Updates in Surgery

Michele Santangelo
Fabio Vistoli *Editors*

Surgery in Uremic Patients

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Updates in Surgery

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The topics addressed by volumes in the series Updates in Surgery have been selected for their broad significance in collaboration with the Italian Society of Surgery. Each volume will assist surgical residents and fellows and practicing surgeons in reaching appropriate treatment decisions and achieving optimal outcomes. The series will also be highly relevant for surgical researchers.

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Surgery in Uremic Patients

Springer

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Foreword

Patients with renal insufficiency are constantly increasing and any associated and/or related surgical pathologies in this patient population often lead to very difficult clinical situations. Surgery in uremic patients is a very complex and challenging matter, with a large number of not well-known problems related to the renal impairment condition and its dependent comorbidities.

This important topic has never been addressed in the Monographs of the Italian Society of Surgery. It is therefore an honor for me to present the work of Professors Michele Santangelo and Fabio Vistoli. I sincerely thank them and all the co-authors for devoting their energies to the realization of this excellent volume enriching the SIC Biennial Reports series.

Their book is a complete guide not only to the management of the most common surgical procedures in patients with renal failure. Indeed, in its 24 chapters it covers aspects ranging from the pathophysiology of uremia to preoperative assessment, from anesthesiological and dialysis considerations to postoperative care, and it offers in-depth insights into the impact of uremia on organ systems, possible postoperative complications, and preventive measures such as the management of infections and fluid imbalances.

For all abdominal surgeries, from minor to major, measures to optimize the procedures in order to minimize complications are outlined, particularly for upper and lower gastrointestinal, hepatobiliary, urological, transplant, endocrine, bariatric, geriatric, and emergency procedures

The book concludes with key findings, clinical implications, and future research avenues, providing a valuable reference resource for those who are already involved in the care of uremic patients. I am sure it will be a milestone for all those, surgeons and non-surgeons alike, who wish to approach this problem or learn more about it.

Rome, Italy
September 2025

Massimo Carlini

Preface

A special interest in the care of patients with chronic renal failure (CRF) has guided much of our working life and prompted us to edit, under the auspices of the Italian Society of Surgery, a monograph dedicated to this topic.

In recent years, the number of patients with uremia has increased dramatically throughout the world, in part as a result of the longer average life expectancy. In Italy alone, there are more than 4,000,000 patients with CRF, 100,000 of whom requiring life-saving treatments: about 60,000 are on dialysis and about 40,000 are kidney transplant recipients. This large population of particularly fragile and high-risk patients requiring specific specialized care often also necessitates surgery to treat diseases arising either as a result of or independently from their uremic state or procedures specifically targeted to CRF (dialysis and transplantation). Considering these data from a different viewpoint, over the course of a lifetime, almost all stage 5 uremic patients will undergo at least one surgical procedure to establish an access for dialysis treatment, and more than 60% of them will undergo at least one other procedure to treat some surgical disease.

In view of their condition and frailty, patients with renal failure require specific care and procedures, which are not, however, always well codified and/or known to all surgeons. Hence the need for this monograph.

Although the title "Surgery in the Uremic Patients" may suggest that the topics covered are relevant to all surgical specialties and their ancillary branches, in the final draft we decided to narrow our scope to focus on topics of interest to general surgery. This, in order to provide a useful reference tool for general surgeons who, at any time in their practice, may be called upon to manage both elective and emergency clinical situations featuring uremia and thus requiring specific solutions.

Therefore, our goals in compiling this edited volume were to:

1. Provide the elements for appropriate preoperative, intraoperative, and postoperative management of CRF patients through an up-to-date and comprehensive review of current knowledge, guidelines, and clinical experience: all elements that we believe should be part of the cultural and technical background of all surgeons. Indeed, we are convinced that this knowledge will enable surgeons to implement safer and more effective medical and surgical practices.
2. Optimize the surgical outcomes of patients with CRF. In fact, enhancing surgeons' understanding and skills in treating these patients is expected to help

reduce postoperative complications, improve surgical outcomes, and optimize the overall management of renal disease, with a significant improvement in the patients' quality of life. In economic/financial terms, these improvements would also help to contain the already burdensome costs of managing these patients, by optimizing healthcare spending.
3. Focus on the indications, diagnoses, and operative techniques of the conditions most frequently associated with CRF and which fall within the remit of general surgeons, including those procedures specifically aimed at the treatment of CRF (e.g., dialysis accesses and kidney transplantation).
4. Examine the extent to which the innovations, technology, and advanced techniques currently available to surgeons (from robots to biomaterials to minimally invasive surgery and more) allow for safer and more effective surgical management of patients with this complex medical condition.
5. Bring residents closer to these topics, so that they can also see this as a potential area of development for their future professional practice.

Until today, despite the tremendous progress made in medical and surgical science in recent decades, an up-to-date and all-inclusive text on this topic has been lacking. For this reason, it has always been our desire to produce a monograph on both routine and frontier surgery in the CRF patient, so as to help bridge this gap in the current international medical literature.

In this sense, the opportunity offered to us by the Italian Society of Surgery to serve as editors for a monograph dedicated to this topic as part of its "Biennial Reports" was a unique chance for us to collect and share best practices, clinical experiences, and scientific evidence in the field of surgery in the patient with CRF.

Since the Italian experience in this specific field of surgery is second to none, we decided to invite chapter contributions from the majority of Italian surgeons who successfully care for these patients. From this point of view, the intent has been achieved: the contributions to the monograph come from almost all of the Italian Regions and from the majority of the centers performing this type of surgery. Unfortunately, the few absences are due both to the limited number of pages available and to unforeseeable circumstances beyond our control.

Our sincere gratitude therefore goes to the colleagues who have shared their in-depth knowledge and experience in this volume, and a special thanks to the Italian Society of Surgery that made the volume possible.

Naples, Italy — Michele Santangelo
L'Aquila, Italy — Fabio Vistoli
September 2025

Acknowledgments

The writing of this monograph would not have been possible without the valuable contributions of the distinguished authors of the individual chapters. We would like to express our sincere gratitude to all the Italian surgeons who have shared their profound knowledge and experience, improving the understanding and management of the surgical care of the patient with CKD. Their dedication to the advancement of surgery in uremic patients was instrumental in the creation of this comprehensive book.

Special thanks also to the Italian Society of Surgery and to all of Italian Surgery, which gave us the opportunity to produce this monograph with the support and contributions of its helpful and wonderful experts.

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Bruno Nardo, Francesco Pata, Roberta Arena, Giuliana Papalia, Michele Provenzano, and Gianluigi Zaza

1.1 Mechanisms Underlying Uremia and Its Systemic Effects

As defined in the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Guidelines [1], chronic kidney disease (CKD) refers to abnormalities of kidney structure or function, present for at least 3 months, with implications for health. CKD is classified based on cause, glomerular filtration rate (GFR) category (G1–G5), and albuminuria category (A1–A3) (Fig. 1.1). Each component of the classification system is critical in the assessment of patients with CKD, allowing evaluation of CKD severity and risk.

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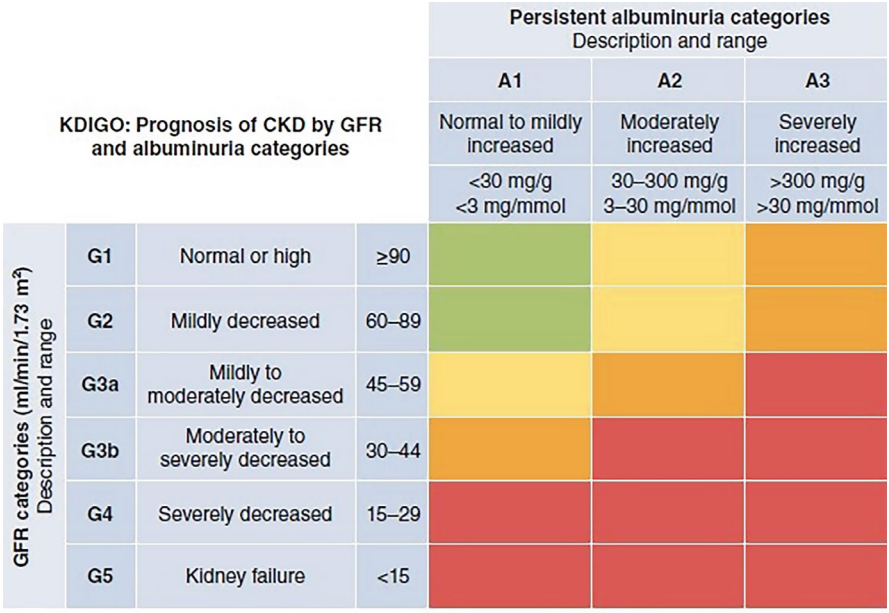


Fig. 1.1 KDIGO prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria categories. (Reproduced with permission from [1])

In 2021, more than 850 million people suffered from some form of kidney disease, reaching a global prevalence of 9.1% of CKD patients. These numbers are showing a growing trend due to aging populations and the increasing burden of risk factors for CKD such as mainly diabetes and hypertension, followed by obesity, cardiovascular disease (CVD), metabolic syndrome, dyslipidemia, and a family history of kidney disease [1–3]. Other less common causes of CKD are primary and secondary glomerulonephritis, autosomal dominant polycystic kidney disease, tubulointerstitial nephritis, obstructive nephropathies, and pyelonephritis [3]. The Global Burden of Disease Study (2019) estimated that 1.42 million people died globally from CKD in that year, revealing the real impact of CKD as a global health problem [4].

End-stage kidney disease in this classification system occurs when GFR stabilizes (the value should be confirmed) at <15 mL/min/1.73 m^2. This clinical condition is also called uremia and is characterized by several systemic complications caused by the irreversible loss of renal function [5].

1.2 Fluid Overload and Sodium Imbalance

Changes in sodium and water intake are normally buffered by the kidneys, thanks to a complex hormonal regulation system (renin-angiotensin-aldosterone system [RAAS], atrial natriuretic peptide, etc.) and activation of the sympathetic nervous

system. In physiologic conditions, an excess of sodium or water intake does not lead to changes in blood volume and blood pressure. In CKD patients, because of hormonal imbalances and reduction in functioning nephrons, external sodium balance is maintained at the expense of extracellular volume (ECV) expansion, which causes the persistence of high blood pressure levels. Generally, ECV expansion is present without peripheral edema when cardiac and hepatic function is normal and the transcapillary Starling forces are not disrupted. Moreover, during CKD progression there is an inability to concentrate urine, followed by impaired urine excretion in response to increased water intake [6, 7].

1.2.1 Hyperkalemia

The normal serum levels of potassium are included in the range of 3.5–5.0 mmol/L. Hyperkalemia is classified into mild (5.5–6.0 mmol/L), moderate (6.0–6.5 mmol/L), and severe (>6.5 mmol/L). Serum potassium levels depend on daily intake and excretion, transcellular shift and acid-base balance. Excretion occurs through the skin, the gastrointestinal tract and the kidneys (almost 90%). The kidneys maintain potassium homeostasis by secreting it through the distal convoluted tubule and the proximal collecting duct. In uremia, the decreased renal ion excretion, the use of some drugs used to slow CKD progression or to treat associated comorbidities and metabolic acidosis (transcellular shift) lead to hyperkalemia. The clinical pictures associated with the condition are weakness, paresthesia, paralysis, nausea, hypotension, arrhythmias or cardiac arrest. The electrocardiographic signs are peaked T waves, prolonged PR interval, shorter QT interval, wider QRS complex, absence of P wave, ventricular fibrillation or tachycardia [8].

1.2.2 Metabolic Acidosis

Metabolic acidosis is defined as a clinical condition with a pH value <7.35 (normal range 7.35–7.45) and a bicarbonate concentration <22 mEq/L (normal range 22–26 mmol/L). It derives from renal inability to excrete the daily acid load as ammonium and titratable acid, with acid retention. Metabolic acidosis causes several complications such as hyperkalemia (transcellular shift of H^+ with K^+), bone demineralization, skeletal muscle catabolism and mortality [9].

1.2.3 Calcium-Phosphorus Imbalance

The reduced excretion of phosphorus causes hyperphosphatemia, defined as a serum concentration > 4.5 mg/dL. Hyperphosphatemia has several consequences. It leads to hypocalcemia (<8.8 mg/dL) for the constancy of the calcium/phosphorus ratio, also as a result of the inability to activate vitamin D. Hypocalcemia can be characterized by muscle cramps, hyperreflexia, tetany, seizures.

Both hyperphosphatemia and hypocalcemia lead to secondary hyperparathyroidism, which stimulates bone reabsorption to increase calcium levels. When the calcium/phosphorus ratio reaches the value of 60, the risk of soft tissue calcifications is enhanced. This increases the risk of cardiovascular diseases and cardiovascular mortality [10].

1.2.4 Hyperuricemia

Uric acid is the final product of purine metabolism, and it is mainly excreted by the proximal tubules. Hyperuricemia is defined as serum uric acid levels >6.0 mg/dL. In uremia, serum uric acid is commonly elevated due to impaired tubular excretion and filtration. Hyperuricemia is the pathogenetic basis for the development of monosodium urate deposits in various organs and tissues, with increased cardiovascular risk. In rare severe cases, it can lead to gout [11].

1.2.5 Anemia

Another sign of uremia is anemia, defined as hemoglobin levels <12 g/dL in women and < 13 g/dL in men. This is a normochromic normocytic anemia that appears mainly as a result of reduced erythropoietin (EPO) production. Other causes can concur to the onset of anemia, such as reduced red blood cell survival and folic acid and vitamin B12 deficiencies. This condition can therefore be considered multifactorial [12].

1.3 Effects of Uremia on Various Organ Systems and Implications for Surgical Outcomes and Complications

Uremia can lead to several signs and symptoms, the combination of which is more appropriately referred to as uremic syndrome. Uremic syndrome is the consequence of the retention of uremic solutes due to their reduced renal clearance, hydroelectrolyte and acid-base disturbances, and endocrine imbalances [13]. The best known uremic solutes are urea, guanidic derivatives, aromatic compounds, aliphatic amines, polyamines, carbohydrate derivatives, polypeptides and proteins, products of nucleic acid metabolism, and many others. Most of these products are considered toxins. These are produced by dysbiosis of the intestinal bacterial flora and by enzymes, especially liver enzymes, and are transported into different organs, where they exert their toxic effects or disrupt key signaling and metabolic pathways. Indeed, these uremic solutes have several effects on cell, organ and system functions and interactions. They are traditionally classified based on their chemical-physical characteristics, such as molecular weight and hydro/lipophilicity [13, 14].

Uremic syndrome includes the following disorders:

- Hemocoagulative disorders. In uremic patients there is a greater tendency to bleeding, most likely related to a platelet dysfunction, and in particular to impaired endothelial adhesion (caused by a lower intracellular content of ADP and serotonin and a reduced production of thrombomodulin). Furthermore, an excess of phosphatidylserine on the platelet surface can promote their phagocytosis by macrophages. Bone marrow activity may also be slowed down by the toxic effect of uremic solutes [15, 16].
- Immune disorders. Both the innate and the adaptative responses are involved. The immune cell functions triggered by factors such as invading microorganisms can be inhibited or constitutively active. Furthermore, an imbalance occurs between the pro-apoptotic and anti-apoptotic factors of immune cells. Solutes, such as guanidines and other medium-high molecular weight uremic toxins, lead to polymorphonuclear dysfunction. The dendritic cells are also affected. The impairment of bone morrow activity plays another important role. Several retained solutes can potentially act as ligands in the activation of toll-like receptors (TLRs), and contribute to chronic inflammation [16].
- Hematopoietic disorders. A typical finding is normocytic and normochromic anemia, the main causes of which include the reduced production of EPO in the kidneys and the reduced survival of red blood cells in the bloodstream resulting from their impaired metabolic health. However, multiple other factors contribute to the onset of anemia, such as the above-mentioned suppressed bone marrow activity. The chronic inflammatory state in uremia also leads to EPO hyporesponsiveness. Iron metabolism is also involved. Vitamin B12 and folate are deficient due to concomitant gastric problems [11, 17].
- Gastrointestinal disorders. Anorexia, nausea, vomiting and taste disturbance are the most frequent symptoms in uremic syndrome. The increase of ammonium in the gastrointestinal tract causes derangement to the bacterial flora with colonization by opportunistic organisms. Ammonium destroys the intestinal tight junctions, thereby affecting parietal permeability. The translocation of bacteria and endotoxins activates an innate immunity response that worsens the intestinal wall damage. The dysbiosis can result in prolonged intestinal transit time and impaired protein assimilation, which may contribute to malnutrition. Distally, the undigested proteins cause proteolytic bacteria proliferation and microbial fermentation with the production of toxic metabolites. Instead, the reduced clearance of intermediate molecular weight solutes, such as leptin, cholecystokinin, indoles and phenols, contributes to anorexia. Hypergastrinemia, on the other hand, causes an increase in gastric acid production and an increased risk of gastroduodenal ulcer disease [18, 19].
- Mineral and bone disorders. Mineral bone disease is characterized by hypocalcemia, hyperphosphatemia, secondary hyperparathyroidism, decreased vitamin D and vascular calcification. These disturbances cause a disruption of the normal mineral homeostasis and may lead to various clinical and radiological pictures such as fibro-cystic osteitis, osteoporosis, osteopenia, osteomalacia, adynamic bone disease and fractures. Accumulation of beta 2 microglobulin is involved in the genesis of cysts and amyloidosis-like conditions [9, 20].

- Cardiovascular disease. CVD is the leading cause of mortality in uremic patients. In uremia, hormones, enzymes and cytokines, are released leading to characteristic cardiac and vascular damage. Hemodynamic alterations also contribute to cardiac and vascular damage.
  Uremic toxins cause the overexpression of genes involved in the inflammatory processes and fibrosis, influencing several signaling pathways. Uremic toxins also affect the endothelial functions, promoting structural damage and inflammation, disrupting cell junctions with subsequent loss of integrity in the endothelial barrier, impairing endothelium-dependent vasodilatation and the pro- and antithrombotic properties. All these factors are associated with the risk of atherosclerosis.
  Vascular smooth muscle cells can switch to a synthetic phenotype. Abnormal arterial stiffness contributes to an increased cardiac afterload, systolic hypertension, left ventricular hypertrophy (LVH) with a decrease in coronary perfusion and thus heart failure.
  Cardiac fibrosis leads to a maladaptive LVH with subsequent dilatation, also supported by an increase of preload. Hyperactivation of RAAS is involved in the onset of hypertension, inflammation, fibrosis, and increased preload.
  Electrical dysfunctions can be present, also caused by electrolyte imbalances [21].
  However, traditional cardiovascular risk factors are highly prevalent in patients with uremia. Hypertension affects the majority of patients, as a cause or consequence of CKD. Moreover, a characteristic lipid pattern is present with low HDL cholesterol levels, normal LDL cholesterol levels and elevated triglycerides. Hyperglycemia is associated with the development of both CKD and CVD [22, 23].
  Another hallmark of cardiovascular involvement in uremia is pericarditis with hyperpyrexia, precordial pain, pericardial rubbing, but without the typical diffuse elevation of the ST segment and the T wave on the electrocardiogram [24].
- Neurological disorders. The condition affects central, peripheral and autonomic nervous systems. The metabolic imbalance caused by uremia exerts its harmful effects through a derangement of several neurotransmitters. In particular, uremic toxins inhibit gamma-aminobutyric acid (GABA) receptors and stimulate N-methyl-D-aspartate (NMDA) receptors. Electrolyte imbalances exert neurotoxic effects as well, resulting in different clinical pictures: encephalopathy, polyneuropathy and mononeuropathy. Encephalopathy can produce signs and symptoms of varying severity, from confusional states to a coma. Typically, the peripheral nervous system is affected by a sensorimotor toxic-degenerative polyneuropathy, which presents with weakness, cramps, restless leg syndrome, distal paresthesias and dysesthesias. Instead, impairment of the autonomic system is characterized by changes in blood pressure and in heart rate, and nocturnal breathing disorders [25].
- Muscle disorders. The responsible mechanisms are still poorly understood. Sarcopenia, atrophy and weakness are attributable to inflammation and the accumulation of reactive oxygen species (ROS), responsible for mitochondrial

uncoupling (decline in ATP production per unit of oxygen consumed) and deficient muscle repair mechanisms. Other factors are comorbidities such as diabetes, malnutrition and vascular disease. EPO, vitamin D, and androgen deficiencies likely contribute to the muscle weakness [26].

