a range of neurological dysfunction from lethargy through to coma, and even generalised grand mal seizures [35). Patients may also suffer muscle weakness, cramps, myoclonic jerks and even flaccid paralysis. Occasionally, rhabdomyolysis may occur following hypotonic fluid therapy.

Although neurological disorders are common in hyponatraemic patients, they are usually reversible unless the clinical course is complicated by an additional cerebral insult, such as hypoxia or hypotension. Hypoxic cardiac arrest usually occurs due to the development of neurogenic pulmonary oedema, rather than pulmonary oedema. The risk of permanent brain damage is increased in prepubescent children, premenopausal women, and also by both the severity and duration of the hyponatraemia. During hyponatraemia, the brain compensates by reducing solute content, both intraneuronal electrolyte and organic osmolyte content are reduced. In addition, glutathione, the most abundant cerebral anti-oxidant, is also reduced. Animal and cell culture experiments have both shown that the osmotic depletion of glutathione renders the brain more susceptible to oxidative injury [36]. Hence, the importance of preventing hypoxic damage to the brain of hyponatraemic patients.

Overzealous correction of hyponatraemia, an increase in serum sodium of 25 mmol/l or greater within 24–48 hours, has been reported to result in cerebral demyelinating lesions [34]. However, most patients who developed central pontine myelinolysis not only had a rapid increase in serum sodium, but either had severe liver disease or another co-morbid

condition, which may have affected the integrity of the blood brain barrier, such as septicaemia or malignancy [37]. Indeed, cerebral demyelinating lesions have been reported in patients following liver transplantation, who were never hyponatraemic, but did have a perioperative increase in serum sodium [38]. Others have also observed that an increased serum sodium is a major risk factor for the development of demyelinating lesions [39].

Management depends upon the clinical state and underlying condition, with the aim of increasing the serum sodium by 1 mmol/hour, until a maximum of 25 mmol/l, or until a target of 125–132 mmol/l has been achieved [40]. In patients who are still passing urine, this can be given as hypertonic saline with, or without loop diuretics, depending upon the fluid status of the patient. For patients with chronic liver disease, fluid restriction and withdrawal of loop diuretics may suffice, but the increase in serum sodium concentration is slow, some 2 mmol/l/day [41]. In patients with chronic liver disease who have been listed for urgent hepatic transplantation, we have used continuous forms of haemofiltration and/or dialysis, using either a low sodium or normal sodium haemofiltration substitution/dialysate fluid to increase the serum sodium in a controlled fashion [42]. Similar treatment schedules have been used in patients with acute renal failure, who were inadvertently given hypotonic fluids, or accidently given hypotonic dialysis/subsitution fluids.

Hypernatraemia

Hypernatraemia can also cause lethargy and coma. In patients with acute renal failure, hypernatraemia may be associated with diabetic nonketotic coma, or following neurosurgical intervention. In most cases in the intensive care unit, hypernatraemia develops due either to an excess intake of sodium compared to water coupled with increased urinary losses of water; or due to excessive losses of water compared to sodium, such as sweating, diarrhoea and burns. Patients recovering from acute tubular necrosis have an impaired response to ADH, and therefore pass urine with an excess of water to sodium, and if bed bound, despite an appropriate thirst drive, may not be able to drink sufficient fluids and become hypernatraemic. In the oliguric patient, hypernatraemia may develop due to the administration of excessive amounts of sodium in the form of drugs (prepared as sodium salts or infused in saline), parenteral nutrition and human albumin solutions, or other plasma expanders.

Hypernatraemia results in an increased plasma osmolality and the passage of water from the cerebral neurones into the plasma, resulting in neuronal contraction and shrinkage of the brain away from the supporting dura, and this may lead to cerebral venous haemorrhage. The response to a reduced intracranial pressure is to decrease cerebrospinal fluid production and increase cerebrospinal fluid reabsorption, the blood-brain barrier becomes more permeable to plasma potassium, and cerebrospinal fluid sodium and chloride, and, in addition, cerebral idiogenic osmoles are created by the production of osmotically active organic acids from glycolysis and the citric acid cycle [43].

Management depends upon renal function and fluid balance. In a patient with recovering ATN, additional hypotonic fluids are required, whereas sodium restriction and loop diuretics would be appropriate for the salt loaded, oliguric patient. Similarly, patients who become hypernatraemic during treatment with continuous forms of haemofiltration and/or dialysis, require a reduction in sodium intake or the sodium concentration of the substitution/dialysis fluids.

Potassium

Hyperkalaemia

Unlike sodium, the brain controls intracellular and cerebrospinal fluid potassium concentrations, and is therefore able to function at extracellular concentrations which cause muscle fasciculations, paralysis and cardiac asystole. Hyperkalaemia develops in acute renal failure and is exacerbated by metabolic acidosis. The causes and treatment of hyperkalaemia are discussed in Section 4.

Hypokalaemia

Hypokalaemia has been reported to cause lethargy and somnolence, but is more commonly associated with muscle weakness, fasciculation and myoclonic jerks. Rhabdomyolysis can occur following exercise, with a serum potassium of 2.0 mmol/l or less. Hypokalaemia is discussed further in Section 4.

Chloride

Hyperchloraemia

Hyperchloraemia usually occurs in the setting of a metabolic acidosis (normal anion gap acidosis). Sim-

ple metabolic acidosis rarely produces coma, however severe acidosis can reduce both cerebral perfusion by causing systemic vasodilatation, and cerebral oxygen delivery by depressing cardiac output.

Hyperchloraemia may develop during treatment with continuous forms of haemofiltration and/or dialysis, when subsitution/dialysate fluids containing too little anionic buffer base (lactate, bicarbonate). There is a corresponding increase in chloride content and this can be corrected by changing the appropriate fluids.

Hypochloraemia

Hypochloraemia similarly, usually develops with a metabolic alkalosis. Severe metabolic alkalosis can result in fitting. Animal experiments have shown that the pial arteries surrounding the brain are sensitive to changes in chloride concentration, hypochloraemia resulting in vasoconstriction and reduced cerebral blood supply [43]. Theoretically, hypochloraemia could reduce red blood cell oxygen tissue delivery, due to changes in the haemoglobin-oxygen dissociation curve.

In the intensive care unit, the most common cause of hypochloraemia with a metabolic alkalosis is the use of continuous forms of haemofiltration and/or dialysis, with substitution/dialysis fluids containing an increased amount of buffer base, with a compensatory reduced chloride content [44]. Treatment is to provide additional chloride, usually in the form of normal saline, although hydrochloric acid has been used occasionally.

Calcium

Calcium is predominantly found in the skeleton (99%), with smaller amounts in muscle (0.3%) and other tissues (0.7%). In plasma, some 44% is free ionised calcium, 47% protein bound (albumin 37%, globulin 10%) and 9% complexed (phosphate, citrate and bicarbonate) [45]. The ratio of free to bound can be affected by changes in plasma pH and protein concentration.

