Perioperative Management of the Patient With Chronic Renal Failure

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Introduction

Chronic renal failure (CRF), or more appropriately chronic kidney disease (CKD), refers to a decline in the glomerular filtration rate (GFR) caused by a variety of diseases, such as diabetes, glomerulonephritis, and polycystic kidney disease. Patients with CKD have a high prevalence of hypertension. Whether hypertension is a cause or a result of CKD remains debatable. CKD may be categorized as mild (GFR of 60-89 mL/min/1.73 m^2), moderate (GFR of 30-59 mL/min/1.73 m^2), severe (GFR of 15-29 mL/min/1.73 m^2), or end-stage renal disease (ESRD). Hemodialysis or peritoneal dialysis is typically initiated as the GFR falls to less than 15 mL/min/1.73 m^2. Some patients with CKD eventually receive kidney transplantation before (a few cases) or after (most recipients) initiation of hemodialysis or peritoneal dialysis.

The progression of renal disease from one stage to the next; the need for emergent or maintenance dialysis; prevention and management of fluid, electrolyte, and acid-base imbalances before and after surgery; prevention of radiocontrast-induced acute renal failure or systemic fibrosis; and the high cardiac risk are issues that must be addressed before a patient with CKD proceeds for elective surgery.

Patients with CKD have a higher incidence of coronary artery disease (CAD) and peripheral vascular disease (PVD) compared to the general population. This is because they have the traditional risk factors for CAD, such as advanced age, diabetes, hypertension, and lipid disorders, as well as a high prevalence of nontraditional risk factors, such as hyperhomocysteinemia, abnormal calcium phosphate metabolism, anemia, increased oxidative stress, and, perhaps, uremic toxins. Based on the updated American College of Cardiology/American Heart Association (ACC/AHA) guidelines on perioperative cardiovascular evaluation of noncardiac surgery, patients with a creatinine level greater than or equal to 2 are considered to have a clinical predictor of at least intermediate pretest probability of increased perioperative cardiovascular risk. This increased risk warrants detailed cardiovascular surveillance before intermediate- or high-risk surgery. (See also New ACC/AHA Guidelines on Perioperative CV Evaluation for Noncardiac Surgery.)

An early nephrologic evaluation is mandatory to assess renal function and the need for renal replacement therapy perioperatively. Thus, the cardiologist, nephrologist, surgeon, primary care physician, nursing staff, and, sometimes, a transplant nephrologist must work as a team to recommend strategies for reducing cardiac and renal risks for the planned procedures (ie, noncardiac).

For excellent patient education resources, visit eMedicine's Diabetes Center. Also, see eMedicine's patient education article Chronic Kidney Failure.

Pathophysiology

Knowledge of the pathophysiologic derangements as well as external (sometimes iatrogenic) insults that can arise in the perioperative period in patients with CKD is vital in the evaluation and management of these patients. Impairment of the excretory function of the kidney results in an elevation in urea nitrogen (BUN), creatinine, and various protein metabolic products. Impairment in the synthetic function results in a decrease in the production of erythropoietin (causing anemia) and active vitamin D-3 (causing hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, and renal osteodystrophy). Impairment in synthetic function also results in a reduction in acid, potassium, salt, and water excretion (causing

acidosis, hyperkalemia, hypertension, and edema) and in platelet dysfunction (leading to an increase in bleeding tendencies [see Azotemia]).
The aforementioned complications that are associated with a decline in renal function and uncontrolled hypertension or sugar levels must be identified and corrected perioperatively.
Drugs normally excreted by the kidney accumulate in patients with CKD, exerting their toxicity in the kidney and other organs. Therefore, dosage adjustments or avoidance of nephrotoxicity, including iodinated contrast in high-risk patients, is a key pathophysiologic principle in patients with CKD. Of note is the avoidance of meperidine (Demerol) in patients with CKD/ESRD because the active metabolite (normeperidine) can accumulate and cause seizures.
CKD can be associated with excess surgical morbidity, the most important of which include acute renal failure, hyperkalemia, volume overload, and infections. The above underscore the need for early involvement of a nephrologist.
Drugs that may cause hyperkalemia or elevation in serum creatinine and are commonly used in the perioperative period include the following:

- Drugs that inhibit renin-angiotensin-aldosterone system
    - Inhibitors of renin synthesis - Aliskiren, beta-blockers (eg, metoprolol, atenolol), clonidine, methyldopa, nonsteroidal anti-inflammatory (NSAIDs, eg, ibuprofen, naproxen), cyclooxygenase-2 (COX-2) inhibitors (eg, celecoxib)
    - Inhibitors of angiotensin II synthesis - ACE inhibitors (eg, enalapril, fosinopril)
    - Inhibitors of aldosterone synthesis - Angiotensin II receptor blockers (eg, losartan, candesartan), heparin, low molecular weight heparin (eg, enoxaparin, nadroparin calcium), immunosuppressive (eg, cyclosporin, tacrolimus)
    - Inhibitors of aldosterone receptor - Potassium-sparing diuretics (eg, spirolactone, eplerenone)
    - Blockers of distal Na^+/K^+ channels - Potassium-sparing diuretics (eg, triamterene, amiloride), antibiotics (eg, trimethoprim/sulfamethoxazole [Bactrim], pentamidine)
- Drugs that cause release of K^+ from muscles - Succinylcholine, antipsychotics (eg, haloperidol)
- Others - Digoxin (overdose)

The deleterious cardiovascular effects of the selective COX-2 inhibitor rofecoxib (Vioxx) have been noted in the literature since 2001. They were again brought to light by deaths caused by rofecoxib-associated thrombotic cardiovascular complications, which mandated a reanalysis of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial.
In summary, this trial, which compared rofecoxib with naproxen in middle-aged men and women with arthritis, showed a 53% decrease in the risk of upper gastrointestinal tract toxicity and a 5-fold increase in the risk of myocardial infarction (MI) for rofecoxib compared with naproxen. The difference was greatest among 58-year-old men. NSAIDs, such as naproxen, block the cyclooxygenase pathway, hence the anti-inflammatory effects of COX-2 receptors and the adverse gastrointestinal effects of COX-1 receptors.
Atherosclerosis is associated with inflammation, and selective COX-2 inhibitors may have antiatherogenic effects by inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. This is most likely a class effect, and, in view of the known inflammatory milieu of the patient with renal failure and the associated high frequency of CAD, the authors recommend that all renal patients avoid the COX inhibitors for analgesia until the exact prothrombotic mechanism is understood.

Effect of anesthesia in persons with CKD
The administration of general anesthesia may induce a reduction in renal blood flow in up to 50% of patients, resulting in the impaired excretion of nephrotoxic drugs. In addition, the function of cholinesterase, an enzyme responsible for breaking down certain anesthetic agents, may be impaired, resulting in prolonged respiratory muscle paralysis if neuromuscular blocking agents are used. *N* -acetyl-procainamide, a metabolite of procainamide, accumulates in persons with CKD and, when used in combination with H2-blockers, causes prolongation of the QTc. The dose should be adjusted, or a substitute should be used.
Fluorinated compounds, such as methoxyflurane and enflurane, are nephrotoxic and should be avoided in patients with CKD. Succinylcholine, a depolarizing blocker, causes hyperkalemia.

Effect of surgery in persons with CKD
Hyperkalemia may be precipitated by tissue breakdown, transfusions, acidosis, ACE inhibitors, beta-blockers, heparin, rhabdomyolysis, and the use of Ringer lactate solution as a replacement fluid. Ringer lactate solution contains potassium, which is often disregarded but can cause hyperkalemia. Third-space fluid loss, diarrhea, vomiting, and nasoenteric suction result in both volume contraction and hypokalemia. Hypokalemia is sometimes followed concomitantly with hypomagnesemia.
Most patients with CKD have chronic acidosis; surgical disease can further complicate the acidemia. Such patients are at a higher risk for hyperkalemia, myocardial depression, and cardiac arrhythmia.
Hypocalcemia and hyperphosphatemia may be caused by rhabdomyolysis. Hyponatremia may occur from hypotonic fluids or inappropriate secretion of antidiuretic hormone.

