The patient with renal disease

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Abstract

The incidence of chronic renal failure is increasing throughout the world. The perioperative management of patients with chronic kidney disease (CKD) is complicated by both the underlying renal dysfunction, with associated disturbances of fluid and electrolyte homeostasis and altered drug clearance, and the presence of associated comorbid conditions. Preoperative assessment for these complex patients requires multidisciplinary approach from anaesthetic, surgical and nephrology teams. Preservation of normal physiology along with prevention of further kidney injury are central to the management of patients with CKD. This article focuses on the perioperative care of patients, including pharmacological considerations of common medications used.

Keywords Acute kidney injury; chronic kidney disease; perioperative; pharmacokinetic

Introduction

Chronic kidney disease (CKD) is a progressive multisystem disease that includes a wide spectrum of kidney dysfunction from mild kidney damage to end-stage renal failure (ESRD). It is defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min^2/1.73/m^2, for 3 months or more, irrespective of cause. The presence of CKD is an independent risk factor for increased morbidity, mortality and intensive care stay. CKD is classified into five stages depending on GFR (Table 1).

The most recent UK Renal registry report suggests more than around Three million people in England have CKD.[1] The prevalence of stage 3–5 CKD in the UK adult population at 8.5 % (10.6% for females and 5.8% for males).[2] Moreover, the NHS in England spent £1.45 billion on CKD in 2009–2010. In the UK, over 3000 kidney transplants take place every year but over 5000 people are still waiting.[3] They have unique pathophysiology relating to both CKD and its underlying cause and therefore present a challenge to surgeons and anaesthetists. As their survival increases, they also present more frequently for surgery unrelated to their renal disease.

The aim of the perioperative management is to control modifiable risk factors associated with acute kidney injury (AKI) and further decline in renal function. This is associated with considerable morbidity and mortality.

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Stages of chronic kidney disease

CKD stage	GFR (ml/min/m^2)	Description
1	≥90	Renal damage[a] with normal GFR.
2	60–89	Renal damage[a] with mild decrease in GFR
3A	45–59	Moderate decrease in GFR
3B	30–44	
4	15–23	Severe decrease in GFR
5	<15 (or dialysis)	Renal failure

[a]Renal damage is defined as pathological abnormalities or markers of damage identified through imaging studies, blood or urine tests.

Table 1

Aetiology

Table 2 indicates the primary cause of established renal failure as reported in the 2017 UK Renal Registry Report. Uncontrolled diabetes and glomerulonephritis are the most common causes in UK. Treatment for chronic kidney disease focuses on slowing the progression of the kidney damage, usually by controlling the underlying cause.

Functions of the kidney

The main functions are summarized below

- salt and water balance or homeostasis
- toxin removal
- calcium and phosphate homeostasis
- acid–base homeostasis
- endocrine function – erythropoietin, renin, vitamin D activation
- blood pressure regulation (long term).

Pathophysiology

CKD is associated with a wide spectrum of multisystem effects which have implications for safe conduct of anaesthesia (Table 3).

Aetiology of established renal failure in the UK[1]

Aetiology	% total
Diabetes	30.1
Glomerulonephritis	14.2
Pyelonephritis	6.7
Hypertension	6.7
Polycystic kidney	7.3
Renal vascular disease	6.8
Other	18.1
Uncertain aetiology	15.4

Table 2

Contrast-induced nephropathy (CIN)

CIN widely defined in the literature as an increase in serum creatinine of more than 44 mmol/litre or 25% above baseline at 48 h following the contrast load.[5] Factors increasing the risk of CI-AKI include pre-existing hypovolaemia and the use of high doses of iodinated, hyper-osmolar contrast media. The benefit of isotonic intravascular volume expansion for the prevention of radiocontrast-induced nephropathy has been clearly demonstrated. Both sodium chloride 0.9% and sodium bicarbonate 4.2% appear to be effective. The use of N-acetylcysteine to prevent radiocontrast-induced nephropathy remains the subject of ongoing investigation.