- Skin disorders. Skin and mucous membranes are xerotic due to impaired tissue trophism, but the mechanism underlying uremic pruritus is not completely understood. Possible causes include: secondary hyperparathyroidism, hyperuricemia, hyperphosphatemia, allergic sensitization, proliferation of skin mast cells, hypervitaminosis A, anemia, neuropathy, or some combination of these. Patients often present with scratching injuries with a risk of infection. Disorders of the skin appendages also develop, such as Terry's nails, with frosted appearance [27].
- Elimination of drugs. Drug side effects are frequent. The reduced renal elimination of medications leads to an accumulation of the medications themselves and their metabolites. Each medication with renal elimination therefore requires a dose adjustment. For patients on dialysis, the dose adjustment must also take into consideration the extracorporeal clearance based on the frequency and duration of treatments [28].

1.4 Assessment of Cardiovascular Status and Fluid and Electrolyte Balance

CVD are the leading cause of morbidity and mortality in patients with CKD. On the other hand, CKD shows an increased cardiovascular risk and many studies suggest that it should be considered a "coronary equivalent" requiring a strict risk factor control as part of the standard of care [21].

Several studies suggest a correlation between reduced eGFR, the presence of proteinuria and an increased risk of cardiovascular events. The presence of other independent risk factors such as hypertension, dyslipidemia and diabetes complicates this scenario.

All things considered, the prevention and management of CVD are of major concern in a nephrological setting. CKD patients generally suffer from atherosclerosis, arrhythmias, heart valve disease, coronary heart disease and, less frequently, uremic pericarditis.

There are many pathophysiological mechanisms that are shared by CVD and CKD. The acute or chronic dysfunction of the kidneys or heart leads to alterations on the other organ as seen in cardio-renal syndromes. The kidneys are the main organs involved in the regulation of fluid homeostasis through the sodium balance. Functional and/or structural alterations at the basis of kidney disease result in loss of concentration, dilution and acidification of urine and of serum levels of major electrolytes.

The reduction of eGFR is responsible for hydrosaline retention so that CKD patients are generally hypervolemic and hypertensive. Volume overload is then responsible for the development of left ventricular hypertrophy, systolic-diastolic dysfunction, and heart failure.

Other pathological mechanisms involved in the genesis of CVD in the context of CKD are represented by electrolyte alterations [29]. Hyperkalemia in CKD patients appears when aldosterone secretion and distal flow are lost. Other common causes are a high-potassium diet and the simultaneous use of angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin II receptor blockers (ARB). Metabolic acidosis also sustains potassium leakage into extracellular fluids. Overall, hyperkalemia exposes to an increased risk of fatal arrhythmias [30].

Primitive and iatrogenic mineral disorders, a typical finding of CKD patients, are involved in atherogenesis. Hyperphosphatemia develops early during the natural course of CKD, due to phosphate retention. It secondarily causes hypocalcemia which requires calcium supplementation for its correction. The overall increase of calcium-phosphorus products promotes the development of coronary arterial calcifications [31].

The general management of CKD involves treatment of the reversible causes of kidney damage, prevention or slowing of the progression of kidney disease, treatment of the complications, and definition of a kidney replacement therapy program.

The diagnostic pathway of the CKD patient should include blood tests to monitor renal function and pro-BNP, blood gas analysis to determine the acid-base balance, chest radiography and kidney ultrasound. Echocardiography and thoracic ultrasound are other essential tools for the diagnosis and follow-up of heart disease and fluid overload.

When considering the therapeutic panorama and the need for risk factor reduction, it is fundamental to control the patient's blood pressure, aiming for a target blood pressure of 130/80 mmHg or less. This has shown to slow the progression of proteinuric CKD and reduce the risk of developing CVD. Volume overload generally responds to dietary sodium restriction (<2 g/day) and diuretic therapy, mainly based on loop diuretics. In cases of primary hypertension, the use of beta blockers, calcium antagonists and alphalytics is recommended [32].

Moreover, all CKD patients should be treated for dyslipidemia, hyperphosphatemia and hyperkalemia. The use of lipid-lowering therapy, mainly based on a statin and ezetimibe, is recommended. Dietary phosphate restriction and oral phosphate binders are used to limit the development of secondary hyperparathyroidism and consequently renal bone disease [33]. Hyperkalemia benefits from the use of potassium chelating drugs and a low-potassium diet [30].

The close correlation between renal and cardiac diseases highlights the complexity of CKD, which has to be intended as a complex systemic disease that not only damages the renal parenchymal but also alters the general balance of the organism. The fragility of the CKD patient requires a close collaboration between the nephrologist and the cardiologist, and a broader assessment of CKD and its complications.

1.5 Risk Prediction Models Specific to Uremic Patients Undergoing Surgery

The identification of a robust risk prediction model is pivotal to predicting mortality, cardiac events, and other serious complications for uremic patients (particularly with CKD or end-stage renal disease) undergoing surgery. Risk prediction models

may inform clinical decision making, informed consent and preoperative planning. Several models have been proposed, but the ideal one has yet to be introduced in clinical practice. The current models are not specific for uremic patients, posing an additional challenge in balancing their complexity and clinical utility, ensuring that they can be effectively applied in routine clinical practice [34].

To predict major cardiac events and/or death, three scores—the Revised Cardiac Risk Index (RCRI) [35], the National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest (MICA) tool [36], and the American College of Surgery (ACS) NSQIP Surgical Risk Calculator (ACS-SRC) [37, 38]—have all been recommended [39, 40], but they present some limitations. RCRI is simply to use, it includes some specific variables for uremic patients, but it does not discriminate moderate CKD and kidney failure (it proposes a dichotomized variable for a serum creatinine level above or below 2 mg/dL or 177 μmol/L), and its performance was suboptimal with a significant risk overestimation when assessed in a cohort of patients with kidney failure [41]. The NSQIP MICA tool stratifies risk according to the type of surgery, but it may underestimate events in patients at high risk and it dichotomizes the serum creatinine level considering a cut-off level of serum concentration > 1.5 mg/dL, 133 μmol/L with the same problem in discriminating CKD stages, although its performance seems superior in identifying patients at high risk of cardiac complications [42]. The NSQIP ACS-SRC is effective for a broad risk assessment, as it also estimates the risk of non-cardiac events, but it is more complex and time-consuming and the variable related to preoperative dialysis does not discriminate between acute kidney injury (AKI) or CKD patients.

To overcome these limitations and introduce a risk prediction tool tailored for uremic patients, a group from Canada [43] derived and internally validated three new prognostic risk prediction models using a retrospective, population-based cohort of 38,541 patients undergoing non-cardiac surgery with an estimated GFR <15 mL/min/1.73 m^2 or under dialysis. Although these models have not yet been externally validated, they all performed well, showing promising results over default strategies, especially when comorbidities and laboratory variables, such as preoperative hemoglobin and albumin, were included.

In a 2024 systematic review of risk prediction models aiming to quantify the risk of developing AKI after non-cardiac surgery, among the nine models identified, only three showed a fair discrimination and potential clinical utility [44]. These conclusions were more positive compared to another review published in 2017, which failed to identify a prediction model adequate for clinical practice among seven models available for postoperative AKI after non-cardiac surgery [45].

1.6 Preoperative Dialysis: When and How

Establishing the correct timing for preoperative dialysis in a patient with renal failure is crucial for mitigating the risk of intraoperative and postoperative complications. "*An equilibrated, euvolemic patient at their dry weight*" should be the target

before surgery, though the precise definition of "dry weight" remains somewhat unclear [46].

A prolonged interval between the last dialysis session and the surgery can lead to:

1. hypervolemia, a cause of hypertension and increased risk of pulmonary edema, heart failure, and myocardial ischemia during the operation and poor wound healing after it;
2. elevated potassium levels, raising the risk of intraoperative arrhythmias;
3. increased uremia and therefore platelet dysfunction, with a higher risk of bleeding.

Furthermore, the increased uremic status related to a longer interval may cause altered taste and anorexia, leading to a malnutritional status (a further risk factor for poor postoperative outcomes) and impaired immune function. While in emergency cases dialysis is usually performed after the surgical procedure, in elective surgeries there is consensus in recommending dialysis the day before surgery, with a minimum interval of at least 6 hours between the session and the operation [47].

Although the evidence is largely based on large retrospective studies, with the inherent biases of such study design, the accumulation of evidence gathered over the past 40 years appears sufficient to support this recommendation [48]. In a retrospective study on 346,828 uremic patients undergoing elective surgery in the US, longer intervals were associated with a higher risk of 90-day postoperative mortality [49]. Other studies showed an increased risk of sudden cardiac death and arrhythmias [50] and overall mortality in patients with longer intervals between preoperative dialysis and surgery [51]. Hence the recommendation, mainly based on expert opinion, to avoid dialysis the same day of surgery or to ensure an interval of at least 6 hours between dialysis and the operation [52]. A shorter interval may lead to hypotension, intraoperative bleeding due to residual anticoagulation, and electrolyte imbalances. For instance, blood samples taken immediately after dialysis may show reduced serum potassium levels, which could lead to improper repletion or temporary arrhythmias [47].

A more aggressive approach, repeating the dialysis at shorter intervals in the preoperative period has not been proven superior in comparison with the standard of care, except for patients that are chronically hypervolemic and underdialyzed (blood urea nitrogen levels exceeding 100 mg/dL), who might experience improved outcomes with daily dialysis sessions for a short period before surgery. Lowering the accumulation of nitrogenous waste could potentially enhance immune system performance, reduce malnutrition, and promote better wound healing [53].

The perioperative management of patients undergoing peritoneal dialysis (PD)—about 11% of the global dialysis population [54]—presents further challenges. Much of the evidence in the literature is from single-center studies or case series, making any definitive recommendations questionable. The key decision revolves around whether to continue PD or switch temporarily to hemodialysis (HD). On the one hand, the use of a temporary venous catheter for HD may be a source of further complications (exit-site bleeding, hematoma, infection, bacteremia or thrombosis

and venous stenosis at the insertion site after removal) [55], on the other hand, in abdominal surgery the occurrence of complications like poor hemostasis and fluid leakage at abdominal wall incision sites leading to peritonitis often suggests temporarily discontinuing PD and switching to HD, removing the catheter only in the case of peritonitis or contaminated field [56].

In cases of non-abdominal or extraperitoneal abdominal surgery, continuation of peritoneal dialysis in the perioperative period may be considered [57], although a shift toward HD may be necessary to allow a tighter control of fluid and electrolyte balance [58]. In these cases, to optimize preoperative status, individuals on continuous cycling peritoneal dialysis (CCPD) should undergo an intensive regimen of nearly continuous dialysis over a 48- to 72-hour period before surgery. Conversely, patients on continuous ambulatory peritoneal dialysis (CAPD) can increase the frequency of exchanges to every 3–4 hours while awake during the 48- to 72-hour preoperative window [59]. This approach ensures optimal fluid and solute balance before surgery, reducing perioperative risks. In the case of a low-risk abdominal surgery procedure when PD is not interrupted, care should be taken to ensure at the time of surgery that the peritoneal cavity is adequately drained, aiming for less than 200 mL of dialysate fluid remaining in the abdomen. This helps to minimize the risk of complications and provides a clearer operative field [56].

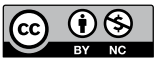
References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4S):S117–314.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3S):S1–87.
3. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389(10075):1238–52.
4. Global Burden of Disease. GBD cause and risk summaries chronic kidney disease. Lancet. 2019;2020(396):S152–3.
5. Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. J Am Soc Nephrol. 2019;30(9):1735–45.
6. Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: core curriculum 2019. Am J Kidney Dis. 2019;74(1):120–31.
7. Borrelli S, Provenzano M, Gagliardi I, et al. Sodium intake and chronic kidney disease. Int J Mol Sci. 2020;21(13):4744.
8. Borrelli S, Matarazzo I, Lembo E, et al. Chronic hyperkaliemia in chronic kidney disease: an old concern with new answers. Int J Mol Sci. 2022;23(12):6378.
9. Raphael KL. Metabolic acidosis in CKD: core curriculum 2019. Am J Kidney Dis. 2019;74(2):263–75.
10. Pazianas M, Miller PD. Osteoporosis and chronic kidney disease-mineral and bone disorder (CKD-MBD): back to basics. Am J Kidney Dis. 2021;78(4):582–9.
11. Vargas-Santos AB, Neogi T. Management of gout and hyperuricemia in CKD. Am J Kidney Dis. 2017;70(3):422–39.
12. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631–4.

13. Nigam SK, Bush KT. Uraemic syndrome of chronic kidney disease: altered remote sensing and signalling. Nat Rev Nephrol. 2019;15(5):301–16.
14. Rosner MH, Reis T, Husain-Syed F, et al. Classification of uremic toxins and their role in kidney failure. Clin J Am Soc Nephrol. 2021;16(12):1918–28.
15. DeLoughery TG. Management of bleeding with uremia and liver disease. Curr Opin Hematol. 1999;6(5):329–33.
16. Hedges SJ, Dehoney SB, Hooper JS, et al. Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol. 2007;3(3):138–53.
17. Cohen G, Hörl WH. Immune dysfunction in uremia - an update. Toxins (Basel). 2012;4(11):962–90.
18. Almeras C, Argilés A. The general picture of uremia. Semin Dial. 2009;22(4):329–33.
19. Rysz J, Franczyk B, Ławiński J, et al. The impact of CKD on uremic toxins and gut microbiota. Toxins (Basel). 2021;13(4):252.
20. Kim JE, Kim HE, Park JI, et al. The association between gut microbiota and uremia of chronic kidney disease. Microorganisms. 2020;8(6):907.
21. Zangeneh F, Clarke BL, Hurley DL, et al. Chronic kidney disease-mineral and bone disorders (CKD-MBDs): what the endocrinologist needs to know. Endocr Pract. 2014;20(5):500–16.
22. Lim YJ, Sidor NA, Tonial NC, et al. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins (Basel). 2021;13(2):142.
23. Reiss AB, Voloshyna I, De Leon J, et al. Cholesterol metabolism in CKD. Am J Kidney Dis. 2015;66(6):1071–82.
24. Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and mechanisms of uremia-related cardiovascular disease. Circulation. 2016;133(5):518–36.
25. Pichler Sekulic S, Sekulic M. Uremia-associated fibrinous pericarditis. Kidney Int. 2023;103(3):643.
26. Rosner MH, Husain-Syed F, Reis T, et al. Uremic encephalopathy. Kidney Int. 2022;101(2):227–41.
27. Kaltsatou A, Sakkas GK, Poulianiti KP, et al. Uremic myopathy: is oxidative stress implicated in muscle dysfunction in uremia? Front Physiol. 2015;6:102.
28. Robertson KE, Mueller BA. Uremic pruritus. Am J Health Syst Pharm. 1996;53(18):2159–70.
29. Aronoff GR. Drugs and the kidney. Curr Opin Nephrol Hypertens. 1993;2(2):187–91.
30. Kovesdy CP, Matsushita K, Sang Y, et al. Serum potassium and adverse outcomes across the range of kidney function: a CKD prognosis consortium meta-analysis. Eur Heart J. 2018;39:1535–42.
31. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7(1):1–59.
32. Molina P, Gavela E, Vizcaino B, et al. Optimizing diet to slow CKD progression. Front Med (Lausanne). 2021;8:654250.
33. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:259–305.
34. van Rijn MHC, van de Luijtgaarden M, van Zuilen AD, et al. Prognostic models for chronic kidney disease: a systematic review and external validation. Nephrol Dial Transplant. 2021;36(10):1837–50.
35. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043–9.

36. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011;124(4):381–7.
37. Cohen ME, Ko CY, Bilimoria KY, et al. Optimizing ACS NSQIP modeling for evaluation of surgical quality and risk: patient risk adjustment, procedure mix adjustment, shrinkage adjustment, and surgical focus. J Am Coll Surg. 2013;217(2):336–46.
38. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217(5):833–842.e1–3.
39. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. Can J Cardiol. 2017;33(1):17–32.
40. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2215–45.
41. Harrison TG, Hemmelgarn BR, James MT, et al. Using the revised cardiac risk index to predict major postoperative events for people with kidney failure: an external validation and update. CJC Open. 2022;4(10):905–12.
42. Cohn SL, Fernandez Ros N. Comparison of 4 cardiac risk calculators in predicting postoperative cardiac complications after noncardiac operations. Am J Cardiol. 2018;121(1):125–30.
43. Harrison TG, Hemmelgarn BR, James MT, et al. Prediction of major postoperative events after non-cardiac surgery for people with kidney failure: derivation and internal validation of risk models. BMC Nephrol. 2023;24:49.
44. Zhuo XY, Lei SH, Sun L, et al. Preoperative risk prediction models for acute kidney injury after noncardiac surgery: an independent external validation cohort study. Br J Anaesth. 2024;133(3):508–18.
45. Wilson T, Quan S, Cheema K, et al. Risk prediction models for acute kidney injury following major noncardiac surgery: systematic review. Nephrol Dial Transplant. 2016;31(2):231–40.
46. Cronin B, Vural C, Maus T, O'Brien EO. Perioperative dialysis: what is "just right"? J Cardiothorac Vasc Anesth. 2023;37(4):501–3.
47. Kanda H, Hirasaki Y, Iida T, et al. Perioperative management of patients with end-stage renal disease. J Cardiothorac Vasc Anesth. 2017;31:2251–67.
48. 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.
49. Fielding-Singh V, Vanneman MW, Grogan T, et al. Association between preoperative hemodialysis timing and postoperative mortality in patients with end-stage kidney disease. JAMA. 2022;328:1837–48.
50. Wong MC, Kalman JM, Pedagogos E, et al. Temporal distribution of arrhythmic events in chronic kidney disease: highest incidence in the long interdialytic period. Heart Rhythm. 2015;12(10):2047–55.
51. Bahrainwala JZ, Gelfand SL, Shah A, et al. Preoperative risk assessment and management in adults receiving maintenance dialysis and those with earlier stages of CKD. Am J Kidney Dis. 2020;75(2):245–55.
52. Trainor D, Borthwick E, Ferguson A. Perioperative management of the hemodialysis patient. Semin Dial. 2011;24:314–26.
53. Yeun JY, Don BR. Surgery in the patient with renal disease. In: Lubin MF, Smith RB, Dodson TF, Spell NO, Walker HK, editors. Medical management of the surgical patient: a textbook of perioperative medicine. Cambridge University Press; 2006. p. 327–52.
54. Auguste BL, Bargman JM. Peritoneal dialysis prescription and adequacy in clinical practice: core curriculum 2023. Am J Kidney Dis. 2023;81(1):100–9.
55. Napalkov P, Felici DM, Chu LK, et al. Incidence of catheter-related complications in patients with central venous or hemodialysis catheters: a health care claims database analysis. BMC Cardiovasc Disord. 2013;13:86.

