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Review Article

Perioperative Management of Patients With End-Stage Renal Disease

Hirotsugu Kanda, MD, PhD[*,1], Yuji Hirasaki, MD[†,‡], Takafumi Iida, MD, PhD[*], Megumi Kanao-Kanda, MD, PhD[*], Yuki Toyama, MD[*], Takashi Chiba, MD[§], Takayuki Kunisawa, MD, PhD[*]

[*]*Department of Anesthesiology and Critical Care Medicine, Asahikawa Medical University, Asahikawa, Hokkaido, Japan*
[†]*Department of Anesthesiology, Tokyo Women's Medical University, Tokyo, Japan*
[‡]*Department of Anatomy, The Jikei University School of Medicine, Tokyo, Japan*
[§]*Iwamizawa Dialysis Center, Jinyukai, Iwamizawa, Hokkaido, Japan*

End-stage renal disease (ESRD) is associated with significant alterations in cardiovascular function; homeostasis of body fluid, electrolytes, and acid-base equilibrium; bone metabolism, erythropoiesis; and blood coagulation. The prevalence of ESRD is increasing rapidly worldwide, as is the number of patients requiring surgery under general anesthesia. Patients with ESRD have significantly higher risks of perioperative morbidity and mortality due to multiple comorbidities. The perioperative management of patients with ESRD under general anesthesia therefore requires special considerations and a careful multidisciplinary approach. In this review, the authors summarize the available literature to address common issues related to patients with ESRD and discuss the best perioperative approach for this patient subgroup.

Key Words: hemodialysis; end-stage renal disease; stroke-volume variation; general anesthesia; goal-directed therapy

THE NUMBER OF patients with chronic kidney disease (CKD) dependent on hemodialysis (HD) is increasing rapidly all over the world due to the increasing prevalence of hypertension, type-2 diabetes mellitus, and the aging population. For example, more than 600,000 patients in the United States currently are receiving long-term HD for end-stage renal disease (ESRD).[1] The extended lifespan prolonged by HD has increased the need for surgery to address complications of the underlying disease. Patients with ESRD have a higher risk of cardiovascular disease and other coexisting diseases[2] and an adjusted all-cause mortality rate at least 10-fold higher than that of the non-ESRD population.[1] As such, perioperative management of patients with ESRD requires special considerations regarding disease pathophysiology, including cardiovascular dysfunction, volume disturbances, anemia, and electrolyte disorders, and pharmacokinetic/pharmacodynamic alterations (Fig 1). In particular, fluid management to prevent both fluid overload and hypovolemia is one of the greatest challenges in ESRD patients. A persistent fluid overload may lead to hypertension, pulmonary edema, and congestive heart failure and a greater risk of mortality.[3] Therefore, ESRD patients usually undergo HD the day before surgery to achieve euvolemia, the so-called "dry weight."[4] On the other hand, ESRD patients sometimes exhibit significant hypotension after the induction of general anesthesia.[5] Surprisingly, little evidence related to perioperative fluid management in ESRD patients has been published.

[1]*Address reprint requests to* Hirotsugu Kanda, MD, PhD, Department of Anesthesiology and Critical Care Medicine, Asahikawa Medical University, Midorigaoka-higashi 2-1-1-1, Asahikawa, Hokkaido, 078-8510, Japan.
E-mail address: h.kanda0629@nifty.com (H. Kanda).

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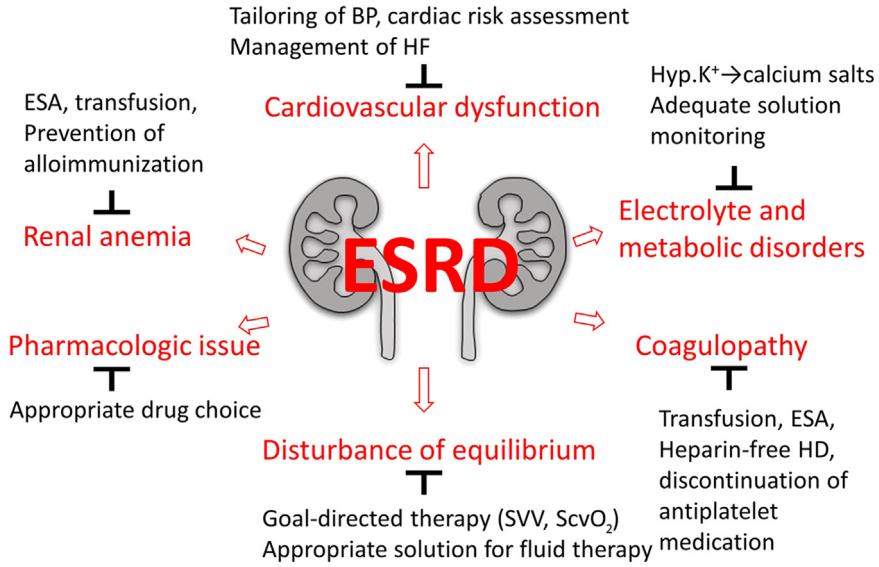

Fig 1. Main systemic complications of ESRD and the treatment of these abnormalities. BP, blood pressure; HF, heart failure; ESA, erythropoietin stimulating agents; SVV, stroke-volume variation; $ScvO_2$, central venous oxygen saturation; $Hyp.K^+$, hyperkalemia.

In this review, the authors summarize the available literature to address common issues related to patients with ESRD and discuss the best perioperative approach for this patient subgroup. In particular, the authors focus on fluid/blood management, including dry weight, choice of fluid, transfusion, and parameters to guide volume replacement therapy.

Definition of CKD

The Kidney Disease Improving Global Outcomes (KDIGO) *2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease* proposed a 5-stage classification for CKD based on the glomerular filtration rate (GFR) (Table 1).[6] CKD is defined as either a history of kidney transplantation or a GFR < 60 mL/min/1.73 m^2 for more than 3 months in the presence of additional markers of kidney damage, such as albuminuria (albumin excretion rate > 30 mg/24 h, albumin-to-creatinine ratio > 30 mg/g [> 3 mg/mmol]); urine sediment abnormalities; electrolyte and other abnormalities due to tubular disorders; tissue abnormalities detected using histology; and structural abnormalities detected using imaging. Patients with a functioning renal transplant still are considered to have CKD. The term "ESRD" corresponds to CKD grade 5, for which lifelong renal replacement therapy (RRT), including peritoneal dialysis, HD, or transplantation, is necessary for survival.

Table 1
GFR Categories in CKD

GFR Category	GFR (mL/min/1.73 m^2)	Terms
Grade 1	≥ 90	Normal or high
Grade 2	60-89	Mildly decreased
Grade 3a	45-59	Mildly to moderately decreased
Grade 3b	30-44	Moderately to severely decreased
Grade 4	15-29	Severely decreased
Grade 5	< 15	Kidney failure

From KDIGO 2012 *Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease*.[6]
Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

Epidemiology

Generation Status and Vital Prognosis

Hill et al performed a systematic review and meta-analysis on 100 articles and reported the prevalence of CKD using the Kidney Disease Outcomes Quality Initiative criteria in a general population.[7] They demonstrated an estimated mean prevalence (95% confidence interval) of CKD at any stage of 13.4% (11.7%-15.1%) worldwide, which is higher than the prevalence of diabetes (8.5% in 2014),[8] and a prevalence of ESRD (CKD stage 5) of 0.1%. The prevalence and prognosis of ESRD are highly modified by socioeconomic background.[9] The main causes of ESRD in the United States, in order, are diabetes, hypertension, glomerulonephritis, and cystic kidney disease.[1] Liyanage et al reported that more than 2.6 million patients with ESRD received RRT in 2010 worldwide,[10] but the actual prevalence of ESRD is deemed to be higher than the reported numbers. Furthermore, they estimated that as many as 9.7 million patients worldwide required RRT in 2010 and the number is projected to double by 2030. The current total Medicare cost for ESRD patients in the United States already has reached $32.8 billion.[1]

Life on dialysis is not straightforward; patients on HD have a higher risk of developing comorbidities such as stroke, acute coronary events, heart failure, vascular access–related infection, endocarditis, cancer, bowel ischemia/bleeding, limb ischemia/necrosis, and bone fractures requiring emergency medical or surgical interventions.[9,11]

The prognosis of ESRD thus is poor. The World Health Organization reported that 864,226 deaths (12.2 deaths per 100,000 people; 1.5% of global deaths) worldwide were

attributable to CKD in 2012.[12] The United States Renal Data System annual data report demonstrated that the expected remaining lifetime and unadjusted annual mortality rate of dialysis patients in 2014 was 6.9 years and 180.0 per 1,000 patient-years, respectively.[1] Robinson et al found high 5-year mortality rates ranging between 39% and 60%, primarily due to cardiovascular complications.[13]

Impact of ESRD on Perioperative Outcomes

Considering their severe comorbidities, it is not surprising that patients with ESRD have considerable perioperative risks. Indeed, the literature consistently demonstrated a higher risk of mortality in ESRD patients compared with non-ESRD patients, both in the cardiac and noncardiac perioperative periods (Table 2).[14–23] Gajdos et al demonstrated that the 30-day mortality rates of patients with ESRD undergoing elective vascular procedures were 4-fold higher than those of their non-ESRD cohorts.[17] Furthermore, they found that older patients (> 65 years) with ESRD had remarkably higher risks of postoperative pulmonary complications and death than the younger subgroup, suggesting that the indications for performing these procedures in this subgroup requires careful consideration. Moran-Atkin et al also reported higher mortality rates in older patients with ESRD in elective and emergency colon surgery for diverticulitis.[18]

Pathophysiology

Kidneys play essential physiologic roles, including excretion of excessive water and water-soluble waste (eg, urea); ion metabolism; acid-base balance; erythropoiesis; and bone metabolism via activation of vitamin D. These functions, however, are disrupted significantly in patients with ESRD, leading to retention of water and urea toxin, hyperkalemia, acidosis, anemia, and osteomalacia, which are discussed in detail in the following.

Cardiovascular Disease

Cardiovascular diseases due to atherosclerosis and cardiac remodeling commonly occur in patients with CKD.[24] Accelerated atherosclerosis is a feature of CKD that may be related to impaired endothelial function, low-grade inflammation, and dyslipidemia.[25] Patients with CKD generally exhibit lower levels of high-density lipoprotein and higher levels of intermediate-density lipoprotein.[25] Another potential contributing factor to cardiovascular disease in CKD is activation of the renin-angiotensin system. Angiotensin II, especially that acting at angiotensin-1 receptors, promotes the production of reactive oxygen species, leading to endothelial dysfunction and vascular remodeling. Under normal conditions, a wide range of systemic mean arterial pressures (MAPs) autoregulate renal blood flow; however, arterial hypertension and renal disease disrupt this autoregulatory mechanism, with renal blood flow becoming more directly proportional to the MAP.[26] The relative risk for ESRD is > 20-fold higher for patients with high-risk hypertension (systolic blood pressure [SBP] > 210 mmHg or diastolic blood pressure > 120 mmHg) than for patients with normal blood pressure (BP) levels.[27,28]

Progressive dysfunction of the cardiovascular system, especially left ventricular hypertrophy (LVH) resulting from high pressure and volume overload, occurs in patients with ESRD.