Hypercalcaemia

Hypercalcaemia can develop rapidly in patients with malignancy, with a vicious cycle of nausea, vomiting, dehydration with renal impairment. Hypercalcaemia can lead to nephrocalcinosis and also to renal tubular damage, reducing the response to ADH, so resulting in further water loss and dehydration. Thus, patients recovering from acute renal failure may also become hypercalcaemic [46].

Patients are often asymptomatic, unless the calcium exceeds 3.3 mmol/l, when a history of a progressive decrease in consciousness, which may result in coma, may be obtained [47]. Hypertension is commonly found in cases of hypercalcaemia due to increased vasomotor tone. Cardiac arrhythmias, ranging from bradycardia through to ventricular tachycardia, may develop, and so compromise cerebral oxygen delivery.

Hypercalcaemia may also occur due to excess calcium administration, in the form of parenteral nutrition and/or using a high calcium dialysate, which may occur when daily intermittent haemodialysis treatment with untreated water is used as dialysate. Patient immobility in the intensive care unit exacerbates hypercalcaemia.

Treatment is based on restoring plasma volume and maintaining a high urine output with a natriuresis, as this maximises urinary calcium excretion [46]. However, this may not be possible in the oligo-anuric patient. Single infusions of the diphosphonate pamidronate, have been reported to be both effective in reducing hypercalcaemia, and safe in patients with established renal failure [47]. Other treatments, such as reducing dialysate calcium concentration in haemofiltration/dialysis fluids, should also be used.

Hypocalcaemia

Hypocalcaemia usually occurs in uncomplicated cases of acute renal failure due to the rapid reduction in renal 1α hydroxylase activity and reduced intestinal calcium absorption. Tetany is unusual, as the plasma ionised calcium to bound calcium ratio is increased by the metabolic acidosis of acute renal failure. [46]. More severe hypocalcaemia may develop following rhabdomyolysis and in other causes of acute renal failure, such as pancreatitis. Ethylene glycol self poisoning results in marked hypocalcaemia due to calcium oxalate deposition in tissues. In addition, renal tubular damage may also lead to hypocalcaemia due to excess urinary calcium losses, as found in patients treated for ovarian and testicular tumours with cisplatin, and also following post-obstructive diuresis.

Although hypocalcaemia may cause delirium and psychosis, in acute renal failure most patients are acidotic and hypoalbuminaemic and therefore, the effective ionised calcium concentration is often maintained. Rapid correction of acidosis and infusion of albumin may lead to hypocalcaemia and provoke tetany [46]. Acute hypocalcaemia may also be associ-

ated with cardiac arrhythmias, due to prolongation of the QT interval, and seziures which require urgent treatment with intravenous calcium gluconate or chloride.

Magnesium

The skeleton contains 55% of the body magnesium, with 45% in soft tissues and 1% in the extracellular fluid. In plasma 55% of the magnesium is free, 30% protein bound and 15% complexed [45].

Hypermagnesaemia

Hypermagnesaemia usually only occurs if patients with acute renal failure have either been given magnesium containing medicament; antacids, enemas, laxatives, or dialysate with a high magnesium concentration. Patients can become lethargic, with muscle weakness when the plasma magnesium exceeds 2mmol/l (4 mEq/l), but can be life threatening when exceeds 3 mmol/l, when bradyarrhythmias and respiratory effort may be affected. Normal treatment is to avoid magnesium containing medications and reducing dialysate magnesium concentration. In an emergency, intravenous calcium can be used to antagonise the cardiac effects of hypermagnesaemia.

Hypomagnesaemia

Hypomagnesaemia often occurs in association with hypokalaemia and hypocalcaemia. It may reflect redistribution from plasma into tissues, as occurs in respiratory alkalosis, patients with diabetic ketoacidosis following insulin administration, and acute pancreatitis. Magnesium deficiency can occur due to chronic gastrointestinal losses following malabsorption or prolonged nasogastric suction, and/or renal tubular losses, due to primary renal tubular defects or secondary to drugs (aminoglycosides, amphotericin B, cyclosporin A, pentamidine, cisplatin). Chronic alcoholics often have a low magnesium dietary intake and increased urinary excretion, and hypomagnesaemia may occur following acute hospital admission and alcohol withdrawl.

Tetany, ventricular arrhythmias and seizures may occur, and treatment with parenteral magnesium is required. In those cases associated with hypokalaemia and hypocalcaemia, all electrolyte deficiencies should be corrected.

Phosphate

85% of body phosphate resides in the skeleton, 6% in skeletal muscle and 9% in other tissues [45]. In plasma 54% is free (44% as HPO_4^{2-} and 10% as $H_2PO_4^-$), 12% is protein bound, and the remainder complexed, usually with sodium (28%), or calcium (3%) and magnesium (3%) [45].

Hyperphosphataemia

Hyperphosphataemia usually develops during acute renal failure due to the reduction in glomerular filtration and renal tubular phosphate secretion. Marked hyperphosphataemia occurs following rhabdomyolysis, and may increase local muscle blood flow.

Hypophosphataemia

Pseudohypophosphataemia often occurs in the patient with acute renal failure in the intensive care unit. Plasma phosphate is redistributed intracellularly following carbohydrate nutrition, respiratory alkalosis, Gram-negative sepsis, severe burns, diabetic ketoacidosis, post renal transplantation and administration of sodium lactate solutions. True hypophosphataemia is due to excessive renal tubular phosphate loss, which may be associated with other electrolyte abnormalities such as hypomagnesaemia, and following drugs such as paracetamol (acetaminophen), diuretics and steroids [48]. In addition, chronic intestinal malabsorption and alcoholism can also result in hypophosphataemia. As all forms of renal replacement therapies do not contain phosphate in the dialysate or subsitution fluids, then these treatments will exacerbate hypophosphataemia [48].

Patients can develop muscle weakness and even rhabdomyolysis, however myocardial dysfunction and cardiomyopathy can be life threatening. Cardiac dysfunction associated with reduced intracellular ATP may be exacerbated by changes in red blood cell deformability and changes in 2,3 DPG, leading to reduced tissue oxygen delivery. The combination of intracellular phosphate depletion and cardiac dysfunction can lead to a generalised encephalopathy.

Pre-existing neurological disease in patients with acute renal failure

Acute renal failure may develop *de novo*, or as acute on chronic renal failure in patients with either acute or

established neurological disease. For example, acute tubular necrosis may complicate major head trauma, or subarachoid haemorrhage in a patient with hypertensive nephropathy or adult polycystic disease, or urinary tract sepsis in patients with established bladder dysfunction, such as spina bifida or demyelinating diseases. Similarly, infection in the immunocompromised renal transplant patient may affect the central nervous systen.

