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REVIEW ARTICLES

Management of the dialysis patient in general intensive care

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Editor's key points

- Chronic kidney disease is increasing and these patients have a significant requirement for intensive care unit care.
- Sepsis is the most common reason for admission.
- Drug handling is altered in these patients and dosages may require adjustment.
- Electrolyte abnormalities are common.

Summary. The incidence of end-stage renal disease (ESRD) is rising and represents an important group of patients admitted to intensive care units (ICU). ESRD patients have significant co-morbidities and specific medical requirements. Renal replacement therapy (RRT), cardiovascular disease, disorders of electrolytes, drug metabolism, and sepsis are discussed. This review provides a practical approach to problems specific to the ESRD patient and common problems on ICU that require special consideration in ESRD patients. ESRD patients are at risk of hyperkalaemia. I.V. insulin and nebulized salbutamol lower serum potassium until definitive treatment with RRT is instituted. ESRD patients are prone to hypocalcaemia, which requires i.v. replacement if associated with complications. Midazolam has delayed metabolism and elimination in renal impairment and should be avoided. Morphine and its derivatives accumulate in renal failure and shorter-acting opiates are preferable. The use of diuretics is limited to patients with residual urine output. When required, therapeutic systemic anticoagulation should be achieved with unfractionated heparin as it is reversible and its metabolism and clearance are independent of renal function. The risk of sepsis is higher among ESRD patients when compared with patients with normal renal function. Empiric treatment should include both Gram-positive and Gram-negative cover, and methicillin-resistant *Staphylococcus aureus* cover if the patient has a dialysis catheter. Cardiovascular events account for the majority of deaths among ESRD patients. Troponin-I and CK-MB in combination should be used as markers of acute myocardial damage in the appropriate context, whereas B-type natriuretic peptide and troponin-T values are of less value.

Keywords: cardiovascular; electrolyte; end-stage renal disease; pharmacology; sepsis

The health-care burden of chronic kidney disease (CKD) is rising,[1 2] reflecting the increasing prevalence of hypertension and type 2 diabetes mellitus, and an ageing population.[3] The incidence of patients reaching end-stage renal failure (ESRD) requiring dialysis is 109 and 354 per million population per year in the UK and the USA, respectively.[1 4] The relative risks of all-cause mortality, cardiovascular events, and hospitalization rates are 5.9, 3.4, and 3.1, respectively, among an ESRD population when compared with patients with normal renal function.[5] Among the ESRD population, mortality is predominantly related to cardiovascular disease[1 6] while sepsis is the most common cause of hospitalization.[1]

The requirement for intensive care unit (ICU) services by the ESRD population is not insignificant. In a cohort of 3420 dialysis patients from a total pool of 276 731 admissions to UK ICU[7], for every 100 patients with ESRD, an ICU bed requirement of 32 days was needed, that is, about 1 month yr^{-1}. In an Australian study of 476 patients with ESRD observed over a 7 yr period, 20% required ICU admission.[8]

Common problems faced among this cohort include cardiovascular disease, sepsis, disorders of electrolytes, and altered drug metabolism. This review summarizes the available literature with an aim of providing the intensive care physician and anaesthetist with a practical approach to problems specific to the ESRD patient on ICU and common problems on ICU that require special consideration in ESRD patients.

Renal replacement therapy and vascular access

Renal replacement therapy

Virtually all patients with ESRD are likely to require renal replacement therapy (RRT) during an ICU admission. The decision to perform continuous veno-venous haemofiltration (CVVHF) or continuous veno-venous haemodiafiltration over haemodialysis or sustained low-efficacy dialysis (SLED) may be determined by the facilities on the ICU, as intermittent haemodialysis or SLED requires an elaborate water purification

facility to produce the dialysate. The use of peritoneal dialysis (PD) may be limited on ICU, as loss of peritoneal function or extensive abdominal adhesions that limit dialysate flow, the absence of a PD nurse, and uncorrectable mechanical defects that prevent effective PD or increase the risk of infection (e.g. surgically irreparable hernia) are all absolute contraindications to PD.[9] Fresh intra-abdominal foreign bodies (e.g. abdominal vascular prostheses), peritoneal leaks, inflammatory or ischaemic bowel disease, abdominal wall or skin infection, intra-abdominal sepsis, and severe malnutrition are all relative contraindications to performing PD.[9]