Table 2
Postoperative Mortality of Patients With ESRD in Various Surgical Settings

Author (yr)	Procedure	Number (With ESRD)	Mortality Rate (Non-ESRD Patients)	Odds Ratio (95% CI)
Parikh et al[14] (2010)	CABG	3485	5.4% in 2003 (1.8%)	NA
Chikwe et al[15] (2010)	CABG	96	7.3% (1.4%)	NA
Thourani et al[16] (2012)	Valve surgery	224	18.3% (5.2%)	1.80 (1.09-2.97)
Gajdos et al[17] (2013)	Major vascular procedures	1409	7.25% (1.4%)	All: 4.46 (3.48-5.72) Abdominal: 4.15 (1.98-8.71) Carotid: 3.52 (1.48-8.40) Peripheral: 3.66 (2.67-5.03)
Moran-Atkin et al[18] (2014)	Colon surgery for diverticulitis	962	Elective: 25.64% (2.56%) Emergency: 31.41% (7.29%)	NA
Smith et al[19] (2015)	Appendectomy	5,712	NA	5.68 (3.96-8.15)
Brakoniecki et al[20] (2017)	General surgeries	1,163	NA	9.05 (4.09-20.0)
De la Garza Ramos et al[21](2016)	Anterior cervical fusion	270	< 4.1% (0.05%)	15.2 (5.67-40.88)
Lin et al[22] (2015)	Fixation of hip fractures	2,680	Mortality rate 354.30/1,000 patient-years (152.04 /1,000 patient-years) Media survival time 1.89 years (4.68 years)	NA
Erkocak et al[23] (2016)	Total joint arthroplasty	359	2% (0.6%)	10.46* (1.67-65.34)

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; ESRD, end-stage renal disease; NA, not applicable.
*Result using multivariate analysis.

Sodium and water retention often lead to volume overload, increasing shunt flow through an arteriovenous fistula, or chronic anemia, with an increased stroke volume and heart rate,[29] whereas hypertension and arteriosclerosis contribute to pressure overload. LVH is related to myocardial fibrosis and myocardial relaxation malfunction, which can cause diastolic dysfunction and arrhythmias.[29] Reduced left ventricular (LV) compliance may increase sensitivity to volume changes and accelerate the development of pulmonary edema.

Diastolic heart failure (ie, heart failure with a preserved ejection fraction) presents clinically with symptoms and signs of heart failure, including fatigue, dyspnea, palpitations, and hypotension due to pulmonary congestion or edema, normal systolic function and evidence of diastolic dysfunction.[30] Glassock et al reported that subclinical diastolic dysfunction is one of the most common echocardiographic findings in asymptomatic CKD patients with ESRD, together with LVH.[31] In fact, a large number of ESRD patients present with diastolic dysfunction and have the potential to develop diastolic heart failure. Moreover, systolic heart failure, dilated LV due to fluid accumulation, decreased ejection fraction, and mitral or tricuspid regurgitation may present with impaired renal function.[32] Eventually, diastolic heart failure contributes to the final form of heart failure in ESRD patients, along with progressive systolic heart failure.[30,32]

Volume Disturbance

ESRD patients are unable to excrete salt and water adequately, which results in chronic volume overload. Chronic volume overload is a common complication in HD patients in relation to hypertension, pulmonary edema, increased arterial stiffness, LVH, and heart failure and may be instrumental in their higher mortality and morbidity.[1,33] The excess fluid must be removed during each dialysis period. These clinical issues, however, have not been resolved due to the adverse effects of dehydration.

Dehydration in the HD patient often is associated with hypotension, tinnitus, and dizziness (Table 3).[34] Moreover, a history of intradialytic hypotension may lead to more severe residual renal dysfunction,[35] occlusion of the arteriovenous access,[36] cerebral or mesenteric infarction,[37,38] and increased morbidity and mortality.[39]

Table 3
Symptoms of Volume Overload and Dehydration

Overload	Dehydration
Increased body mass	Decreased body mass
Hypertension	Hypotension
Edema	Dizziness
Palpitation	Nausea and vomiting
Dyspnea	Unsteadiness
Breath shortness	Torpor
Headache	Syncope

Metabolic Acidosis and Electrolyte Abnormalities

Metabolic Acidosis

In CKD patients, impaired GFR (40-50 mL/min) limits the ability of the kidneys to excrete acid.[40–42] This disability initially leads to hyperchloremic (normal anion gap) metabolic acidosis, which may convert to a mixed normal anion gap and high anion gap metabolic state when the GFR falls < 15 mL/min.[43] Additional abnormalities caused by acidemia and metabolic acidosis include insulin resistance, thyroid dysfunction, high cortisol levels, and reduced insulin-like growth factor-1 [44–46] in conjunction with increased protein turnover,[47] leading to a low serum albumin concentration.

Hyperkalemia

Ninety percent of potassium is excreted by the kidneys and 10% by the intestine.[48] The ability to excrete excessive potassium is affected by CKD. Plasma potassium levels, however, are maintained within normal limits until the onset of CKD grade 5. Patients have an impaired ability to excrete potassium load, which leads to the development of hyperkalemia.

Disorder of Calcium, Phosphate, and Bone Metabolism

The presence of ESRD affects the excretion of phosphate ions and activation of vitamin D at the kidneys, which decelerates the absorption of calcium from the small intestine and leads to an initial drop in the blood calcium level. Hypocalcemia may result in laryngospasm, a prolonged QT, and cardiac arrhythmias.[49] This leads to secondary hyperparathyroidism, in which excessive excretion of parathyroid hormone occurs to compensate for the hypocalcemia, leading to hypercalcemia and hyperphosphatemia via the mobilization of calcium and phosphate from the bone matrix.[50,51] As a result, the bone becomes fragile and more prone to fracture. On the other hand, an elevated blood calcium level leads to an ectopic deposition of calcium phosphate in systemic vessels (vascular calcification)[52] or soft tissues (calciphylaxis).[53]

Renal Anemia and Alloimmunization

Anemia is a common complication in moderate-to-severe CKD,[54–56] usually due to the reduced production of endogenous erythropoietin by the impaired kidneys.[57] The reduced aerobic capacity results in symptoms of anemia, such as fatigue, dizziness, and palpitations, and potential aggravation of myocardial dysfunction.[58] Therefore, adequate therapies, erythropoiesis stimulating agents (ESA), red blood cell (RBC) transfusion, and iron supplements are required to improve the patient's quality of life and outcome.[59]

Alloimmunization is defined as an immune response to foreign antigens after exposure to genetically different cells or tissues. Transfusion may induce alloimmunization targeting the human leukocyte antigen or RBCs, with sensitization rates ranging from 2% to 21%.[60–62] Sensitized patients who undergo kidney transplantation have a greater risk of graft

loss.[63] Therefore, transfusions should be performed only in transplantation candidates under special consideration. In particular, the balance of risk and benefits before transfusion should be assessed for potential recipients in cases of high-risk allosensitization, previous transplantation, pregnancy, and previous transfusion.[59]

Coagulopathy

ESRD patients are at increased risk for perioperative bleeding.[64] The accumulated uremic toxins inhibit normal platelet function and platelet–vessel wall interactions.[65] Moreover, anemia, which commonly is seen in ESRD patients, also interferes with normal coagulation.[59] A study using thromboelastography reported that coagulation abnormalities were detected in 42.9% of patients with ESRD.[66]

Pharmacology

Loss of kidney function affects drug pharmacokinetics and pharmacodynamics, requiring anesthesiologists to carefully consider potential alterations in the distribution, metabolism and elimination, and protein binding, as discussed later.

Preoperative Considerations

Preoperative Evaluation and Surgical Decision-Making

As mentioned previously, patients with ESRD carry higher risks of perioperative morbidity and mortality, regardless of the type of surgery. As such, a multidisciplinary team approach involving all medical and surgical specialties is essential to achieve a successful postoperative outcome. The patient's past and present history should be reviewed thoroughly (Table 4).[67] Physical examination focusing on the patient's cardiovascular status should be performed carefully to identify any clinical findings of cardiovascular disease. Despite a high prevalence of coronary artery disease in patients with ESRD, many are asymptomatic due to the presence of diabetes or exercise intolerance.[68] The assessment, therefore, should include objective diagnostic modalities, namely, cardiac troponin T,[69] stress myocardial perfusion single-photon emission computed tomography,[70] dobutamine stress echocardiography,[71] and coronary artery calcium score,[72] to detect unidentified cardiovascular disease preoperatively.[73,74] In this context, invasive diagnostic imaging, including coronary angiography, may be justified. The results should be reviewed by all care team members and indications for the surgery should be discussed as long as time allows. Less-invasive catheter-based cardiovascular interventions (percutaneous coronary intervention,[75] endovascular stent,[76] and transcatheter aortic valve implantation[77]) may lead to a lower risk of periprocedural mortalities in some settings. Whether these procedures are associated with better long-term outcomes in this patient group, however, remains controversial. Marui et al demonstrated that coronary stenting was associated with a lower 30-day mortality, whereas surgical revascularization was associated with a reduced risk of cardiac death in a 5-year postoperative period.[75] Similarly, Yuo et al demonstrated that endovascular stenting for abdominal aortic aneurysms was associated with a lower postprocedural mortality compared with open repair, but they found no significant difference in 1-year mortality.[76] The decision as to whether surgery is indicated or the type of surgery that might be beneficial for the patient should be made with consideration of the patient's condition, will, and ultimate goal of treatment in each case.

Table 4
Preoperative Considerations for Patients With ESRD

Patients should be informed regarding an increased risk of complication and mortality
Blood pressure should be controlled with predialysis and postdialysis goals of $< 140/90$ and 130/80 mmHg, respectively.
Patients with < 4 METs or unknown functional capacity require a cardiology consultation[67]
Hemoglobin level should be maintained at 9.0-10.0 g/dL using an ESA
Hemodialysis should be performed the day before surgery (elective surgery at least 6 h after dialysis with heparin)
Target range of HbA1c in ESRD patients is 6.0% to 8.0%
Transfusion or ESA to maintain hematocrit around 30% preoperatively reduces the bleeding risk

Abbreviations: ESA, erythropoiesis stimulating agents; ESRD, end-stage renal disease; HbA1c, hemoglobin A1c; METs, metabolic equivalents.

Management of Hypertension and Heart Failure

Tailoring of BP is very important for ESRD patients to reduce perioperative morbidity. The KDIGO clinical practice guidelines recommend treatment for blood pressure $< 130/80$ mmHg in patients with CKD.[78] Moreover, other guidelines recommend predialysis and postdialysis BP goals of $< 140/90$ mmHg or $< 130/80$ mmHg.[79]

Heart failure, combined systolic heart failure and diastolic failure, is the final form of cardiovascular disease in ESRD patients. In patients with acute pulmonary edema or congestion, an intravenous bolus of loop diuretics should be administered initially if urination is preserved.[80] Continued administration of dobutamine is needed in patients with an SBP < 85 mmHg, or a vasodilator, such as nitroglycerin, is necessary in patients with an SBP > 115 mmHg.[80] Moreover, consideration of emergency HD is required when the hemodynamics are not stable. According to the European Society of Cardiology guidelines, pharmacologic treatment of diastolic heart failure is limited. In general, diuretics are used to control sodium and water retention and relieve breathlessness and edema, but the effects of diuretics are not clear in HD patients.[80] A small study indicated that the heart rate–limiting calcium-channel blocker verapamil may improve exercise capacity and symptoms in diastolic heart failure patients.[81,82] Beta-blockers also may be used to control the ventricular rate in patients with atrial fibrillation.[80]

Preoperative Dialysis

In general, preoperative dialysis is required to correct the fluid status and electrolyte abnormality and to remove the uremic toxins. The appropriate timing of preoperative dialysis,

however, still is unclear due to the scarcity of clinical data. A retrospective study reported that HD within 24 hours before surgery was associated with a lower potassium level on the day of surgery.[4]

Heparin is used as the first-choice anticoagulant for HD. Because the heparin effect lasts 4 hours, elective surgery should be scheduled at least 6 hours after dialysis to avoid perioperative bleeding if heparin is used during HD.[83] Heparin-free dialysis is excluded in this recommendation.