History and Physical Examination
Conduct a thorough history and physical examination because they are essential in the evaluation of patients with CKD prior to surgery. Obtain information on the following during the history and physical examination:

- Blood pressure and sugar trends
- Presence of anemia
- Radiocontrast exposure
- Prior surgical experiences
- Bleeding tendencies
- Allergies
- Use of potentially nephrotoxic drugs
- Nutritional and volume status
- Significant history of cardiac disease or peripheral arterial disease (PAD)
- Presence of comorbid disease
- Functional capacity

Other important history
Obtain the patient's history related to the following conditions because this information is important in the perioperative treatment of patients with CKD:

- Stable or unstable angina, history of myocardial infarction
- Arrhythmias (atrial fibrillation)
- Comorbid disease (eg, pulmonary disease, history of stroke, transient ischemic attacks)

Obtain the patient's functional capacity by using simplified questions of usual daily activities (eg, climbing flights of stairs, playing tennis, shoveling snow in the winter). Strenuous activities, such as swimming, tennis, or basketball, have estimated energy requirements of at least 10 metabolic equivalents (METs).
Also, inquire about the patient's history of previous surgeries, which helps to determine the effects of general anesthesia and the presence of allergies to medications.
Perform a thorough physical examination, particularly to obtain evidence of volume overload and cardiovascular abnormalities (eg, murmurs, carotid bruits, pericardial effusion, abnormal peripheral pulses). Note the presence or absence of hair on the lower extremities because this information may herald undiagnosed PAD. Record all extremity pressures, and calculate the ankle-brachial index (ABI).
Abnormal calcium metabolism is observed in secondary and tertiary hyperparathyroidism, which is prevalent in patients with ESRD. In one retrospective study, the annual incidence of severe valvular heart disease was estimated at 15-19 cases per 10,000 patients who were on dialysis. Of these patients, the most common etiology was calcific valvular disease (69%) and endocarditis (19%). Calcific valvular disease manifested primarily as aortic stenosis endocarditis and mitral regurgitation, which could primarily be due to calcific valvular disease or secondary to endocarditis; therefore, a history of syncope, heart failure, or chest pain should imply not only ischemic heart disease but also the possibility of significant aortic valvular disease. These patients benefit from preoperative noninvasive imaging (ie, transthoracic echocardiography).

Workup
Laboratory studies and other tests

- Perform a CBC, particularly to investigate for the presence of anemia of CKD, which can be treated with recombinant erythropoietin therapy. This therapy helps optimize the hematocrit value prior to elective surgery.
- Conduct iron studies to determine if an iron deficiency or anemia is present, which can be treated with intravenous iron therapy. Also, perform a thorough gastrointestinal and gynecologic (in women) evaluation to investigate the cause of the iron deficiency.
- Study the patient's serum chemistry results, including potassium, magnesium, and phosphate concentrations, to establish the level of renal function and electrolyte concentrations. Also, obtain digoxin and other levels.
- Perform a urinalysis to help detect a urinary infection or active glomerular disease (red and white cells and their casts).
- Perform a baseline electrocardiogram (ECG) to investigate for arrhythmias, conduction system abnormalities (eg, left bundle-branch block), evidence of silent MI or ischemia, electrolyte abnormalities (eg, hypokalemia, hyperkalemia), and hypocalcemia or hypercalcemia.