Other factors determining the mode of RRT include the patient's haemodynamic status, existing vascular access, and physician experience. The optimum mode and dose of renal replacement in acute kidney injury is an extensive topic beyond the scope of this paper. There are no studies evaluating the optimal mode of renal replacement in the critically ill chronic dialysis patient in the ICU.

Vascular access

Arteriovenous fistulae and grafts are inappropriate for use in continuous haemofiltration as needles cannot be placed for prolonged periods. This increases the chances of trauma to the fistula and also limits the movement of the patient's arm. Furthermore, the use of an arteriovenous fistula with the lower pump speeds used in continuous haemofiltration may result in fistula thrombosis. However, it is possible to use the arteriovenous fistula for intermittent haemodialysis or SLED in the ICU.

Haemodialysis catheters ('Permacaths') are intended for RRT and, to minimize infection risk, should not be used as vascular access for routine administration of drugs. Insertion of a dialysis line into the subclavian vein should be avoided where possible in view of the risk of central venous stenosis or thrombosis of the outflow vein.[10] Patients on chronic haemodialysis may have had a number of changes of vascular access sites resulting from previous episodes of line sepsis, venous thrombosis or stenosis, or inadequate flows through the vascular access device. A proportion of these patients develop superior vena cava stenosis that may lead to obstruction. Superior vena cava stenosis/obstruction affects central venous pressure readings, making it difficult to gauge intravascular filling in this population.

Cardiovascular disease in ESRD

Circulating volume and pulmonary oedema

Individuals with normal kidney function can regulate their sodium and water balance. Patients on dialysis have minimal, if any, residual renal function and have to rely virtually entirely on the dialysis procedure for salt and water elimination. Failure of salt and water excretion results in chronic hypertension and its secondary effects.[11] ESRD patients with elevated arterial pressures often have increased intravascular salt and water. Their hypertension therefore responds to ultrafiltration.[12] The patient's 'dry weight' (the weight of the patient when deemed to be clinically euvolaemic)[13] is unlikely to be applicable in the setting of critical illness with large third-space fluid losses.

Many chronic haemodialysis patients are anuric[14] and are much more likely to develop pulmonary oedema secondary to volume overload. Repeated fluid boluses using cardiac output monitoring devices in the resuscitation of a hypotensive dialysis patient have not been specifically evaluated in this cohort of patients. Common triggers for acute pulmonary oedema requiring ICU admission among the ESRD population include acute pulmonary infection, excessive inter-dialytic weight gain, inappropriate dry weight prescription, and primary cardiac events.[15] Anuric patients on dialysis presenting with pulmonary oedema are unlikely to respond to furosemide (as described earlier). If facilities for RRT are not immediately available, a nitrate infusion and continuous positive airway pressure may be required as 'holding measures' in pulmonary oedema, where appropriate.[16] *In extremis*, venesection can decrease circulating volume though this is rarely performed in practice.[17]

Sudden cardiac death

Cardiovascular disease, including sudden death, myocardial infarction, cardiac arrest, and malignant arrhythmias, is the major cause of death in haemodialysis patients accounting for 43% of all-cause mortality.[18] Sudden cardiac death accounts for ~60% of this total.[19] Dialysis patients in ICUs are twice as likely as other patients to have had cardiopulmonary resuscitation before admission to ICU.[7]

There are a number of 'non-traditional' risk factors that predispose ESRD patients to cardiovascular disease. These include left ventricular hypertrophy, rapid electrolyte shifts during dialysis, QT dispersion, sympathetic over-activity, and deposition of calcium-phosphate precipitants within arteries.[18] QT dispersion is a marker of homogeneity of cardiac repolarization. Hypertension, coronary artery disease, and QT dispersion are independent predictors of complex ventricular arrhythmias in patients with ESRD.[20 21] Factors relating to haemodialysis that are strongly associated with cardiac arrest include low-potassium dialysate (≤2 mEq litre^{-1}), increased ultrafiltration volumes, exposure to low-calcium dialysate, and pre-dialysis serum creatinine levels.[22] Modifications of the haemodialysis prescription may decrease the risk of cardiac arrest in patients with ESRD, though there are no clear guidelines as yet.