56. Lew SQ. Peritoneal dialysis immediately after abdominal surgery. Perit Dial Int. 2018;38(1):5–8.
57. Zhang Y, Feng S, Lu Y, et al. Efficacy of APD in perioperative period of non-abdominal operation for peritoneal dialysis patients. Int J Gen Med. 2019;12:207–12.
58. Imam TH. Non-catheter related abdominal surgeries in patients on peritoneal dialysis. J Clin Nephrol Res. 2014;1(1):1005.
59. Kleinpeter MA, Krane NK. Perioperative management of peritoneal dialysis patients: review of abdominal surgery. Adv Perit Dial. 2006;22:119–23.



Anesthetic Considerations: Postoperative Care and Complications

2

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2.1 Monitoring and Management of Anesthesia in Uremic Patients with a Focus on Management of Fluid and Electrolyte Imbalance

Anesthesia management in uremic patients presents distinct challenges, primarily due to the fluid and electrolyte imbalances that are common in these individuals. Renal dysfunction in these patients impairs the kidneys' ability to eliminate waste products and regulate key electrolytes, leading to problems such as hyperkalemia, metabolic acidosis, and sodium disturbances, all of which can compromise cardiovascular and metabolic stability [1]. These conditions increase the likelihood of severe complications during surgery, so careful anesthesia management is essential. A critical aspect is assessing and correcting fluid and electrolyte imbalances. Uremic patients often experience fluid overload, which can result in pulmonary edema and hemodynamic instability or dehydration, particularly if they have undergone recent dialysis or have difficulty maintaining proper fluid intake [2]. Thus, fluid management must be carefully balanced, with continuous monitoring of central venous pressure (CVP), urine output, and blood pressure to avoid both fluid excess and deficits [2].

Electrolyte disturbances also require significant attention. Hyperkalemia, in particular, increases the risk of life-threatening arrhythmias, such as ventricular fibrillation. This condition must be corrected prior to surgery through interventions such as administering sodium bicarbonate, calcium gluconate, or a combination of insulin and glucose [3]. Similarly, metabolic acidosis must be addressed promptly as it can interfere with the effectiveness of anesthetic agents [4]. Sodium balance must

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also be carefully monitored since both hyponatremia and hypernatremia can lead to neurological complications such as seizures and confusion [4]. Furthermore, anesthetic agents must be chosen carefully, considering their renal metabolism. Drugs that are primarily eliminated through the kidneys, such as succinylcholine, should be used cautiously, while volatile anesthetics like sevoflurane are often preferred as they do not rely on renal clearance [5].

Preoperative dialysis is another important aspect of managing uremic patients. Hemodialysis, performed ideally within 24 hours before surgery, helps remove uremic toxins and correct fluid and electrolyte imbalances [4]. However, the timing of dialysis must be carefully considered, as dialysis too close to the procedure may lead to intraoperative hypotension, while insufficient dialysis might not effectively correct metabolic abnormalities. In certain cases, intraoperative dialysis may be required if problems such as fluid imbalance or persistent acidosis arise especially in patients undergoing cardiopulmonary bypass [6]. During surgery, continuous monitoring of fluid and electrolyte status is essential. Invasive monitoring tools, such as arterial lines for continuous blood pressure measurement and central venous catheters for fluid management, may be necessary for more accurate assessment of the patient's condition [4]. Postoperatively, the management of fluid and electrolyte balance remains a priority. Careful tracking of fluid intake and output is essential to avoid both overhydration and dehydration. Hyperkalemia and calcium disturbances are common complications that require continuous monitoring, and pain management must be adjusted for renal function as many analgesic medications, such as morphine, are renally cleared and can accumulate, leading to toxicity. Alternative pain management strategies, including regional anesthesia, may offer a safer option for these patients [7, 8].

In conclusion, managing anesthesia in uremic patients requires a multidisciplinary approach with a detailed focus on fluid, electrolyte, and anesthetic drug management. With careful planning and vigilant monitoring, safe and effective care can be provided for these high-risk patients.

2.2 Effects of Uremia on Drug Metabolism and Pharmacokinetics

Uremia significantly affects the metabolism and pharmacokinetics of anesthetic drugs due to impaired kidney function, leading to the accumulation of waste products in the bloodstream. The kidneys are essential for the elimination of many drugs, including anesthetics, and when their function is compromised in patients with uremia, the pharmacokinetic characteristics of these drugs are altered [9]. These changes can result in the accumulation of anesthetic agents in the body, raising the risk of both toxicity and insufficient drug effects, which makes it crucial to adjust dosages and carefully monitor patients throughout the perioperative period [10].

One of the most notable impacts of uremia is on drug metabolism. While the liver is primarily responsible for metabolizing many anesthetic drugs through

enzymes like cytochrome P450 (CYP450), the accumulation of uremic toxins such as urea and creatinine can inhibit the function of these enzymes, slowing the breakdown of certain medications [11]. As a result, drugs such as propofol, which are primarily metabolized by the liver, may have prolonged effects in uremic patients, leading to prolonged sedation and potential cardiovascular instability; it is recommended to start with a lower dose [12].

The distribution of anesthetic drugs is also affected in uremic patients. Renal failure often causes a drop in plasma protein levels, particularly albumin. Many anesthetic drugs, such as opioids and benzodiazepines, rely on protein binding to circulate in the bloodstream. When albumin levels are reduced, a greater proportion of the drug remains in its free form, increasing its pharmacological activity. This leads to heightened drug effects and an increased risk of adverse reactions, such as respiratory depression or excessive sedation. Furthermore, changes in fluid distribution due to edema or altered body composition in uremic patients can alter the volume of distribution of certain anesthetics, potentially requiring further adjustments in drug dosing [13].

The elimination of anesthetic drugs is heavily influenced by renal function, and this is particularly problematic in uremic patients. Since the kidneys are responsible for excreting many drugs, a decrease in glomerular filtration rate (GFR) results in slower clearance and accumulation of drugs like morphine [14] and certain muscle relaxants [15] that are primarily eliminated through renal pathways. As these drugs accumulate, their effects may be prolonged, leading to extended sedation and respiratory depression. In cases of severe renal impairment, the active metabolites of drugs, such as morphine-6-glucuronide, may accumulate and increase the risk of adverse effects [14]. For these reasons, anesthetic drugs that are predominantly renally cleared may require significant dose reductions or substitution with alternatives that are metabolized by the liver.

Additionally, uremia can alter the pharmacodynamic response to anesthetic agents. The accumulation of uremic toxins can make the central nervous system more sensitive to the depressant effects of anesthetic agents, increasing the likelihood of complications like excessive sedation, hypotension, or respiratory depression [16]. This heightened sensitivity is particularly significant when using drugs like opioids or benzodiazepines. The response to muscle relaxants may also be altered, as uremic patients may exhibit increased sensitivity at the neuromuscular junction, leading to prolonged paralysis if standard doses are used [15]. Succinylcholine can increase serum potassium and is contraindicated in hyperkalemic patients; however, it can safely be used following dialysis [17, 18].

Regional anesthesia techniques may offer an alternative in uremic patients, as these approaches typically use lower doses of anesthetic agents, reducing the overall impact on the body's metabolism and pharmacokinetics. However, these techniques come with their own set of risks and need to be carefully considered based on the patient's overall condition and coagulation function [10].

Close monitoring of vital signs, drug effects, and metabolic status is crucial. Preoperative hemodialysis or peritoneal dialysis may help reduce the accumulation of uremic toxins and improve drug clearance, thereby facilitating safer anesthesia management [19].

In conclusion, uremia alters the way anesthetic drugs are absorbed, distributed, metabolized, and eliminated, making it essential to adjust the approach to anesthesia in these patients.

2.3 Strategies for Intraoperative Monitoring

Intraoperative monitoring plays a critical role in ensuring the safety and stability of patients undergoing surgery, particularly those with complex comorbidities such as uremia, cardiovascular disease, or respiratory dysfunction. The strategies employed during intraoperative monitoring vary depending on the patient's underlying medical conditions, the type of surgery, and the anesthetic techniques used. For patients with uremia or renal dysfunction, intraoperative monitoring becomes even more crucial due to the potential for fluid and electrolyte imbalances, metabolic disturbances, and the altered pharmacokinetics of anesthetic and other drugs [20].

A cornerstone of intraoperative monitoring is continuous cardiovascular monitoring. This includes measurement of heart rate, blood pressure, and electrocardiographic (ECG) monitoring, which are essential for detecting changes in hemodynamics during the perioperative period. For patients with renal failure or uremia, it is particularly important to closely monitor blood pressure to avoid both hypertension and hypotension, as these extremes can lead to renal hypoperfusion, exacerbating kidney injury. Blood pressure should be maintained within a target range to ensure adequate perfusion to vital organs, including the kidneys [4]. Additionally, continuous ECG monitoring helps detect arrhythmia, which is more common in uremic patients due to electrolyte imbalances, especially hyperkalemia [4, 21]. Abnormal rhythms such as ventricular arrhythmias can occur rapidly, requiring immediate intervention to prevent more severe cardiac events [4].

Invasive techniques, such as the use of an arterial line, allow for continuous measurement of blood pressure and provide easy access to arterial blood sampling for laboratory analysis. For example, in patients with severe renal dysfunction, an arterial line can facilitate frequent monitoring of arterial blood gases and electrolytes, particularly potassium, calcium, and bicarbonate, all of which may fluctuate during surgery. This continuous blood pressure monitoring is also critical for assessing fluid status and guiding fluid therapy, which is especially important in uremic patients who are at risk for both volume overload and dehydration [21].

Another key parameter to monitor in uremic patients is urine output, which can serve as an indicator of renal function during the intraoperative period. Monitoring urine output is particularly vital in patients with renal impairment or those undergoing nephrectomies, major abdominal surgeries, or vascular surgeries [22]. A decrease in urine output, particularly if it falls below 0.5 mL/kg/h, may signal worsening renal function or hemodynamic instability, such as inadequate perfusion or shock [22]. This could indicate the need for interventions such as fluid resuscitation, adjustments in anesthetic agents, or the initiation of renal replacement therapy, including hemodialysis if necessary.

In addition to cardiovascular and renal monitoring, assessment of respiratory function is equally critical during surgery. This involves monitoring the patient's oxygen saturation (SpO_2), end-tidal carbon dioxide ($ETCO_2$), and respiratory rate to ensure adequate ventilation and gas exchange. In uremic patients, respiratory function may be compromised due to fluid retention, non-cardiogenic pulmonary edema, or the effects of anesthetic agents [4]. The use of a pulse oximeter and capnography provides real-time data on oxygenation and ventilation, which is crucial for detecting early signs of respiratory distress or failure.

One of the key challenges in uremic patients is managing their fluid and electrolyte balance intraoperatively. Monitoring fluid balance should be meticulous as patients with renal dysfunction are prone to both dehydration and fluid overload. In addition to urine output, other strategies include monitoring the CVP or using a pulmonary artery catheter to assess intravascular volume status.

Continuous invasive monitoring of core body temperature can help detect hypothermia or hyperthermia, which can be common in uremic patients undergoing surgery due to changes in thermoregulation or fluid shifts. Temperature regulation is particularly important in these patients, as either extreme can have a detrimental effect on kidney function [23] and anesthetic drug metabolism [24].

In summary, intraoperative monitoring is a fundamental aspect of anesthesia management in all patients, but it is especially critical in those with uremia or renal dysfunction due to their altered pharmacokinetics, fluid and electrolyte imbalances, and the potential for hemodynamic instability. Comprehensive monitoring strategies, including continuous cardiovascular monitoring, urine output measurement, fluid balance assessment, and electrolyte monitoring, allow for early detection of complications and timely interventions. The use of advanced monitoring technologies, combined with a tailored approach to anesthesia and fluid management, can help optimize patient outcomes and reduce the risks associated with surgery in this high-risk population. Close collaboration with the surgical team and nephrologists ensures that the patient's overall management remains coordinated, and that intraoperative care is optimized for their specific needs.

2.4 Monitoring and Management of Postoperative Complications Specific to Uremic Patients

Patients with end-stage renal disease (ESRD) are exposed to a greater risk of postoperative morbidity and mortality. Chronic kidney disease within the non-surgical setting is a long-time unbiased predictor of mortality [25–27], but it is also an independent risk factor for postoperative mortality and morbidity [28, 29]. Uremic patients, whose kidneys struggle to eliminate metabolic waste and regulate fluid and electrolyte levels, are at a higher risk for complications after surgery. Uremic patients often have a complicated medical history including several comorbidities. These conditions can influence post-operative recovery and heighten the risk of

adverse events [30, 31]. Therefore, meticulous perioperative planning, close monitoring, and customized interventions are essential to managing these patients effectively during the postoperative period.

2.5 Key Postoperative Complications in Uremic Patients

2.5.1 Electrolyte Imbalance

Hyperkalemia is a complication that can occur in uremic patients after surgery. As kidney function declines, the body's ability to eliminate potassium decreases, making even small changes in potassium levels potentially life-threatening due to the risk of arrhythmias. Factors such as drugs (like non-steroidal anti-inflammatory drugs [NSAIDs] and angiotensin converting enzyme [ACE] inhibitors) [32], fluid shifts or insufficient dialysis can increase the likelihood of hyperkalemia [33]. It is crucial to monitor serum potassium levels frequently. If hyperkalemia is identified, prompt actions such as administering sodium bicarbonate, calcium gluconate, or insulin with glucose should be taken. In more severe instances, hemodialysis may be necessary.

2.5.2 Cardiovascular Complications

Cardiovascular events, inclusive of arrhythmias, myocardial infarction, and congestive heart failure, pose major postoperative risks for uremic patients [34, 35]. Uremic toxins produce endothelial dysfunction, increased vascular stiffness, and dyslipidemia, all of which heighten the risk of cardiovascular events. It is critical to monitor cardiac rhythm and conduct frequent ECGs during the immediate postoperative period. Additionally, careful monitoring of blood pressure is vital, as both hypotension and severe hypertension can trigger cardiovascular events. Blood pressure should be monitored regularly, aiming for a target value of less than 140/90 mmHg. If high blood pressure is identified, antihypertensive medications which include calcium channel blockers, beta-blockers, and ACE inhibitors or angiotensin receptor blockers should be considered based on the patient's individual circumstances. Diuretics also can be useful in dealing with fluid overload.

Patients with renal failure are at a heightened risk of arrhythmias consequent to electrolyte imbalances (especially hyperkalemia and hypocalcemia). Postoperative arrhythmias can range from benign atrial fibrillation to potentially life-threatening ventricular arrhythmias. Continuous ECG monitoring is crucial for the early detection of arrhythmia.

Uremic patients have a notably higher risk of coronary artery disease because of factors such as atherosclerosis, vascular calcification, and other contributing elements. During the postoperative period, surgical stress, fluid shifts, and

inflammation can trigger an acute coronary event. For patients suspected of developing acute coronary syndrome, immediate evaluation with an ECG and cardiac biomarkers is essential. Treatment may involve aspirin, nitroglycerin, and heparin, along with angiography if necessary, and postoperative care may also include revascularization procedures.

2.5.3 Infections

Patients with uremia are particularly vulnerable to infections [36] due to changes in immune function [37], such as reduced neutrophil activity, and a higher probability of having diabetes. The most common infections include surgical site infections (SSIs), pneumonia, urinary tract infections, and sepsis. Prophylactic antibiotics should be given based on the type of surgical procedure and the patient's kidney function. If any sign of infection arises, postoperative cultures should be obtained without delay. Additionally, all indwelling catheters, including those used for dialysis, need to be carefully monitored for signs of infection, and appropriate antimicrobial treatment should be adjusted based on culture findings.

2.6 Strategies for Preventing and Managing Surgical Site Infections, Fluid Overload and Electrolyte Disturbances

SSIs are a significant cause of complications and death after surgery for all patients [38], but they pose an even greater risk for patients with CKD and ESRD [39]. Renal failure impacts immune function, making patients more susceptible to infections. Factors like uremic toxins, fluid imbalances and reduced metabolic responses can further slow recovery and heighten the risk of infections on the surgical site [19, 40]. To efficaciously manage infections a comprehensive strategy is essential, involving preoperative optimization, cautious intraoperative techniques, and attentive postoperative care.

A thorough preoperative evaluation is crucial for identifying modifiable risk factors for SSIs in patients with renal failure. Key issues include:

- Optimization of dialysis. For patients undergoing dialysis, it is important to schedule the procedure appropriately around the time of surgery. Ideally, hemodialysis ought to take place the day before the operation [41] to eliminate excess uremic toxins, correct electrolyte imbalances, and optimize fluid status [42]. Dialysis on the day of surgery can increase the danger of hypotension and hypoperfusion during the procedure, so it should be avoided unless necessary.
- Correction of anemia. Anemia is often present in patients with renal failure. It is important to deal with anemia before surgery, either using erythropoiesis-stimulating agents (ESAs) or iron supplementation to enhance oxygen delivery to tissues and promote better wound healing [43].

- Nutritional support. Inadequate nutritional status can hinder wound healing and heighten the risk of infection [44]. Patients' nutritional requirements should be evaluated.
- Glycemic control. In diabetic patients, maintaining tight control of glucose levels before and after surgery is essential to reduce the risk of infection. Elevated blood sugar levels can impair neutrophil function and increase the likelihood of wound infections. Preoperative blood glucose levels should be optimized, and careful monitoring should continue throughout the recovery period [45].

Prophylactic antibiotics play a crucial role in preventing SSIs, but their management should be customized for patients with renal failure. The selection of antibiotics should reflect the predicted pathogens associated with the specific surgical procedure. Dosing may need to be adjusted based on renal function, as some antibiotics are excreted through the kidneys. It is important to administer prophylactic antibiotics within 60 minutes before the incision to achieve sufficient tissue levels during surgery [46, 47]. For patients on dialysis, antibiotics should be given after the dialysis session to avoid being removed by the dialysis process.

Minimizing the duration of the procedure helps reduce exposure to potential pathogens. It is important to take care to minimize tissue injury during surgery, as excessive dissection and retraction can disrupt blood flow and heighten the risk of infection.

Attention to fluid management during surgery is vital. Overhydration should be avoided to prevent tissue edema and an increased risk of infection, while dehydration can negatively impact renal function.

Using appropriate surgical techniques for wound closure is essential to prevent infection. Whenever possible, subcuticular closure should be employed to reduce the risk of contamination at the skin surface [48].

Patients with renal failure need careful monitoring for early signs of SSIs. This includes daily wound inspection: the surgical site should be checked daily for any signs of infection. Fever, rapid heart rate, and low blood pressure can be early indicators of systemic infection or sepsis. If there is any suspicion of infection, it is important to promptly obtain cultures from the wound and blood to identify the organism responsible.

In the event of a SSI, prompt management is essential to avoid further complications [49]. The choice of antibiotics should be based on culture results. For patients with renal failure, it is important to adjust doses according to renal function and to avoid nephrotoxic antibiotics whenever possible. Wounds must be kept clean and dry, and in some instances debridement of necrotic tissue may be necessary.

Uremia is linked to a disrupted fluid balance, and the changes in fluid status that occur postoperatively as a result of anesthesia and surgical stress can exacerbate this problem, increasing the risk of cardiovascular and pulmonary complications. In uremic patients, fluid overload can result in complications such as pulmonary edema, heart failure, and potentially fatal outcomes. It is of primary importance to monitor fluid status: keeping a close eye on urine output is crucial for the early identification of fluid retention. If there is insufficient diuresis, diuretics or dialysis

should be considered. It is essential to closely monitor patients for signs of fluid overload, such as weight gain, breathing difficulties, and rising blood pressure. Regularly measuring body weight is a simple yet effective method for monitoring changes in fluid status. Additionally, invasive monitoring techniques, such as CVP, along with non-invasive tools like point-of-care ultrasound, can effectively guide fluid therapy [50].