Head Injuries

Following trauma that produces localised cortical contusion and laceration, there will also be some diffuse axonal injury. This may be complicated by intracranial haematoma and infection, leading to brain oedema, increased intracranial pressure, mid-line brain shift and further hypoxic/ischaemic brain damage. If the patient is not adequately resuscitated, hypoxia can supervene due to a combination of airway obstruction, chest trauma followed by infection, collapse, or fat emboli and neurogenic pulmonary oedema. Similarly, inadequate management of such injuries will result in hypotension, and thus may lead to renal failure.

Hypertension, atherosclerosis and diabetes mellitus

Severely hypertensive patients may have a history of stroke, focal neurological defects and subarachnoid haemorrhage. Similarly, patients with atherosclerosis may have arterial bruits, carotid, femoral and renal, and also have a history of stroke or focal neurological damage. Patients with diabetes mellitus may have evidence of both macro and microvascular cerebrovascular disease. All these patients are more susceptible to develop acute renal failure when exposed to a circulatory insult, such as hypovolaemia or sepsis, as renal perfusion pressures are more critical than in patients without vascular disease.

Infection

Immunocompromised host

Acute renal failure can develop following infection in the immunocompromised host. Patients with renal, heart, liver, pancreas and bone marrow transplants often do not have normal renal function, due to the effects of drug therapy (for example cyclosporin A, tacrolimus, amphotericin B), and secondary complications including hypertension and diabetes mellitus. Thus infections, coupled [24] with the use of nephrotoxic antibiotics or the development of other complications, such as haemolytic uraemic syndrome post bone marrow transplantation, can lead to acute renal failure. Cerebral complications in the immunocompromised host are set out in Table 4.

Renal allograft transplant recipients with deteriorating renal graft function due to acute vascular or cellular rejection, are often treated with a variety of polyclonal antibodies to T and/or B lymphocytes. These agents are also used to treat rejection in other

Table 4. Neurological disorders in the immunocompromised host.

Encephalitis/coma	viral	Herpes simplex
		Herpes varicella/zoster
		CMV
		Papova virus
	malignant	post transplant lymphoproliferative disorder
Meningitis	bacterial	Listeria
		Legionella
		Nocardia
		Mycobacteria
	parasitic	Toxoplasma
	fungal	Candida
		Crytococcus
		Aspergillus
Epileptic seizures	bacterial	Cerebral abscess
	parasitic	Toxoplasma
		Strongyloides
	viral	Herpes viruses
		Papova virus

solid organ transplantation and include OKT3, ATG and ALG. They result in sudden lymphocyte lysis and the release of lympho-, cyto- and chemokines. This may result in a variety of neurological syndromes ranging from headache to aseptic meningitis and frank encephalopathy.

Ventriculo-atrial/peritoneal shunt infection

Cerebral ventriculo-atrial shunts were the preferred surgical choice for the treatment for hydrocephalus. Approximately 30% of juguloatrial catheters become colonised with bacteria, usually *S. epidermidis* [49] which produces a biofilm on the plastic surface of the catheter, so protecting the micro-organism from host defences. Mico-organisms migrate down the catheter due to the development of an electrical gradient which is set up at the time of the surgical operation [50]. Once the wound has healed the gradient disappears, and this is in keeping with the clinical situation where the vast majority of catheter infections occurred within the first two months following insertion. Infection was often associated with the development of microscopic haematuria and proteinuria, due to the host response to low grade persistent bacteraemia. Renal biopsy characteristically showed the appearances of type I mesangiocapillary glomerulonephritis, although a variety of histological diagnoses have been reported, ranging from minor mesangial proliferation, focal segmental lesions through to diffuse exudative proliferative glomerulonephritis, and even occasionally, crescentic lesions [51].

IgM and C3 were demonstrated in the subendothelial immune complexes, and some patients developed circulating rheumatoid factors and cryoglobulins. Following a change in surgical practice, to place the distal end of the shunt into the peritoneal cavity, the incidence of shunt nephritis has markedly declined [52].

Bacterial infections

Patients with secondary and tertiary syphilis may develop a membranous type of glomerulonephritis, with predominantly IgM mesangial deposits. Some will progress to develop neurological disease, tabes dorsalis and neurosyphilis. Acute renal failure is rare, but syphilis may reactivate in the HIV-1 patient with AIDS, and progress to renal failure in the setting of multiple organ failure.

Viral infections

The human immunodeficiency retroviruses, HIV-1 and HTLV-1 can both affect the nervous system. HIV-1 can directly cause neurological disease at both the time of the primary infection and also both in the asymptomatic period and then when the patient develops AIDS. Patients may present with encephalitis, meninigitis and cranial nerve paralises. In addition, both cord lesions and also peripheral nerve lesions have been described [33]. HIV-1 infected patients who progress to develop AIDS, are also susceptible to opportunistic infections (Table 4).

Recently, a variety of renal glomerular lesions have been described in patients with HIV-1 [53], ranging from minimal change, to focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, and even crescentic disease. One of these, focal segmental glomerulosclerosis, which typically affects Afro-Caribeans, can present with nephrotic range proteinuria and often proceeds to end-stage renal failure within 6 months of diagnosis [54]. Ultrasound examination of the kidneys in this condition shows a characteristic bright renal cortex, with preserved renal size. Preliminary studies have suggested that steroids (1 mg/kg · day) may be effective in reducing the rate of decline in renal function [53].

Renal failure may also occur in HIV-1 patients treated for CMV infection with acyclovir, gancyclovir and the newer antiherpes virus agents. All these drugs are potentially toxic to the renal tubules, and dose modification is required according to renal function. Despite dose reduction some patients develop acute renal failure, with a characteristic vacuolation of the renal proximal tubular cells. In addition, accumulation of these drugs can result in an encephalopathy [55]. Neither acyclovir nor gancyclovir are appreciably removed by peritoneal dialysis, and therefore, if neurotoxicty is suspected, intermittent or continuous forms of haemodialysis and/or haemofiltration are required for effective drug elimination [55].

HTLV-1 infection predominantly occurs in patients from the Carribean and Japan. Progressive spastic paraparesis develops, more commonly in women, and most patients are wheel chair bound within 10 years of the onset of the intial symptoms. Most patients have bladder involvement, with urinary frequency, urgency and incontinence. Recurrent urinary tract sepsis may result in interstitial renal disease and chronic renal impairment. As with HIV-1 patients, they have a polyclonal increase in gammaglobulins and may be more susceptible to infection, which may precipitate

acute renal failure. Occasionally, patients with HTLV-1 can develop polymyositis, and muscle breakdown coupled with dehydration may also result in acute renal failure [56].

Demyelinating diseases

Multiple sclerosis is the classic demyelinating disease, and many patients will develop disturbed urinary sphincter function. Patients with spinal cord disease can often achieve reasonable bladder emptying by abdominal pressure, whereas those with detrusor and sphincter inco-ordination may need intermittent self catheterisation or an indwelling catheter. Many patients with multiple sclerosis die of unrelated causes, and up to 30% of disease relapses are triggered following infection, many of which are from the urinary tract.