The utility of implantable cardioversion-defibrillators (ICDs) on patients undergoing chronic haemodialysis had not been evaluated prospectively. However, retrospective analyses suggest that patients receiving ICDs for secondary prevention had an overall lower mortality risk compared with matched controls, but the benefits seemed to be restricted to the early post-implantation period.[23] Device infections were a common complication.

Cardiac biomarkers

Patients with ESRD may have an elevated troponin T in the absence of any acute myocardial damage. However, there

is little difference in troponin I levels between healthy controls and those on dialysis. This may be related to the shorter half-life of troponin I.[24] Myocardial injury should be suspected if the troponin-I level is >0.8 ng dl^{-1}.[25] Compared with troponin I, myocardial creatinine kinase (CK-MB) may have an even lower positivity in the dialysis population without acute myocardial damage.[26] It therefore seems reasonable to use both troponin I and CK-MB in combination as markers of acute myocardial damage in the appropriate clinical context.

Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T values are of less diagnostic value in the acute setting in chronic dialysis patients, as both markers depend on volume status. Relative to the general population, plasma levels of troponin T and NT-proBNP levels are elevated in up to 40% and 100% of asymptomatic chronic haemodialysis patients, respectively.[27] Furthermore, the modality of dialysis and the use of non-native fistulae (catheter or graft) affect both serum NT-proBNP and troponin T values.[28] High-flux dialysers may increase clearance of these biomarkers and should be taken into account, especially in patients with acute onset of cardiac ischaemia. Patients dialysed with a low-flux dialyser may have elevation of troponin T and NT-proBNP levels after haemodialysis due to haemoconcentration. There is also a significant association between these biomarkers and non-native fistulae (catheter or graft), possibly due to the chronic inflammation commonly driven by these devices.[28] Increased NT-proBNP and troponin T are useful tools for long-term risk stratification in chronic haemodialysis patients.[29] Annual increases in serum BNP $>40\%$ are associated with a seven-fold increased risk for all-cause and cardiac death in haemodialysis patients.[30]

Elevated cardiac enzymes in haemodialysis patients with sepsis are also associated with an increase in both short- and long-term mortality. An elevated cardiac troponin I >0.2 ng ml^{-1} at the onset of sepsis was independently associated with an increased risk of 5.13 for short-term mortality and 5.90 for long-term mortality.[31] Short-term mortality (death within 90 days of onset of sepsis) was predominantly related to sepsis, whereas long-term mortality (death after 90 days from onset of sepsis) was primarily related to cardiovascular disease.

Sepsis in ESRD

Sepsis remains the most common cause of hospitalization of ESRD patients and, compared with the general population, is associated with a high mortality and morbidity.[32] Various factors are implicated in the increased susceptibility of CKD and dialysis patients to sepsis. These include the presence of plasma tumour necrosis factor soluble receptors, anti-IL-1α autoantibodies, the accumulation of an endogenous inhibitor of nitric oxide synthase, opsonization defects, anaemia, and deficiencies of trace elements and vitamins.[33–36]

The optimal haemodynamic management of ESRD patients with severe sepsis and septic shock has not been evaluated in any large randomized control trial. A *post hoc* analysis from the Rivers' study[37] included 10 ESRD patients receiving chronic dialysis in the control group and eight in the treatment group.[38] Baseline variables were similar between these two groups; yet, there was a significant improvement in arterial pressure, central venous saturation, lactate, and APACHE score in the early goal-directed therapy (EGDT) group. Seven of the 10 control group patients died in contrast to only one of the eight EGDT group patients. Though numbers were small, this difference was statistically significant. Clearly, further trials are needed in this patient cohort; yet, these early data are encouraging. Existing data are, however, insufficient to make any recommendations in the ESRD patient group.