It is crucial to cautiously manage intravenous fluid administration to prevent fluid overload during and after surgery. A restrictive fluid approach, where the patient receives just enough fluids to maintain stable blood pressure, with a preference for balanced crystalloids, is the best practice [51]. For patients who still have some kidney function, diuretics like furosemide can help control mild fluid overload. However, it is important to be careful to avoid excessive diuresis and any electrolyte imbalances [52]. When fluid retention is significant or does not respond to diuretics, dialysis may be necessary [53]. It is essential to closely monitor patients for signs of fluid overload, such as weight gain, breathing difficulties, and rising blood pressure, adjusting fluid management as needed.

Electrolyte homeostasis is a significant concern for uremic patients, especially those undergoing surgery, as impaired kidney function can result in imbalances in sodium, potassium, calcium, and acid-base levels. Due to the high risk of complications associated with electrolyte disturbances, a well-planned approach to perioperative management is crucial [54].

Uremic patients face electrolyte imbalances stemming from decreased kidney function, which can lead to problems such as hyperkalemia, hyponatremia, hypocalcemia, hyperphosphatemia, and metabolic acidosis. The kidneys' inability to eliminate potassium and phosphate, along with a disrupted calcium balance, plays a role in neuromuscular and cardiovascular dysfunction [55]. Due to the significant risks associated with these disturbances, a well-planned approach to perioperative care is of primary importance:

- During the preoperative period, ensuring that patients receive adequate dialysis sessions before surgery can help address problems such as hyperkalemia, hyperphosphatemia, and metabolic acidosis. Adjusting levels of electrolytes before surgery can help minimize the chances of complications during the procedure.
- During the intraoperative period, consistent monitoring of electrolyte levels, including sodium, potassium, calcium, magnesium, and phosphate, can inform necessary preoperative actions. It is recommended to undertake frequent electrolyte monitoring. Continuous invasive hemodynamic monitoring is recommended for unstable patients. Point-of-care blood gas analysis alongside regular laboratory tests allows for the identification and correction of electrolyte imbalances. Implementing balanced crystalloids, careful sodium administration, and strategies for calcium correction can help minimize disturbances.
- During the postoperative period, regular assessments of serum electrolytes and acid-base balance are essential, particularly during the first 48 hours after surgery. Avoiding potassium-rich fluids, using potassium-binding agents, and possibly administering glucose-insulin infusions can aid in preventing hyperkalemia.

Potassium-binding resins, sodium bicarbonate for metabolic acidosis, and calcium supplementation for hypocalcemia should be tailored to meet the individual patient's needs. Early postoperative dialysis should be considered for patients facing ongoing hyperkalemia, acidosis, or significant electrolyte disturbances.

2.7 Postoperative Pain Management

Effective management of postoperative pain is crucial in surgical care as it enhances patient comfort, encourages early movement, and helps prevent complications after surgery. In patients with uremia, however, managing pain becomes more challenging due to reduced kidney function, metabolic imbalances, and a higher likelihood of drug toxicity. Therefore, it is vital to choose analgesic medications carefully and employ a multimodal approach to pain management to achieve optimal outcomes while minimizing potential side effects.

Uremia triggers a series of physiological changes that influence how pain is perceived and how effectively analgesics work:

- Altered drug metabolism. With reduced renal clearance, there is a prolonged half-life and accumulation of drugs that are typically excreted by the kidneys.
- Neuropathy and hyperalgesia. Uremic neuropathy and central sensitization can heighten pain perception, making management more challenging.
- Platelet dysfunction. An increased risk of bleeding impacts the selection of analgesic medications.

The use of NSAIDs for managing postoperative pain in patients with renal dysfunction is generally avoided. NSAIDs can lead to further deterioration of kidney function with consequent fluid retention and imbalances in electrolytes. Furthermore, there is an increased risk of bleeding associated with NSAID use, particularly in patients who may have platelet dysfunction as a result of uremia. Uremic patients are more susceptible to gastrointestinal complications, which can be aggravated by NSAIDs. If NSAIDs are deemed necessary, it is advisable to use lower doses and select those with minimal renal impact, such as ibuprofen or naproxen.

Due to these risks, non-opioid analgesics like acetaminophen or weak opioids are often preferred. Opioids are frequently utilized for postoperative pain relief but necessitate careful adjustments in dosing for patients with uremia. Preferred agents are fentanyl and methadone due to their minimal renal excretion. Morphine and codeine should be avoided as they can lead to the accumulation of toxic metabolites. Strategies that minimize opioid use are commonly implemented in uremic patients to prevent complications such as respiratory depression or sedation. Regional and multimodal analgesia are essential strategies for optimizing pain control while minimizing systemic opioid exposure. Epidural anesthesia provides effective pain relief for major surgeries. However, due to the increased risk of bleeding in uremic patients, careful monitoring of coagulation status and individualized risk assessment are necessary before proceeding with this

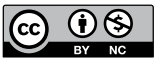
technique. Peripheral nerve blocks provide targeted pain relief with reduced systemic side effects. Continuous peripheral nerve catheters may be used postoperatively for prolonged analgesia, minimizing the need for systemic opioids. Continuous wound infiltration with local anesthetics or regional catheter-based delivery (e.g., transversus abdominis plane [TAP] blocks) can provide prolonged analgesia and reduce reliance on opioids. A multimodal approach that combines regional anesthesia, local anesthetics, and adjunct medications tailored to the individual patient's needs can significantly enhance postoperative pain control and reduce complications [56–58].

References

1. Alfrey AC. Chronic renal failure: manifestations and pathogenesis. In: Schrier RW, editor. Renal and electrolyte disorders. Boston: Little, Brown and Company; 1976. p. 319–47.
2. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol. 2016;17(1):109.
3. Bianchi S, Aucella F, De Nicola L, et al. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2019;32(4):499–516.
4. Sladen RN. Anesthetic considerations for the patient with renal failure. Anesthesiol Clin North Am. 2000;18(4):863–82.
5. Prough DS, Foreman AS. Anesthesia and the renal system. In: Barash PG, Cullen BF, Stoelting RK, editors. Clinical anesthesia. 2nd ed. Philadelphia: JB Lippincott; 1992. p. 1125–56.
6. Murkin JM, Murphy DA, Finlayson DC, Waller JL. Hemodialysis during cardiopulmonary bypass: report of twelve cases. Anesth Analg. 1987;66(9):899–901.
7. Mouquet C, Bitker MO, Bailliart O, et al. Anesthesia for creation of a forearm fistula in patients with endstage renal failure. Anesthesiology. 1989;70(6):909–14.
8. Linke CL. Anesthesia considerations for renal transplantation. Contemp Anesth Prac. 1987;10:183–231.
9. Gupta B, Gupta L. Anesthesia consideration for renal disease. ARC J Anesth. 2018;3(1):9–14.
10. Chowdhury SR, McLure HA. Chronic kidney disease and anaesthesia. BJA Educ. 2022;22(8):321–8.
11. Ladda MA, Goralski KB. The effects of CKD on cytochrome P450-mediated drug metabolism. Adv Chronic Kidney Dis. 2016;23(2):67–75.
12. Jun MR, Kim MG, Han KS, et al. Potency of propofol for inducing loss of consciousness in end-stage kidney disease patients. PLoS One. 2021;16(8):e0254520.
13. Klammt S, Wojak HJ, Mitzner A, et al. Albumin-binding capacity (ABiC) is reduced in patients with chronic kidney disease along with an accumulation of protein-bound uraemic toxins. Nephrol Dial Transplant. 2012;27(6):2377–83.
14. Odoma VA, Pitliya A, AlEdani E, et al. Opioid prescription in patients with chronic kidney disease: a systematic review of comparing safety and efficacy of opioid use in chronic kidney disease patients. Cureus. 2023;15(9):e45485.
15. Radkowski P, Krupiniewicz KJ, Suchcicki M, et al. Navigating anesthesia: muscle relaxants and reversal agents in patients with renal impairment. Med Sci Monit. 2024;30:e945141.
16. Liabeuf S, Pešić V, Spasovski G, et al. Drugs with a negative impact on cognitive function (part 1): chronic kidney disease as a risk factor. Clin Kidney J. 2023;16(12):2365–77.
17. Miller RD, Way WL, Hamilton WK, Layzer RB. Succinylcholine-induced hyperkalemia in patients with renal failure. Anesthesiology. 1972;36:138–41.
18. Powell DR, Miller R. The effect of repeated doses of succinylcholine on serum potassium in patients with renal failure. Anesth Analg. 1976;54:746.

19. Nasr R, Chilimuri S. Preoperative evaluation in patients with end-stage renal disease and chronic kidney disease. Health Serv Insights. 2017;10:1178632917713020.
20. Kanda H, Hirasaki Y, Iida T, et al. Perioperative management of patients with end-stage renal disease. J Cardiothorac Vasc Anesth. 2017;31(6):2251–67.
21. Meersch M, Schmidt C, Zarbock A. Patient with chronic renal failure undergoing surgery. Curr Opin Anaesthesiol. 2016;29(3):413–20.
22. Myles PS, McIlroy DR, Bellomo R, Wallace S. Importance of intraoperative oliguria during major abdominal surgery: findings of the restrictive versus liberal fluid therapy in major abdominal surgery trial. Br J Anaesth. 2019;122(6):726–33.
23. De Rosa S, Antonelli M, Ronco C. Hypothermia and kidney: a focus on ischaemia-reperfusion injury. Nephrol Dial Transplant. 2017;32(2):241–7.
24. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med. 2007;35(9):2196–204.
25. Culleton BF, Larson MG, Wilson PWF, et al. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int. 1999;56:2214–9.
26. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17:2034–47.
27. Weiner DE, Tighiouart H, Amin MG, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol. 2004;15:1307–15.
28. Mathew A, Devereaux PJ, O'Hare A, et al. Chronic kidney disease and postoperative mortality: a systematic review and meta-analysis. Kidney Int. 2008;73(9):1069–81.
29. Liao CC, Liu CC, Lee YW, et al. Complications and mortality after surgery in patients with chronic kidney disease: a retrospective cohort study based on a multicenter clinical database. J Multidiscip Healthc. 2024;17:3535–44.
30. Tonelli M, Wiebe N, Guthrie B, et al. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. Kidney Int. 2015;88(4):859–66.
31. Stevens LA, Li S, Wang C, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2010;55(3 Suppl 2):S23–33.
32. Rimmer JM, Horn JF, Gennari FJ. Hyperkalemia as a complication of drug therapy. Arch Intern Med. 1987;147(5):867–9.
33. Ayach T, Nappo RW, Paugh-Miller JL, Ross EA. Postoperative hyperkalemia. Eur J Intern Med. 2015;26(2):106–11.
34. Ozrazgat-Baslanti T, Thottakkara P, Huber M, et al. Acute and chronic kidney disease and cardiovascular mortality after major surgery. Ann Surg. 2016;264(6):987–96.
35. Cherng YG, Chang CC, Yeh CC, et al. Adverse outcomes after non urological surgeries in patients with chronic kidney disease: a propensity-score-matched study. Clin Epidemiol. 2019;11:707–19.
36. Minnaganti VR, Cunha BA. Infections associated with uremia and dialysis. Infect Dis Clin N Am. 2001;15:385–406.
37. Asaka M, Iida H, Izumino K, Sasayama S. Depressed natural killer cell activity in uremia. Evidence for immunosuppressive factor in uremic sera. Nephron. 1988;49(4):291–5.
38. DiPiro JT, Martindale RG, Bakst A, et al. Infection in surgical patients: effects on mortality, hospitalization, and postdischarge care. Am J Health Syst Pharm. 1998;55(8):777–81.
39. Cheung AH, Wong LM. Surgical infections in patients with chronic renal failure. Infect Dis Clin N Am. 2001;15(3):775–96.
40. Maroz N, Simman R. Wound healing in patients with impaired kidney function. J Am Coll Clin Wound Spec. 2014;5(1):2–7.
41. Nicolini F, Fragnito C, Molardi A, et al. Heart surgery in patients on chronic dialysis: is there still room for improvement in early and long-term outcome? Heart Vessel. 2011;26:46–54.
42. Kloeser R, Buser A, Bolliger D. Treatment strategies in anemic patients before cardiac surgery. J Cardiothorac Vasc Anesth. 2023;37(2):266–75.

43. Russell L. The importance of patients' nutritional status in wound healing. Br J Nurs. 2001;10(6 Suppl):S42, S44–9.
44. Patel KL. Impact of tight glucose control on postoperative infection rates and wound healing in cardiac surgery patients. J Wound Ostomy Continence Nurs. 2008;35(4):397–404.
45. Nichols RL. Use of prophylactic antibiotics in surgical practice. Am J Med. 1981;70(3):686–92.
46. Hawn MT, Richman JS, Vick CC, et al. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. JAMA Surg. 2013;148(7):649–57.
47. CDC Guidelines for the prevention and control of nosocomial infections. Guidelines for prevention of surgical wound infections, 1985. Am J Infect Control. 1986;14(2):71–82.
48. Rubin RH. Surgical wound infection: epidemiology, pathogenesis, diagnosis and management. BMC Infect Dis. 2006;6:171.
49. Lobo DN, Macafee DA, Allison SP. How perioperative fluid balance influences postoperative outcomes. Best Pract Res Clin Anaesthesiol. 2006;20(3):439–55.
50. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003;238(5):641–8.
51. Risler T, Krämer B, Müller GA. The efficacy of diuretics in acute and chronic renal failure. Focus Torasemide Drugs. 1991;41(Suppl 3):69–79.
52. Lopez T, Banerjee D. Management of fluid overload in hemodialysis patients. Kidney Int. 2021;100(6):1170–3.
53. Prough DS. Physiologic acid-base and electrolyte changes in acute and chronic renal failure patients. Anesthesiol Clin North Am. 2000;18(4):809–33. ix
54. Dhondup T, Qian Q. Electrolyte and acid-base disorders in chronic kidney disease and end-stage kidney failure. Blood Purif. 2017;43(1–3):179–88.
55. Tawfic QA, Bellingham G. Postoperative pain management in patients with chronic kidney disease. J Anaesthesiol Clin Pharmacol. 2015;31(1):6–13.
56. Muir MA, Szempruch KR, Dupuis R, et al. Utilizing multimodal analgesia to evaluate postoperative analgesic requirements in kidney transplant recipients. Clin Transpl. 2021;35:e14240.
57. Pham PC, Toscano E, Pham PM, et al. Pain management in patients with chronic kidney disease. NDT Plus. 2009;2(2):111–8.
58. Dolati S, Tarighat F, Pashazadeh F, et al. The role of opioids in pain management in elderly patients with chronic kidney disease: a review article. Anesth Pain Med. 2020;10(5):e105754.



Dialysis Access Surgery

3

Massimo Del Gaudio, Chiara Bonatti, Francesca Rizzo, and Matteo Ravaioli

3.1 Direct Arteriovenous Fistulas

Clinical and imaging assessments are essential for selecting the appropriate vascular access (VA) type, surgical approach, and monitoring complications early [1]. Arteriovenous fistulas (AVF) can alter blood flow, pulmonary pressure, and cardiac output, particularly when flow rates exceed 2000 mL/min. The preferred diagnostic tool for VA planning is duplex ultrasound, which evaluates arterial and venous diameters. A vein diameter of >2 mm and an artery diameter of >1.6 mm are considered optimal for AVF maturation [2]. According to the National Kidney Foundation (NKF-K/DOQI) guidelines [3], the preferred AVF locations are the forearm (radiocephalic AVF), elbow (brachiocephalic AVF), and upper arm (brachiobasilic AVF with transposition). The wrist AVF is the gold standard due to its simplicity, low complication rate, and long-term viability [4].

Various anastomotic configurations exist, with the vein side-to-end anastomosis being the most common. Proximal AVFs provide a larger caliber for venous cannulation and improved patency rates but are associated with higher complication risks, including steal syndrome and cardiac alterations. The brachiobasilic AVF necessitates additional surgical intervention to superficialize the vein for cannulation [5]. Before use, AVFs require a maturation period to allow venous structural changes due to increased flow turbulence. An AVF is considered functional when flow exceeds 600 mL/min, the vein diameter reaches 0.6 cm, and the depth remains below 0.6 cm^3. Maturation typically takes 1–3 months post-surgery. AVF failure is

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often due to arterial or venous stenosis, which can be treated via endovascular or surgical interventions. With an increasing number of dialysis patients aged 75 and older, the presence of multiple comorbidities, particularly cardiovascular diseases, presents additional challenges [6].

3.2 Prosthetic Arteriovenous Fistulas

A prosthetic arteriovenous fistula (PAF) involves connecting an artery and vein using a prosthetic conduit, serving two primary purposes: bridging vessels that are otherwise too distant for direct anastomosis [7] and providing a robust segment for hemodialysis (HD) catheter insertion. PAFs are a secondary option after native AVFs [8] but may be the first choice in patients with insufficient native vessels, obesity, or fragile vasculature [9]. Prosthetic AV grafts (AVPs) can be biological (homologous vein allografts, cryopreserved veins, bovine grafts) or synthetic (Dacron, PTFE). Biological grafts, while effective, are costly and limited in availability.

PAFs have a shorter functional lifespan due to thrombosis from venous stenosis and neointimal hyperplasia. Thrombosis risk increases with reduced blood flow, hypotension, and excessive compression post-dialysis. Infection is a major concern, with AVP-related bacteremia occurring at rates significantly higher than AVFs [10]. Treatment involves intravenous antibiotics and, in severe cases, complete graft removal [11]. Pseudoaneurysms may require surgical intervention if they enlarge significantly or if overlying skin integrity is compromised. Ischemic complications are more frequent in PAFs than AVFs. Endovascular stent grafts offer a minimally invasive solution for complex cases, preserving access function and reducing the need for central catheters [12].

3.3 Venous Catheters

Non-tunneled central venous catheters (CVCs) are suitable for urgent HD initiation or when permanent access is not available. Preferred insertion sites include the internal jugular and femoral veins, with the subclavian vein as a last resort. Ultrasound guidance enhances placement accuracy and reduces complications such as vascular injury, hematoma, air embolism, pneumothorax, and catheter malposition. Complication rates range from 5% to 19% [13], with the highest risk being associated with subclavian vein access due to its proximity to the pleura [14].

Tunneled CVCs, designed for long-term use, incorporate a subcutaneous cuff to prevent bacterial migration and infection. While these catheters provide a durable option for patients ineligible for AVF or PAF placement, their use requires careful management to minimize infection and thrombosis risks.

3.4 Peritoneal Catheters

Peritoneal dialysis (PD) is an established treatment for end-stage renal disease (ESRD), facilitated by the development of permanent silicone-rubber catheters with Dacron cuffs [15]. The introduction of continuous ambulatory peritoneal dialysis (CAPD) has provided a simple, cost-effective alternative to in-hospital HD [16]. CAPD involves instilling dialysate into the peritoneal cavity via a closed system and draining it after several hours. It is more affordable than HD and enables home-based therapy.

Despite advances in delivery systems, peritonitis remains a significant risk, often necessitating a transition to HD [17]. Surgical placement of PD catheters via mini-laparotomy or laparoscopy ensures proper positioning within the peritoneal cavity [18]. Laparoscopic techniques allow for direct visualization, reducing complications associated with blind placement. Once implanted, the catheter is tunneled subcutaneously to its exit site, ensuring functional integrity and minimizing infection risks.