Recombinant interleukin-I_β has recently been used to treat multiple sclerosis. Earlier studies using interferons α and γ for the treatment of hepatitis B, lymphoproliferative disorders and renal cell carcinoma, have reported a range of renal effects varying from interstitial renal disease, with increased renal tubular enzymuria, through to various forms of glomerulonephritis often with proteinuria, and even cases of acute renal failure [57, 58].

Spinal cord injury and paraplegia

The survival of patients following spinal cord injury is greater for those with incomplete lesions and those with low lesions. In a long term follow-up study, urinary tract sepsis and its complications was the most common cause of death [59]. Following the initial injury there may be extensive damage to other internal organs and hypotension, leading to acute renal failure. Nursing care is paramount during the period of flaccid paralysis to prevent the development of pressure sores. Initially the bladder is atonic, and then will develop reflex detrusor activity, unless there is a lower motor neurone or cauda equina lesion. Depending on the exact neurological problem, patients achieve urinary drainage by condom drainage, urethral sphincterotomy, intermittent self catheterisation, or long-term indwelling urinary catheter. There is an increased incidence of bladder calculi with indwelling urinary catheters.

Despite the improvements in urinary drainage, renal function can deteriorate with time. In addition, ischial pressure sores may develop and become additional sources of recurrent sepsis, with the possibility of secondary amyloidosis and renal amyloid deposition. Not surprisingly, episodes of acute renal failure may be precipitated by urinary tract sepsis.

Patients with chronic renal failure who have been treated by haemodialysis for more than ten years, can develop neurological problems due to the deposition of β_2-microglobulin, which has been structurally modified in a post-translational process to result in a form of amyloid. Characteristically, this dialysis associated amyloid is deposited in the cervical and lumbosacral vertebrae. This may result in cord compression requiring acute neurosurgical decompression.

Congenital/inherited diseases

Spina bifida

Children with hydrocephalus are now treated by ventriculoperitoneal shunting (see shunt nephritis above). Most children with menigomyelocoeles develop neuropathic bladders, and therefore suffer from urinary incontinence, repeated infections and urinary reflux [60]. Regular monitoring of renal function and development is required. Intermittent self catheterisation is the treatment of choice [61], and rotating antibiotics may be indicated for those with reflux and scarring. However, childhood renal scarring can result in the failure of normal renal development, and progressive renal failure with hypertension may then develop.

Adult polycystic kidney disease

Adult polycystic kidney disease is (APKD) an autosomal dominant condition. In addition to renal and hepatic cysts, some patients develop mitral valve prolapse and intracranial aneurysms. Subarachnoid haemorrhage or intracranial haemorrhage can occur in 1–2% of patients with APKD.

Tuberous sclerosis

In addition to the development of cerebral tuberous masses, areas of glial cell proliferation, which result in mental retardation and epilepsy, hamartomas and cysts may also develop in the kidneys. Occasionally progressive renal failure occurs in association with multiple renal cysts.

Fabry's disease

α-galactosidase A deficiency is an inborn error of glycosphingolipid metabolism, and is inherited as an X-linked recessive condition. Homozygous females may develop cerebral infarcts and/or haemorrhage. Deposition also occurs in the kidney and can lead to progressive renal failure.

Muscle diseases

Myasthenia gravis

Plasma exchange is often used in severe cases of myasthenia gravis which have not responded to prednisolone or intravenous immunoglobulin therapy. In this condition antibodies to the acetyl-choline synaptic receptor reduce neuromuscular transmission, resulting in muscle weakness. Standard plasma exchange with human albumin solutions can result in a reduction in extracellular calcium and magnesium and may exacerbate muscle weakness, particularly intercostal muscles, with a sudden deterioration in respiratory function. Thus calcium supplementation of replacement solutions should be considered.

Malignant hyperthermia

This is a dominantly inherited condition that is characterised by acute hypercatabolic reaction in skeletal muscle, triggered by any potent inhalational agent and depolarising muscle relaxants. Halothane and suxamethonium are the most commonly implicated agents [62]. Following administration of the anaesthetic agents muscle contraction develops, due to a postsynaptic effect as muscle relaxants are ineffective. There is an increase in the free, intracellular calcium concentration due to release from intracellular stores [63].

Malignant hyperpyrexia has a clinical spectrum ranging from mild to severe cases, when the temperature can increase by 1°C in a few minutes, and is associated with marked rhabdomyolysis, profound metabolic acidosis with hyperkalaemia and hyperphosphataemia. Some patients also develop disseminated intravascular coagulation, pulmonary oedema, acute renal failure and die. Emergency treatment is required. Anaesthesia must be discontinued, the patient hyperventilated, intravenous sodium dantrolene administered and the patient cooled [62]. Peritoneal dialysis and continuous haemofiltration using room temperature, or cooled substitution and dialysate fluids have been used.

Patients with mitochondrial myopathies, myotonic dystrophy and muscular dystrophies are also potentially more prone to develop hyperpyrexia during anaesthesia.

Neuroleptic malignant syndrome

This is an idiosyncratic reaction to therapeutic doses of phenothiazines, butyrophenones, thioxanthenes and other antipsychotic agents such as loxapine. Unlike malignant hyperthermia, the increase in core temperature can develop between 1 and 3 days after starting a course of treatment. The increased muscle tone appears to be presynaptic, as neuromuscular blocking agents can cause paralysis and be used for treatment in conjunction with dantrolene [64]. However, many patients develop acute renal failure due to the myoglobinuric renal injury, and occasionally patients die due to respiratory failure.

3,4-methylenediozymethamphetamine (MDMA)

3,4-methylenedioxymethamphetamine (''ecstasy'') is a synthetic derivative of amphetamine and is used as a recreational drug amongst the young. It can produce hyperpyrexia, dehydration, rhabdomyolysis, and disseminated intravascular coagulation, resulting in acute renal failure [65]. However, it is now clear that it has other actions, in particular, it causes an increase in ADH. Young people are encouraged to drink large volumes of water at ''rave parties''. When combined with MDMA this results in water retention, hyponatraemia and cerebral oedema which may prove fatal.

Neurological problems as a consequence of dialysis

Dialysis disequilibrium

Haemodialysis

Investigation of patients with chronic renal failure treated by regular haemodialysis, has shown that there is an increase in brain water content in the majority of subjects following a standard haemodialysis treatment [66]. This increase in brain water content is usually asymptomatic, unless there is some additional cerebral abnormality [67].