The most common infections in ESRD patients are pneumonia, cellulitis, and bacteraemia.[1] Another unusual but important source of infection in ESRD patients is pyocystis. Patients with ESRD often pass very little urine and thus risk retaining small volumes of urine within the bladder for prolonged periods, which may become infected.[39] Patients with polycystic kidney disease may develop infected kidney and liver cysts. Furthermore, some patients on chronic haemodialysis may have had previous renal transplants that are no longer functioning but remain *in situ*. Failed renal allografts have the potential to become infected (graft pyelonephritis), as do native kidneys.

Indwelling dialysis catheters (both for haemodialysis and PD) are a significant source of sepsis. Haemodialysis patients have a greater rate of early infectious complications, primarily attributable to the use of haemodialysis catheters.[40] On the other hand, PD patients have a higher rate of late infectious complications and a higher associated mortality.[41] Antibiotic choice should be determined by a combination of initial broad-spectrum cover and knowledge of local pathogens and resistance patterns. Specialist advice should be sought with regard to removal of an infected dialysis catheter.

Catheter-related bloodstream infections

Complications relating to haemodialysis catheter-related bloodstream infections (CRBSIs) vary from centre to centre. CRBSIs have an estimated incidence of 0.7–5.5 episodes per 1000 catheter-days[42 43] and account for 0.28 admissions per 1000 catheter-days.[44] This variability in incidence may be due to different haemodialysis catheter types and care practices. Approximately half of all CRBSIs are caused by Gram-positive cocci, a third by Gram-negative rods, including a wide variety of enteric organisms, and $\sim$20% are polymicrobial.[42] It is therefore prudent to provide both Gram-positive and Gram-negative antimicrobial cover in a haemodialysis patient with a suspected bacteraemia until an organism is isolated.

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is an obvious concern as the relative risk is 100-fold

higher for a dialysis patient compared with the general population and eight-fold higher for a patient using a dialysis catheter in comparison with a fistula.[45] Up to 9.5% of haemodialysis patients are carriers of MRSA, and the adjusted hazard ratio of infection-related mortality was five-fold greater among MRSA carriers.[46] It therefore seems reasonable to provide MRSA cover with vancomycin or teicoplanin for ESRD patients with a bacteraemia. The risk of MRSA bacteraemia is greater in ESRD patients who dialyse with an i.v. dialysis catheter. Of all patients on established dialysis who had a documented episode of MRSA bacteraemia in the UK, 30.2% were utilizing an arteriovenous fistula or graft and 69.8% were dialysing on a non-tunnelled or tunnelled venous catheter.[47]

PD peritonitis

Peritonitis is a significant complication of PD with a mortality of 3.5–10%.[48] PD peritonitis (PDP) is defined by the International Society of Peritoneal Dialysis (ISPD) as two or more of the following: (i) signs and symptoms; (ii) white cell count >100 ml^{-1} of PD effluent and $>50\%$ neutrophils after a dwell of at least 2 h, and (iii) a positive culture of an organism from the PD effluent.[49] Typical symptoms include fever, abdominal pain, nausea and vomiting, and a cloudy peritoneal effluent. A Cochrane review found that intraperitoneal antibiotics are superior to i.v. antibiotics in the treatment of PD-associated peritonitis.[50] Patients on PD admitted to the ICU have high rates of death and technique failure.[51] Approximately, a quarter of PD patients are admitted with PDP.