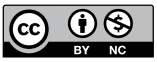
3.5 Conclusions

The choice of dialysis access method depends on individual patient factors, including vascular condition, anticipated treatment duration, and risk of complications. While AVFs remain the gold standard, alternative options such as PAFs and CVCs provide viable solutions for specific patient populations. Advances in surgical techniques and infection control continue to enhance the longevity and functionality of dialysis access, improving overall patient outcomes.

References

1. Brescia MJ, Cimino JE, Appel K, et al. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. N Engl J Med. 1966;275(20):1089–92.
2. Mendes RR, Farber MA, Marston WA, et al. Prediction of wrist arteriovenous fistula maturation with preoperative vein mapping with ultrasonography. J Vasc Surg. 2002;36(3):460–3.
3. National Kidney Foundation. 2006 Updates Clinical Practice Guidelines and Recommendations [Internet]. National Kidney Foundation; 2006 [cited 2025 Jan 15]. Available from: https://www.kidney.org/sites/default/files/docs/12-50-0210_jag_dcp_guidelines-va_oct06_sectionc_ofc.pdf
4. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. Am J Kidney Dis. 2006;48 Suppl 1:S176–247.
5. Korkut AK, Kosem M. Superficialization of the basilic vein technique in brachiobasilic arteriovenous fistula: surgical experience of 350 cases during 4 years period. Ann Vasc Surg. 2010;24(6):762–7.
6. US Renal Data System, USRDS 2005 Annual Data Report. Atlas of end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda; 2005.
7. Polo JR, Vazquez R, Polo J, et al. Brachiocephalic jump graft fistula: an alternative for dialysis use of elbow crease veins. Am J Kidney Dis. 1999;33(5):904–9.

8. Stehman-Breen CO, Sherrard DJ, et al. Determinants of type and timing of initial permanent hemodialysis vascular access. Kidney Int. 2000;57(2):639–45.
9. Davidson I, Gallieni M, Saxena R, et al. A patient centered decision making dialysis access algorithm. J Vasc Access. 2007;8:59–68.
10. Taylor G, Gravel D, Johnston L, et al. Prospective surveillance for primary bloodstream infections occurring in Canadian hemodialysis units. Infect Control Hosp Epidemiol. 2002;23:716–20.
11. Ryan SV, Calligaro KD, Scharff J, et al. Management of infected prosthetic dialysis arteriovenous grafts. J Vasc Surg. 2004;39:73–8.
12. Shah AS, Valdes J, Charlton-Ouw KM, et al. Endovascular treatment of hemodialysis access pseudoaneurysms. J Vasc Surg. 2012;55:1058–62.
13. McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med. 2003;348(12):1123–33.
14. Lamperti M, Bodenham AR, Pittiruti M, et al. International evidence-based recommendations on ultrasound-guided vascular access. Intensive Care Med. 2012;38(7):1105–17.
15. Tenckhoff H, Blagg CR, Curtis KF, Hickman RO. Chronic peritoneal dialysis. Proc Eur Dial Transplant Assoc. 1973;10:363–71.
16. Popovich RP, Moncrief JW, Decherd JF, et al. The definition of a novel portable/wearable equilibrium dialysis technique. Trans Am Soc Artif Intern Organs. 1976;5:64. (abstract).
17. Gokal R. CAPD overview. Perit Dial Int. 1996;16 Suppl 1:S13–8.
18. Chow KM, Szeto CC, Leung CB, et al. Tenckhoff catheter insertion by nephrologists: open dissection technique. Perit Dial Int. 2010;30(5):524–7.



Common General Surgical Procedures: Wall Defects in Kidney Transplant Patients

4

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4.1 Introduction

Incisional hernia (IH) occurring in the early postoperative period correlates with inadequate fascia closure or imperfect surgical technique, whereas late postoperative onset of IH relates to disorganization of the extracellular matrix (ECM) and altered equilibrium between collagen synthesis and breakdown [1]. Alterations in tissue architecture, fibroblast morphology and ECM organization are reported in hernia fascial and sack tissue harvested form IH, and compared with normal fascia tissue [2]. The adverse effects of uremia on fibroblast proliferation, hydroxyproline level and collagen production in wounds were identified in the 1960s and 1970s [3]. Moreover, renal replacement therapy predisposes patients to significant protein loss: hemodialysis patients lose 6– 8 grams of amino acids per procedure, while peritoneal dialysis patients lose 8- 20 grams of proteins per day from the peritoneal cavity, leading to a negative impact on wound healing [3]. Heller et al. reported on the results of a study on 251 patients who underwent elective abdominal surgery, identifying chronic kidney disease (CKD) as an independent risk factor for IH development (odds ratio [OR] 2.8) and impaired wound healing (OR 2.3). In multivariate analyses, CKD proved to be an independent risk factor for the development of IH with an OR similar to obesity [4].

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4.2 Hernia and Incisional Hernia: Technique and Optimization Strategies in Perioperative Care to Minimize Complications

IH is defined as any abdominal wall gap, with or without a bulge in the area of a postoperative scar, perceptible or palpable on clinical examination or radiologic imaging; it is a frequent surgical problem resulting from the loss of integrity of the abdominal wall at the site of a previous surgical incision [5]. The incidence of IH for transverse or oblique laparotomy in the general population is up to 4% [5]. The reported incidence of IH after kidney transplantation (KTx) is 1.6% to 18% [6].

In the non-transplanted population, risk factors for IH are: a high body mass index (BMI), older age, diabetes mellitus, and surgical factors [5, 7]. Surgical site infection plays a prominent role in the development of IH [8]. Several studies have identified multiple different risk factors for developing IH after KTx. These belong either to donor or to recipient factors: deceased donor graft, lymphocele, reoperation, smoking and female sex, immunosuppression, and delayed graft function [5, 9].

After KTx, patients receive immunosuppressive medications with impairment of wound healing. Corticosteroids have an important role in impeding wound healing, especially when used at high doses to contrast acute rejection [8]. The most commonly used drugs in transplanted patients are steroids associated with mycophenolic acid as well as mammalian target of rapamycin (mTOR) inhibitors, which have an antiproliferative effect and impair fibroblast growth. All these drugs interfere with the production of vascular endothelial growth factor and impede local angiogenesis and tissue repair mechanisms [10].

The negative effect of immunosuppression can contribute to the high incidence of surgical site infection [8]. A recent study by Druinka et al. found delayed graft function and wound infection to be strong predictors of IH on univariate analysis [8].

Repair of IH in KTx recipients requires a complex surgical procedure owing to the alteration of the native tissue layers caused by previous surgeries and the unconventional non-midline incision used in the KTx. There is no consensus on the best therapeutic strategy for transplanted patients with IH: conservative treatments such as weight loss and abdominal binder for patients not suitable for surgery can be considered an alternative therapeutic option to surgery; surgical repair is required in 52–71% of patients affected by IH with a recurrence rate of 4–33% [11]. Surgery is associated with better patient survival compared to patients who undergo conservative treatment. Many surgical procedures have been proposed for IH repair after KTx. The most commonly used procedures are primary suture and the use of synthetic or biological mesh, either with open or with laparoscopic technique. Literature data demonstrate that hernia repair with prosthetics is associated with a significant reduction in recurrence compared with primary closure alone [12, 13]. An increased risk of recurrence is associated with male sex, primary repair, tacrolimus and sirolimus use, smoking history, and diabetes [8].

To prevent IH, the use of a prophylactic mesh on abdominal wall closure has been proposed but it is still controversial owing to the increased risk of mesh infection and because it could complicate exploration of the iliac fossa if there are

surgical complications after the transplant [9]. There is no reported evidence that the closure method (single-layer closure vs layered fascial closure) can play a central role in predicting the rate of IH formation. By contrast, the type of incision may play a role in the prevention of IH [9].

Studies have demonstrated that an oblique Rutherford-Morrison incision has a better outcome in terms of IH incidence compared to a paramedian hockey-stick incision, which is associated with a higher rate of IH [14–16]. A full understanding of the anatomic layers involved in this wall defect is mandatory before proceeding to hernia repair. The presence of the graft itself, the proximity to the inguinal area and iliac bones could make it difficult to fix the mesh and increase the complexity of the repair [10].

In most cases, the muscular layers of the lateral abdominal wall are retracted and the wall defect can be diagnosed along the inguinal ligament: the internal oblique and transversus abdominus muscles are retracted laterally and caudally. A careful dissection of the external oblique muscle is needed to expose the fascia and to prepare for mesh placement. If the transversus abdominus and the internal oblique muscles cannot be reapproximated, the external oblique must be used as the primary fascia to cover the mesh.

The use of biological mesh is associated with a lower risk of recurrence compared with IH repair without a mesh or with synthetic mesh, thanks to a better integration into the abdominal wall that minimizes the risk of bacterial infection and to a better neovascularization that reduces the risk of infections and wound complications [13, 17]. There is no consensus on the correct position of the mesh and there are only few reported experiences on this issue. The underlay position exposes patients to a higher risk of bowel occlusion and enterocutaneous fistula. The onlay position has a higher risk of mesh bacterial contaminations caused by superficial wound infections [13, 17]. When comparing the results for the underlay and onlay mesh positions, there are no significant differences in terms of morbidity, infectious complications or recurrence [12, 13].

In KTx recipients, laparoscopic repair has the potential advantage of reducing tissue trauma and reducing fluid accumulation causing seroma and potential infections, contributing to a reduced recurrence rate. A laparoscopic procedure can be easier in these patients, who are less prone to developing peritoneal adhesions probably as a result of immunosuppressive therapy. Moreover, laparoscopic repair may be useful to close wall defects close to bone prominences, which are frequent in KTx recipients [12, 17]. Lastly, the laparoscopic technique could be useful even in obese patients.

Reported data suggest that mesh graft repair, either open or laparoscopic, may be considered a valid therapeutic option in renal recipients with IH, resulting in a significant lower recurrence rate compared with primary suture alone, although the hernia recurrence rate remains high [12].

In conclusion, the Rutheford-Morison incision with double-layer closure seems to be the preferred method for preventing IHs. For patients with IH, either open or laparoscopic mesh repairs are safe procedures and are associated with a low rate of postoperative complications and a reasonable recurrence rate. Biologic mesh repair

is a useful alternative for patients with larger defects, infected wounds or recurrent hernias. Strategies to reduce the risk factors in KTx recipients should be put in place through a multidisciplinary approach aimed at reducing patient-related risk factors such as weight loss and smoking cessation, adopting a careful surgical technique and implementing a tailored management of immunosuppression.

References

1. Omar I, Zaimis T, Townsend A, et al. Incisional hernia: a surgical complication or medical disease? Cureus. 2023;15(12):e50568.
2. Thankam FG, Larsen NK, Varghese A, et al. Biomarkers and heterogeneous fibroblast phenotype associated with incisional hernia. Mol Cell Biochem. 2021;476:3353–6.
3. Maroz N, Simman R. Wound healing in patients with impaired kidney function. J Am Coll Clin Wound Spec. 2014;5(1):2–7.
4. Heller A, Saskia E, Westphal PB, et al. Chronic kidney disease is associated with abdominal incisional hernia rates and wound healing disturbances. Int Urol Nephrol. 2014;46:1175–81.
5. Gioco R, Sanfilippo C, Veroux P, et al. Abdominal wall complications after kidney transplantation: a clinical review. Clin Transpl. 2021;35(12):e14506.
6. Smith C, Katz MG, Foley D, et al. Incidence and risk factors of incisional hernia formation following abdominal organ transplantation. Surg Endosc. 2015;29(2):398–404.
7. Nasham B, Citterio F. Wound healing complications and the use of mammalian target of rapamycin inhibitors in kidney transplantation: a critical review of the literature. Transplantation. 2012;94(6):547–61.
8. Durinka JB, Parsikia F, Karipineni F, et al. Association between delayed graft function and incisional hernia after renal transplant. Exp Clin Transplant. 2017;15(1):27–33.
9. Gomez-Dos-Santos V, Lopez-Plaza JA, Molina-Villar JM, et al. Prevention of incisional hernia after kidney transplantation: study protocol for randomized controlled trial. Trials. 2023;24(1):528.
10. Costa L, Martin D, Zingg T, et al. Incidence, risk factors, and management of incisional hernias after kidney transplant: a 20 year single center experience. Transplant Proc. 2023;55:337–41.
11. Simson N, Parker S, Stonier T, et al. Incisional hernia in renal transplantation: a systematic review. Am Surg. 2018;84(6):930–7.
12. Yennam GR, Gutti TL, High R, et al. Experience of laparoscopic incisional hernia repair in kidney and/or kidney pancreas transplant recipients. Am J Transplant. 2011;11(2):279–86.
13. Varga M, Matia I, Kucera M, et al. Polypropylene mesh repair of incisional hernia after kidney transplantation: a single center experience and review of the literature. Ann Transplant. 2011;16(3):121–5.
14. Nanni G, Tondolo V, Citterio F, et al. Comparison of oblique versus hockey stick surgical incision for kidney transplantation. Transplant Proc. 2005;37(6):2479–81.
15. Chio U-C, Liu Y-L, Siow T-F, et al. Endoscopic totally extraperitoneal repair of combined Gibson incisional and inguinal hernia in a kidney transplant recipient. Asian J Surg. 2023;46(7):2800–1.
16. Yildiz I, Savas Koka Y. What kind of incision should be made to reduce the risk of incisional hernia in kidney transplantation? Ann Transplant. 2017;22:989–93.
17. Wagenaar S, Nederhoed JH, Hoksbergen AWJ, et al. Minimally invasive, laparoscopic, and robotic assisted techniques versus open techniques for kidney transplant recipients: a systematic review. Eur Urol. 2017;72(2):205–17.

5 Common General Surgical Procedures: Cholecystectomy, Appendectomy, Anal Surgery

Roberta Angelico, Claudia Quaranta, Luca Toti, Tommaso Maria Manzia, and Giuseppe Tisone

5.1 Cholecystectomy: Technique and Optimization Strategies in Perioperative Care to Minimize Complications

Cholecystectomy is mainly indicated for cholelithiasis, which is one of the most common gastroenterological diseases affecting 10–15% of the general population [1]. The incidence of cholelithiasis increases in end-stage renal disease (ESRD) patients, being about 18% because of altered endocrine function and uremic toxins. Patients with ESRD and cholelithiasis may be asymptomatic or develop acute or chronic cholecystitis and acute pancreatitis, with an incidence rate of 5.8 per 1000 person-years and 0.67–14.10 per 1000 person-years, respectively [2] (Fig. 5.1).

The major international guidelines, including those from the European Association of the Study of the Liver (EASL) [1] and the Society of American Gastrointestinal and Endoscopic Surgeons [3], and the more recent Tokyo 2018 guidelines [4] recommend that in the general population symptomatic cholelithiasis should be treated by laparoscopic cholecystectomy (LC). In acute cholecystitis (AC), early LC (i.e., within 72 hours since onset) should be the standard of care whenever possible, even in fragile patients [5]. According to the Tokyo guidelines, treatment selection should be based on risk stratification according to the Charlson Comorbidity Index (CCI) score and the American Society of Anesthesiologists (ASA) score [4]. In this regard, ESRD patients usually have high ASA and CCI scores due to their underlying associated disease. Therefore, in ESRD patients with

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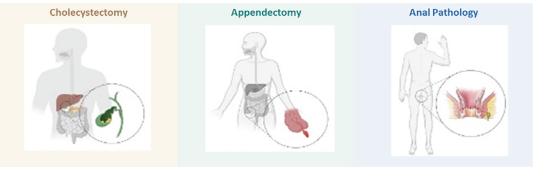


Cholecystectomy	Appendectomy	Anal Pathology
Epidemiology	**Epidemiology**	**Epidemiology**
Gallstone disease: 18% Acute cholecystitis: 5.8 per 1000 person-years	Acute appendicitis: 16.9 per 10,000 person-years	Anal Fistula: 39.5%
Indication for surgery	**Indication for surgery**	**Indication for surgery**
Symptomatic gallstone disease and AC	Scoring systems (Alvarado score, AIR score, AAS) allow risk stratification of patients with suspected AA	Anal abscess with or without fistula
Surgical treatment	**Surgical treatment**	**Surgical treatment**
LC is the standard method for symptomatic gallstones including AC In high risk ESRD patients consider PBD	LPS appendectomy is the preferred approach over open appendectomy	Surgical incision and drainage
Postoperative complications	**Postoperative complications**	**Postoperative complications**
SSI, wound disruption, unplanned intubation, bleeding, return to OR, cardiac arrest	Mechanical wound complication, bleeding	SSI, bleeding

AA, acute appendicitis; AAS, adult appendicitis score; AC, acute cholecystitis; AIR score, appendicitis inflammatory response score; ESRD, end-stage renal disease; LC, laparoscopic cholecystectomy; LPS, laparoscopic; OR, operating room; PBD, percutaneous biliary drainage; SSI, surgical site infection

Fig. 5.1 General surgical procedures in uremic patients

grade I (mild) AC, upfront conservative treatment (based on antibiotic therapy) followed by delayed surgery after 4–6 weeks should be performed; in ESRD patients with grade II (moderate) and grade III (severe) AC, conservative treatment, associated with percutaneous biliary drainage in cases of sepsis, should be considered.

However, in clinical practice, treatment of gallstone disease in ESRD still remains controversial. In a large study by Tam et al. dialysis was associated with a higher risk of 30-day postoperative morbidity (16.1% vs 3.8%) and longer hospital stays (5.5 vs 1.4 days, $p = 0.0001$) in patients on dialysis compared with patients without ESRD. The postoperative morbidities after LC in the dialysis patients mainly included wound disruption, pneumonia, cardiac arrest, bleeding, sepsis, and reoperation [6]. Specifically, complications such as infections and bleeding are connected to the uremia-related alterations in immune response, which increase the risk of bacterial infection and have a direct effect on platelet function.

In kidney transplant (KTx) recipients, prophylactic LC may be considered in cases of high-risk of cholelithiasis-related severe complications due to the post-transplant immunosuppressive status; however, recent studies suggest that the risk of developing complications from asymptomatic cholelithiasis remains very low and does not support prophylactic LC in these patients [1].

Appropriate preoperative preparation including prophylactic antibiotics and elective surgery within 24 hours from the last dialysis is required. Resumption of dialysis 24–36 hours postoperatively, or if hyperkalemia is detected, is common practice after LC in ESRD patients. In patients on peritoneal dialysis, LC can be performed taking special care not to compromise the peritoneal catheter and, although there is no consensus on the timing of resumption of peritoneal dialysis, a 4-week switch to hemodialysis seemed to produce safer outcomes [7]. In addition, across the spectrum of severity, there is evidence that goal-directed moderate fluid

resuscitation decreases the risk of fluid overload and mortality compared with aggressive resuscitation. Caution in chronically anticoagulated patients is warranted, being aware of late bleeding because of a "heparin rebound" due to regional heparin during dialysis.

The gold standard for cholecystectomy is the laparoscopic approach, and its surgical technique has been extensively described [1]. The main principle for a safe LC is correct identification of the relevant anatomy achieving a "critical view" of the cholecystic hilum. If it is not possible to safely proceed with the identification of the cystic duct and artery, a subtotal cholecystectomy may be performed [5]. The free, peritonealized portion of the gallbladder is excised. The portion of the gallbladder adherent to the liver may be left situ or partially excised. The lowest portion of the gallbladder is closed with sutures or staples, reconstituting an intact lumen.