Acute removal of urea may cause dialysis disequilibrium syndrome, a potentially lethal syndrome associated with various neurologic symptoms (restlessness, headache, or coma) after HD.[84] Therefore, patients undergoing surgery should have an adequate set period before surgery to confirm the absence of these symptoms.[4]

Taken together, the available information suggests that HD on the day before surgery is preferable to correct electrolyte imbalance, uremia, and excess body fluid and to minimize the perioperative bleeding risk.

Provisions for Bleeding Risk

Adequate heparin-free dialysis that reduces the accumulated urea improves platelet function.[65] Preoperative transfusion or administration of ESA to maintain the hematocrit at approximately 30% may reduce the bleeding risk.[85] The use of point-of-care tests, including thromboelastography, is expected to improve perioperative coagulation management in patients with ESRD.[66,86] If antiplatelet agents are administered to prevent stroke or myocardial infarction, aspirin should be discontinued 6 days before surgery, clopidogrel should be discontinued 7 days before surgery, and intravenous heparin should be discontinued 4 hours before surgery.[87]Administration of 1-desamino-8-D-arginine vasopressin may reduce bleeding by improving platelet function and clotting factor activity in ESRD patients.[88–90] However, 1-desamino-8-D-arginine vasopressin should be used with caution or avoided entirely in patients with ESRD because it may lead to fluid retention and increase BP.

Treatment of Hyperkalemia and Hypercalcemia

Bolus infusion of calcium salts, calcium gluconate, or calcium chloride immediately decreases the potassium level.[91] This intervention, however, increases serum calcium concentration and thus increases the threshold for the cardiac muscle action potential, leading to decreased excitability.[92] Several published studies, however, suggested that calcium should be administered when the serum potassium concentration is $>$ 6.0-to-6.5 mmol/L, even in the absence of electrocardiogram abnormalities.[92,93] Bicarbonate infusion is the most reliable treatment for acute hyperkalemia after calcium salt infusion. Hypertonic sodium bicarbonate (2 mmol/min over 1 h) or isotonic bicarbonate (1.5 mmol/min over 1 h) is effective for hyperkalemia.[94,95] Therapies to increase the intracellular uptake of potassium, such as intravenous administration of insulin and nebulized salbutamol, may be administered to prevent hyperkalemia. Combination therapy with insulin and salbutamol has synergistic effects and appears to be safe for ESRD patients.[96] Emergency dialysis sometimes is required in the case of severe and treatment-resistant hyperkalemia.

The infusion of calcium salts is an appropriate therapy for hypocalcemia that is comorbid with hyperkalemia. Calcitonin, bisphosphonate, and cinacalcet should be considered for treatment in the case of hypercalcemia.[97–99]

In any case, frequent electrolyte checks are necessary to monitor these abnormalities during the perioperative period.

Management of Renal Anemia

In 1989, the US Food and Drug Administration approved the use of recombinant human erythropoietin to boost hemoglobin (Hb) levels and ameliorate symptoms of anemia in patients with ESRD.[100] Before the availability of ESAs, treatment options for anemia were limited mainly to RBC transfusions and, in some cases, androgen and iron therapy.[57] ESA therapy increases the mean Hb level in HD patients from 9.8-to-11.2 g/dL and has cut the RBC transfusion rate by half.[101] Unfortunately, however, several randomized studies reported that ESA treatment in predialysis patients with CKD increased the risk of mortality and major cardiovascular events.[102–104] Due to the accumulation of findings that ESA therapy increased the risk of adverse events, the US Food and Drug Administration introduced several major ESRD-related regulatory and reimbursement changes in 2011 that eventually led to revisions of the ESA label information. The primary label changes were removal of the Hb target range of 10-to-12 g/dL and new dosing and administration language recommending that ESA dosing be reduced or interrupted at Hb concentrations $\sim$11 g/dL.[105,106] Revisions of the regulatory and reimbursement policies in 2011 led to subsequent decreases in ESA doses and Hb concentrations in dialysis patients in the United States and increases in the use of RBC transfusions in chronic dialysis patients.

The 2012 KDIGO *Clinical Practice Guidelines for Anemia in Chronic Kidney Disease* recommended initiating ESA therapy for ESRD patients when Hb is between 9.0 and 10.0 g/dL to avoid a decrease in the Hb concentration to $<$ 9.0 g/dL.[59] In general, the KDIGO guidelines stated that ESAs should not be used to maintain Hb concentrations $>$ 11.5 g/dL in adult patients with CKD.[59] Iron therapy is considered suitable adjuvant therapy for ESA therapy, whereas treatment with androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline is not.[59]

Intravenous administration of ESA (500 IU/kg) and an iron supplement (200 mg) 1 day before surgery was reported to significantly reduce the need for perioperative transfusion in anemic patients undergoing cardiac surgery.[107] Moreover, the administration of ESA before anesthesia was correlated with a reduction in cardiac surgery–associated acute kidney injury.[108]

Blood Glucose Control

The KDIGO clinical practice guidelines suggest a target hemoglobin A1c (HbA1c) of $< 7.0\%$ to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease.[6] On the other hand, these guidelines also recommend that the target HbA1c be extended to $> 7.0\%$ in individuals with comorbidities or limited life expectancy and risk of hypoglycemia.[6]

Up to one-third of diabetic HD patients are considered to have "burnt-out diabetes."[109,110] Burnt-out diabetes presents with a low HbA1c level ($< 6.0\%$) even if the diabetes mellitus is long term. Moreover, these patients have an adverse prognosis despite HbA1c $< 6.0\%$.[109,110] This adverse condition is due to multiple factors, such as malnutrition, protein-energy wasting, reduced clearance of exogenous insulin, and antihyperglycemic effects of the accumulated uremic toxins.[109–111] The clinical significance of this condition, however, remains unclear. Ricks et al reported that HD patients with HbA1c levels between $< 6.0\%$ and $> 8.0\%$ had increased mortality.[112] These findings indicated that ESRD patients with HbA1c levels $< 6.0\%$ have a poor outcome from the viewpoint of burnt-out diabetes.[112] As previously suggested, the authors of this review recommend a target range of HbA1c in ESRD patients of 6.0% to 8.0%, especially in diabetic dialysis patients.

Tight glucose control (81-108 mg/dL) in critically ill patients, including those with renal failure, is associated with an increased risk of hypoglycemia and adverse events compared with conventional glucose control, which targets a blood glucose level of 180 mg/dL.[113] Several studies have revealed that a target level < 180 mg/dL reduced perioperative morbidity and mortality.[114,115] The authors recommend moderate glucose control (< 180 mg/dL), acceptable in general, as a suitable strategy for ESRD patients because these patients have a risk for hypoglycemia, as represented by burnt-out diabetes.

Intraoperative Considerations

Fluid Management

Dry Weight and Fluid Removal

Anesthesiologists must estimate each patient's fluid status consistently and provide appropriate fluid therapy to maintain an adequate perfusion pressure for microcirculation (Table 5). What constitutes dry weight and euvolemia, however, is not clear.

Dry weight is defined as "the lowest tolerated post-dialysis weight achieved with minimal signs or symptoms of hypo- or hypervolemia."[116] This definition, however, does not adequately apply to all patients. Fluid overload also may result from intradialytic hypotension and/or symptoms related to dialysis and ultrafiltration. Intradialytic hypotension (decrease in SBP ≥ 20 mmHg or MAP by ≥ 10 mmHg)[117] commonly is detected in dialysis patients (15%-30% of all dialysis treatments) and complicates HD therapy.[118] Several conditions, including hypovolemia, an inadequate hemodynamic response from the sympathetic nervous system, diastolic dysfunction, autonomic dysfunction, and underlying cardiac disease, are potential causes of intradialytic hypotension.

Table 5
Intraoperative Considerations for Patients With ESRD

Moderate glucose control (< 180 mg/dL) is recommended
Special attention must be paid to both the type and quantity of fluid to be administered
Stroke-volume variation is a useful indicator of hypovolemia
Caution is advised to prevent acute fluid overload after preoperative fluid removal, bleeding, and predicted insensible water loss.
RBC transfusion should be considered for patients with Hb < 7 g/dL
Caution is advised when performing regional blocks and neuraxial anesthesia due to the bleeding risk
Appropriate sites should be selected for arteriovenous fistulae, arteriovenous grafts, a venous or arterial catheter cannulation
Intraoperative HD is not necessary except under specific situations in cardiac surgery
ε-aminocaproic acid and tranexamic acid are useful against post-CPB bleeding

Abbreviations: CPB, cardiopulmonary bypass; ESRD, end-stage renal disease; HD, hemodialysis; RBC, red blood cells.

Information obtained from physical examinations, such as body mass, BP, and edema, is not adequate for accurately determining the fluid status. The quantitative methods, such as cardiothoracic ratio, human atrial natriuretic peptide, or brain natriuretic peptides, and inferior vena cava diameter are more credible predictors of fluid status and informative for determining the dry weight.[119] The equation Kt/V can be used to estimate the volume of blood cleansed during HD and to calculate the appropriate dialysis dose, where K, t, and V are urea clearance, dialysis time, and body fluid volume, respectively. That is, Kt/V indicates the volume of the HD dose. The KDIGO clinical practice guidelines suggest a minimally adequate Kt/V of 1.2 for HD treatment 3 times a week, with a target dose of 1.4 per session.[120]

There currently is no gold standard measurement for dry weight, and therefore it may be difficult for anesthesiologists to establish the preoperative fluid status. Furthermore, it is very difficult to manage fluids in HD patients intraoperatively.

What is the Best Intravenous Solution for Fluid Therapy in Patients With ESRD?

To date, various types of intravenous solution have been developed for fluid therapy.[121] The effect of intravenous fluid therapy on clinical outcomes has been studied extensively over the last several decades. Perel et al performed a systematic review of randomized controlled trials comparing colloids and crystalloids and found no beneficial effect of colloids on survival in critically ill patients.[122] Furthermore, hydroxyethyl starch (HES) is associated with a higher risk of developing acute renal insufficiency in this cohort.[123,124] In the setting of kidney transplantation, Cittanova et al demonstrated that the use of high-molecular HES (200/0.6) for volume expansion in a brain-dead donor was associated with a higher incidence of postoperative graft kidney dysfunction.[125] On the other hand, Blasco et al revealed that the use of low-molecular

HES (130/0.4) was associated with better postoperative graft function compared with high-molecular HES.[126]

As for crystalloids, studies have demonstrated that hyperchloremia secondary to the use of 0.9% saline was associated with poor postoperative outcomes in noncardiac surgery.[127,128] On the other hand, the use of balanced solutions was associated with better kidney function and a better 24-hour survival rate in a rat sepsis model.[129] In clinical trials, the use of balanced solutions was associated with better control of the plasma acid-base and electrolyte balances;[130,131] it remains unclear, however, whether the use of balanced solutions is associated with better clinical outcomes.