Preoperative

The aim of preoperative preparation of patients with CKD is to identify and optimize any pre-existing pathophysiology in order to minimize the risk of anaesthesia and surgery. This requires a multidisciplinary approach involving anaesthetists, surgeons and renal physicians. Because CKD affects all organ systems, it is important to the aim is to optimize medical condition and address potentially reversible manifestations of uraemia.

Clinical assessment

The clinical assessment of renal patients, like any other patient group, should follow the structure of history, examination and investigations, with particular emphasis being placed upon the causes, complications and perioperative consequences of renal disease.

History

A full history should be taken including a review of other conditions and their management to date.

The cause and stage of a patient's CKD can be identified as well as any other comorbidities.

In patients with CKD stage V, does the patient receive renal replacement therapy (RRT)? If this is the case, the following information is crucial:

Complications of CKD

Cardiovascular system

- Salt and water retention, hypertension, and left ventricular hypertrophy
- Cardiomyopathy, congestive cardiac failure, and subclinical pulmonary oedema
- Accelerated atherosclerosis and stiffening of large capacitative arteries, Altered lipoprotein metabolism
- Complications of arteriovenous fistula or shunts,[4] e.g. heart failure, limb ischaemia, steal syndrome, pulmonary atheroembolism
- Uraemic pericarditis
- Cardiovascular autonomic neuropathy with reduced baroreceptor sensitivity, sympathetic hyperactivity, and parasympathetic dysfunction
- Calciphylaxis and vascular calcification resulting in valvular heart disease and calcified atherosclerotic lesions
- Anaemia

Haemostasis and coagulation

- Uraemic thrombocytopathy Prothrombotic tendency/hypercoagulation and reduced fibrinolysis Vascular access thrombosis

Metabolic acidosis

- Bone resorption
- Negative nitrogen balance, muscle wasting, growth retardation

Musculoskeletal system

- Renal osteodystrophy
- Rhabdomyolysis after major surgery

Endocrine system

- Secondary and tertiary hyperparathyroidism, vitamin D deficiency diabetes mellitus

Gastrointestinal system

- Delayed gastric emptying
- Anorexia, vomiting, reduced protein intake, malnutrition Reduced calcium absorption

Immune system

- Immunosuppression due to uraemia or drugs

Fluid and electrolyte homeostasis

- Hyperkalaemia
- Volume overload
- Dehydration

Central nervous system

- Myoclonus, mental slowing, convulsions, coma
- Autonomic and Peripheral neuropathy

Dialysis related

- Sudden cardiac death -Hypotension, arrhythmias
- Residual heparinzation
- Dialysis disequilibrium syndrome, cerebral oedema
- Dialysis amyloidosis

Table 3

- What modality of RRT (haemodialysis or peritoneal dialysis) do they receive and via what access is it provided (e.g. arteriovenous fistula, long-term haemodialysis catheter or a Tenckhoff peritoneal dialysis catheter)
- When was RRT last provided, and when it is next due?
- What is the patient's 'dry weight?' This is the patient's normal weight following RRT and may be used to calculate the extent of fluid overload/deficit by comparison with the patient's current weight.
- Is the patient formerly restricted in the volume of fluid they drink per day?
- What volume (if any) of urine does the patient produce per day?

Unless surgery is urgent, it is usually possible to provide RRT prior to theatre. For emergency procedures the period for optimization may be considerably shorter, and could even involve a period of optimization in the critical care unit, including renal replacement therapy (Table 4). There may need to be consideration of transfer of the patient to a tertiary centre for renal care in the perioperative period.