Imaging studies and other specific noninvasive testing

- Obtain a chest radiograph to help rule out volume overload or active pulmonary disease.
- Conduct noninvasive diagnostic testing on patients who are about to receive intermediate-risk procedures and have a poor functional capacity or on patients with minor clinical predictors who are about to receive high-risk surgery and have poor functional capacity. Noninvasive assessment can be achieved using the tests described below.
    - Exercise ECG testing: Patients who are able to achieve greater than 85% of the maximum predicted heart rate with good exercise capacity (>6 METs) without showing ischemic changes in the ECG findings or developing hypotension are at a very low risk of a perioperative infarct. Test results also help estimate the functional capacity of the patient. Limitations include difficulty interpreting ECG findings in the presence of bundle block, hypertensive ECG changes, and the effect of digoxin. The test has a sensitivity and specificity of 68% and 77%, respectively; however, in patients with renal disease, this testing is much less applicable because of limitations in exercise capacity and baseline ECG abnormalities.
    - Stress thallium or sestamibi testing: Advantages of this test are its applicability in patients with abnormal ECG findings, left ventricular hypertrophy, or documented CAD. A positive test result is documented as perfusion defects on images in combination with ECG findings. This combination of findings bolsters the clinical picture and has an overall sensitivity and specificity of 92% and 93%, respectively. This study has limitations in patients who are unable to attain their target heart rates, and some clinicians consider the findings to be of low predictive value in patients with diabetes and ESRD, who have limited exercise capacity.
    - Persantine or dipyridamole pharmacologic myocardial perfusion imaging with thallium or sestamibi: This study is used in patients who are unable to exercise and/or are undergoing major vascular or orthopedic procedures. Positive test results are quantified as reversible defects. Fixed defects do not convey risk. The finding of a reversible dilated left ventricular cavity is also considered a high-risk profile. Several randomized studies have shown that the results of this test can help predict the risk of a perioperative cardiac event in patients with ESRD. Limitations include patients with pulmonary obstructive disease, use of theophylline, and critical carotid stenosis.
    - Dobutamine stress echocardiography: This test is used to detect wall motion abnormalities on echocardiography findings after infusing dobutamine to increase the heart rate to at least 85% of the maximal heart rate. Findings include wall motion abnormalities and ECG changes at different infusion rates. This study is found to be comparable to the Persantine thallium study in several randomized trials. Limitations include patients who are obese, have severe chronic obstructive pulmonary disease, and have severe hypertension and arrhythmias. In one study, a negative test result in selected patients helped

identify a very low-risk population, with a 97% probability of no cardiac complications after surgery.
    - Coronary angiography: This study is indicated in patients with profoundly abnormal stress test results, evidence of significant left ventricular dysfunction after echocardiography testing, the possibility of significant aortic valvular pathology, and symptoms suggestive of worsening chronic stable angina or unstable angina.

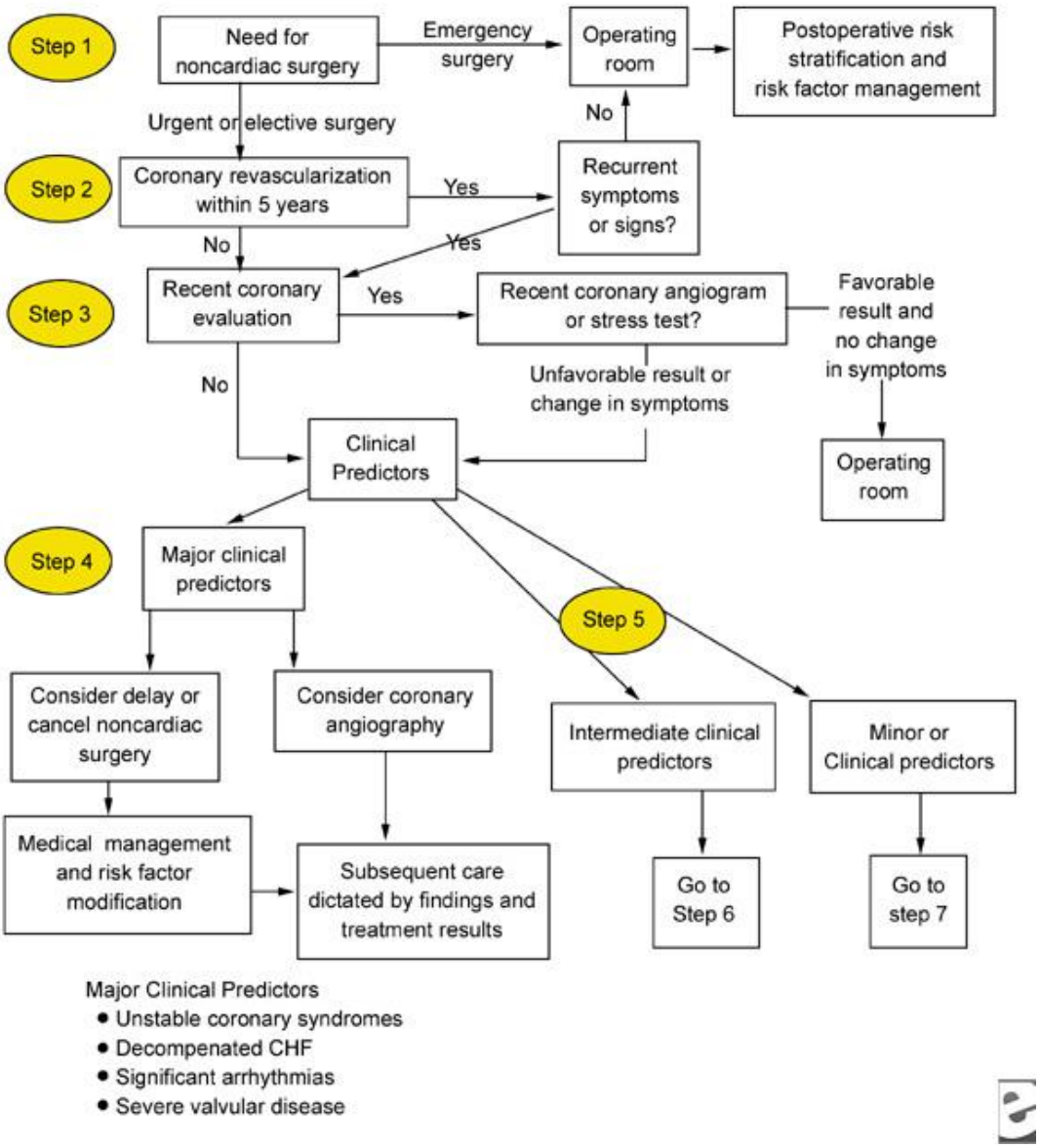
Clinical Decision Making and Management
Preoperative decision making and management
Cardiovascular risk
In light of the high prevalence of cardiovascular disease and increased perioperative morbidity in patients with CKD, a thorough cardiovascular risk assessment is indicated and should be performed in accordance with the ACC/AHA guidelines, as outlined below.
Clinical predictors of preoperative cardiovascular risk (eg, MI, congestive heart failure [CHF]) can be described as major, intermediate, or minor risk factors.