Scarce information is available regarding the best practice for intravenous fluid therapy in patients with ESRD. It is unknown whether colloid solutions have any adverse effects in patients with ESRD who already have limited renal function. Colloid infusions, including HES, however, should not be used in ESRD patients. Crystalloids should be used as first-line fluid replacement therapy. Considering the presence of metabolic acidosis de novo, a balanced solution may be preferable to prevent further exacerbation of acidosis. On the other hand, balanced solutions often contain potassium, which potentially can lead to potassium retention. These issues should be addressed in future studies. Therefore, the type of fluids administered intraoperatively should be selected carefully on the basis of the patient's perioperative status, including volume, electrolyte status, and hemodynamics.

Intraoperative Transfusion

RBC transfusion increases the oxygen-carrying capacity, thereby improving anemia-related symptoms.[132] In patients with symptomatic anemia, RBC transfusion leads to an immediate increase in the RBC mass and, as mentioned previously, transfusion of RBCs again has become more common on the basis of findings from clinical trial data and the recent revision of regulatory and reimbursement policies for ESA. The use of RBC transfusions again should be considered with regard to the risk and benefit, based on the guidelines.

According to the 2012 KDIGO clinical practice guidelines, acute clinical situations, acute severe hemorrhage, unstable coronary artery disease, and the need for rapid preoperative Hb correction should be treated with RBC transfusion.[59] Unfortunately, the Hb threshold for transfusion in these situations is unclear, but the current guidelines recommend that RBC transfusion be considered for patients with Hb < 7 g/dL.[59] RBC transfusion also is necessary for clinical conditions such as hemoglobinopathies, bone marrow failure, and ESA resistance. Indications for transfusion outside of acute situations are not established, but the rate of transfusion markedly increases when Hb falls < 10 g/dL (100 g/L).[59] The guidelines recommend that RBC transfusion in a CKD patient with nonacute anemia should be based on symptoms of anemia rather than an arbitrary Hb threshold.[59] Taken together, acute transfusion is absolutely necessary for ESRD patients in the perioperative period if Hb < 7 g/dL, and even earlier in some severe cases.

Table 6
Estimated Risks Associated With Blood Transfusions per Unit Transfused

Risks Associated with Transfusions	Estimated Risk
Infections	
Hepatitis B	1 in 282,000 to 1 in 357,000
West Nile virus	1 in 350,000
Death from bacterial sepsis	1 in 1,000,000
Hepatitis C	1 in 1,149,000
Human immunodeficiency virus	1 in 1,467,000
Immunologic response	
Fever/allergic reaction	1 in 100-200
Hemolytic reaction	1 in 6,000
Transfusion-related acute lung injury	1 in 12,350
Anaphylaxis	1 in 50,000
Fatal hemolysis	1 in 1,250,000
Graft-versus-host disease	Rare
Other	
Mistransfusion	1 in 14,000-19,000

Taken from the *KDIGO Clinical Practice Guidelines for Anemia in Chronic Kidney Disease*.[60]

The risk of blood transfusion must be considered in clinical practice. Improved blood screening methods through the donor history questionnaire and strict laboratory screening have decreased the risk of transfusion-transmitted viral infections greatly (Table 6).[59] Bacterial and parasitic contamination now pose a greater threat in transfusion medicine than does viral contamination.[133] The risks associated with blood transfusion include hemolytic or febrile transfusion reactions, allergic reaction, transfusion-related acute lung injury, transfusion-associated circulatory overload, post-transfusion purpura, graft-versus-host disease, iron overload, alloimmunization, citrate toxicity, and hyperkalemia.[133]

Hemodynamic Management and Monitoring

In general, hemodynamic management in ESRD patients means achieving the appropriate preload and afterload and maintaining BP. There are no available data, however, regarding the outcome of ESRD patients undergoing perioperative hemodynamic management. Currently, both static and dynamic monitoring are used for hemodynamic management, especially fluid responsiveness.

Static monitoring or invasive monitoring requires a catheter placement into the central veins or pulmonary artery. These methods essentially require reaching and maintaining a certain central venous pressure (CVP) or pulmonary arterial wedge pressure (PAWP), indicating an adequate preload. Evaluating intravascular volume status based on CVP or PAWP is of limited use, however, because the measures are poorly related to the patient's fluid responsiveness.[134,135] Moreover, insertion of a pulmonary artery catheter, which is invasive, does not improve the outcome in critically ill patients.[136] Therefore, pulmonary artery catheters are not recommended for perioperative hemodynamic monitoring in ESRD patients. Goal-directed therapy (GDT) based on dynamic monitoring of systolic-pressure variation, pulse-pressure variation, and stroke-volume variation (SVV) improves outcomes in high-risk patients compared with a standard management protocol

with static monitoring.[137,138] In other words, these dynamic parameters could be better correlated with fluid responsiveness than static measurements, CVP, and PAWP.[139,140] SVV can be used to replace CVP in the volume management of patients who have undergone kidney transplantation.[141] The authors of this study found that SVV was decreased after a 500-mL fluid infusion in patients with ESRD, but LV end-diastolic volume measured using 3-dimensional transesophageal echocardiography was not changed after infusion in these patients due to diastolic disfunction.[142] In addition, low venous oxygen saturation (SvO_2) was associated with high mortality in cardiac or major surgery and sepsis patients.[143] In fact, adequate tissue oxygenation is dependent on oxygen delivery (cardiac output or Hb) and extraction (metabolic demands).[144] Impaired tissue oxygenation results in hypoxic tissue injury and organ dysfunction. Therefore, it is important to maintain tissue oxygenation using SvO_2 as an indicator, even if the MAP targets are achieved using vasopressors.[143] There were several protocols and studies of GDT using SVV, cardiac index, or SvO_2 showing improved outcome, including in-hospital mortality, hospital stay, and transfusion dose.[145] Taken together, vasopressors or rapid fluid infusion should be performed if the cardiac index is < 2.5 L/m^2 or SVV is $> 10\%$. In addition, if central venous oxygen saturation ($ScvO_2$) is $< 70\%$, transfusion or inotropic agents should be administered.

Inducing general anesthesia in ESRD patients is a clinical challenge because anesthetic agents reduce both cardiac output and afterload (ie, systemic vascular resistance). Ickx et al reported that there was no major hemodynamic instability in ESRD patients without cardiac complications compared with a healthy control group if low-dose and long-term infusion of propofol was administered for induction anesthesia.[146] In that study, however, treatment with ephedrine was more common in the ESRD group. There is no gold standard anesthetic agent for ESRD patients. The details of anesthetic agents are described in the Pharmacology section. It is very important to monitor the hemodynamic status and to be prepared to provide the appropriate treatment, infusion, or vasopressor during induction anesthesia. The authors' institutional policy suggests that an arterial line catheter be inserted before anesthesia to provide real-time BP, SVV, cardiac output, or cardiac index monitoring and that a novel CV catheter, which is able to measure $ScvO_2$, be inserted to administer vasopressor or inotropes in ESRD patients with the severe clinical triad of severe aortic valve stenosis, atrial fibrillation, and low ejection fraction. The authors of the study presented here revealed that SVV is a useful indicator of hypovolemia or fluid responsiveness in ESRD patients.[142] Although there is no suitable method for monitoring perioperative fluid overload, anesthesiologists should be alert to the potential for acute fluid overload, including congestion or hemodynamic instability, if the volume of intravenous infusion exceeds the total dose of preoperative fluid removal, bleeding, and predicted insensible water loss.

Specific Considerations for Cardiac Surgery

There are no randomized clinical trials evaluating whether intraoperative dialysis should be performed during cardiopulmonary bypass (CPB) in cardiac surgery. Takami et al reported a retrospective study finding that regular intermittent HD after cardiac surgery could be performed safely in most HD-dependent patients compared with intraoperative hemofiltration during CPB.[147] On the other hand, some studies have indicated that intraoperative HD could be used to manage the water and electrolyte balance in case of emergency surgery with severe hyperkalemia or CPB with potassium-rich cardioplegia.[148,149] Taken together, intraoperative HD is not necessary, except under specific conditions.

Postbypass bleeding is a common problem in cardiac surgery, especially in ESRD patients, due to coagulation abnormalities.[150] Several studies have revealed that ε-aminocaproic acid and tranexamic acid reduced bleeding and improved patient outcome in cardiac surgery.[151–153] Moreover, appropriate use of clotting factor replacement therapy or blood transfusions has the potential to decrease the postoperative bleeding risk and redo surgery. On the other hand, antifibrinolytic therapy using aprotinin to limit blood loss should not be performed in cardiac surgery because aprotinin is associated with the risk of renal failure requiring dialysis.[153,154]

Regional and Neuraxial Anesthesia

Brachial plexus block is useful for the formation of an arteriovenous fistula in patients with ESRD.[155] Moreover, regional or neuraxial anesthesia or in combination with general anesthesia are an appropriate anesthetic management for other types of surgery.[156–158] Special attention, however, is required when using local anesthetic agents or neuraxial anesthesia to avoid adverse complications. Low bicarbonate value due to ESRD leads to a delayed onset of local anesthetics, and a low protein binding effect increases the duration of their effects.[159] These pharmacodynamic changes may increase the possibility of local anesthetic intoxication, and careful administration is required. Epidural anesthesia has been performed successfully for surgery of body trunk and inferior limbs to achieve safe and effective analgesia. The risks and benefits must be considered carefully when administering epidural anesthesia to a patient with a platelet count of $< 100{,}000$/mm. That is, these patients have an increased risk of neuraxial hematoma associated with neuraxial anesthesia.[160,161]

ESRD patients frequently receive antiplatelet medication (eg, aspirin or clopidogrel) because of coronary artery disease or cerebrovascular disease. As discussed, the antiplatelet medication must be discontinued if a neuraxial block or deep plexus block is indicated.[87]

Vascular Access

Appropriate vascular access is required for long-term survival and quality of life. Anesthesiologists must be familiar with vascular access sites to prevent complications. Arteriovenous fistula (AVF), arteriovenous grafts (AVG), tunneled cuffed catheters, and port catheter systems are well-known options for permanent access.[162] Short-term noncuffed catheters are used for acute dialysis and for a limited duration in hospitalized patients.

Arteriovenous Fistula

AVF is the first choice for permanent vascular access, providing longer survival of the access, the lowest rate of thrombosis, and a lower cost of implantation, and it is less prone to infection compared with AVG or other catheters.[162] The mortality risk also is reduced in HD patients using an AVF.[163] A wrist primary fistula is preferred because the access should be placed distally and in the upper extremities whenever possible. The disadvantage of AVF is long maturation times: 1-to-4 months. The anesthesiologist should protect vascular channels with the potential to become fistula contraction sites, if possible.

Arteriovenous Grafts

AVG should be considered if fistula placement is not possible because of abnormal superficial veins or an exhausted AVF. The synthetic or biologic material selected for conduits should be based on the surgeon's experience and preference.

Catheters for HD

Tunneled cuffed catheters are considered only if AVF and AVG cannot be used because there is a greater risk of infection, susceptibility to thrombosis, and blood flow delivery inconsistencies compared with AVF or AVG.[162] The preferred insertion site for tunneled cuffed venous dialysis catheters is the right internal jugular vein.[162] Other options include the right external jugular vein, left internal and external jugular veins, subclavian veins, femoral veins, and translumbar and transhepatic access to the inferior vena cava. Ultrasound imaging is useful for catheter placement. Port catheter systems sometimes are used as a bridge device until AVF maturation. Noncuffed catheters are used for acute dialysis and short term (< 1 week) because of the risk of infection.