In a UK-based nationwide study, the most common organism implicated in PDP was coagulase-negative *Staphylococcus*, accounting for around 30% of all episodes, followed by non-*Pseudomonas* Gram-negative bacteria and *Staphylococcus aureus*. Cure rates varied from 77.2% for coagulase-negative *Staphylococcus* to 21.4% for *Pseudomonas*. The combination of intraperitoneal gentamicin and cephalosporins yielded a higher cure rate than oral-based regimens, with an overall mortality rate of 3.5%.[52] A similar study in Australia demonstrated that adverse clinical outcomes were associated with MRSA peritonitis and that empiric initial therapy with either vancomycin or cephazolin resulted in comparable outcomes, provided that vancomycin is prescribed when MRSA is isolated and identified.[53]

Electrolyte disorders in ESRD patients

The ICU clinician is faced with challenging fluid and electrolyte problems in virtually all critically ill patients. These problems may arise from the underlying pathological process or from iatrogenic causes. Disorders of different electrolytes are not mutually exclusive. In patients with normal renal function, regulation of fluid and electrolytes is predominantly by the kidneys. Common electrolyte problems in patients with ESRD include disorders of potassium, calcium, and magnesium and phosphate. In addition to these electrolyte disorders, problems with acid–base balance and fluid management are often testing.

Potassium

The normal Western daily diet contains ~100 mmol of potassium. Patients with ESRD should consume less than half of this as under normal circumstances. Ninety per cent of potassium excretion is via the kidneys and 10% via the gut.[54] Potassium loss via the skin and lungs is negligible. Patients with ESRD have a compensatory increased potassium excretion via the gut, though this is inadequate to compensate for impaired renal excretion.[55] Life-threatening hyperkalaemia in ESRD patients who are not dialysed regularly is therefore a significant risk.[16]

The initial management of hyperkalaemia should focus on measures to 'stabilize the myocardium' and increase the intracellular shift of potassium. I.V. calcium gluconate (10 ml of 10% i.v. calcium gluconate) antagonizes the depolarizing effect of hyperkalaemia and should be administered first to reduce the risk of arrhythmia. Potassium is the major intracellular cation and 98% of the body's potassium is in intracellular compartments. Due to this uneven distribution of potassium across cell membranes, a 1% shift in its distribution can cause a 50% change in plasma potassium concentration.[56] Therapies to increase intracellular uptake of potassium, including i.v. insulin or nebulized salbutamol, are therefore often instituted in hyperkalaemia.[57 58] The potassium-lowering effect of nebulized salbutamol is maximal at 90 min and lasts at least 3 h.[57] Combination treatment of hyperkalaemia with insulin and salbutamol is synergistic and safe in patients with ESRD.[59] Patients with ESRD are unable to eliminate significant amounts of potassium via the kidneys to reduce their total body potassium. Definitive treatment with RRT therefore needs to be instituted promptly. If RRT is delayed, the ESRD patient may experience 'rebound hyperkalaemia' as the potassium ions return into the extracellular space but are not excreted by the kidneys.[16]

Succinylcholine acts on nicotinic acetylcholine receptors on skeletal myocytes and results in sodium and calcium influx and potassium efflux. Succinylcholine administration results in an increase in serum potassium of up to 1 mmol litre^{-1}, occurring 3–5 min after administration.[60] This has raised concerns in patients with renal failure due to their impaired ability to excrete potassium. The risk of succinylcholine-induced hyperkalaemia is greater in patients with sepsis, inflammation, and direct muscle trauma.[61] Succinylcholine is safe in renal impairment, providing that there are no additional risk factors for succinylcholine-induced hyperkalaemia, and potassium levels are not already elevated.[62]

Patients on intermittent haemodialysis often have low plasma potassium levels immediately after the completion of dialysis due to depletion of plasma potassium. Over the next few hours, intracellular potassium re-equilibrates with extracellular potassium.[63] Thus, unless the patient is

suffering from cardiac arrhythmias related to hypokalaemia, replacement of potassium soon after haemodialysis is not required. Should patients suffer from arrhythmias related to hypokalaemia, a 'high potassium dialysate' (3 mmol litre^{-1} potassium) may be used.[63] When patients are on CVVHF, 'post-dialysis hypokalaemia' is not an issue as potassium is continuously replaced.