In the early 1960s, a clinical syndrome of dialysis disequilibrium was recognised [68]. During haemodialysis, patients were noted to develop headache, nausea and vomiting which could progress to blurring of vision, muscle twitching, hypertension, tremors, and even grand mal fitting [69]. This syndrome was more commonly observed in children, severely uraemic patients, those treated with rapid haemodialysis of more than four hours, and those with pre-existing neurological disease. Early investigation showed that cerebrospinal fluid pressure increased during haemodialysis in patients with the dialysis disequilibrium syndrome, and that the urea concentration was greater in the cerebrospinal fluid than plasma after dialysis [68, 70]. These changes were accompanied by an increase in brain water content [71]. Several theories were suggested to account for this increase in cerebral water. One effect of rapid haemodialysis is the removal of urea and other small molecules resulting in a decrease in plasma osmolality, as the decrease in plasma urea is much greater than that in the cerebrospinal fluid and cerebral tissues, it was suggested that this produces a ''urea gradient'', with a consequent movement of water from the intravascular compartment into the brain, along an osmotic urea gradient [68, 71]. More recently, other studies have questioned the validity of extrapolating changes in the cerebrospinal fluid and those within the cerebral tissues, as the cerbrospinal fluid, brain extracellular space and intracellular space may not be in equilibrium during a haemodialysis treatment [69]. Other studies reported that whereas plasma pH increased during haemodialysis, cerebrospinal fluid pH decreased [70], due mainly to a reduction in cerebrospinal fluid bicarbonate. One explanation for this finding would be that during haemodialysis, either cerebral blood flow was reduced, or that the distribution of cerebral blood flow was altered, resulting in a mismatch between neuronal oxygen requirement and supply. This is supported by studies which have observed a reduction in brain intracellular pH following haemodialysis [72]. By producing local areas of cerebral hypoxia, there will be a change from aerobic to anaerobic cellular metabolism, with the consequent breakdown of intracellular proteins and the production of small molecular weight organic acids. The combination of local cerebral hypoxia and increased neuronal osmolality secondary to a reduction in intracellular pH, would predispose to areas of cytotoxic oedema and intracellular swelling.

With the advent of improvement in haemodialysis technology; introduction of volumetrically controlled dialysis machines, bicarbonate dialysate coupled with dialysate sodium profiling, and on-line haematocrit measurement with ultrafiltration profiling, the frequency of the dialysis disequilibrium syndrome in patients with chronic renal failure attending for regular haemodialysis treatment is rare [69]. However, despite these advances coupled with reducing blood pump speeds, dialysate flow rates, increased sodium dialysate concentration and using shorter, but more frequent, haemodialysis treatments with prophylactic mannitol, intermittent haemodialysis treatment in acute renal failure patients with acute neurosurgical problems or hepatic coma, remains frought with difficulty. The introduction of haemodialysis to treat acute renal failure in patients with acute and chronic liver disease did not improve survival [73]. Similarly, in neurosurgical patients requiring haemodialysis, an overall mortality of around 67% has been reported [74–86]. Although some patients in these studies died directly as a result of brain stem coning and cerebral oedema, the majority of post-mortem examinations did not suggest cerebral oedema as the cause of death. Instead, the majority of patients died from cerebral hypoxia, consequent upon increased ICP with reduced cerebral oxygen delivery and/or reduced CPP.

With the advent of intracranial pressure monitoring it became quite clear that treatment with haemodialysis could result in an increase in intracranial pressure. Changes in ICP during haemodialysis in patients, with both acute liver failure and following neurosurgery are often observed within the first hour of treatment [76, 86, 87], when the changes in plasma and cerebrospinal fluid osmolality and pH are small. Despite ensuring that patients are volume replete, haemodialysis is often associated with hypotensive episodes, particularly at the initiation of treatment, which do not always respond to volume replacement [87]. As patients with severe sepsis and acute liver failure are markedly vasodilatated, they are unable to increase their systemic vascular resistance [88], as would normally occur in a patient with end-stage renal failure. In these patients, the reduction in mean arterial blood pressure is accompanied by reduced cardiac filling pressures, and often there is no compensatory increase in cardiac rate. The net effect is a reduction in cardiac output, coupled with increased pulmonary vascular resistance and intrapulmonary shunting, and reduced mean arterial blood pressure. Consequently, this leads to a reduction in both cerebral oxygen delivery and cerebral blood flow, coupled with a reduction in the cerebral perfusion pressure which results in brain ischaemia. As the cerebral circulation may already be compromised [88] and the blood brain barrier damaged, due to both vasogenic and cytotoxic

mechanisms (Fig. 1), further ischaemic damage at the neuronal level occurs, resulting in local vasodilatation and a further increase in intracranial pressure, so compromising the cerebral perfusion pressure further. Similarly, in the postoperative neurosurgical patient, cerebral autoregulation will be defective around the damaged area, with localised damage to the blood brain barrier, and therefore, in this area, cerebral perfusion will be flow and pressure dependent (Fig. 2).

Cerebral electrical activity, as recorded by flash visual evoked potentials, shows that intermittent haemodialysis treatments, in patients at risk of cerebral oedema, are associated with a deterioration in cerebral function, as evidenced by both a prolongation of the latencies and a decrease in the height of the potentials. This is supportive evidence of increasing cerebral neuronal hypoxia as a consequence of treatment with haemodialysis [20].

These adverse effects of haemodialysis on cardiac output, tissue oxygen delivery and mean arterial blood pressure result in cerebral hypoxia, which in the susceptible patient results in further cerebral ischaemia and accounts for the high mortality of both neurosurgical patients and those with hepatic coma treated by haemodialysis [73–80].

Peritoneal Dialysis/CAPD

Peritoneal dialysis using either a hard acute dialysis catheter, or a soft Tenchkoff catheter, inserted using a Seldinger technique, have been advocated by several groups as providing renal replacement therapy for patients with acute or chronic renal failure at risk from cerebral oedema/hypoxia [73, 77, 84, 85, 86, 89, 90]. The overall survival rate from these published series is approximately 66%, superior to that for haemodialysis. Peritoneal dialysis is much less efficient than haemodialysis in terms of urea removal and changes in plasma osmolality, and thereby would not be expected to result in developing marked gradients between the plasma and brain extracellular space [69, 77].