Postoperative Considerations

There is no evidence regarding the optimal time to restart postoperative dialysis to reduce the incidence of postoperative complications (Table 7). In general, regular HD should be continued 3 times per week as a routine schedule except for urgent indications, and heparin administration should be resumed 12 hours after surgery until stable hemostasis is reached to reduce the risk of bleeding.

Special attention must be paid to fluid status, electrolyte balance, and blood glucose concentration. As with intraoperative fluid infusion, volume overload and hypovolemia must be avoided, and frequent checks of electrolyte status, especially potassium, are needed to reduce complications. Fluid and electrolyte status and urea and creatinine levels can facilitate decisions regarding the solution type or dose and need for urgent postoperative dialysis.

A multidisciplinary approach to analgesia is required to alleviate postoperative pain. Regional and neuraxial anesthesia should be used from the intraoperative period to reduce postoperative pain.[155–158] These techniques diminish the requirements for opioids, such as morphine, and thus help avoid the risk of accumulation of the drug and its metabolites. Intravenous patient-controlled analgesia with fentanyl may be effective for postoperative pain in ESRD patients, with monitoring for respiratory depression.[164]

A retrospective study revealed that central venous vascular access and a higher hepatic Sequential Organ Failure Assessment subscore were independently associated with an increased risk of mortality, whereas a residual urinary output > 500 mL was associated with a decreased risk of mortality in HD patients in the intensive care unit.[165] These findings are helpful for postoperative management in ESRD patients to reduce complications.

Table 7
Postoperative Considerations for Patients With ESRD

Fluid status, electrolyte data, urea, and creatinine levels facilitate decisions regarding the solution type or dose and need for urgent postoperative dialysis
Regular hemodialysis should be continued on a routine schedule of 3 times per week
Heparin injections should be resumed 12 h after surgery until stable hemostasis to reduce the risk of bleeding
A multidisciplinary approach to analgesia is required for alleviating postoperative pain

Abbreviation: ESRD, end-stage renal disease.

Pharmacology

Propofol

Propofol commonly is used to induce and maintain perioperative anesthesia. Ickx et al reported that ESRD did not markedly affect the pharmacokinetic and pharmacodynamic profiles of propofol.[146] Dahaba et al also reported that end-stage renal failure did not increase the recovery time from total intravenous anesthesia with propofol and remifentanil; in their study, there was no difference in the time to maintenance of adequate respiration and extubation in patients with ESRD.[5] Taken together, these findings suggest that propofol can be used safely in individuals receiving HD.

Etomidate

Etomidate is a short-acting intravenous anesthetic with a stable hemodynamic status for cardiac surgery compared with propofol because etomidate has little or no effect on cardiac output, peripheral resistance, and pulmonary circulation.[166] Etomidate causes adrenal insufficiency, however, and therefore long-term administration for anesthesia maintenance is not recommended.[167] The possibility of adrenal inhibition by a single dose of etomidate remains unclear. There is a case report of anesthesia induction with etomidate for HD patients with myocardial revascularization.[168]

The risks and benefits must be considered carefully if etomidate is selected as the induction agent.

Ketamine

Ketamine, an N-methyl-D-aspartate receptor agonist, is administered to induce or maintain anesthesia and pain control for chronic pain. Ketamine has the safest pharmacologic profile in patients with renal failure.[169] Several studies have reported that ketamine is a useful anesthetic agent for renal transplant recipients or for pain management in ESRD patients.[170–172]

Dexmedetomidine

Dexmedetomidine is a highly selective α2-agonist with sedative, analgesic, and sympatholytic properties. Because of its minimal effects on the respiratory system, dexmedetomidine is used widely as sedative agent with or without intubation. Rutkowska et al reported that intravenous dexmedetomidine prolonged the duration of brachial plexus block in patients with ESRD with appropriate sedation.[173] De Wolf et al reported that CKD patients may be more sedated because of the lower plasma protein binding of dexmedetomidine, although the elimination half-life was shortened in renal disease.[174] In their study, there were no differences between the CKD and control groups in either the volume of distribution at steady state or elimination clearance. Dexmedetomidine can be useful for ESRD patients but must be used with caution due to its sedation-enhancing effects.

Inhalation Agents

The most commonly used inhalation anesthetic agent is sevoflurane, which reacts with carbon dioxide absorbents to produce compound A, a substance that is nephrotoxic in animal models.[175] A retrospective study of renal laboratory data, however, pooled from 22 clinical trials performed to compare sevoflurane with isoflurane, enflurane, or propofol reported a similar incidence of increased serum creatinine and blood urea nitrogen concentrations.[176] Isoflurane and desflurane are not associated with nephrotoxic potential and are considered safe to use in CKD patients.[177,178] In conclusion, sevoflurane, desflurane, and isoflurane can be used safely in ESRD patients.

Opioids

Opioids do not have direct toxic effects on the kidney. It is important to identify the pharmacokinetics of both the parent drug and metabolites, however, before opioids are administered to ESRD patients as a perioperative analgesic agent.

Morphine is metabolized to morphine-3-glucuronide and morphine-6-glucuronide by hepatic glucuronidation. Morphine-6-glucuronide is a potent μ-receptor agonist that effectively provides analgesia and sedation.[179] In contrast, morphine-3-glucuronide has minimal analgesic effects and is neuroexcitatory.[180] Renal function strongly affects the metabolism of morphine-6-glucuronide, and in patients with CKD, the half-life of morphine-6-glucuronide increases from 2 to 27 hours.[181] Thus, CKD patients should receive a minimum dose of morphine and be monitored closely postoperatively for respiratory depression. Although ESRD is not an absolute contraindication for morphine use, the drug should be administered to these patients with caution. A rather large fraction of morphine can be eliminated by dialysis.[182]

Hydromorphone has approximately 10 times greater analgesic effects and a shorter duration of action than morphine. Hydromorphone does not accumulate significantly in ESRD patients, but it is metabolized to hydromorphone-3-glucoronide, which has neuroexcitatory effects and accumulates in these patients.[183] Therefore, hydromorphone should be used with caution and the dosage adjusted. Hydromorphone-3-glucoronide can be eliminated by dialysis.[184]

Meperidine is a synthetic opioid that is metabolized to normeperidine, which is dependent on the GFR.[164] The use of meperidine in CKD patients may lead to central nervous system and respiratory depression, seizures, and psychosis.[185] Although naloxone or HD are able to reverse these side effects,[186] the use of meperidine in ESRD patients should be avoided if possible.

Codeine and dihydrocodeine have a significantly prolonged elimination half-life in dialysis patients and sometimes cause central nervous system depression.[164,187,188] Therefore, these drugs should be used with caution in patients with ESRD or avoided entirely, if possible.

Fentanyl is metabolized largely by the hepatic system with no active metabolites. Fentanyl clearance is reduced in patients with moderate-to-severe uremia and could depress respirations postoperatively as a result.[189] Although fentanyl can be used in patients with renal failure, such patients should be monitored for signs of gradual accumulation of the parent drug. Fentanyl is not cleared by HD because of its high protein-binding properties and low water solubility.[182] Remifentanil clearance does not depend on renal function because it has an esterase-dependent metabolism. On the other hand, patients with renal failure may accumulate the remifentanil metabolite remifentanil acid.[190] Because the effect of remifentanil acid is 1/4,600 that of remifentanil, remifentanil does not have toxic effects in renal impairment.[190,191] Paradoxically, Dahaba et al reported that remifentanil had reduced clearance and a prolonged elimination half-life in HD patients.[192] They also reported that a lower infusion rate of remifentanil was needed in total intravenous anesthesia with propofol and remifentanil, but the recovery time from general anesthesia was not prolonged significantly.[5]

Neuromuscular Relaxants

The neuromuscular-blocking agents rocuronium and vecuronium have enhanced effects in patients with CKD as a result of decreased clearance.[193–195] Robertson et al reported that the effects of rocuronium tended to be enhanced when combined with propofol, but not when combined with inhalation agents, in ESRD patients.[195] Moreover, endogenous compounds bind to rocuronium; the plasma concentration is increased by the urea level, concomitant medication, and diabetes, etc.[195]

Intraoperative use of long-acting neuromuscular blocking agents or agents eliminated through the kidney should be minimized, and continuous neuromuscular monitoring should be performed to prevent postoperative residual curarization. A significant hyperkalemic response to the depolarizing muscle relaxant suxamethonium was not observed in CKD patients if the preoperative potassium level was within the normal range.[196] Cisatracurium, the 1R cis-10R cis isomer of atracurium, is subject to Hofmann elimination, which is independent of renal and hepatic function, making these agents useful neuromuscular blockers for renal failure patients.[197] Although the clearance is reduced by 13% and the terminal elimination half-life prolonged by 4.2 minutes,[198] Dahaba et al reported that ESRD did not prolong recovery from total intravenous anesthesia with remifentanil and propofol or recovery from cisatracurium neuromuscular block.[5] These neuromuscular relaxants should be administered with neuromuscular monitoring if possible.

Sugammadex is a selective relaxant-binding agent that encapsulates the neuromuscular blocking agent rocuronium for elimination by the kidneys as a sugammadex-rocuronium complex. Staals et al reported no significant difference between the mean time to recovery of the train-of-4 ratio to 0.9 in ESRD patients and control patients after administering sugammadex.[199] They also reported that clearance of both rocuronium and sugammadex was reduced in patients with ESRD compared with healthy individuals.[200] The sugammadex-rocuronium complex remains in the body for a longer period in patients with ESRD. Clinical data regarding the pharmacokinetics of this complex, however, are not yet available. Although it is considered that sugammadex can be used safely in clinical practice in patients treated with HD, detailed studies should be conducted to determine whether the rocuronium-sugammadex complex is harmful over the long term in a larger population of ESRD patients.

Neostigmine clearance is reduced and its elimination half-life time prolonged in CKD, including in ESRD patients.[201] Several studies, however, revealed that combined use of neostigmine and atropine or glycopyrronium had adequate reversal effects on neuromuscular blockade.[202,203] On the other hand, the prolonged effect of neostigmine may initiate a parasympathomimetic response, including bradycardia and heart block, especially when combined with atropine, a short-acting muscarinic antagonist, rather than long-acting glycopyrronium.[204]

Acetaminophen

Acetaminophen administered orally to healthy volunteers and CKD patients did not affect renal function, including tubular and glomerular function.[205] A rat model of adenine-induced renal failure also demonstrated that acetaminophen did not affect the progression of renal disease.[206] Based on these findings, administering acetaminophen for intraoperative or postoperative analgesia is considered safe, and the dose does not need to be altered for ESRD patients.

Nonsteroidal Anti-Inflammatory Agents (NSAIDS)

Whether the use of NSAIDs increases the risk of ESRD remains a controversial issue because previous studies have demonstrated conflicting results. Perneger et al reported that a cumulative dose of 5,000 or more NSAID-containing pills was associated with increased odds of developing ESRD.[207] Schneider et al found that both selective and nonselective NSAIDs were associated significantly with acute renal failure.[208] On the other hand, Murray et al demonstrated that regular analgesic agents, including NSAIDs, did not increase the risk of developing ESRD.[209] According to a recent study of more than 100,000 selected HD patients, however, NSAID use was a significant risk factor for dialysis.[210] Thus, NSAIDs should be prescribed cautiously, especially in patients at high risk for ESRD.