- Major predictors
    - Unstable coronary syndromes - Recent MI with evidence of important ischemic risk based on clinical symptoms or the results of noninvasive testing or unstable or severe angina (Canadian Heart Association class III or IV)
    - Decompensated CHF
    - Significant arrhythmias - High-grade atrioventricular block, symptomatic ventricular arrhythmias in the presence of underlying heart disease, supraventricular arrhythmias with uncontrolled ventricular rate
    - Severe valvular disease
- Intermediate predictors
    - Mild angina pectoris (Canadian Heart Association class I or II)
    - Prior MI based on history findings or the presence of pathological Q waves
    - Compensated or prior CHF
    - Diabetes mellitus
- Minor predictors
    - Advanced age
    - Abnormal ECG findings (eg, left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities)
    - Rhythm other than sinus (eg, atrial fibrillation)
    - Low functional capacity (eg, inability to climb one flight of stairs with bag of groceries)
    - History of stroke
    - Uncontrolled systemic hypertension

Surgical risk for noncardiac procedures can be divided into high-risk, intermediate-risk, or low-risk surgery. The type of surgery, the duration of the surgical procedure, and, occasionally, the choice of anesthesia can make a difference in patient outcome. Allowing the anesthesiologist to choose the mode of anesthesia is always advisable.