5.2 Appendectomy: Technique and Optimization Strategies in Perioperative Care to Minimize Complications

Acute appendicitis (AA) is a common cause of acute abdominal pain leading to perforation and peritonitis. Its lifetime risk is approximately 8.6% for males and 6.7% for females [8]. The diagnosis is based on clinical history, physical examination, laboratory tests and imaging (US or CT scan) in combination with different scoring systems which consider factors such as nausea or vomiting, right iliac fossa pain, temperature, white blood cell count, C-reactive protein (i.e., Alvarado score, appendicitis inflammatory response [AIR] score, adult appendicitis score [AAS]) [9]. As in the general population, patients with ESRD have an incidence rate of AA of 16.9 per 10,000 person-years [10] (Fig. 5.1).

However, after appendectomy, ESRD patients have a higher risk of postoperative complications such as hyperkalemia, hypotension, sepsis and poor wound healing, as well as hemorrhage due to uremia-related impaired platelet function.

In a large study analyzing 3,620,103 patients who underwent appendectomy, 0.16% patients had ESRD and had an increased risk of postoperative death during the hospital stay (5.2% of ESRD patients vs 0.1% of controls). ESRD patients also had an increased risk of mechanical wound complication ($p = 0.040$) and a mean length of stay (LOS) 34% greater than controls ($p < 0.001$). In addition, in the ESRD group the risk of death was also greater for patients undergoing open appendectomy compared to laparoscopic appendectomy ($p = 0.060$) [11].

As in the general population, the therapeutic management of ESRD patients with uncomplicated AA includes antibiotics and appendectomy within 48 hours from admission [12]; this approach allows for optimal timing of dialysis and stabilization of the patient before surgery. The preferred surgical approach is laparoscopic appendectomy, using three ports and dividing the appendix with a loop suture or endoscopic stapler.

5.3 Surgical Anal Pathology: Technique and Optimization Strategies in Perioperative Care to Minimize Complications

The principal anorectal diseases include anal abscess, anal fistula and hemorrhoids. In the general population, anal abscess represents the most common anorectal disease with an incidence of 16.1–20.2 per 100,000 per year and a 15.5% rate of subsequent fistula formation [13]. According to Hsieh et al., ESRD patients with anal abscess have a high incidence of fistula formation (39.5%) [14] (Fig. 5.1). In cases of anorectal disease, surgical incision and drainage are usually recommended [15]. Thus, ESRD patients have an increased risk for anorectal surgery because of comorbidities, anemia and uremia-related platelet dysfunction. Therefore, considering intraoperative risk and postoperative care, the treatment of anal abscess in dialysis patients tends to be more conservative than in the general population.

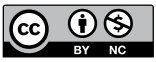
Only few small case series can be found in the literature about the outcomes of ESRD patients with anal abscess. A recent retrospective study by Hsieh et al. reviewed 43 ESRD patients with anal abscess divided into two groups according to whether they received surgical intervention (n = 27) or medical treatment alone (n = 16). There was no significant difference in LOS, one-year survival or recurrence rate between the surgical group and non-surgical group, suggesting that anorectal surgery is safe in ESRD patients on a well-managed dialysis program [14].

Although postoperative antibiotics had a limited role in uncomplicated anal abscess, a broad-spectrum therapy may be considered in all dialysis patients because of their immunocompromised status. Careful hemostasis should be obtained, and postoperative care should be within a tertiary care center. The surgical technique for anorectal disease is well standardized for the different types of lesions [15]:

1. Perianal abscess: an incision is made at the maximum point of tenderness and placed either parallel or radial to the anus.
2. Simple anal fistula: a probe is introduced into the external opening and passed down the tract into the internal opening; then an incision is made, and the tract is laid open.
3. Complex anal fistulae follow a more devious route with several openings and may be treated by: a) Seton drainage: if a large trans-sphincteric fistula is present, a seton should be placed. The fistula is slowly drawn out by the seton. b) Endorectal advancement flap: the infected tissue around the internal opening of anal fistula is cut out and then covered by a flap of healthy tissue from the inside of the rectum above it. The fistula should continue to drain out of the outside opening. c) Ligation of the intersphincteric fistula tract (LIFT) procedure: the part of fistula that passes between the two sphincter muscles is ligated with stitches. The entire fistula tract is then removed from this space.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol. 2016;65(1):146–81.
2. Chen YT, Ou SM, Chao PW, et al. Acute cholecystitis in end-stage renal disease patients: a nation-wide longitudinal study. Dig Liver Dis. 2013;45(2):142–6.
3. Overby DW, Apelgren KN, Richardson W, et al. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. Surg Endosc. 2010;24:2368–86.
4. Wakabayashi G, Iwashita Y, Hibi T, et al. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25(1):73–86.
5. Pisano M, Allevi N, Gurusamy K, et al. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. World J Emerg Surg. 2020;15(1):61.
6. Tam SF, Au JT, Sako W, et al. How sick are dialysis patients undergoing cholecystectomy? Analysis of 92,672 patients from the American College of Surgeons National Surgical Quality Improvement Program database. Am J Surg. 2015;210(5):864–70.
7. Mari G, Scanziani R, Auricchio S, et al. Laparoscopic surgery in patients on peritoneal dialysis: a review of the literature. Surg Innov. 2017;24(4):397–401.
8. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990;132(5):910–25.
9. Di Saverio S, Birindelli A, Kelly MD, et al. WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. World J Emerg Surg. 2016;11:34.
10. Chao PW, Ou SM, Chen YT, et al. Acute appendicitis in patients with end-stage renal disease. J Gastrointest Surg. 2012;16(10):1940–6.
11. Smith MC, Boylan MR, Tam SF, et al. End-stage renal disease increases the risk of mortality after appendectomy. Surgery. 2015;158(3):722–7.
12. Fair BA, Kubasiak JC, Janssen I, et al. The impact of operative timing on outcomes of appendicitis: a National Surgical Quality Improvement Project analysis. Am J Surg. 2015;209:498–502.
13. Adamo K, Sandblom G, Brännström F, Strigård K. Prevalence and recurrence rate of perianal abscess—a population-based study, Sweden 1997-2009. Int J Color Dis. 2016;31(3):669–73.
14. Hsieh MH, Lu YA, Kuo G, et al. Epidemiology and outcomes of anal abscess in patients on chronic dialysis: a 14-year retrospective study. Clinics (Sao Paulo). 2019;74:e638.
15. Ommer A, Herold A, Berg E, et al. German S3 guidelines: anal abscess and fistula (second revised version). Langenbeck's Arch Surg. 2017;402(2):191–201.



Upper Gastrointestinal Non-Oncologic Surgery

6

Marco Vivarelli and Paolo Vincenzi

6.1 Introduction

An increased incidence of acid-related gastrointestinal (GI) dysfunctions—namely, peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD)—has been constantly reported among patients with chronic kidney disease (CKD) compared to the general population [1, 2]. Several underlying pathophysiological mechanisms have been proposed, though still not well defined, including uremic toxicity, fluid overload, electrolyte abnormalities, hemodialysis (HD) effects on splanchnic perfusion, endocrine disorders, and hormonal changes [1, 2]. At the same time, CKD represents one of the most significant risk factors for morbidity and mortality after elective and emergent surgery for these conditions [3].

6.2 Peptic Ulcer Disease

6.2.1 Epidemiology and Pathophysiology

The prevalence of PUD has steadily decreased over the past 50 years, currently ranging between 0.2–0.5% and 2–3% in Western and Eastern countries, respectively [4]. The advent of gastric antisecretory drugs, first histamine-2 receptor antagonists

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and then proton-pump inhibitors (PPIs), together with a better understanding of *Helicobacter pylori* (*H. pylori*) infection pathophysiology leading to specific treatment regimens, have greatly contributed to this decrease.

However, the incidence of PUD in patients affected by CKD has been constantly increasing, with an almost ten-fold higher risk of developing the disease than patients with normal renal function [1, 5]. Similarly, the rates of ulcer complications, i.e., bleeding and perforation, together with the related morbidity, mortality and recurrence rates, have been shown to be significantly higher than in the normal population, leading to assume that other causative factors might play a role in the etiology of PUD in patients with CKD [6].

Accordingly, several studies have reported a weak association between *H. pylori* infection and PUD in this specific population, as confirmed by lower frequencies of infection in CKD and end-stage renal disease (ESRD) patients on HD [5]. Indeed, elevated levels of serum urea nitrogen and inflammatory cytokines, causing decreased gastric acid secretion, higher pH and mucosal damage, might contribute to create an adverse environment for the growth of *H. pylori* [5]. Similarly, other well-known risk factors for PUD in the general population, such as use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), have still not been proven to be risk factors for peptic ulcers in CKD patients [5].

On the other hand, HD represents one of the strongest risk factors for the occurrence of PUD; intradialytic hypotension, leading to splanchnic hypoperfusion and gastrointestinal mucosal ischemia, might induce stress ulcer-like mucosal lesions that subsequently evolve into definite ulcers [5]. Likewise, the impaired gastric emptying secondary to uremia might contribute to gastric mucosal damage, thus increasing the risk of gastric ulcers (GUs), more common than duodenal ulcers (DUs), among patients receiving HD [1].

6.2.2 Elective Surgical Management

The constant decrease in the prevalence of PUD has led inevitably to a reduction in the need for elective surgical management of this condition. Current indications for surgery include inability to interrupt NSAIDs, intolerance to PPIs, or recurrence of the disease while on PPI therapy. The primary goals of an elective operation for PUD include eradication and/or healing of the ulcer through acid-reducing surgery, while ensuring low morbidity, mortality and recurrence rates.

The current strategy of choice should combine truncal vagotomy with antrectomy, allowing an 85% overall reduction in basal acid production, the former procedure by eliminating the cholinergic stimulation to parietal cells and the latter by reducing the gastrin-induced acid secretion by parietal cells through removal of the gastric antrum, i.e., the main location of gastrin-secreting cells [4]. This procedure has been reported to have lower recurrence rates of PUD, when compared with truncal vagotomy and pyloroplasty, despite common GI side effects, including early fullness (approximately 30%), diarrhea (up to 20%) and dumping (8–10%) [4].

Technically, truncal vagotomy requires first the mobilization of the distal esophagus approximately 4 to 5 cm above the gastroesophageal junction (GEJ). At this level, the anterior trunk gives rise to branches that innervate the hepatobiliary system and follows the lesser curve and can be identified first. It should be mobilized at least 2 cm, clipped proximally and distally, and divided including at least a 2 cm specimen. The posterior vagal trunk is usually found along the right edge of the esophagus, it innervates the celiac plexus and continues along the posterior aspect of the lesser curve. The first branch of the posterior trunk is the criminal nerve of Grassi which, if left undivided, may lead to recurrent ulcers. The posterior trunk is similarly mobilized 2 cm, clipped, and divided with a 2 cm specimen. Pathologic confirmation, if available, is recommended (Fig. 6.1).

Technically, during antrectomy the stomach is divided from just proximal to the incisura angularis on the lesser curvature to a point on the greater curvature that is two-thirds from the GEJ to the pylorus, whereas, in the case of DUs, the duodenum is divided distal to all ulceration but proximal to the ampulla of Vater. Reconstruction techniques include Billroth I or II, depending on the grade of inflammation involving the duodenum.

Laparoscopic or robotic-assisted procedures have been emerging as the current mainstay of treatment [7]. Historical operations, including selective vagotomy, first described by Wertheimer and Latarjet in 1922 and highly selective vagotomy, first introduced by Griffith and Harkins in 1957, though complicated by minor post-vagotomy side effects such as dumping and diarrhea due to preservation of the vagal nerve's hepatic and celiac branches, have been completely abandoned because of high recurrence rates and technical complexity (Fig. 6.1).

6.2.3 Complications and Surgical Management

The main complications of PUD are perforation and bleeding. Despite a perforated peptic ulcer (PPU) occurring with one-sixth the frequency of bleeding, it still carries a perioperative mortality rate ranging between 10% and 25%, significantly higher in the case of concomitant renal dysfunction, and an estimated recurrence rate of approximately 12% [8]. The main location of PPU is the duodenal bulb, followed by the pyloric region [8].

Apart from extremely selected pauci-symptomatic cases where the perforation has sealed as confirmed on water-soluble contrast study allowing a non-operative management to be pursued, emergent surgery is strongly recommended [9], with each hour of surgical delay associated with an adjusted 2.4% decreased probability of survival compared to the previous hour [10].

In the presence of small PPUs (<2 cm), laparoscopic primary repair represents the standard treatment, as proven by a recent metanalysis demonstrating similar mortality and leakage rates to open surgery, though with significantly lower morbidity and length of stay [11]. Moreover, the addition of an omental patch seems not to add any further benefit, prolonging exclusively the operative time [12] (Fig. 6.2).

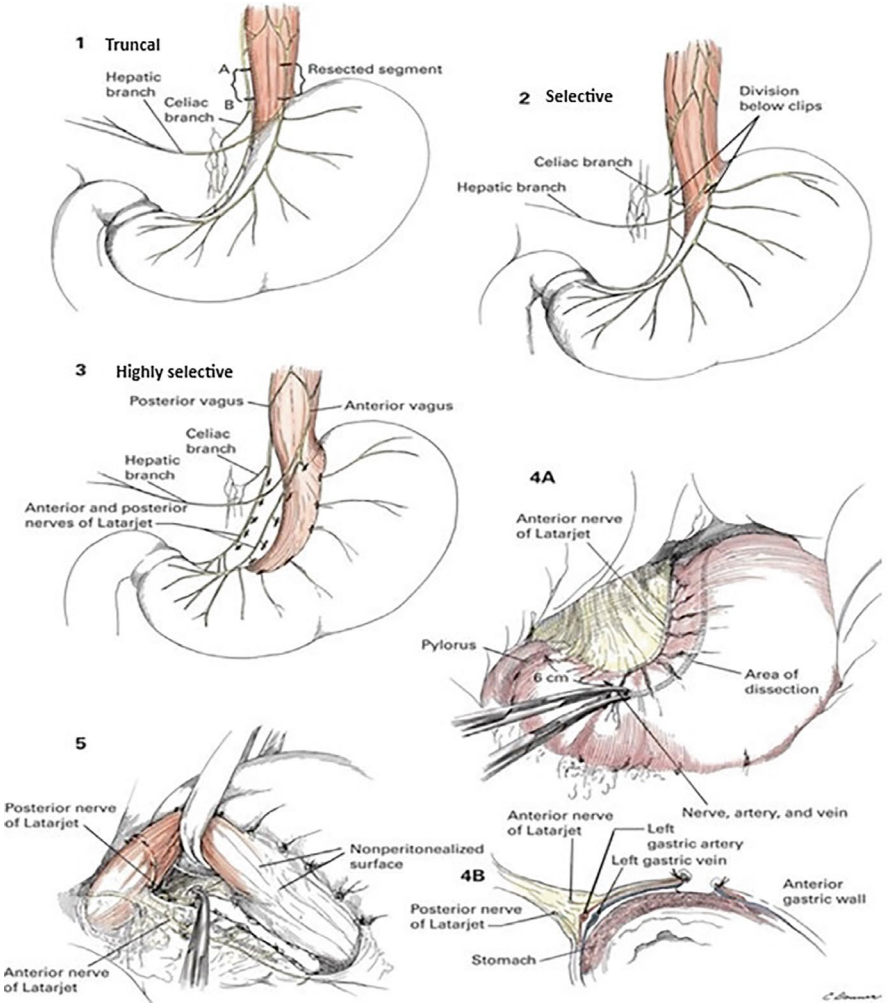


Fig. 6.1 (1) Truncal vagotomy. (2) Selective vagotomy. (3) Highly selective vagotomy (HSS). (4) (**a**, **b**) Denervation with preservation of the anterior nerve of Latarjet during HSS. (5) Preservation of the posterior nerve of Latarjet during HSS. (Reproduced from [4] with permission from Elsevier)

In the presence of large PPUs (>2 cm), a tailored approach should be pursued, depending on the location. Antrectomy plus or minus D1–D2 resection with diversion is the classic and most commonly described intervention, if the ampullary region is not involved [4, 9]. If a duodenal repair is thought to be at high risk for leakage complications, reported to be above 10% in these circumstances, a damage control procedure such as pyloric exclusion and gastrojejunostomy and, if necessary, external biliary diversion via T-tube, represents the safest and most appropriate operation [4, 9].

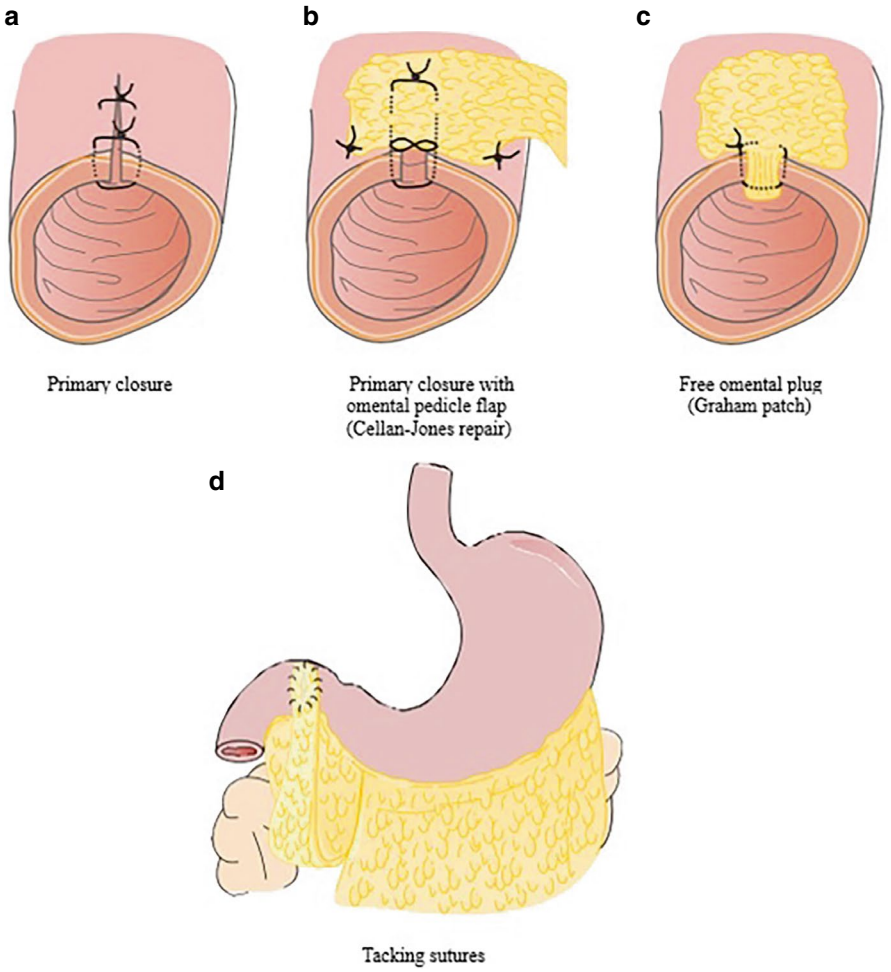


Fig. 6.2 Alternative techniques for suture of a perforated ulcer: (**a**) primary suture; (**b**) primary closure with pedicled omental flap sutured into the perforation (Cellan–Jones repair); (**c**) primary closure with free omental plug sutured into the perforation (Graham patch); (**d**) use of tacking sutures around the perforation (for example when friable edges or a large perforation may not allow approximation of wound edges). (Reproduced from [8] with permission from Oxford Academic)

On the other hand, the incidence of PUD-related acute GI bleeding requiring hospitalization has been constantly increasing in the population of ESRD patients and is associated with worse outcomes such as increased mortality and re-bleeding risk, the latter being three-fold higher than in the general population [6, 13]. Indeed, in several studies, HD emerged as a significant risk factor for ulcer bleeding, independently from first or recurrent episodes [6, 14].