Local Anesthetics

As mentioned earlier, regional and neuraxial anesthesia are effective analgesia techniques for ESRD patients. Delayed onset and prolonged duration of local anesthetics should be considered. Renal clearance of metabolites from lidocaine or ropivacaine is reduced in ESRD patients.[211,212]

Attention must be paid to the nervous system symptoms, especially with large doses or prolonged administration, because these metabolites have central nervous system toxicity.

Conclusion

In this article, the authors reviewed the literature to address the issues related to patients with ESRD undergoing general anesthesia. A careful multidisciplinary approach is mandatory to achieve a successful surgical outcome for this high-risk patient subgroup, considering comorbidities, including cardiovascular diseases; the risk of anemia, fluid and electrolyte disturbances; and drug handling malfunctions during the perioperative period.

The authors propose that dynamic parameter stroke-volume variability is a useful indicator of hypovolemia for the intraoperative fluid management of ESRD. “Goal-directed therapy” based on cardiac output, SVV, and $ScvO_2$ has a special potential to improve patient outcome in ESRD patients. Additional studies are needed to determine the optimal fluid management to prevent or attenuate hypovolemia or fluid overload, which worsens the outcome of HD patients intraoperatively. The authors believe that these special efforts can facilitate the management of ESRD patients and maximize patient outcome.

References

1 United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. End-stage renal disease (ESRD) in the United States, Volume 2. Bethesda, MD: National

Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 215–602.
2 Brown JH, Hunt LP, Vites NP, et al. Comparative mortality from cardiovascular disease in patients with chronic renal failure. Nephrol Dial Transplant 1994;9:1136–42.
3 Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. Nephrol Dial Transplant 2009;24:1574–9.
4 Renew JR, Pai SL. A simple protocol to improve safety and reduce cost in hemodialysis patients undergoing elective surgery. Middle East J Anaesthesiol 2014;22:487–92.
5 Dahaba AA, von Klobucar F, Rehak PH, et al. Total intravenous anesthesia with remifentanil, propofol and cisatracurium in end-stage renal failure. Can J Anaesth 1999;46:696–700.
6 KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150.
7 Hill NR, Fatoba ST, Hirst JA, et al. Global prevalence of chronic kidney disease-A systematic review and meta-analysis. PloS ONE 11:e0158765.
8 World Health Organization. Global report on diabetes: Executive summary. Available at: http://apps.who.int/iris/bitstream/10665/204874/1/WHO_NMH_NVI_16.3_eng.pdf?ua=1. Accessed March 26, 2017.
9 Webster AC, Nagler E, Morton RM, et al. Chronic kidney disease. Lancet 2016;389:1238–52.
10 Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: A systematic review. Lancet 2015;385:1975–82.
11 Venkat A, Kaufmann KR, Venkat KK. Care of the end-stage renal disease patient on dialysis in the ED. Am J Emerg Med 2006;24:847–58.
12 World Health Organization. Global health estimates 2015: Deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.
13 Robinson BM, Akizawa T, Jager K, et al. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: Differences in access to renal replacement therapy, modality use, and haemodialysis practices. Lancet 2016;388:294–306.
14 Parikh DS, Swaminathan M, Archer LE, et al. Perioperative outcomes among patients with end-stage renal disease following coronary artery bypass surgery in the USA. Nephrol Dial Transplant 2010;25:2275–83.
15 Chikwe J, Castillo JG, Rahmanian PB, et al. The impact of moderate-to-end-stage renal failure on outcomes after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2010;24:574–9.
16 Thourani VH, Sarin EL, Kilgo PD, et al. Short- and long-term outcomes in patients undergoing valve surgery with end-stage renal failure receiving chronic hemodialysis. J Thorac Cardiovasc Surg 2012;144:117–23.
17 Gajdos C, Hawn MT, Kile D, et al. The risk of major elective vascular surgical procedures in patients with end-stage renal disease. Ann Surg 2013;257:766–73.
18 Moran-Atkin E, Stem M, Lidor AO. Surgery for diverticulitis is associated with high risk of in-hospital mortality and morbidity in older patients with end-stage renal disease. Surgery 2014;156:361–70.
19 Smith MC, Boylan MR, Tam SF, et al. End-stage renal disease increases the risk of mortality after appendectomy. Surgery 2015;158:722–7.
20 Brakoniecki K, Tam S, Chung P, et al. Mortality in patients with end-stage renal disease and the risk of returning to the operating room after common general surgery procedures. Am J Surg 2017;213:395–8.
21 De la Garza Ramos R, Jain A, Nakhla J, et al. Postoperative morbidity and mortality after elective anterior cervical fusion in patients with chronic and end-stage renal disease. World Neurosurg 2016;95:480–5.
22 Lin JC, Liang WM. Mortality and complications after hip fracture among elderly patients undergoing hemodialysis. BMC Nephrol 2015;16:100.
23 Erkocak OF, Yoo JY, Restrepo C, et al. Incidence of infection and inhospital mortality in patients with chronic renal failure after total joint arthroplasty. J Arthroplasty 2016;31:2437–41.
24 Miller L, Sood M, Sood A, et al. Cardiovascular disease in end-stage renal disease: The challenge of assessing and managing cardiac disease in dialysis patients. Int Urol Nephrol 2010;42:1007–14.
25 Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. Circulation 2007;116:85–97.
26 Bidani AK, Griffin KA, Williamson G, et al. Protective importance of the myogenic response in the renal circulation. Hypertension 2009;54:393–8.
27 Tozawa M, Iseki K, Iseki C, et al. Blood pressure predicts risk of developing end-stage renal disease in men and women. Hypertension 2003;41:1341–5.
28 Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996;334:13–8.
29 London GM. Cardiovascular disease in chronic renal failure: Pathophysiologic aspects. Semin Dial 2003;16:85–94.
30 Dorhout Mees EJ. Diastolic heart failure: A confusing concept. Heart Fail Rev 2013;18:503–9.
31 Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol 2009;4(Suppl 1):S79–91.
32 Curtis BM, Parfrey PS. Congestive heart failure in chronic kidney disease: Disease-specific mechanisms of systolic and diastolic heart failure and management. Cardiol Clin 2005;23:275–84.
33 Barsoum RS. Chronic kidney disease in the developing world. N Engl J Med 2006;354:997–9.
34 Daugirdas JT. Chronic hemodialysis prescription: A urea kinetic approach. In: Daugirdas JT, Blake PG, Ing TS, editors. Handbook of dialysis. Baltimore, MD: Lippincott Williams & Wilkins; 2007. p. 146–69.
35 Jansen MA, Hart AA, Korevaar JC, et al. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int 2002;62:1046–53.
36 Puskar D, Pasini J, Savic I, et al. Survival of primary arteriovenous fistula in 463 patients on chronic hemodialysis. Croat Med J 2002;43:306–11.
37 Mizumasa T, Hirakata H, Yoshimitsu T, et al. Dialysis-related hypotension as a cause of progressive frontal lobe atrophy in chronic hemodialysis patients: A 3-year prospective study. Nephron Clin Pract 2004;97:c23–30.
38 John AS, Tuerff SD, Kerstein MD. Nonocclusive mesenteric infarction in hemodialysis patients. J Am Coll Surg 2000;190:84–8.
39 Shoji T, Tsubakihara Y, Fujii M, et al. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int 2004;66:1212–20.
40 Warnock DG. Uremic acidosis. Kidney Int 1988;34:278–87.
41 Bailey JL. Metabolic acidosis: An unrecognized cause of morbidity in the patient with chronic kidney disease. Kidney Int Suppl 2005:S15–23.
42 Widmer B, Gerhardt RE, Harrington JT, et al. Serum electrolyte and acid base composition. The influence of graded degrees of chronic renal failure. Arch Intern Med 1979;139:1099–102.
43 Gautheir P, Simmons EE, Lemann J. Acidosis of chronic renal failure. In: DuBose TD, Hamm L, editors. Acid-base and electrolyte disorders: A companion to Brenner and Rector's the kidney. Philadelphia, PA: Saunders; 2002. p. 207–16.
44 Williams B, Hattersley J, Layward E, et al. Metabolic acidosis and skeletal muscle adaptation to low protein diets in chronic uremia. Kidney Int 1991;40:779–86.
45 Ballmer PE, McNurlan MA, Hulter HN, et al. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. J Clin Investig 1995;95:39–45.
46 Bailey JL, Wang X, England BK, et al. The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP dependent ubiquitin-proteasome pathway. J Clin Investig 1996;97:1447–53.
47 May RC, Bailey JL, Mitch WE, et al. Glucocorticoids and acidosis stimulate protein and amino acid catabolism in vivo. Kidney Int 1996;49:679–83.
48 Halperin ML, Kamel KS. Potassium. Lancet 1998;352:135–40.
49 Cooper MS, Gittoes NJ. Diagnosis and management of hypocalcaemia. Br Med J 2008;336:1298–302.
50 Lemann J Jr, Litzow JR, Lennon EJ. The effects of chronic acid loads in normal man: Further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J Clin Investig 1966;45:1608–14.
51 Babayev R, Nickolas TL. Bone disorders in chronic kidney disease: An update in diagnosis and management. Semin Dial 2015;28:645–53.
52 Vervloet M, Cozzolino M. Vascular calcification in chronic kidney disease: Different bricks in the wall? Kidney Int 2017;91:808–17.