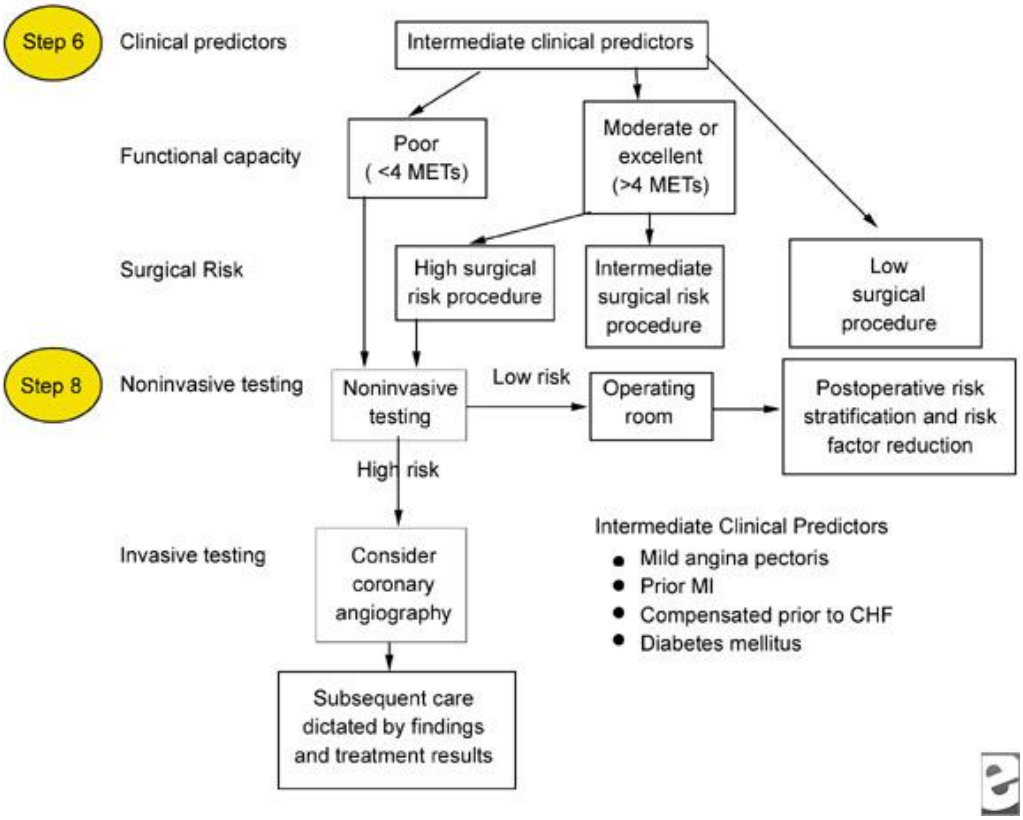
- High risk (reported cardiac risk often >5%)
    - Emergency operations, particularly in elderly persons
    - Aortic and other major vascular procedures
    - Peripheral vascular procedures
    - Anticipated prolonged surgical procedures associated with large fluid shifts, blood loss, or both
- Intermediate risk (reported cardiac risk generally <5%)
    - Carotid endarterectomy
    - Head and neck procedures
    - Intraperitoneal and intrathoracic procedures
    - Orthopedic procedures
    - Prostate surgery
- Low risk (reported cardiac risk generally <1%)
    - Endoscopic procedures
    - Superficial procedures
    - Cataract surgery
    - Breast surgery

Patients with major clinical predictors of cardiac morbidity can be assessed using the flow chart from the ACC/AHA guidelines on preoperative management (see image below). Preoperatively, patients who are undergoing elective surgery can be treated by identifying their risk profile for surgery and their risk of the intended procedure, as indicated above. Patients with decompensated heart failure or unstable coronary syndromes should have their procedures postponed until their medical management is optimized.