Treatment of upper GI bleeding in CKD patients is similar to the general population, with surgical hemostasis, or angiographic embolization if immediately available and with appropriate skills, indicated after failure of second endoscopy, according to the most recent World Society of Emergent Surgery guidelines [9]. The choice of the appropriate surgical procedure for bleeding peptic ulcer—ulcer oversew vs resection—should be made on the basis of the location and extension of the ulcer and the characteristics of the bleeding vessel [9]. Surgical management of DUs is much more complex than GUs, with higher mortality and reoperation rates [15].

6.3 Gastroesophageal Reflux Disease

6.3.1 Epidemiology and Pathophysiology

An increased incidence and risk of GERD together with its main complications, i.e., esophageal stricture and Barrett's esophagus, have been clearly documented in patients with CKD compared to those without [2].

Hormonal changes, including secondary hyperparathyroidism and persistent activation of the renin-angiotensin-aldosterone system, and electrolyte abnormalities, such as vitamin D deficiency-induced hypocalcemia, might play a major role in GERD development, whereas the cytokine accumulation and oxidative stress linked to CKD might promote progression to the intestinal metaplasia of Barrett's esophagus [2].

6.3.2 Elective Surgical Management

The main indications for elective surgery of GERD include symptoms not controlled by PPIs, intolerance to PPIs, extra-esophageal GERD complications, severe peptic complications like recurrent esophageal ulcer, peptic stricture, Barrett's esophagus, refusal of long-term medical management, especially by young patients, and GERD associated with hiatal hernia [16].

A laparoscopic fundoplication reinforcing the lower esophageal sphincter (LES) has been considered the procedure of choice for the surgical treatment of GERD, with reflux control and symptomatic relief achieved in about 80–90% of patients [16]. Even in this setting, renal insufficiency emerged as a significant risk factor for complications after antireflux surgery [3].

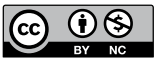
There are three main fundoplication methods: posterior 360°–Nissen, the most common, posterior 270°–Toupet and anterior 180°–Dor. The first one, being a complete fundoplication, consists of completely wrapping the gastric fundus around the lower esophagus, whereas the other two, as partial fundoplications, leave the anterior (Toupet) or the posterior (Dor) wall of the esophagus free. Posterior fundoplications, i.e., Nissen and Toupet, have better long-term control of GERD symptoms than the anterior one, i.e. Dor [16].

According to recent single center retrospective series and metanalysis, robot-assisted antireflux surgery appears to be a safe and feasible technique, with equal efficacy to the conventional laparoscopic approach [17, 18]. Other new minimally invasive surgical and endoscopic options have been developed over the last two decades. Among these, magnetic sphincter augmentation (MSA) is a surgical procedure wherein a string of titanium-encased magnets is wrapped and secured around the GEJ laparoscopically; the magnetic force between these beads is just strong enough to provide LES reinforcement in the resting state but allows for separation of the beads while swallowing [19]. The transoral incisionless fundoplication (TIF) is an endoscopic procedure designed to mimic a surgical fundoplication by creating a high-pressure zone at the level of GEJ in the configuration of a flap valve [20]. According to a recent systematic review and metanalysis conducted by Pasam et al. [21] comparing the above methods with classic fundoplication, data on MSA were still not sufficient to provide definitive conclusions, whereas TIF did not demonstrate significantly inferior short-term outcomes compared with surgical fundoplication. The authors concluded that TIF should be considered on a case-by-case basis, especially in patients with GERD associated with a small hiatal hernia (<2 cm), who are poor surgical candidates or do not want to undergo a surgical fundoplication.

References

1. Liang CC, Muo CH, Wang IK, et al. Peptic ulcer disease risk in chronic kidney disease: ten-year incidence, ulcer location, and ulcerogenic effect of medications. PLoS One. 2014;9(2):e87952.
2. Wang X, Wright Z, Patton-Tackett ED, Song G. The relationship between gastroesophageal reflux disease and chronic kidney disease. J Pers Med. 2023;13(5):827.
3. Schlottmann F, Strassle PD, Patti MG. Surgery for benign esophageal disorders in the US: risk factors for complications and trends of morbidity. Surg Endosc. 2018;32(8):3675–82.
4. Wang A, Yerxa J, Agarwal S, et al. Surgical management of peptic ulcer disease. Curr Probl Surg. 2020;57(2):100728.
5. Kim M, Kim CS, Bae EH, et al. Risk factors for peptic ulcer disease in patients with end-stage renal disease receiving dialysis. Kidney Res Clin Pract. 2019;38(1):81–9.
6. Niikura R, Aoki T, Kojima T, et al. Natural history of upper and lower gastrointestinal bleeding in hemodialysis patients: a dual-center long-term cohort study. J Gastroenterol Hepatol. 2021;36(1):112–7.
7. Yu LJ, Maxfield MW, Chow OS, et al. Video- and robotic-assisted thoracoscopic truncal vagotomy. Am Surg. 2023;89(6):2955–9.
8. Søreide K, Thorsen K, Søreide JA. Strategies to improve the outcome of emergency surgery for perforated peptic ulcer. Br J Surg. 2014;101(1):e51–64.
9. Tarasconi A, Coccolini F, Biffl WL, et al. Perforated and bleeding peptic ulcer: WSES guidelines. World J Emerg Surg. 2020;15:3.
10. Buck DL, Vester-Andersen M, Møller MH. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg. 2013;100(8):1045–9.
11. Cirocchi R, Soreide K, Di Saverio S, et al. Meta-analysis of perioperative outcomes of acute laparoscopic versus open repair of perforated gastroduodenal ulcers. J Trauma Acute Care Surg. 2018;85(2):417–25.
12. Lin BC, Liao CH, Wang SY, Hwang TL. Laparoscopic repair of perforated peptic ulcer: simple closure versus omentopexy. J Surg Res. 2017;220:341–5.

13. Trivedi H, Yang J, Szabo A. Gastrointestinal bleeding in patients on long-term dialysis. J Nephrol. 2015;28(2):235–43.
14. Ogiyama H, Tsutsui S, Murayama Y, et al. Renal dysfunction is an independent risk factor for rebleeding after endoscopic hemostasis in patients with peptic ulcer bleeding. Turk J Gastroenterol. 2021;32(8):622–30.
15. Lolle I, Møller MH, Rosenstock SJ. Association between ulcer site and outcome in complicated peptic ulcer disease: a Danish nationwide cohort study. Scand J Gastroenterol. 2016;51(10):1165–71.
16. Schlottmann F, Herbella FA, Allaix ME, et al. Surgical treatment of gastroesophageal reflux disease. World J Surg. 2017;41(7):1685–90.
17. Vertaldi S, D'Amore A, Manigrasso M, et al. Robotic surgery and functional esophageal disorders: a systematic review and meta-analysis. J Pers Med. 2023;13(2):231.
18. Liu L, Lewis N, Mhaskar R, et al. Robotic-assisted foregut surgery is associated with lower rates of complication and shorter post-operative length of stay. Surg Endosc. 2023;37(4):2800–5.
19. Dunn C, Bildzukewicz N, Lipham J. Magnetic sphincter augmentation for gastroesophageal reflux disease. Gastrointest Endosc Clin N Am. 2020;30(2):325–42.
20. Chang KJ, Bell R. Transoral incisionless fundoplication. Gastrointest Endosc Clin N Am. 2020;30(2):267–89.
21. Pasam RT, Osman KT, Mohan BP, Adler DG. Endoscopic versus surgical therapies for GERD: a systematic review and network meta-analysis. iGIE. 2023;2(4):510–21.



Upper Gastrointestinal Oncologic Surgery

7

Silvia Quaresima, Quirino Lai, Massimo Rossi, and Fabio Melandro

7.1 Introduction

End-stage renal disease (ESRD) requiring dialysis is associated with poor outcomes, including a ten-fold higher risk of hospital admission and a 13–26% shorter expected lifespan compared to that of the general healthy population [1]. Despite the well-described outcomes for ESRD, poor data are available in the literature about the impact of hemodialysis on the risks of complications and death due to malignancies. An extensive nationwide study of ESRD patients undergoing dialysis in the United States revealed a high cumulative incidence of cancer, with >9% of such patients being diagnosed with cancer within five years of initiating hemodialysis [2]. However, studies exploring in detail the impact of surgery on the treatment of the different types of tumors in dialyzed patients are lacking.

The present chapter aims to explore the specific impact of malignant tumors involving the upper gastrointestinal tract in patients with ESRD requiring dialysis.

7.2 Esophageal Cancer

Data concerning the management and outcomes of esophageal cancer (EC) surgery in dialyzed patients are still lacking. This is presumably due to the surgeon's reluctance to perform aggressive procedures in ESRD patients on regular dialysis due to their higher risk of postoperative death or cardiovascular events compared to individuals with normal renal function [3–5]. For this reason, there are only few reports about surgical resection of EC and they involve a minimal number of patients.

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Surgery for EC is considered one of the most invasive and challenging procedures in dialyzed patients [6–8]. There are two possible significant factors explaining why EC surgery has been rarely reported and discussed in dialysis patients with chronic kidney disease (CKD). First, as stated, CKD requiring regular dialysis leads to higher postoperative morbidity and mortality rates when associated with major surgery, regardless of the type of operation [3–5]. Second, the risk of developing EC is reported to be significantly lower in patients with ESRD than in the general population, although the underlying protective mechanism remains unknown [9].

Esophageal resection for cancer is often correlated with relatively poor surgical outcomes, with a mortality rate of 4–10% and a morbidity rate of 26–41% [10]. Therefore, the surgeon is inclined to avoid such risky procedures, especially in patients with an increased complexity like dialyzed patients [6].

Irradiation of the primary tumor can be an efficacious alternative for managing EC in ESRD patients. However, radiotherapy carries a possible risk of severe infections and adverse effects, especially in chronically dialyzed individuals [11]. The safety and efficacy of chemoradiation or radiation therapy for EC in dialysis patients have yet to be established due to the limited number of reports in which they have been evaluated [11, 12]. It seems feasible for dialyzed patients to receive chemotherapy with appropriate dosage adjustments to assure safety [13]. Nevertheless, its ability to achieve a radical cure remains uncertain when compared to surgical removal [14].

Consequently, surgery should be considered the only curative option. With the intent to reduce surgical stress, two-field nodal dissection or a two-stage operation can be considered in dialysis patients. The limited available reports suggest that EC surgery for dialysis-dependent patients is feasible with a selection of less invasive approaches and that the postoperative comorbidity risks remain relatively high. The dialyzed population is highly susceptible to anastomotic leakage, surgical site infection, cardiopulmonary disorder, and hemorrhage, imputable to their impaired wound healing capability, unstable hemodynamic condition, and platelet dysfunction [3]. Given these considerations, therapeutic decision-making tailored to each patient based on a meticulous pre-treatment assessment may be relevant to minimize the risk of severe complications. Dialysis is known to be associated with a higher mortality rate. Therefore, it is mandatory to balance the possibility of cure and safety when choosing therapeutic approaches for EC patients on maintenance dialysis. When treating EC patients receiving regular dialysis, surgeons should select therapeutic modalities considering tumor curability and patient tolerance to this challenging surgery.

7.3 Gastric Cancer

Gastric cancer (GC) is the second most common malignancy worldwide, and surgical treatment remains the only curative management option [15, 16]. Although advances in surgical techniques and perioperative management have made gastrectomy for GC a safe surgical procedure, the outcomes in dialyzed patients remain

unclear due to the limited data reported in the literature provided mainly by retrospective series (Table 7.1).

Due to the rising use of maintainance dialysis [21], cancer surgery in these patients is expected to increase in the future [22]. Surgeons often hesitate to plan the established standard of care in patients receiving dialysis because of the reported increased risk of adverse outcomes after major abdominal surgery [23–25]. In a recently published Japanese case series of 75 patients on maintainance hemodialysis undergoing gastric resection for GC, the overall morbidity (Clavien-Dindo grade II or higher) and 30-day mortality rates were 25.3% and 1.3%, respectively [17]. Such findings are in line with some Japanese nationwide surveys, which report that patients on hemodialysis had higher 30-day mortality rates after distal gastrectomy (4.0%) and total gastrectomy (6.0%) [26, 27]. The previously cited case series also showed a high incidence of anastomotic leakage (6.7%), consistent with prior studies showing ESRD to be significantly associated with this complication [5, 18–20, 28, 29]. Survival outcomes in hemodialysis patients undergoing gastrectomy were notably poor. The 5-year overall survival (OS) rates in patients with pathological stages I, II, III, and IV were 59.2%, 42.9%, 32.3%, and 0%, respectively [17]. Of relevance, OS rates were extremely poor when compared with the Japanese nationwide database and in the case of less advanced tumor stages. In detail, 5-year OS rates in patients not requiring hemodialysis with stage IA, IB, and II diseases were 91.5%, 83.6%, and 70.6%, respectively [30]. The leading causes of death in dialysis patients undergoing GC surgery were infectious diseases and heart failure, as previously described in a nationwide dialysis data report from Japan [31] and the United States [32]. This observation suggests that most patients with pathological stage I and II disease died of causes other than GC. According to these data, the surgical indications should be carefully evaluated based on the balance between survival

Table 7.1 Summary of published reports about surgical treatment of gastric cancer in hemodialysis patients

Author (year)	Treatment	Patients (n)	Mortality (%)	30-day morbidity (%)	5-year survival (%)
Sugawara (2021) [17]	Gastrectomy	75	1.5%	25.3%	59.2% (stage I) 42.9% (stage II) 32.3% (stage III) 0% (stage IV)
Lee (2018) [18]	Gastrectomy	38	41.0% (VLS) 33.0% (open)	-	82.4% (VLS) 67.4% (open)
Otani (2017) [19]	Gastrectomy	12	0.0%	33.3%	22.2%
Liu (2015) [20]	Gastrectomy	26	11.5%	38.5%	83.6%
Matsumoto (2014) [5]	Gastrectomy	49	36.7%	6.1%	48.6% (3-year)

VLS videolaparoscopic surgery

benefits from surgery and life expectancy. Advanced age and comorbidities such as diabetes and cardiovascular disease are mainly associated with poor survival outcomes in dialysis patients [33–35].

Given the extremely low relapse rate in early GC and poor survival of ESRD patients, radical surgery seems unlikely to maximize survival benefits, at least for hemodialysis patients with early GC. Endoscopic submucosal dissection (ESD) alone, even if non-curative and without additional treatment, might be an alternative option for treating this population [36]. Although endoscopic resection can reduce the risk of non GC-related deaths compared with surgery, definitive data are not available due to the scarce number of reports. In the non-hemodialysis population, ESD seems to help improve outcomes in frail patients with early GC presenting comorbidities and advanced age [37]. However, some studies suggest caution in using ESD in hemodialysis patients, given the high incidence of delayed bleeding after gastric endoscopic treatment in patients with severe CKD [38]. Additionally, the prognosis of GC patients with severe comorbidities was inferior, even when they were treated by endoscopic resection, and endoscopic treatment results were inferior to radical surgery in terms of disease-specific survival [39].

Further, anticancer drug treatment is generally tricky in terms of dosage adjustment and time of administration relative to dialysis sessions. Some case reports have been published about possibly treating GC in hemodialysis patients with 5-fluorouracil, irinotecan, or a taxane derivate, by reducing and monitoring the administration dose without increasing hematopoietic toxic effects [40–45]. However, definitive data and standardized administration protocols are not yet available due to the lack of consistent case series.

Surgery for GC cancer patients with ESRD is expected to be improved in the future due to the increasing number of patients undergoing hemodialysis and the aging of this population. However, the adverse effects caused by the dialytic treatment impairing physical function (including wound healing, immunity, body fluid regulation, and hemostasis) must be carefully evaluated to plan a multidisciplinary treatment approach.

7.4 Small Intestine

Small intestine cancers are rare gastrointestinal cancers, often recognized lately and affected by a poor prognosis. For a long time, adenocarcinoma has been the most common histologic type among small intestine malignancies, but neuroendocrine tumors (NET) have remarkably increased in recent years, surpassing adenocarcinomas as the most frequent tumor type of the small bowel [46]. Of note. Adenocarcinomas are most frequently diagnosed in the duodenum, while NET is most frequently found in the jejunum and ileum. Other tumors involving the small intestine are gastrointestinal stromal tumors (GISTs), sarcomas, and lymphomas.

Very few case reports exist reporting the development of small bowel tumors in patients with ESRD [47–53]. According to a population-based case-control study (1,029,695 cancer patients and 99,610 controls) among the United States elderly

using SEER-Medicare linked data, ESRD was associated with a significantly elevated risk for cancers of the small bowel (odds ratio [OR] =1.92, 95% confidence interval [CI] =1.27–2.92; p-value = 0.002) [54]. Despite these results, the number of reported cases is minimal.

As for the duodenal carcinoma, a cohort study of 150 patients from six hepatopancreatic centers in the United Kingdom showed 1-year, 3-year, and 5-year survival rates of 83.9%, 66.7%, and 51.2%, respectively, in non-CKD patients treated with pancreatoduodenectomy (PD) [55]. PD represents the preferred surgical treatment option. Only one case of pylorus-preserving PD has been reported in a patient with duodenal carcinoma and ESRD [47]. A more extensive series also including cases with pancreatic cancer based on a national Japanese inpatient database (n = 30,495 eligible patients, of whom 307 receiving hemodialysis) showed that patients undergoing hemodialysis had a higher risk of postoperative complications (OR = 1.62, 95% CI = 1.23–2.14; p-value = 0.001), 30-day mortality (OR = 7.45, 95% CI = 3.26–17.0; p-value <0.001), and 90-day mortality (OR = 10.9, 95% CI = 6.58–18.2; p-value <0.001) than those not undergoing hemodialysis [4].

Segmental resection of the duodenum has been recently supported, and it should be considered in ESRD patients with tumors located in the distal part of the duodenum, with the aim of minimizing the morbidity and mortality rates of these frail patients [56, 57].

Articles describing ESRD patients with NET, GIST, or lymphomas involving the small bowel are anecdotal, making it impossible to clarify the impact of surgery on the management of these tumors in patients on dialysis [51–53].

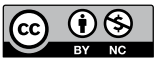
References

1. Gajdos C, Hawn MT, Kile D, et al. Risk of major nonemergent inpatient general surgical procedures in patients on long-term hemodialysis. JAMA Surg. 2013;148:137–43.
2. Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. Am J Kidney Dis. 2015;65:763–72.
3. Mathew A, Devereaux PJ, O'Hare A, et al. Chronic kidney disease and postoperative mortality: a systematic review and meta-analysis. Kidney Int. 2008;73:1069–81.
4. Shinkawa H, Yasunaga H, Hasegawa K, et al. Mortality and morbidity after pancreatoduodenectomy in patients undergoing hemodialysis: analysis using a national inpatient database. Surgery. 2019;165(4):747–50.
5. Matsumoto S, Takayama T, Wakatsuki K, et al. Short-term and long-term outcomes after gastrectomy for gastric cancer in patients with chronic kidney disease. World J Surg. 2014;38(6):1453–60.
6. Abdelsattar ZM, Habermann E, Borah BJ, et al. Understanding failure to rescue after esophagectomy in the United States. Ann Thorac Surg. 2020;109:865–71.
7. Kitamura M, Hiraga S, Takamiya T, et al. Radical esophagectomy on a maintenance hemodialysis patient. Nephron. 1990;56:103–4.
8. Zaza M, Gaur P, Chan EY, et al. Minimally invasive esophagectomy in a patient with end-stage renal disease. BMJ Case Rep. 2016;2016:bcr2016214551.
9. Liang JA, Sun LM, Yeh JJ, et al. The association between malignancy and end-stage renal disease in Taiwan. Jpn J Clin Oncol. 2011;41:752–7.