Treatment with small volume cycles results in greater intracranial stability than haemodialysis. Similarly MAP and CPP were not as labile during peritoneal dialysis treatment compared to haemodialysis [91]. In earlier studies, peritoneal dialysis has been reported to cause a reduction in cardiac output and stroke volume, with compensatory increases in heart rate, MAP, and systemic vascular resistance [92]. In acutely ill patients who are vasodilated, with evidence of tissue hypoxia due to a mismatch in oxygen delivery

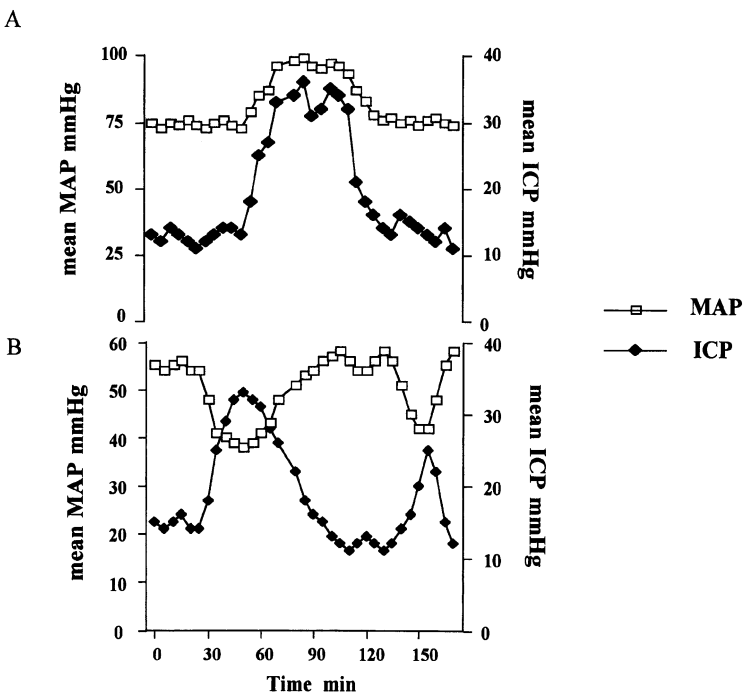

Figure 2. (A) recording from a patient showing normal cerebral autoregulation; mean arterial blood pressure increases with an increase in intracranial pressure, an intact Cushing reflex: (B) Recording from a patient showing defective cerebral autoregulation; mean arterial blood pressure decreases and is followed by an increase in intracranial pressure, resulting in an abnormally low cerebral perfusion pressure, a failed Cushing reflex.

and supply [90], compensatory increases in systemic vascular resistance may not occur, and so account for a reduction in cardiac output. Peritoneal dialysis also has an effect on pulmonary function by restricting diaphragmatic movement and increasing intrapulmonary shunting [93]. In our own studies, peritoneal dialysis was associated with an increase in pulmonary vascular resistance, and a reduction in tissue oxygen delivery, due to both changes in cardiac ouput and pulmonary function [91].

Although peritoneal dialysis could be seen as advantageous in terms of removing gut derived endo- and exotoxins in septic patients [88], no improvement in patient survival has been demonstrated [76, 90]. Indeed, most studies have reported technical problems, from leakage at the exit site, bacterial and culture-negative peritonitis, loss of plasma proteins, orthostatic pneumonia, increased gastrointestinal haemorrhage, aggravation of the "pulmonary septic syndrome", to life threatening intraperitoneal haemorrhage [85, 86, 94]. In our own experience, although intracranial pressure was not adversely affected by peritoneal dialysis, the major disadvantage with both acute manual peritoneal dialysis and/or a peritoneal cycling machine, has been the inability to maintain accurate fluid balance [91]. In part, this may be due to the changes in blood flow that occur throughout the portal circulation as a consequence of severe sepsis and liver failure [88], and also the use of vasoconstrictors such as dopamine, adrenaline and noradrenaline, which are used to maintain an adequate mean arterial blood and cerebral perfusion pressure, but also reduce blood flow to the gastrointestinal tract. Patients with liver failure are prone to sepsis, for example, they have impaired bacterial opsonisation due to reduced amounts of fibronectin and complement proteins. The reported incidence of peritonitis in patients with liver failure treated with peritoneal dialysis has been high (up to 87%), and most of the organisms came from the gastrointestinal tract (*Ps. aerogenes*, *S. faecalis*, *E. coli*, *C. albicans*) [94]. One of the major problems with peritoneal infections is eradication. As, when hepatic function does not spontaneously improve in these patients, then orthotopic liver transplantation becomes the treatment of choice, but this can not be undertaken in the presence of peritoneal infection.

Peritoneal dialysis usually requires no anticoagulant. This would appear to be an advantage in both those with liver failure and following neurosurgery. Despite using no anticoagulant, several studies have reported upon a high incidence of haemorrhage both in those with liver failure [94] and following neurosurgery [85,86]. This may be due to the low clearances of uraemic toxins achieved with peritoneal dialysis, and therefore reflects the increased risk of uraemic bleeding.

Intermittent machine haemofiltration

Studies on patients with chronic renal failure treated by intermittent machine haemofiltration, were reported to show a reduction in both the incidence of the dialysis disequilibrium syndrome and improved cardiovascular stability, compared to standard haemodialysis [95, 96]. Whereas the total amount of urea removed was similar in both treatments, the rate of plasma urea removal was less during haemofiltration, and the amount of urea removed from the cerebrospinal fluid greater, so resulting in a reduced plasmal/cerebrospinal fluid urea gradient compared to haemodialysis [95]. In addition, cerebrospinal fluid pH was significantly greater following haemofiltration compared to haemodialysis [95]. The improved cardiovascular stability with haemofiltration was confirmed by other investigators who demonstrated an increased systemic vascular resistance during treatment, which thereby maintained cardiovascular stability [96].

However, in patients with acute liver failure, intermittent haemofiltration, although superior to haemodialysis, was associated with an increase in ICP [97]. Treatment with intermittent haemofiltration produced a reduction in cardiac filling pressures. As there was no compensatory increase in heart rate, stroke volume or systemic vascular resistance, this resulted in a decreased cardiac output and MAP [98]. In addition, as with peritoneal and haemodialysis, there was an increase in pulmonary vascular resistance, and intrapulmonary shunting, with a net effect of reducing tissue oxygen delivery. As the changes in ICP often occurred within the first hour of treatment, before significant changes in plasma urea and osmolality had developed, they were thought most likely to be due to cerebral hypoxia, as there was no demonstrable compensatory increase in tissue oxygen extraction or the tissue oxygen uptake ratio.

Continuous arterio-venous haemofiltration and/or dialysis

As intermittent machine haemofiltration was superior to haemodialysis, several groups pioneered the use of continuous arteriovenous haemofiltration (CAVH) [99] in patients with hepatic coma complicated by cerebral oedema [100, 101]. CAVH was shown to provide the most stable form of renal replacement therapy for

these critically ill patients, by both maintaining cardiac output, tissue oxygen delivery, and also by maintaining MAP and CPP. Many patients with liver failure are not as catabolic as those with sepsis, and CAVH alone usually provides adequate therapy in terms of urea and creatinine clearance. CAVH is at least, if not more, efficient than peritoneal dialysis. Although CAVH has been successfully used in the management of acute renal failure in neurosurgical patients [85, 86], in some cases, particularly when renal failure occurs in the setting of sepsis and/or multiple trauma, CAVH may not achieve adequate clearances. Under these circumstances, the CAVH circuit can be modified to allow additional dialysis (continuous arteriovenous haemodialysis or CAVHD) which will increase the efficiency of the extracorporeal circuit. CAVHD has been reported to be similar to CAVH in achieving improved cardiac and intracranial stability compared to the intermittent forms of haemofiltration and/or haemodialysis [98].