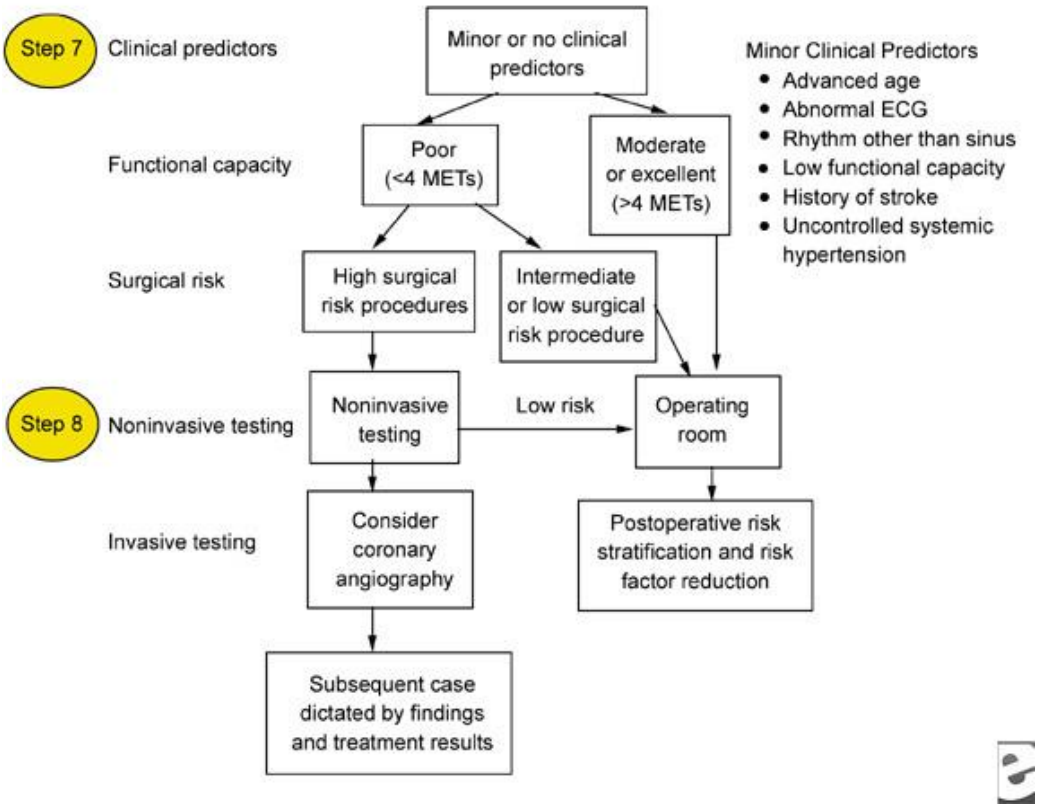


Major clinical predictors to be used for the perioperative management of a patient with chronic renal failure.

Patients with intermediate or minor clinical predictors (see images below) who are undergoing elective noncardiac surgery should be evaluated based on their functional capacity and type of surgery. Functional capacity is defined in METs, which are usually self-reported; however, this capacity can also be assessed based on the results from exercise treadmill testing. Patients who achieve at least 6 METs have a significantly better prognosis. Patients with poor functional capacity should be evaluated with noninvasive testing methods, while patients with good functional capacity can proceed to surgery.



Intermediate clinical predictors to be used for the perioperative management of a patient with chronic renal failure.



Minor clinical predictors to be used for the perioperative management of a patient with chronic renal failure.

Based on the updated ACC/AHA guidelines on perioperative cardiovascular evaluation of noncardiac surgery, all patients with renal insufficiency who have a creatinine level greater than or equal to 2 are considered to have an intermediate clinical predictor of increased perioperative cardiovascular risk.

Renal risk assessment and interventions
Patients with CKD treated conservatively
Rapidly establish the duration of CKD; level of renal function impairment; and whether the elevation in BUN and creatinine is prerenal, intrarenal, postrenal, or a combination of these on a background of CKD. Patients who are euvolemic, responsive to diuretic therapy, and/or have no significant electrolyte abnormalities or bleeding tendencies are uncomplicated and do not require dialysis before surgery.
Patients with edema, CHF, or pulmonary congestion or those who are responsive to diuretic therapy require further cardiovascular evaluation. If the results of the cardiovascular evaluation are optimal, then fluid overload can be attributed to CKD. Combination diuretic therapy can help treat these patients to achieve euvolemia prior to surgery. Patients with diabetes have a greater tendency of having volume overload or cardiovascular disease. CKD may be so advanced that the patient develops diuretic resistance, with progressive edema. Preoperative dialysis may be considered in these patients. If postoperative dialysis is imminent, the surgeons should be advised to place a temporary catheter intraoperatively. This avoids the use of femoral cannulation, which carries a higher risk of infection. Permanent vascular access placement can then be arranged when the patient is more stable.
Further deterioration in renal function can be avoided by identifying and eliminating potential nephrotoxic agents. These include substitution or dosage adjustment for antibiotics (eg, aminoglycosides, acyclovir, amphotericin), sedatives, and muscle relaxants. NSAIDs and COX-2 inhibitors should be avoided, as should radiocontrast material.

Iodinated radiocontrast material can induce acute renal failure by causing vasoconstriction and direct renal tubular epithelial cell damage and should be avoided as much as possible. The use of gadolinium in patients with CKD or ESRD has been shown to be associated with diffuse fibrosis, mostly of the skin, known as nephrogenic systemic fibrosis. Therefore, unless there is no alternative method of diagnosis, gadolinium should be avoided as much as possible. If iodinated radiocontrast material must be used, prophylactic oral administration of the antioxidant acetylcysteine, or administration of sodium bicarbonate along with hydration (0.45% saline), may reduce the risk of acute renal failure.