Calcium

The kidneys are responsible for phosphate excretion and for hydroxylation of vitamin D to its active form (and therefore calcium absorption).[64] Severe hypocalcaemia may result in seizures, laryngospasm, prolongation of the QT interval, and cardiac arrhythmias.[65] In the acute setting, calcium can be replaced i.v. Calcium infusions may result in thrombophlebitis and therefore should be given via a central vein or large peripheral vein. Ten millilitres of calcium gluconate 10% (94 mg calcium) may be given over 10 min, followed by a slow infusion of calcium at a rate not exceeding 1.5 mEq min^{-1}. Hypomagnesaemia often co-exists with and exacerbates hypocalcaemia and should be corrected.[66] The mechanism behind hypocalcaemia secondary to hypomagnesaemia may be related to impaired parathyroid hormone (PTH) release. The use of citrate anticoagulation for RRT may exacerbate underlying hypocalcaemia due to chelation of serum calcium. Citrate anticoagulation often results in a net calcium deficit, despite supplementation to maintain ionized calcium levels.[67]

Hypercalcaemia, defined as a total serum calcium of >2.55 mmol litre^{-1}, may be a consequence of excessive calcium supplementation or related to the underlying cause of renal failure such as multiple myeloma or sarcoidosis. In chronic ESRD patients, tertiary hyperparathyroidism may result in hypercalcaemia. Patients with residual renal function and preserved urine output may suffer from severe volume depletion, as hypercalcaemia results in an osmotic diuresis.

Calcitonin, an inhibitor of osteoclast activity, is reserved for severe hypercalcaemia (>3 mmol litre^{-1})[68], but tachyphylaxis does occur. Bisphosphonates have a more sustained duration of action by reducing bone resorption of calcium.[69] For hypercalcaemia secondary to hyperparathyroidism, cinacalcet 60 mg may be given orally. Cinacalcet acts by reducing parathyroid gland secretion of excessive PTH.[70] In the context of ESRD, RRT ameliorates hypercalcaemia. The use of regional citrate anticoagulation for RRT, but without calcium replacement, results in hypocalcaemia due to calcium chelation. This strategy has been used as a therapeutic measure in hypercalcaemia and renal failure.[71]

Phosphate and magnesium

Phosphate is absorbed via the small intestine and excreted via the kidneys. Patients with ESRD are therefore at risk of hyperphosphataemia. Management of hyperphosphataemia in ESRD includes RRT, dietary phosphate restriction, and administration of phosphate binders during meals.

Magnesium is absorbed from the gastrointestinal tract and excreted predominantly via the kidneys. There is a close association between hypermagnesaemia and renal failure.[72] Hydration or thiazide diuretics may enhance renal elimination of magnesium. In the anuric ESRD patient, haemofiltration may be required to correct hypermagnesaemia.

Altered pharmacokinetics and pharmacodynamics in ESRD

Drug prescription must take account of altered pharmacokinetics resulting from a reduced glomerular filtration rate (GFR), altered protein binding, and a variable volume of distribution. The mode of RRT used is the key determinant of drug dosage. Relevant dosages of medications for the appropriate mode of RRT can be found in a number of formularies. However, we will focus on analgesics and sedatives, diuretics, erythropoiesis-stimulating agents (ESAs), anticoagulation, and antimicrobials.

Analgesics and sedatives

Propofol metabolism is primarily achieved by rapid hepatic metabolic clearance linked to glucuronidation by the cytochrome P450 system.[73] Metabolic clearance of propofol by the kidneys, however, accounts for up to one-third of total body clearance, so dose reductions may be required.[74 75] Haemodiafiltration does not substantially influence propofol clearance, but the initial introduction of an extracorporeal circuit reduces plasma concentrations due to haemodilution alone or adsorption of plasma albumin (with propofol) onto its membrane.[76] Although the required dose of propofol may be decreased, in practice the dose of propofol is titrated to effect. This varies even for patients with normal renal function, unless specifically indicated; patients on ICU should be kept on the minimum amount of sedation compatible with comfort.