Clinical examination: it is especially helpful in assessing volume status, physiological compromise and the nature and extent of any complications of kidney disease. Particular attention should be paid to the following areas:

- volume status: dry mucous membranes, postural hypotension, tachycardia and increased capillary refill time suggest hypovolaemia. While fluid overload may be characterized by oedema, weight gain, hypertension and elevated jugular venous pressure.
- cardiovascular system: including heart rate, blood pressure, and auscultation for any pericardial rub (uraemia) or abnormal heart sounds (gallop rhythm in heart failure).
- respiratory system: auscultation for chest crepitation's and pleural effusions (pulmonary oedema), Kussmaul breathing and tachypnoea suggest respiratory compensation for metabolic acidosis.
- abdominal examination: hepatic congestion, enlargement of the kidneys and renal artery bruits are recognized findings in patients with CKD.
- neurological examination: is there confusion or other signs of uraemia? Look for signs of micro-vascular diabetic complications such as peripheral neuropathy.
- assessment of potential sites for IV access, noting the presence of arteriovenous fistulae and long-term lines which will likely preclude further access at these sites.

Investigations: specific clinical investigation in addition to those performed routinely in the preoperative period, should be guided by history and examination findings, urgency of surgery (immediate, urgent, expedited, elective) and grade of surgery (minor, moderate, major or major+). The National Institute for Health and Care Excellence has produced guidance regarding this and the following recommendations are based upon this:[6]

- complete blood count to evaluate for anaemia, thrombocytopenia.
- coagulation studies if significant platelet dysfunction or recent heparinization.
- estimated GFR: allows modification of drug to compensate for reduced clearance.
- renal panel: sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium, and bicarbonate levels.
- arterial blood gas measurements for pH and acid–base balance
- chest radiograph to evaluate fluid status, cardiomegaly or metastatic calcification
- electrocardiogram: Resting 12 lead may demonstrate the presence of established myocardial infarction, uraemic pericarditis or cardiac chamber hypertrophy.

Other tests – resting or stress echocardiogram depending upon symptoms/signs of heart failure and ECG findings.

Coronary angiography may be indicated, but must be justified over the risk of CI-AKI. CPET has become increasingly widespread in assessing the patients risk prior to many types of major surgery. Data for patients with kidney disease are limited, but a small single-centre study reported lower maximal and submaximal exercise tolerance in patients with CKD compared to healthy controls.[7]

Indications of emergency preoperative dialysis

- Hyperkalaemia (K >60 mmol/)
- Fluid overload and pulmonary oedema
- Metabolic acidosis
- 'Uraemic' toxicity and coma

Table 4

Intraoperative management

During the operative period, the aim is to prevent further injury to the kidney. Modifiable factors should be controlled to prevent AKI in patients with CKD.

Intravascular volume expansion

Perioperative hypovolaemia should be rapidly corrected by volume expansion with intravenous fluids, whether occurring before, during, or after surgery. Composition of the resuscitation fluid remains an area of controversy. Evidence of increased harm with starches and lack of clear benefit compared with crystalloids or albumin led to its withdrawal in June 2013.[8] However, there is currently no clear consensus on superiority between albumin and crystalloids. For crystalloids, there is evidence that balanced salt solutions should be given in preference to 0.9% saline, which has been associated with development of hyperchloraemic acidosis, decreased renal blood flow (RBF), and increase risk of AKI. The balance needs to be made between the risks of hypotension versus the potential risks of fluid therapy.

Maintenance of renal blood flow and renal perfusion pressure

Maintenance of adequate renal blood flow and perfusion pressure involves the defence of both cardiac output and systemic arterial pressure.[9] The mainstay of improving MAP is with intravascular filling. Inotropic and vasopressor therapy may then be initiated for the management of low cardiac output and systemic arterial hypotension, respectively. It is suggested that goal-directed perioperative fluid management

should be considered in patients deemed at high risk of AKI and all patients undergoing high-risk surgery. Such goal-directed therapy (GDT) strategies involve titrating fluid boluses and/or inotropic drugs to endpoints such as cardiac output (as provided by oesophageal Doppler, pulse contour waveform analysis, or dilutional techniques) or markers of end organ perfusion (such as arterial lactate). Despite historic concerns, norepinephrine is an excellent first-line vasopressor agent. There is no firm evidence to suggest that the drug compromises renal, hepatic, or gastrointestinal blood flow when used to treat arterial hypotension. Vasopressin and terlipressin may be useful agents in the treatment of post-operative catecholamine-resistant vasodilatory shock. The optimal therapeutic target for systemic arterial pressure for renal protection has not been established. A minimum mean arterial pressure of 65–75 mmHg is often targeted in clinical practice; however, a higher target may be necessary in patients with pre-existing hypertension.