Mannitol remains the most effective therapeutic agent for treating surges in ICP [28]. However, mannitol is less effective in oliguric/anuric patients, and may also not be as effective when administered as a bolus to patients during intermittent haemodialysis and/or haemofiltration treatments, due to its removal [76). It is more effective when given to patients treated with CAVH and/or CAVHD.

With the advent of these forms of renal replacement therapy and other improvements in general intensive care management, including nursing patients supine or with minimal head elevation to maximise CPP [6], and the introduction of sedatives to control ICP, the survival of patients with acute liver failure has increased, and more importantly, patients can be stabilised prior to emergency orthotopic hepatic transplantation.

Continuous veno-venous haemofiltration (CVVH) and/or dialysis (CVVHD)

Although the spontaneous techniques of CAVH and CAVHD can often achieve adequate control of blood chemistries, filter clotting can be problematical, especially in those patients at risk of haemorrhage in whom minimal or no anticoagulation is used. In addition, in critically ill patients with hyperacute liver failure who are often hypotensive despite inotropic support [88], there may be unpredictable reductions in systemic blood pressure, resulting in filter clotting. To achieve the maximal blood flow in the spontaneous CAVH circuit, large bore femoral arterial catheters are needed. As patients with liver failure have a coagulopathy [88], catheter insertion may result in haemorrhage [99] and vessel wall damage, with local thrombosis [99, 102]. Previous reports have suggested improved survival for those patients with acute renal failure treated with CVVH compared to CAVH [103]. In theory, removal of venous blood into an extracorporeal circuit should have less of an effect on circulatory haemodynamics than an arterial source. Our initial results, in terms of cardiovascular and intracranial stability, although better than those for intermittent haemodialysis and/or haemofiltration, were as not as good as those achieved with CAVH and/or CAVHD [98], However, despite these findings, several patients who had fitted secondary to cerebral oedema following treatment with haemodialysis, have been successfully managed with CVVHF and walked out of hospital [22, 99]. The major problem with CVVH and CVVHD was one of accurate control of fluid balance. Patients with acute liver failure and those post-operative neurosurgical patients with perfusion dependent cerebral tissue, were often too unstable to tolerate large ultrafiltrate losses (Fig. 3). The occlusion and/or continuous ripple pumps (Imed 999; Imed Gemini, Imed, Abingdon, UK) we initially used to regulate the ultrafiltrate, dialysate and fluid replacement volumes, had not been specifically designed to operate at the pressures present within the extracorporeal circuit, and therefore did not have the necessary degree of accuracy required. To improve the cardiovascular and intracranial stability in this group of patients continuous haemofiltration and/or dialysis machines, more accurate pumps were needed [104]. These have now been commercially developed and will hopefully provide the stability of the spontanoeus extracorporeal system, combined with the advantages of the pumped circuit (Quantum SED, Renalaid, Huddersfield, UK; Prisma, Hospal, Denver, Colorado, USA).

Dialyser/haemofilter membrane bioincompatibility

The effect of repeated exposure to extracorporeal materials on patients with chronic renal failure is a well known cause of morbidity and mortality in the haemodialysis population [105]. More recently, there have been reports of increased patient survival and a reduction in the duration of renal failure, in patients with acute renal failure treated with synthetic, dialyzer membranes, compared to the standard cellulose cuprophan membranes [106]. Similar improvements in patient outcome were reported using polyacrylonitrile membrane haemodialysis compared to cuprophan, in patients with acute liver and renal failure [87]. These

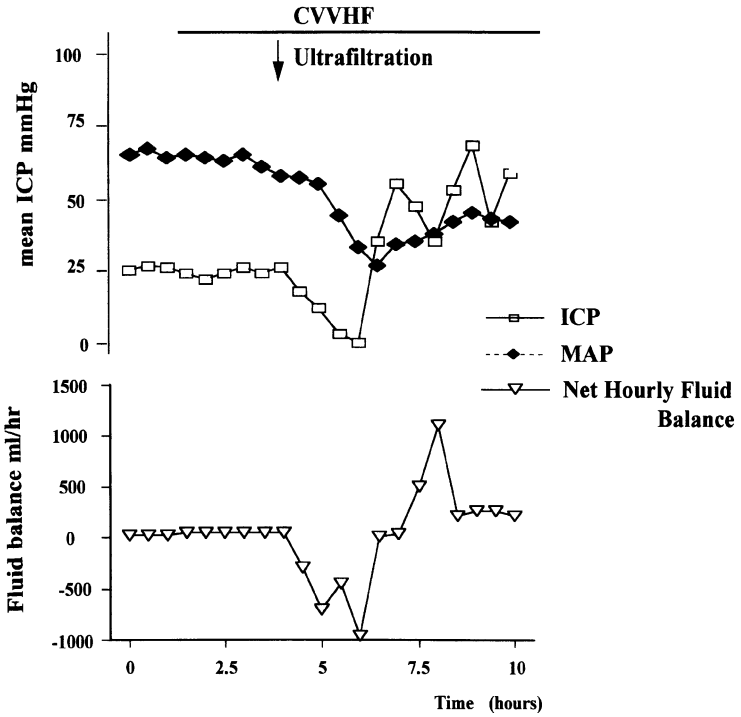

Figure 3. The effect of forced ultrafiltration in a patient with impaired cerebral autoregulation. Ultrafiltration was associated with an initial reduction in both mean intracranial pressure (ICP) and mean arterial blood pressure (MAP). This was then followed by a surge in ICP that was refractory to treatment, and despite fluid repletion, MAP did not recover promptly. The patient died 24 hrs later.

initial observations have been confirmed by more recent studies, which showed that haemofiltration using the more biocompatible, polycrylonitrile membrane, resulted in smaller adverse changes in intracranial pressure, mean arterial blood pressure, cerebral perfusion pressure and tissue oxygen delivery [107].

Continuous modes of haemofiltration and/or dialysis using polyacrylonitrile or polysulphone membranes, have been shown to result in less pro-inflammatory cytokine production, complement, platelet and inflammatory cell activation [108]. In addition, these membranes have also been reported not only to adsorb activated complement fragments, cytokines and platelet derived growth factor onto their surface, but also allow greater plasma clearance into the ultrafiltrate, with predominant losses of IL-6 [109]. The use of these more biocompatibile membranes, by reducing endothelial and macrophage activation [105], may reduce local nitric oxide synthesis; and thereby reduce some of the post capillary vascular dilatation, that accounts for the cardiovascular instability during the first hour of dialysis observed in those patients with acute liver failure [87, 97].

Interestingly, in the reports of patients with acute renal failure treated with the synthetic, more biocompatible membranes, the frequency of infection and the number of deaths attributable to sepsis were reduced [106], suggesting that the effect of biocompatibility may have significant *in vivo* effects. This may be even more important in those patients with acute liver failure who are at risk of sepsis, not only from gut derived pathogens, but also because they have reduced levels of fibronectin and complement proteins, resulting in defective bacterial opsonisation.