Midazolam is metabolized to its active metabolite, α_1-hydroxymidazolam in the liver by cytochrome P450 enzymes and by glucuronide conjugation. There is a close correlation between plasma concentrations of both midazolam and α_1-hydroxymidazolam and the degree of sedation.[77] In healthy volunteers, midazolam is rapidly cleared from the blood with an elimination half-life of 1.5–3.5 h.[78] However, in critical care patients, there is a wide variation of the main pharmacokinetic parameters of midazolam, with a prolonged elimination half-life of 4.5–5.5 h.[79] The elimination of α_1-hydroxymidazolam is also reduced in renal impairment compared with patients without renal impairment (136 *vs* 3.9 ml min^{-1}).[80] Furthermore, protein binding of midazolam is decreased in renal failure, resulting in an increased free midazolam.[81] Neither lorazepam nor midazolam is removed efficiently by CVVHF. Bolus doses of midazolam should therefore be reduced and titrated according to the effect in patients with ESRD. The use of midazolam infusions in critically ill patients with ESRD should therefore be avoided, where

possible. Nevertheless, CVVHF does contribute significantly to the removal of their respective glucuronide metabolites.[82]

A range of opioids is used in the intensive care setting including hydromorphones, morphine, fentanyl, alfentanil, and remifentanil. Morphine is metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) by hepatic glucuronidation. M6G is a potent μ-receptor agonist and it therefore produces analgesia and sedation.[83] M3G has a minimal analgesic effect but may be a potent neuro-excitatory compound.[84] Morphine and its glucuronides are eliminated via the kidneys, and thus accumulate in renal failure[85], as do codeine and its metabolites.[86] Despite the very high ultrafiltrability/diffusability of free morphine across high-efficiency or high-flux membranes, only a minimal amount of the total amount of morphine is removed in 24 h in patients requiring haemofiltration or haemodiafiltration. However, a significant quantity of free morphine may be removed in haemodialysis due to a much higher dialysate flow rate.[87 88] Hydromorphones do not substantially accumulate in ESRD, most likely due to their rapid conversion to hydromorphone-3-glucoronide (H3G). H3G, however, accumulates between dialysis treatments but appears to be effectively removed during haemodialysis.[89] Although morphine use is not an absolute contraindication in ESRD, it should be used with caution.

Fentanyl-based regimens are often preferred in patients with renal impairment as the short plasma half-lives of fentanyl and alfentanil are related to redistribution rather than metabolism.[90] Nevertheless, in patients with ESRD, dose reduction in fentanyl is still required as accumulation will result in toxicity.[91] Fentanyl is not cleared by haemodialysis.[88] The elimination half-life and plasma clearance of alfentanil are unaffected by renal impairment; however, its volume of distribution and free fraction are increased in patients with renal failure.[92] Remifentanil clearance is clinically independent of renal function because of its esterase-dependent metabolism though its metabolite, remifentanil acid, does accumulate in renal failure.[93] As this metabolite is 1/4600 less potent than remifentanil, this agent does not have a toxic effect in renal impairment.[93 94]

Diuretics

In the few haemodialysis patients with residual renal function, furosemide may be used to increase urine output with a view to maintaining fluid balance. Decreased renal diuretic delivery, decreased basal fractional NaCl reabsorption, and decreased proximal tubule diuretic secretion contribute to the relative resistance to the effect of diuretics in patients with ESRD and CKD.[95]

Increasing diuretic dosage may overcome diuretic resistance. Up to 200 mg furosemide may be given as a slow infusion. Furosemide is dependent on renal function for clearance, and thus, the risk of diuretic toxicity (such as ototoxicity) is increased.[96] The exact incidence of deafness secondary to high-dose loop diuretic use is not known. Bumetanide and torsemide are therefore advantageous due to their non-renal metabolism. I.V. and oral doses of bumetanide (up to 10 mg) and torsemide (up to 100 mg) are equivalent due to their high bioavailability. The concurrent use of a thiazide diuretic in addition to a loop diuretic to inhibit downstream NaCl reabsorption may improve loop diuretic responsiveness.[95] Administration of diuretics that continuously maintain effective rates of excretion into the urine may produce a greater overall diuretic effect than the same amount of diuretic administered in intermittent doses.[97] Therefore, an i.v. infusion is more likely to have a greater effect.[98] Many haemodialysis patients will not achieve a significant diuresis despite these measures, as they lack an adequate GFR. Patients on PD often have some residual renal function, unlike most patients on maintenance haemodialysis.[14] The use of diuretics in patients with ESRD is limited to patients with residual urine output. This may be a valuable therapeutic strategy in the management of a patient with pulmonary oedema until RRT facilities are available.