Avoidance of nephrotoxic drugs – Use of nephrotoxic drugs (e.g. gentamicin) for antibiotic prophylaxis and other nephrotoxic drugs should be avoided (Table 5). For detailed information, it is advisable to use a relevant pharmacological formulary.

Glycaemic control – Perioperative hyperglycaemia especially during cardiac and vascular surgery is associated with increased renal morbidity and overall mortality. Although the current evidence suggests that strict norm glycaemia is required for optimum benefit, this approach increases the risk of hypoglycaemia, the clinical significance of which is unknown in the ICU setting. It is not yet clear whether rigorous intraoperative glycaemic control reduces morbidity and mortality in patients undergoing cardiac and vascular surgery.

Treatment of urinary tract obstruction

A urinary catheter is essential to monitor urine output and to rule out urinary tract obstruction. Other considerations include careful identification of the ureters in pelvic surgery. If post-renal obstruction is suspected an ultrasound of the renal tract and urgent urological opinion/intervention is essential.

Postoperative

Avoid renal dysfunction

Renal dysfunction after surgery is associated with multiple organ dysfunction syndrome and may result in a mortality of up to 6%. A number of postoperative complications are known to be associated with renal dysfunction. Prompt diagnosis and management of acute cardiac dysfunction, haemorrhage, sepsis, rhabdomyolysis, and intra-abdominal hypertension are essential to prevent the development of AKI.

- Rhabdomyolysis should be initially treated with aggressive intravascular volume expansion; diuretic therapy and urinary alkalinization may be considered.
- Abdominal compression syndrome caused by intra-abdominal hypertension is associated with diminished renal perfusion and may precipitate ischaemic ATN. Timely recognition of abdominal compression syndrome, by intravesical pressure measurement, followed by decompressive laparotomy may provide the optimal management of this condition.

Admission to high-dependency or intensive care facilities may be suitable for patients with significant comorbidity and after major surgical procedures.

Other organ systems should be supported as appropriate and homeostasis maintained for example diabetic patients should have their blood glucose controlled until they are able to restart their normal insulin regimes and re-start oral nutrition. Electrolytes need close monitoring.

Pharmacological considerations

In patients with CKD, the effect of altered clearance, the production and accumulation of active metabolites, and the risk of aggravating pre-existing kidney disease on drug administration must be considered. Dose adjustment is not usually necessary until the GFR is 50 ml/min/1.73m^2. CKD may influence both the pharmacokinetics and the pharmacodynamics of a drug (Table 6).

Perioperative drugs: many anaesthetic drugs reduce renal blood flow, GFR, and urine output and are excreted by the kidneys, either unchanged or as metabolites. It is also important that the

Risk factors for perioperative AKI

Patient	Operative	Pharmacological
Age	Emergency surgery	Non-steroidal anti-inflammatory agents
Male sex	Cardiac surgery liver transplant surgery	Angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers
CKD	Vascular surgery	Antibiotics (aminoglycosides, glycopeptides, etc.)
Chronic cardiac failure	Intraperitoneal surgery duration of surgery	Immunosuppressive drugs (calcineurin inhibitors)
Hypertension	Major haemorrhage	Hydroxyethyl starch solutions
Chronic liver disease	Sepsis	Radiocontrast agents
Diabetes mellitus	Blood transfusion	
Limited cardiovascular reserve	Intraoperative hypovolaemia and hypotension	