53 Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: Risk factors, diagnosis, and treatment. Am J Kidney Dis 2015;66:133–46.
54 Obrador GT, Roberts T, St. Peter WL, et al. Trends in anemia at initiation of dialysis in the United States. Kidney Int 2001;60:1875–84.
55 Hsu CY. Epidemiology of anemia associated with chronic renal insufficiency. Curr Opin Nephrol Hypertens 2002;11:337–41.
56 McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:1501–10.
57 Eschbach JW, Adamson JW. Anemia of end-stage renal disease (ESRD). Kidney Int 1985;28:1–5.
58 Kalra PR, Greenlaw N, Ferrari R, et al. Hemoglobin and change in hemoglobin status predict mortality, cardiovascular events and bleeding in stable coronary artery disease. Am J Med 2017 Jan 19 [e-pub ahead of print].
59 KDIGO clinical practice guideline for anemia in chronic kidney disease. Available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf. Accessed May 15, 2017.
60 Opelz G, Vanrenterghem Y, Kirste G, et al. Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. Transplantation 1997;63:964–7.
61 Reed A, Pirsch J, Armbrust MJ, et al. Multivariate analysis of donor-specific versus random transfusion protocols in haploidentical living-related transplants. Transplantation 1991;51:382–4.
62 Vanrenterghem Y, Waer M, Roels L, et al. A prospective, randomized trial of pretransplant blood transfusions in cadaver kidney transplant candidates. Leuven Collaborative Group for Transplantation. Transpl Int 1994;7(Suppl 1):S243–6.
63 Thiyagarajan UM, Bagul A, Frost J, et al. Role of human leukocyte antigen, donor-specific antibodies, and their impact in renal transplantation. Transplant Proc 2012;44:1231–5.
64 Folsom AR, Lutsey PL, Astor BC, et al. Atherosclerosis Risk in Communities Study. Chronic kidney disease and venous thromboembolism: A prospective study. Nephrol Dial Transplant 2010;25:3296–301.
65 Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial 2006;19:317–22.
66 Darlington A, Ferreiro JL, Ueno M, et al. Haemostatic profiles assessed by thromboelastography in patients with end-stage renal disease. Thromb Haemost 2011;106:67–74.
67 Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2215–45.
68 De Vriese AS, Vandecasteele SJ, Van den Bergh B, et al. Should we screen for coronary artery disease in asymptomatic chronic dialysis patients?. Kidney Int 2012;81:143–51.
69 Khan NA, Hemmelgarn BR, Tonelli M, et al. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: A meta-analysis. Circulation 2005;112:3088–96.
70 Kim JK, Kim SG, Kim HJ, et al. Cardiac risk assessment by gated single-photon emission computed tomography in asymptomatic end-stage renal disease patients at the start of dialysis. J Nucl Cardiol 2012;19:438–47.
71 Wang LW, Fahim MA, Hayen A, et al. Cardiac testing for coronary artery disease in potential kidney transplant recipients: A systematic review of test accuracy studies. Am J Kidney Dis 2011;57:476–87.
72 Chang SM, Nabi F, Xu J, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. J Am Coll Cardiol 2009;54:1872–82.
73 Hakeem A, Bhatti S, Chang SM. Screening and risk stratification of coronary artery disease in end-stage renal disease. JACC Cardiovasc Imaging 2014;7:715–28.
74 Bhatti NK, Karimi Galougahi K, et al. Diagnosis and management of cardiovascular disease in advanced and end-stage renal disease. J Am Heart Assoc 2016;5:e003648.
75 Marui A, Kimura T, Nishiwaki N, et al. (CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators). Percutaneous coronary intervention versus coronary artery bypass grafting in patients with end-stage renal disease requiring dialysis (5-year outcomes of the CREDO-Kyoto PCI/CABG Registry Cohort-2). Am J Cardiol 2014;114:555–61.
76 Yuo TH, Sidaoui J, Marone LK, et al. Limited survival in dialysis patients undergoing intact abdominal aortic aneurysm repair. J Vasc Surg 2014;60:908–13.
77 Ohno Y, Attizzani GF, Barbanti M, et al. (OBSERVANT Research Group). Transcatheter aortic valve replacement for severe aortic stenosis patients undergoing chronic dialysis. J Am Coll Cardiol 2015;66:93–4.
78 Taler SJ, Agarwal R, Bakris GL, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. Am J Kidney Dis 2013;62:201–13.
79 National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45(4 Suppl 3):S16–45.
80 McMurray JJ, Adamopoulos S, Anker SD, et al. (ESC Committee for Practice Guidelines). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803–69.
81 Setaro JF, Zaret BL, Schulman DS, et al. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990;66:981–6.
82 Hung MJ, Cherng WJ, Kuo LT, et al. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. Int J Clin Pract 2002;56:57–62.
83 Carlo JO, Phisitkul P, Phisitkul K, et al. Perioperative implications of end-stage renal disease in orthopaedic surgery. J Am Acad Orthop Surg 2015;23:107–18.
84 Zepeda-Orozco D, Quigley R. Dialysis disequilibrium syndrome. Pediatr Nephrol 2012;27:2205–11.
85 Hedges SJ, Dehoney SB, Hooper JS, et al. Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol 2007;3:138–53.
86 Wikkelsø A, Wetterslev J, Møller AM, et al. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev 2016. CD:007871.
87 Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: Guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2015;40:182–212.
88 Soslau G, Schwartz AB, Putatunda B, et al. Desmopressin-induced improvement in bleeding times in chronic renal failure patients correlates with platelet serotonin uptake and ATP release. Am J Med Sci 1990;300:372–9.
89 Mannucci PM. Desmopressin: A nontransfusional hemostatic agent. Annu Rev Med 1990;41:55–64.
90 Tramma D, O'Brien C, Hulton SA. Effect on early graft function of high-dose desmopressin in transplant recipients with bleeding disorders. Saudi J Kidney Dis Transpl 2013;24:364–5.
91 Putcha N, Allon M. Management of hyperkalemia in dialysis patients. Semin Dial 2007;20:431–9.
92 Mount DB, Zandi-Nejad K. Hyperkalemia. In: Brenner BM, editor. The kidney, ed 7. Philadelphia, PA: Saunders; 2004. p. 1017–25.
93 Crews D, Chi P, Choi M. Disorders of potassium homeostasis. In: Piccini JP, Nilsson KR, editors. The Osler medical handbook, ed 2. Baltimore, MA: The Johns Hopkins University Press; 2006. p. 800–4.
94 Kim HJ. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron 1996;72:476–82.
95 Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: Interactions with insulin and albuterol. Am J Kidney Dis 1996;28:508–14.

96 Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. Kidney Int 1990;38:869–72.
97 Sekine M, Takami H. Combination of calcitonin and pamidronate for emergency treatment of malignant hypercalcemia. Oncol Rep 1998;5:197–9.
98 Drake MT, Clarke BL, Khosla S. Bisphosphonates: Mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032–45.
99 Frazão JM, Messa P, Mellotte GJ, et al. Cinacalcet reduces plasma intact parathyroid hormone, serum phosphate and calcium levels in patients with secondary hyperparathyroidism irrespective of its severity. Clin Nephrol 2011;76:233–43.
100 Kliger AS, Fishbane S, Finkelstein FO. Erythropoietic stimulating agents and quality of a patient's life: Individualizing anemia treatment. Clin J Am Soc Nephrol 2012;7:354–7.
101 Ibrahim HN1, Ishani A, Foley RN, et al. Temporal trends in red blood transfusion among US dialysis patients, 1992-2005. Am J Kidney Dis 2008;52:1115–21.
102 Drueke TB, Locatelli F, Clyne N, et al. CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–84.
103 Singh AK, Szczech L, Tang KL, et al. CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98.
104 Pfeffer MA, Burdmann EA, Chen CY, et al. The TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019–32.
105 Epogen (epoetin alfa) [package insert]. Thousand Oaks, CA: Amgen Inc; 2012.
106 Aranesp (darbepoetin alfa) [package insert]. Thousand Oaks, CA: Amgen Inc; 2012.
107 Poulsen TD, Andersen LW, Steinbrüchel D, et al. Two large preoperative doses of erythropoietin do not reduce the systemic inflammatory response to cardiac surgery. J Cardiothorac Vasc Anesth 2009;23:316–23.
108 Penny-Dimri JC, Cochrane AD, Perry LA, et al. Characterising the role of perioperative erythropoietin for preventing acute kidney injury after cardiac surgery: Systematic review and meta-analysis. Heart Lung Circ 2016;25:1067–76.
109 Kalantar-Zadeh K, Kopple JD, Regidor DL, et al. A1C and survival in maintenance hemodialysis patients. Diabetes Care 2007;30:1049–55.
110 Kalantar-Zadeh K, Derose SF, Nicholas S, et al. Burnt-out diabetes: Impact of chronic kidney disease progression on the natural course of diabetes mellitus. J Ren Nutr 2009;19:33–7.
111 Rhee CM, Leung AM, Kovesdy CP, et al. Updates on the management of diabetes in dialysis patients. Semin Dial 2014;27:135–45.
112 Ricks J, Molnar MZ, Kovesdy CP, et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: A 6-year cohort study. Diabetes 2012;61:708–15.
113 Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.
114 Sheehy AM, Gabbay RA. An overview of preoperative glucose evaluation, management, and perioperative impact. J Diabetes Sci Technol 2009;3:1261–9.
115 Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical EndocrinologistsAmerican Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract 2009;15:353–69.
116 Sinha AD, Agarwal R. Can chronic volume overload be recognized and prevented in hemodialysis patients? The pitfalls of the clinical examination in assessing volume status. Semin Dial 2009;22:480–2.
117 Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. Nephrol Dial Transplant 2007;22(Suppl 2):ii22–44.
118 Santos SF, Peixoto AJ, Perazella MA. How should we manage adverse intradialytic blood pressure changes? Adv Chronic Kidney Dis 2012;19:158–65.
119 Goldfarb-Rumyantzev AS, Chelamcharla M, Bray BE, et al. Volume indicators and left ventricular mass during aggressive volume management in patients on thrice-weekly hemodialysis. Nephron Clin Pract 2009;113:c270–80.
120 Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. Am J Kidney Dis 2006;48 (Suppl 1):S2–90.
121 Kampmeier T, Rehberg S, Ertmer C. Evolution of fluid therapy. Best Pract Res Clin Anaesthesiol 2014;28:207–16.
122 Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013. CD:000567.
123 Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125–39.
124 Myburgh JA, Finfer S, Bellomo R, et al. CHEST InvestigatorsAustralian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901–11.
125 Cittanova ML, Leblanc I, Legendre C, et al. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996;348:1620–2.
126 Blasco V, Leone M, Antonini F, et al. Comparison of the novel hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6 in brain-dead donor resuscitation on renal function after transplantation. Br J Anaesth 2008;100:504–8.
127 Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg 2012;255:821–9.
128 McCluskey SA, Karkouti K, Wijeysundera D, et al. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: A propensity-matched cohort study. Anesth Analg 2013;117:412–21.
129 Zhou F, Peng ZY, Bishop JV, et al. Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis. Crit Care Med 2014;42:e270–8.
130 Roquilly A, Loutrel O, Cinotti R, et al. Balanced versus chloride-rich solutions for fluid resuscitation in brain-injured patients: A randomised double-blind pilot study. Crit Care 2013;17:R77.
131 Disma N, Mameli L, Pistorio A, et al. A novel balanced isotonic sodium solution vs normal saline during major surgery in children up to 36 months: A multicenter RCT. Paediatr Anaesth 2014;24:980–6.
132 Linman JW. Physiologic and pathophysiologic effects of anemia. N Engl J Med 1968;279:812–8.
133 Tanhehco YC, Berns JS. Red blood cell transfusion risks in patients with end-stage renal disease. Sem Dial 2012;25:539–44.
134 Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008;134:172–8.
135 Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med 2007;35:64–8.
136 Harvey S, Harrison DA, Singer M, et al. PAC-Man Study Collaboration. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): A randomised controlled trial. Lancet 2005;366:472–7.
137 Waldron NH, Miller TE, Gan TJ. Perioperative goal-directed therapy. J Cardiothorac Vasc Anesth 2014;28:1635–41.
138 Scheeren TW, Wiesenack C, Gerlach H, et al. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: A prospective randomized multicentre study. J Clin Monit Comput 2013;27:225–33.
139 Cannesson M, Musard H, Desebbe O, et al. The ability of stroke volume variations obtained with Vigileo/FloTrac system to monitor fluid responsiveness in mechanically ventilated patients. Anesth Analg 2009;108:513–7.
140 Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. Crit Care Med 2009;37:2642–7.
141 Chin JH, Jun IG, Lee J, et al. Can stroke volume variation be an alternative to central venous pressure in patients undergoing kidney transplantation? Transplant Proc 2014;46:3363–6.