Erythropoiesis-stimulating agents

ESRD patients are usually prescribed ESAs to maintain their haemoglobin levels. However, there is a relative resistance to the haemopoetic effect of ESAs during an inflammatory response.[99] The benefit of continuing ESAs in critically ill patients with ESRD is debatable and has not been properly evaluated. However, increasing the dose of ESAs in haemodialysis patients with severe sepsis or septic shock is not routinely recommended as ESA doses >40 000 units per week produced an increased incidence of deep vein thrombosis and myocardial infarction.[100]

Anticoagulants

Chronic uraemia carries an increased risk of bleeding. Abnormal prolongation of bleeding time and haemorrhagic symptoms have characterized the bleeding tendency seen in uraemic dialysis patients.[101] Impaired adhesion and decreased aggregation of platelets resulting in their dysfunction have been attributed to intrinsic platelet defects, anaemia, uraemic toxins, von Willebrand factor, and vessel abnormalities.[101] The most common sites of bleeding secondary to uraemia include petechial haemorrhage, ecchymoses at the arteriovenous fistula needling or venous access insertion sites, and upper gastrointestinal bleeding.[102]

The use of low-molecular-weight heparin to maintain patency of the extracorporeal dialysis circuit is of similar efficacy and safety to unfractionated heparin in chronic stable haemodialysis patients.[103] However, unfractionated heparin is the anticoagulant of choice for therapeutic anticoagulation in the acute setting as it is readily reversible and its metabolism and clearance are independent of renal function. Low-molecular-weight heparins have limited use when therapeutic anticoagulation is required as elimination will be impaired, leading to a prolonged and unpredictable anticoagulant effect.[104]

Sodium citrate may be used for 'regional anticoagulation' of the extracorporeal circuit in instances where systemic anticoagulation is undesirable. This is safe in CVVHF, SLED, and intermittent haemodialysis.[105–107] Among critically ill patients requiring CVVHF, regional citrate anticoagulation increased haemofilter survival time and decreased bleeding risk compared with systemic heparin anticoagulation.[106] During SLED treatment, the calcium infusion rate may need to be increased because of the more efficient removal of the calcium citrate complex in SLED compared with CVVHF.[105] However, during intermittent haemodialysis on the ICU, a low-calcium dialysate (1 mmol litre^{-1}) used in conjunction with citrate anticoagulation may not require routine calcium substitution when citrate dosing is adjusted according to the post-filter ionized calcium concentration.[107]

Antibiotics

The mode of RRT determines antibiotic dosage.[108 109] However, as discussed above, the choice of antibiotics must be based upon the most likely source of infection (including the presence of a haemodialysis or PD catheter) and organism, local antibiotic resistance patterns. Empiric treatment should generally include both Gram-positive and Gram-negative cover. MRSA cover may be needed if the patient has an indwelling haemodialysis or PD catheter.

In conclusion, the incidence of ESRD is increasing with the ageing population and it is likely that an increasing number of patients with ESRD will be admitted to ICU. There is a paucity of data from existing studies that specifically address the management of this specific population in the ICU setting. This highlights the need for more prospective clinical trials in this specific patient cohort. Fundamental differences between patients with normal function and those with ESRD include electrolyte disorders and altered drug handling. Cardiovascular disease and sepsis account for a significant proportion of mortality and morbidity in patients with ESRD. The underlying aetiology of cardiac pathology and sepsis in this cohort is different and therefore may require a different approach to management. We have summarized the available literature with the aim of providing the intensive care physician and anaesthetist with a practical approach to problems specific to the ESRD patient on ICU and commonplace problems on ICU that require special consideration in ESRD patients.

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