Extracorporeal anticoagulation

Intracranial pressure is often measured in post-operative neurosurgical patients using intraventricular, sub- and extradural devices. In addition to the risk of haemorrhage around these, there are the risks of intracranial haemorrhage from the wound, and re-bleeding in cases of primary intracranial haemorrhage. ICP is also often measured in patients with acute liver failure and encephalopathy, who are at risk of bleeding due to clotting factor deficencies, thrombocytopenia, low-grade fibrinolysis with or without intravascular coagulation [88]. Intracranial haemorrhage secondary to problems with extracorporeal anticoagulation has invariably proved fatal [78, 81, 85, 86, 109].

Standard heparin has been the main anticoagulant

used by most groups. Two major problems have been encountered: firstly haemorrhage [87], which may be life threatening [109]. Secondly, heparin has also been reported to aggrevate the thrombocytopenia found in those patients with liver failure [87]. Alternatives to standard heparin include low molecular weight heparin, nafamostat mesilate, citrate and epoprostenol. One study using low molecular weight heparin during CVVH, reported a high incidence of haemorrhage at high infusion rates, and increased clotting within the dialyzer at low infusion rates, suggesting no overall benefit from standard heparin [110]. Nafamostat mesylate, a potent protease inhibitor, has been used as an extracorporeal anticoagulant [111]. Clinical experience has mainly been limited to Japan, but has been reported to be an effective anticoagulant, without increased risk of haemorrhage in neurosurgical patients with acute renal failure (Y. Ohtake, personal communication). However, the cost is currently prohibitive and there are reports of bone marrow suppression. Citrate has been used successfully by several groups [112], but in addition to potential problems with calcium homeostasis, specially prepared dialysate/haemofiltration fluid is required, because of the high sodium load (hypertonic trisodium citrate (TSC)), and the risk of alkalosis (each citrate molecule is converted through to three bicarbonates, provided hepatic function is adequate). More recently, isotonic citrate dextrose-A, which is used as the standard anticoagulant by blood banks, has been used for intermittent haemodialysis and appears to have fewer side effects than TSC [113]. Dermatan sulphate and hirudin have also been recently used as extracorporeal anticoagulants, but as yet there are no substantial data on treating neurosurgical or liver failure patients at risk of intracranial haemorrhage.

Epoprostenol has been used for some years as an extracorporeal anticoagulant and has been reported to reduce thrombocytopenia [87]. In addition, in one study of CAVH/CAVHD anticoagulation with epoprostenol, proved to be superior to heparin, in terms of both the duration of the extracorporeal circuit and also in reducing the number of bleeding episodes [93]. Epoprostenol has been reported to improve tissue oxygen delivery at the cellular level, in patients with acute hepatic failure. By acting as a local vasodilator, epoprostenol may alter the distribution of blood flow through a tissue, and thereby increase tissue oxygen uptake [114]. This may be an important additional benefit to patients with liver failure, who have evidence of tissue hypoxia, and in the neurosurgical patient, who has an area of flow dependent cerebral tissue [114].

As intracranial haemorrhage secondary to problems with extracorporeal anticoagulation has invariably proved fatal [78, 85, 109], we and others explored the possibility of using no anticoagulant. Several studies have reported similar duration of the extracorporeal circuit using both standard heparin and no anticoagulant [115], which is keeping with our own experience. Our current standard practice in neurosurgical and acute liver failure cases, is to use no anticoagulant, but to infuse 0.5 l of 0.9% saline prior to the haemodiafilter (1.0–1.5 l dialysis cycles), to reduce the haematocrit in the circuit. When clotting does occur, it usually starts in the venous bubble chamber, due to the blood-air interface [116]. Experience with heparin bonded haemofilters has similarly shown that clotting in the venous bubble trap causes circuit failure.

Dialysate/haemofiltration substitution fluids

The majority of the currently commercially available substitution fluids are lactate based. Racemic lactate solutions contain both the naturally occurring L-lactate and also D-lactate. D-lactate is mainly metabolised in skeletal muscle, at a slower rate than L-lactate. In patients with hepatic failure, or those in circulatory shock lactate, particularly D-lactate, could accumulate. As most lactate assays are based on lactate dehydrogenase, only L-lactate can be measured, and therefore D-lactate accumulation can pass unnoticed. D-lactate accumulation is also more likely to occur in small children and those with a short bowel syndrome, due to the effect of intestinal bacteria. Occasionally, D-lactate accumulation has been reported to cause an encephalopathy [117]. The effects of the various anionic bases used in dialysate and/or haemofiltration substitution fluids are further discussed in Section 19.

Summary

Although patients with acute liver failure, and those following neurosurgical operations, are at risk of cerebral oedema, only a minority of patients die from brain stem coning, the majority die from cerebral hypoxia. Therefore, any acceptable mode of renal replacement therapy should cause the minimum disturbance to cerebral oxygen delivery and cerebral perfusion pressure, as these patients may have defective cerebral autoregulation and a damaged blood-brain barrier. Thus, a reduction in either cerebral oxygen delivery or a reduction in cerebral perfusion pressure, can lead to further cerebral hypoxia, fol-

lowed by a secondary increase in ICP, and a greater cerebral hypoxic insult, which may be fatal.

CAVH and CAVHD are currently the treatment of choice in this group of patients, as they provide the greatest cardiac and intracranial stability. In the future, they may well be replaced by CVVH and CVVHD as a new generation of continuous slow haemofiltration/dialysis machines with volumetric control, will be commercially available. If CAVH and CAVHD can not be provided, then peritoneal dialysis using a Tenchkoff catheter is to be preferred, using small (1.0 litre) volume exchanges, to minimise the cardiorespiratory effects.

Bioincompatibility can result in both adverse cardiovascular and intracranial effects. Therefore, a biocompatible membrane such as polysulfone or polyacrylonitrile, should be used. The effect of biocompatibility is greater during CVVHD than CAVH, and this may be related to the faster blood flow causing greater complement, platelet and leukocyte activation, and also leeching of plasticisers and other chemicals from the extracorporeal circuit. It is therefore recommended that the extracorporeal circuit is well rinsed prior to use, and ethylene oxide sterilised components are avoided.

The anticoagulant of choice should minimise the risk of haemorrhage and prevent clotting in the extracorporeal circuit. Standard heparin will probably remain as the most used anticoagulant, as the difficulty and cost of checking antifactor Xa activity on a regular basis, will probably preclude the widespread use of low molecular weight heparins. Heparin does increase the risk of haemorrhage in both patients with liver failure and those following neurosurgery, and, if used, should be carefully and regularly monitored. Epoprostenol is used by many liver units, as it not only reduces the risk of haemorrhage, but may also increase tissue oxygenation. In the future, no extracorporeal anticoagulation should be possible, using combinations of predilution with heparin bonded lines and dialyzers.

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