142 Kanda H, Hirasaki Y, Iida T, et al. Effect of fluid loading on left ventricular volume and stroke volume variability in patients with end-stage renal disease: A pilot study. Ther Clin Risk Manag 2015;11:1619–25.
143 Chemtob RA, Eskesen TG, Moeller-Soerensen H, et al. Systematic review of the association of venous oxygenation and outcome in adult hospitalized patients. Acta Anaesthesiol Scand 2016;60:1367–78.
144 Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med 2011;184:514–20.
145 Kapoor PM, Kakani M, Chowdhury U, et al. Early goal-directed therapy in moderate to high-risk cardiac surgery patients. Ann Card Anaesth 2008;11:27–34.
146 Ickx B, Cockshott ID, Barvais L, et al. Propofol infusion for induction and maintenance of anaesthesia in patients with end-stage renal disease. Br J Anaesth 1998;81:854–60.
147 Takami Y, Tajima K, Okada N, et al. Simplified management of hemodialysis-dependent patients undergoing cardiac surgery. Ann Thorac Surg 2009;88:1515–9.
148 Okamoto K, Shimizu H, Ueda T, et al. Aggressive surgical strategy should be used for the treatment of thoracic aortic disease in patients with end-stage renal disease. Interact Cardiovasc Thorac Surg 2011;12:384–8.
149 Khoo MS, Braden GL, Deaton D, et al. Outcome and complications of intraoperative hemodialysis during cardiopulmonary bypass with potassium-rich cardioplegia. Am J Kidney Dis 2003;41:1247–56.
150 Edmunds LH Jr, Colman RW. Thrombin during cardiopulmonary bypass. Ann Thorac Surg 2006;82:2315–22.
151 Blaine KP, Press C, Lau K, et al. Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage. J Clin Anesth 2016;35:516–23.
152 Martin K, Gertler R, MacGuill M, et al. Replacement of aprotinin by ε-aminocaproic acid in infants undergoing cardiac surgery: Consequences for blood loss and outcome. Br J Anaesth 2013;110:615–21.
153 Fergusson DA, Hébert PC, Mazer CD, et al. BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–31.
154 Mangano DT, Tudor IC, Dietzel C, Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006;354:353–65.
155 Misiolek HD, Kucia HJ, Knapik P, et al. Brachial plexus block with ropivacaine and bupivacaine for the formation of arteriovenous fistula in patients with end-stage renal failure. Eur J Anaesthesiol 2005;22:473–5.
156 Hadimioglu N, Ertug Z, Bigat Z, et al. A randomized study comparing combined spinal epidural or general anesthesia for renal transplant surgery. Transplant Proc 2005;37:2020–2.
157 Freir NM, Murphy C, Mugawar M, et al. Transversus abdominis plane block for analgesia in renal transplantation: A randomized controlled trial. Anesth Analg 2012;115:953–7.
158 Dhir S, Fuller J. Case report: Pregnancy in hemodialysis-dependent end-stage renal disease: Anesthetic considerations. Can J Anaesth 2007;54:556–60.
159 Al-mustafa MM, Massad I, Alsmady M, et al. The effect of low serum bicarbonate values on the onset of action of local anesthesia with vertical infraclavicular brachial plexus block in patients with end-stage renal failure. Saudi J Kidney Dis Transpl 2010;21:494–500.
160 Goodier CG, Lu JT, Hebbar L, et al. Neuraxial anesthesia in parturients with thrombocytopenia: A multisite retrospective cohort study. Anesth Analg 2015;121:988–91.
161 Bernstein J, Hua B, Kahana M, et al. Neuraxial anesthesia in parturients with low platelet counts. Anesth Analg 2016;123:165–7.
162 National Kidney Foundation. K/DOQI guidelines, clinical practice guidelines for vascular access. Available at: http://kidneyfoundation.cachefly.net/professionals/KDOQI/guideline_upHD_PD_VA/index.htm. Accessed April 25, 2017.
163 Polkinghorne KR, McDonald SP, Atkins RC, et al. Vascular access and all-cause mortality: A propensity score analysis. J Am Soc Nephrol 2004;15:477–86.
164 Kurella M, Bennett WM, Chertow GM. Analgesia in patients with ESRD: A review of available evidence. Am J Kidney Dis 2003;42:217–28.
165 Apel M, Maia VP, Zeidan M, et al. End-stage renal disease and outcome in a surgical intensive care unit. Crit Care 2013;17:R298.
166 Buddle AO, Mets B. Pro: Etomidate is the ideal induction agent for a cardiac anesthetic. J Cardiothorac Vasc Anesth 2013;27:180–3.
167 Shehabi Y, Bellomo R, Mehta S, et al. Intensive care sedation: The past, present and the future. Crit Care 2013;17:322.
168 Nascimento MS, Bernardes CF, de Medeiros RL. Marked hypercapnia during cardiopulmonary bypass for myocardial revascularization. Case report. Rev Bras Anestesiol 2002;52:231–5.
169 Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care 2005;33:311–22.
170 Javid MJ, Rahimi M, Keshvari A. Dissociative conscious sedation, an alternative to general anesthesia for laparoscopic peritoneal dialysis catheter implantation: A randomized trial comparing intravenous and subcutaneous ketamine. Perit Dial Int 2011;31:308–14.
171 Hashimoto Y, Takagi Y, Amano N, et al. A case report of total intravenous anesthesia for renal transplantation [in Japanese]. Masui 1993;42:435–40.
172 Capel MM, Jenkins R, Jefferson M, et al. Use of ketamine for ischemic pain in end-stage renal failure. J Pain Symptom Manage 2008;35:232–4.
173 Rutkowska K, Knapik P, Misiolek H. The effect of dexmedetomidine sedation on brachial plexus block in patients with end-stage renal disease. Eur J Anaesthesiol 2009;26:851–5.
174 De Wolf AM, Fragen RJ, Avram MJ, et al. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 2001;93:1205–9.
175 Gonsowski CT, Laster MJ, Eger EI 2nd, et al. Toxicity of compound A in rats. Effect of increasing duration of administration. Anesthesiology 1994;80:566–73.
176 Mazze RI, Callan CM, Galvez ST, et al. The effects of sevoflurane on serum creatinine and blood urea nitrogen concentrations: A retrospective, twenty-two-center, comparative evaluation of renal function in adult surgical patients. Anesth Analg 2000;90:683–8.
177 Litz RJ, Hubler M, Lorenz W, et al. Renal responses to desflurane and isoflurane in patients with renal insufficiency. Anesthesiology 2002;97:1133–6.
178 Zaleski L, Abello D, Gold MI. Desflurane versus isoflurane in patients with chronic hepatic and renal disease. Anesth Analg 1993;76:353–6.
179 Dahan A, van Dorp E, Smith T, et al. Morphine-6-glucuronide (M6G) for postoperative pain relief. Eur J Pain 2008;12:403–11.
180 Smith MT. Neuroexcitatory effects of morphine and hydromorphone: Evidence implicating the 3-glucuronide metabolites. Clin Exp Pharmacol Physiol 2000;27:524–8.
181 Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care 2005;33:311–22.
182 Bastani B, Jamal JA. Removal of morphine but not fentanyl during haemodialysis. Nephrol Dial Transplant 1997;12:2802–4.
183 Babul N, Darke AC, Hagen N. Hydromorphone metabolite accumulation in renal failure. J Pain Symptom Manage 1995;10:184–6.
184 Davison SN, Mayo PR. Pain management in chronic kidney disease: The pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. J Opioid Manag 2008;4(335–6):339–44.
185 Stock SL, Catalano G, Catalano MC. Meperidine associated mental status changes in a patient with chronic renal failure. J Fla Med Assoc 1996;83:315–9.
186 Hassan H, Bastani B, Gellens M. Successful treatment of normeperidine neurotoxicity by hemodialysis. Am J Kidney Dis 2000;35:146–9.
187 Chan GL, Matzke GR. Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. Drug Intell Clin Pharm 1987;21:773–83.
188 Guay DR, Awni WM, Findlay JW, et al. Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease. Clin Pharmacol Ther 1988;43:63–71.
189 Koehntop DE, Rodman JH. Fentanyl pharmacokinetics in patients undergoing renal transplantation. Pharmacotherapy 1997;17:746–52.

190 Hoke JF, Shlugman D, Dershwitz M, et al. Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. Anesthesiology 1997;87:533–41.
191 Breen D, Wilmer A, Bodenham A, et al. Offset of pharmacodynamics effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. Crit Care 2004;8:R21–30.
192 Dahaba AA, Oettl K, Von Klobucar F, et al. End-stage renal failure reduces central clearance and prolongs the elimination half life of remifentanil. Can J Anaesth 2002;49:369–74.
193 Lynam DP, Cronnelly R, Castagnoli KP, et al. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 1988;69:227–31.
194 Cooper RA, Maddineni VR, Mirakhur RK, et al. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure. Br J Anaesth 1993;71:222–6.
195 Robertson EN, Driessen JJ, Booij LH. Pharmacokinetics and pharmacodynamics of rocuronium in patients with and without renal failure. Eur J Anaesthesiol 2005;22:4–10.
196 Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: An old question revisited. Anesth Analg 2000;91:237–41.
197 Boyd AH, Eastwood NB, Parker CJ, et al. Pharmacodynamics of the 1R cis-1'R cis isomer of atracurium (51W89) in health and chronic renal failure. Br J Anaesth 1995;74:400–4.
198 Eastwood NB, Boyd AH, Parker CJ, et al. Pharmacokinetics of 1R-cis 1'R-cis atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. Br J Anaesth 1995;75:431–5.
199 Staals LM, Snoeck MM, Driessen JJ, et al. Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function. Br J Anaesth 2008;101:492–7.
200 Staals LM, Snoeck MM, Driessen JJ, et al. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: A pharmacokinetic study. Br J Anaesth 2010;104:31–9.
201 Cronnelly R, Stanski DR, Miller RD, et al. Renal function and the pharmacokinetics of neostigmine in anesthetized man. Anesthesiology 1979;51:222–6.
202 Fisher DM, Dempsey GA, Atherton DP, et al. Effect of renal failure and cirrhosis on the pharmacokinetics and neuromuscular effects of rapacuronium administered by bolus followed by infusion. Anesthesiology 2000;93:1384–91.
203 Hunter JM, Jones RS, Utting JE. Use of atracurium in patients with no renal function. Br J Anaesth 1982;54:1251–8.
204 Webb MD. Type I second-degree AV block after neostigmine administration in a child with renal failure. Anesth Prog 1995;42:21–2.
205 Berg KJ, Djoseland O, Gjellan A, et al. Acute effects of paracetamol on prostaglandin synthesis and renal function in normal man and in patients with renal failure. Clin Nephrol 1990;34:255–62.
206 Kadowaki D, Sumikawa S, Arimizu K, et al. Effect of acetaminophen on the progression of renal damage in adenine induced renal failure model rats. Life Sci 2012;91:1304–8.
207 Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 1994;331:1675–9.
208 Schneider V, Levesque LE, Zhang B, et al. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. Am J Epidemiol 2006;164:881–9.
209 Murray TG, Stolley PD, Anthony JC, et al. Epidemiologic study of regular analgesic use and end-stage renal disease. Arch Intern Med 1983;143:1687–93.
210 Chang YK, Liu JS, Hsu YH, et al. Increased risk of end-stage renal disease (ESRD) requiring chronic dialysis is associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs). Medicine (Baltimore) 2015;94:e1362.
211 De Martin S, Orlando R, Bertoli M, et al. Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. Clin Pharmacol Ther 2006;80:597–606.
212 Pere P, Salonen M, Jokinen M, et al. Pharmacokinetics of ropivacaine in uremic and nonuremic patients after axillary brachial plexus block. Anesth Analg 2003;96:563–9.