Table 5

Pharmacokinetic changes due to CKD

Pharmacokinetic parameter	Chronic kidney disease changes	Impact on drug dosing
Absorbtion	Decreased intestinal metabolism and raised gastric emptying time and pH	Minimal: no dosing impact
Distribution	Decreased serum albumin, increase total body water	Moderate for some drugs, (phenytoin, theophylline, digoxin, aminoglycosides
Metabolism	Decreased function of Cytochrome P-450 enzymes[10] and drug transporter proteins. Decreased Phase I & I metabolism[11]	Moderate for some drugs, (Nortriptiline, morphine, warfarin
Excretion	Decreased GFR, impaired tubular secretion and reabsorption; increased proteinuria Decreased non-renal excretion:biliary, pulmonary and salivary	Major for some drugs with extensive renal elimination (cimetidine, sitagliptin, Lisinopril) Biliary (Erythromycin)

Minimal: no dosing impact anticipated, Moderate: some drugs require monitoring and dose adjustment, Major: accurate dose adjustment and drug monitoring is required.

Table 6

doses may need to modified again when the patient is undergoing dialysis or hemofiltration.

- **Induction agents**: reduce dose of benzodiazepines, thiopental and intimidate by 30% because of changes in protein binding, volume of distribution, and cardiac function. Less reduction is required with propofol.[12]
- **Inhalation agents:** the elimination of volatile anaesthetic agents is not dependent on renal function. Isoflurane, halothane, and desflurane are all safe. Both sevoflurane and enflurane will theoretically produce nephrotoxic fluoride ions and their use should be discouraged for prolonged durations. Nitrous oxide has little effect on kidney.[12]
- **Muscle relaxants**: atracurium and cisatracurium are obvious choices. Around 90% is metabolized by ester hydrolysis and Hoffman elimination.[13] plasma cholinesterase activity is unchanged in CRF and therefore and mivacurium and suxamethonium (in the absence of hyperkalaemia). Limited doses of vecuronium and rocuronium are acceptable alternatives. Acidosis prolongs the duration of all muscle relaxants are acceptable alternatives. Sugammadex is excreted in urine unchanged. It appears to be safe in to use in CRF but is not recommended for GFR<30 ml/min. It is unpredictably removed by dialysis.
- **Local anaesthetics**: duration of action of local anaesthetics is reduced. Reduce maximum doses by 25% because of decreased protein binding and a lower seizure threshold. This seems to be especially apparent for bupivacaine.[14]
- **Analgesia**: simple paracetamol is safe in normal doses for short-term use in the perioperative period. It should be avoided long term as there is an association with analgesic neuropathy, especially if combined with codeine or caffeine. Non-steroidal anti-inflammatory drugs (NSAIDs) are nephrotoxic and should therefore be avoided in CKD patients.
- **Analgesia: Opioids** Half-lives of codeine and dihydrocodeine are prolonged five times so should be avoided if possible. Avoid pethidine as nor-pethidne can cause convulsions. Tramadol is partially excreted unchanged by the kidney and has a renally-excreted active metabolite resulting in an enhanced action and prolonged duration of action. The doses need to be reduced and the interval between them prolonged. Tramadol may be epileptogenic in the presence of uraemia. Oxycodone has active metabolites so reduce dose and increase interval. Fentanyl has inactive metabolites, but accumulates with prolonged use. Alfentanil and remifentanil are not particularly affected. Morphine has an active metabolite (morphine-6-glucuronide) which is significantly more potent than morphine and is entirely dependent upon renal function for elimination. Consequently, its half-life increases from 2 to 27 hours in CKD. This metabolite is implicated in the sedative and respiratory depressive side-effects of morphine and these signs need to be closely monitored for. Morphine and morphine-6-glucuronide are removed by haemodialysis.[15]
- **Antibiotics**: Most antibiotics are excreted by kidney. It is common to use normal loading dose with reduce and/or delayed maintenance doses. If in doubt check with BNF or with a microbiologist.

Summary

Patients with CKD are complex medical cases and present unique challenges to surgeon and anaesthetist. Management priorities are to exclude acute kidney injury, avoid nephrotoxic drugs, preserve vascular access and pay fastidious attendance to fluid balance. A number of key principles remaining common to all. The pharmacokinetic and pharmacodynamic changes must be taken into consideration: many drugs having reduced renal and non-renal clearance. Nephrological advice should be sought early and should be provided cheerfully! ◆

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