Controversy exists on the effectiveness of acetylcysteine and sodium bicarbonate and the superiority of one over the other; nonetheless, until rigorous clinical trials are conducted, the use of these agents in clinical practice is likely to continue, as these agents are benign and have been shown in some (if not most) studies to reduce acute renal failure.

Demerol (meperidine) used for postoperative pain should be avoided because accumulation of its metabolite normeperidine can cause seizures in patients with CKD, especially those on dialysis.

All drug interactions and potential nephrotoxicity must be identified and either stopped or the dose of the drug adjusted for the level of renal function. Electrolyte abnormalities must be identified and corrected perioperatively.

Patients already on dialysis or those who have a renal transplant
For patients already on dialysis, dialysis adequacy, preoperative dialysis needs, postoperative dialysis timing, and dosage requirements for all medications should be determined. Patients on hemodialysis usually require preoperative dialysis within 24 hours before surgery to reduce the risk of volume overload, hyperkalemia, and excessive bleeding. Patients with peritoneal dialysis who are undergoing abdominal surgery should be switched to hemodialysis until wound healing is complete. Peritoneal dialysis should be continued for those undergoing nonabdominal surgery.

Because of complicated interactions and immunosuppressive dosing, monitoring, and adjustment, a nephrologist with specialized knowledge of renal transplantation should be involved in the preoperative evaluation of patients with CKD who have received kidney transplantation. Cyclosporine or tacrolimus taken by renal transplant recipients for immunosuppression are metabolized by the cytochrome P-450 system in the liver and, thus, interact with a wide variety of agents. Diltiazem, hepatic 3-methylglutaryl coenzyme A reductase inhibitors, macrolides, and antifungal drugs inhibit the system, elevate levels, and can precipitate nephrotoxicity. Others, such as carbamazepine (Tegretol), barbiturates, and theophylline, induce the system, reduce levels, and can precipitate rejection. Drug levels must be monitored in this setting. Intravenous cyclosporine or tacrolimus should be given at one third the oral dose until the patient is able to tolerate oral medications.

Postoperative decision making and management

No preoperative cardiac assessment is indicated for emergency surgery; however, postoperative cardiac assessment must be performed and continued for 3-5 days with daily ECGs and screening of cardiac enzyme levels to detect and treat possible perioperative MI. Perioperative MI occurs mostly within the first 72 hours; however, most occurrences are silent. The incidence rate of perioperative MI is approximately 1% but carries a high mortality rate of almost 50%.

Be aware of discordant testing results of total creatine kinase (CK), myocardial band enzymes of CK (CK-MB), and troponin. Total CK levels are elevated in patients with CKD, but CK-MB levels are not; thus, elevation in CK-MB levels is due to myocardial injury. Elevation of troponin levels without a corresponding elevation in total CK levels has been shown to reflect enzyme elimination kinetics due to renal failure or cross-reactivity of the troponin I assay with noncardiac antigens.

Therefore, any enzyme elevations are not diagnostic in and of themselves. The diagnosis of postoperative MI should be made based on a combination of clinical, laboratory, and ECG evidence.

The preoperative use of beta-blocker therapy (eg, metoprolol, atenolol) may be beneficial. The risks of developing or worsening hyperkalemia have been mentioned previously. At least 2 randomized placebo-controlled trials have demonstrated reduced perioperative cardiac events and up to 6 months' improved survival.

The ACC/AHA guidelines for perioperative cardiovascular evaluation for noncardiac surgery recommend definite benefit (ie, class 1 classification) in beta-blocker therapy in patients at high cardiac risk for events because of the presence of ischemia in those undergoing vascular surgery or who have required them in the past for angina or hypertension disease; however, no data are available on patients with CKD.

The authors suggest beta-blocker therapy with a target heart rate of 50-60 beats per minute for patients at high or intermediate risk for cardiac events if no absolute or significant relative contraindications exist, although larger placebo-controlled trials are needed to better define benefits and risks in patients with CKD or ESRD.

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