10. Wright CD, Kucharczuk JC, O'Brien SM, et al. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg. 2009;137:587–95.
11. Hirota H, Ito K, Kageyama SI, et al. Safety of radiotherapy for hemodialysis patients with cancer. Int J Clin Oncol. 2020;25:978–83.
12. Rebibou JM, Chauffert B, Dumas M, et al. Combined chemotherapy and radiotherapy for esophageal carcinoma in a hemodialyzed patient. Long-term survival. Nephron. 1996;74:611–2.
13. Janus N, Thariat J, Boulanger H, et al. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol. 2010;21:1395–403.
14. Ter Veer E, Haj Mohammad N, van Valkenhoef G, et al. The efficacy and safety of first-line chemotherapy in advanced esophagogastric cancer: a network meta-analysis. J Natl Cancer Inst. 2016;108(10):djw166.
15. Brar SS, Mahar AL, Helyer LK, et al. Processes of care in the multidisciplinary treatment of gastric cancer: results of a RAND/UCLA expert panel. JAMA Surg. 2014;149:18–25.
16. Chen LT. Management of gastric cancer in Asia: resource-stratified guidelines. Lancet Oncol. 2013;14(12):e535–47.
17. Sugawara K, Yamashita H, Yajima S, et al. Prognosis of hemodialysis patients undergoing surgery for gastric cancer: results of a multicenter retrospective study. Surgery. 2021;170(1):249–56.
18. Lee H, Park CH, Park SM, et al. Safety of laparoscopic radical gastrectomy in gastric cancer patients with end-stage renal disease. J Gastric Cancer. 2018;18(3):287–95.
19. Otani Y, Okabayashi T, Shima Y, et al. Safety and efficacy of the surgical management of hemodialysis patients with gastric cancer. Acta Med Okayama. 2017;71(4):333–9.
20. Liu YY, Tsai CY, Yeh CN, et al. Gastric cancer patients with end-stage renal disease who underwent radical gastrectomy. Anticancer Res. 2015;35(4):2263–8.
21. Malyszko J, Tesarova P, Capasso G, Capasso A. The link between kidney disease and cancer: complications and treatment. Lancet. 2020;396(10246):277–87.
22. Yamamoto Y, Kanzaki R, Ose N, et al. Lung cancer surgery for patients on hemodialysis: a decade of experience at multicenter institutions. Ann Thorac Surg. 2020;109(5):1558–65.
23. Ito T, Maekawa H, Sakurada M, et al. Risk factors for postoperative complication in on maintenance hemodialysis who undergo abdominal surgery. Asian J Surg. 2016;39(4):211–7.
24. Yasuda K, Tahara K, Kume M, et al. Risk factors for morbidity and mortality following abdominal surgery in patients on maintenance hemodialysis. Hepato-Gastroenterology. 2007;54(80):2282–4.
25. Abe H, Mafune K. Risk factors for maintenance hemodialysis patients undergoing elective and emergency abdominal surgery. Surg Today. 2014;44(10):1906–11.
26. Kurita N, Miyata H, Gotoh M, et al. Risk model for distal gastrectomy when treating gastric cancer on the basis of data from 33,917 Japanese patients collected using a nationwide web-based data entry system. Ann Surg. 2015;262(2):295–303.
27. Watanabe M, Miyata H, Gotoh M, et al. Total gastrectomy risk model: data from 20,011 Japanese patients in a nationwide internet-based database. Ann Surg. 2014;260(6):1034–9.
28. Tanaka Y, Kanda M, Tanaka C, et al. Usefulness of preoperative estimated glomerular filtration rate to predict complications after curative gastrectomy in patients with clinical T2-4 gastric cancer. Gastric Cancer. 2017;20(4):736–43.
29. Migita K, Takayama T, Matsumoto S, et al. Risk factors for esophagojejunal anastomotic leakage after elective gastrectomy for gastric cancer. J Gastrointest Surg. 2012;16(9):1659–65.
30. Katai H, Ishikawa T, Akazawa K, et al. Five-year survival analysis of surgically resected gastric cancer cases in Japan: a retrospective analysis of more than 100,000 patients from the nationwide registry of the Japanese Gastric Cancer Association (2001-2007). Gastric Cancer. 2018;21(1):144–54.
31. Nitta K, Goto S, Masakane I, et al. Annual dialysis data report for 2018, JSDT Renal Data Registry: survey methods, facility data, incidence, prevalence, and mortality. Ren Replace Ther. 2020;6:41.

32. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2019 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020;75(1 Suppl 1):A6–7.
33. Cohen LM, Ruthazer R, Moss AH, Germain MJ. Predicting six-month mortality for patients who are on maintenance hemodialysis. Clin J Am Soc Nephrol. 2010;5(1):72–9.
34. Wagner M, Ansell D, Kent DM, et al. Predicting mortality in incident dialysis patients: an analysis of the United Kingdom Renal Registry. Am J Kidney Dis. 2011;57(6):894–902.
35. Miskulin D, Bragg-Gresham J, Gillespie BW, et al. Key comorbid conditions that are predictive of survival among hemodialysis patients. Clin J Am Soc Nephrol. 2009;4(11):1818–26.
36. Kwon YL, Kim ES, Lee KI, et al. Endoscopic treatments of gastric mucosal lesions are not riskier in patients with chronic renal failure or liver cirrhosis. Surg Endosc. 2011;25(6):1994–9.
37. Toya Y, Endo M, Nakamura S, et al. Long-term outcomes and prognostic factors with non-curative endoscopic submucosal dissection for gastric cancer in elderly patients aged ≥ 75 years. Gastric Cancer. 2019;22(4):838–44.
38. Choi YK, Ahn JY, Na HK, et al. Outcomes of endoscopic submucosal dissection for gastric epithelial neoplasm in chronic kidney disease patients: propensity score-matched case-control analysis. Gastric Cancer. 2019;22(1):164–71.
39. Tanoue K, Fukunaga S, Nagami Y, et al. Long-term outcome of endoscopic submucosal dissection for early gastric cancer in patients with severe comorbidities: a comparative propensity score analysis. Gastric Cancer. 2019;22(3):558–66.
40. Yamamoto T, Miyazaki T, Kurashima Y, et al. A case report of successful chemotherapy with tegafur/gimeracil/oteracil and nab-paclitaxel for gastric cancer with chronic renal failure. Gan To Kagaku Ryoho. 2015;42(6):735–8.
41. Kanematsu K, Tsujimoto H, Nomura S, et al. Weekly paclitaxel therapy for gastric cancer in patients with renal dysfunction: a case report. Ann Med Surg (Lond). 2016;11:26–8.
42. Yang MJ, Choi YJ, Kim HJ, et al. Treatment with ramucirumab-paclitaxel in a metastatic gastric cancer patient undergoing hemodialysis: a case report. Medicine (Baltimore). 2021;100(7):e24795.
43. Cho H, Imada T, Masudo K, et al. Combined 5-FU and CDDP in a gastric cancer patient undergoing hemodialysis--pharmacokinetics of 5-FU and CDDP. Gan To Kagaku Ryoho. 2000;27(13):2135–8.
44. Ashizawa T, Iwahori T, Yokoyama T, et al. Irinotecan hydrochloride (CPT-11) in dialysis patients with gastrointestinal cancer. Acta Med Okayama. 2010;64(1):19–26.
45. Janus N, Launay-Vacher V, Thyss A, et al. Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study. Ann Oncol. 2013;24(2):501–7.
46. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1):63–71.
47. Uchida H, Shibata K, Kai S, et al. Pylorus-preserving pancreaticoduodenectomy in patients undergoing chronic hemodialysis. Surg Today. 2008;38(12):1152–4.
48. Miach PJ, Dawborn JK, Xipell J. Neoplasia in patients with chronic renal failure on long-term dialysis. Clin Nephrol. 1976;5(3):101–4.
49. Jarrett RA, Block CA. Peritoneal dialysis masking symptoms of an insulinoma uncovered during the perioperative period: a case report. South Med J. 2009;102(2):214–5.
50. Shimizu M, Suzuki K, Tsuchida K, et al. Insulinoma in a patient with chronic renal failure due to type 2 diabetes mellitus treated effectively with diazoxide. Intern Med. 2015;54(6):621–5.
51. Niikura R, Serizawa T, Yamada A, et al. Safety of regular-dose imatinib therapy in patients with gastrointestinal stromal tumors undergoing dialysis. Case Rep Gastroenterol. 2016;10(1):17–23.
52. De Luca I, Miliziano D, Guerra G, et al. Hemodialysis and imatinib: plasma levels, efficacy and tolerability in a patient with metastatic GIST - case report. Heliyon. 2024;10(7):e28494.
53. Coorey CP, Aarabi A, Kumar K. Mixed cryoglobulinaemia vasculitis secondary to marginal zone lymphoma in a patient with end-stage renal failure on haemodialysis. CEN Case Rep. 2024;13(3):168–73.

54. Shebl FM, Warren JL, Eggers PW, Engels EA. Cancer risk among elderly persons with end-stage renal disease: a population-based case-control study. BMC Nephrol. 2012;13:65.
55. Solaini L, Jamieson NB, Metcalfe M, et al. Outcome after surgical resection for duodenal adenocarcinoma in the UK. Br J Surg. 2015;102(6):676–81.
56. Bennett CM, Coleman HG, Veal PG, et al. Lifestyle factors and small intestine adenocarcinoma risk: a systematic review and meta-analysis. Cancer Epidemiol. 2015;39(3):265–73.
57. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol Ther. 2006;23(8):1097–104.



Diverticulitis and Other Colitis in Kidney Transplant Patients

8

Massimiliano Veroux, Alessia Giaquinta, Martina Giambra, Domenico Zerbo, and Pierfrancesco Veroux

8.1 Introduction

Kidney transplantation is the best replacement therapy for patients with end-stage renal disease [1]. The incidence of gastrointestinal complications in kidney transplantation may be as high as 56% [2–5], with more than 10% of patients displaying a severe course [5–7]. Kidney transplant recipients (KTRs) undergoing colorectal surgery may be exposed to an increased risk of postoperative mortality and surgical complications compared with the general population, but also with end-stage renal disease patients, mainly due to the use of immunosuppression [8]. DiBrito et al. [8] evaluated the postoperative morbidity and mortality rates following colorectal resection in KTRs compared with the general population: KTRs had a higher mortality rate compared to non-KTRs (11.1% vs 4.3%, $p < 0.001$), and KTRs had a 3.59-fold higher risk of death than non-KTRs. Moreover, KTRs were more likely than non-KTRs to have postoperative complications during their surgical hospitalization (38.5% vs 31.5%, $p = 0.001$), particularly wound complications (6.2% vs 2.4%, $p < 0.001$), infectious complications (7.7% vs 4.2%, $p < 0.001$), and cardiovascular complications (5.2% vs 2.7%, $p < 0.001$). Interestingly, colorectal resection in KTRs resulted in higher costs and length of stay, and KTRs were more likely to be treated in transplant centers than in other surgical units [8]. Similar findings were reported by Halabi et al. [9] who reported higher rates of mortality (6.29% vs 3.64%), wound complications (8.02% vs 5.37%), and acute renal failure (17.14% vs 7.10%) in KTRs compared with the general population, although the rate of anastomotic leakage was similar between the two groups [9]. KTRs have a higher rate of acute complicated diverticulitis compared to the general population [9, 10], with a

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potential higher rate of anastomotic leakage after colorectal surgery, both for benign and malignant diseases [8, 11], as well as a higher mortality rate in emergency colectomy [12]. In a recent study, Bardol et al. [13] found that KTRs undergoing elective left colectomy have a fourfold higher rate of anastomotic leakage and a higher incidence of intra-abdominal septic complications and re-operation compared to non-transplant patients.

8.2 Diverticular Disease and Colonic Perforation

The incidence of acute diverticulitis in KTRs is believed to be higher than in general population [9, 10]: a recent review [10] reported an incidence of 1% of acute diverticulitis in KTRs, with an overall mortality of 25%. The progression to diverticulitis in KTRs with a known diverticulosis was 16%, and up to 57% in patients with autosomal dominant polycystic kidney disease (ADPKD) [14]. Acute diverticulitis, together with intestinal ischemia, is the most frequent cause of colonic perforation in KTRs, affecting up to 60% of patients, with a mortality rate up to 33% [7, 10].

Few studies compared the incidence of acute diverticulitis in transplant patients compared to the general population: in a study by Qasabian et al. [15], 0.94% of transplant patients developed acute diverticulitis compared with 0.02% of the general population.

While there is a general consensus on the surgical indications of complicated diverticulitis in immunocompetent patients, the management of diverticulitis in KTRs remains controversial: in the study of Rencuzogullari et al. [16], among the 15 KTRs with acute diverticulitis, six (40%) patients required a surgical intervention (two during the first attack due to perforation and four for recurrent or refractory diverticulitis), while nine patients were successfully treated conservatively. However, when a colonic perforation is suspected, an aggressive diagnostic evaluation and surgical treatment is recommended, together with broad spectrum antibiotics, to improve the outcome of these patients [7, 14]: the Hartmann procedure is generally performed, since a primary anastomosis in immunosuppressed patients may be associated with a greater risk of post-surgical morbidity [17].

Traditionally, a higher incidence of diverticulosis and acute diverticulitis in KTRs has been associated with ADPKD [10, 14, 18–21] because of the underlying alterations in connective tissue that put ADPKD patients at higher risk for formation of diverticula [10]. However, the data are from small series and are conflicting: some epidemiologic studies found a 7–40% prevalence of diverticular disease in ADPKD patients [20, 21], although a prospective study of 55 ADPKD and 71 non-ADPKD patients did not find any difference in prevalence, size, or distribution of colonic diverticula between the two groups [21]. A large nationwide analysis [22] reported a 4.6% prevalence of diverticulosis in the ADPKD population compared with 2.3% of the general population ($p < 0.0001$); moreover, ADPKD patients with diverticulosis were younger, and the difference in prevalence was more evident as age increased. ADPKD was also a risk factor for diverticulitis: the prevalence in ADPKD patients was 1.5%, compared with 0.8% among patients without ADPKD ($p < 0.0001$), and 2.6% of KTRs with ADPKD developed an acute diverticulitis

[22]; however, patients with ADPKD and diverticulitis had a lower prevalence of colonic surgery when compared with patients without ADPKD, probably because of the associated comorbidities that suggested adopting a non-operative approach [22].

In an interesting study, Parker et al. [14] evaluated the outcome of acute diverticulitis in 14 polycystic KTRs compared with 27 non-transplant patients, and they were not able to find significant differences between the two groups in the rates of recurrent diverticulitis, diverticulitis complications, or operative intervention, although KTRs had a higher rate of recurrent, complicated diverticulitis. Similar results were reported by Domínguez Fernández et al. [11], while Scotti et al. [23] reported a higher incidence of colonic perforation after acute diverticulitis in ADPKD patients.

The management of acute diverticulitis in KTRs is similar to that in immunocompetent patients, although the use of immunosuppression may increase the risk of infective complications, progression of diverticulitis and failure of non-operative management [12]. While an aggressive surgical approach was reported in earlier studies, a wider use of non-operative approaches is now preferred [16, 17, 24, 25]: a large proportion of KTRs could be treated conservatively, although a higher rate of readmission, need for surgical operation, drainage and death is reported in KTRs compared with the non-transplant population [26]. However, these events occur in a small fraction of KTRs and most recurrent episodes may be also managed non-operatively [26].

A point of discussion is the possibility of performing a pre-transplant prophylactic colectomy in ADPKD patients with diverticulosis [26]. However, most authors agree that a prophylactic colectomy would be impractical due to the low incidence of acute diverticulitis in this population and the long-term wait for kidney transplantation; however, patients should be counseled about the early signs and symptoms of diverticulitis and encouraged to seek medical care, possibly in a transplant center [10, 16, 17, 26].

8.3 Post-transplant Colitis

The chronic use of immunosuppression in KTRs may be associated with chronic injury to the gastrointestinal mucosa leading to the development of post-transplant colitis, usually related to the use of mycophenolate mofetil and mycophenolic acid. These gastrointestinal complications usually do not require a surgical intervention, and adjustment of levels of immunosuppression is generally needed to improve the gastrointestinal symptoms [5, 7].

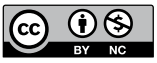
Post-transplant inflammatory bowel disease (IBD) may arise from an inappropriate immune response to intestinal antigens, resulting in continuous intestinal inflammation [27]. In KTRs, the immunosuppressive therapy, which could theoretically contrast this inflammatory process, may paradoxically allow for dysregulation of the intestinal immune system, finally resulting in the development of post-transplant *de novo* IBD, despite being immunosuppressed [5, 7, 27].

De novo IBDs are an uncommon complication of kidney transplantation, with only 46 cases reported in a recent review [5]. *De novo* IBDs usually present late after transplantation, suggesting a potential etiopathogenetic role of chronic exposure of the intestinal mucosa to immunosuppressive therapy [5, 7]. Clinical, endoscopic and histological features resemble those observed in general population but, in KTRs, *de novo* IBDs could have a more aggressive course than in the general population [5, 28], and about half of patients may require a surgical intervention during the post-transplant follow-up [5].

References

1. Veroux M, Corona D, Veroux P. Kidney transplantation: future challenges. Minerva Chir. 2009;64:75–100.
2. Veroux P, Veroux M, Puliatti C, et al. Tacrolimus-induced neurotoxicity in kidney transplant recipients. Transplant Proc. 2002;34(8):3188–90.
3. Gioco R, Puzzo L, Patanè M, et al. Post-transplant colitis after kidney transplantation: clinical, endoscopic and histological features. Aging (Albany NY). 2020;12(24):24709–20.
4. Hardinger K, Brennan DC, Lowell J, et al. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. Transpl Int. 2004;17(10):609–16.
5. Gioco R, Corona D, Ekser B, et al. Gastrointestinal complications after kidney transplantation. World J Gastroenterol. 2020;26(38):5797–811.
6. Sarkio S, Halme L, Kyllönen L, Salmela K. Severe gastrointestinal complications after 1,515 adult kidney transplantations. Transpl Int. 2004;17(9):505–10.
7. Coccolini F, Catena F, Di Saverio S, et al. Colonic perforation after renal transplantation: risk factor analysis. Transplant Proc. 2009;41(4):1189–90.
8. DiBrito SR, Alimi Y, Olorundare IO, et al. Outcomes following colorectal resection in kidney transplant recipients. J Gastrointest Surg. 2018;22(9):1603–10.
9. Halabi WJ, Jafari MD, Nguyen VQ, et al. Colorectal surgery in kidney transplant recipients: a decade of trends and outcomes in the United States. Am Surg. 2013;79(10):1026–33.
10. Hwang SS, Cannom RR, Abbas MA, Etzioni D. Diverticulitis in transplant patients and patients on chronic corticosteroid therapy: a systematic review. Dis Colon Rectum. 2010;53(12):1699–707.
11. Domínguez Fernández E, Albrecht KH, Heemann U, et al. Prevalence of diverticulosis and incidence of bowel perforation after kidney transplantation in patients with polycystic kidney disease. Transpl Int. 1998;11:28–31.
12. Al-Khamis A, Abou Khalil J, Demian M, et al. Sigmoid colectomy for acute diverticulitis in immunosuppressed vs immunocompetent patients: outcomes from the ACS-NSQIP database. Dis Colon Rectum. 2016;59(2):101–9.
13. Bardol T, Souche R, Genet D, et al. Outcomes of elective left colectomy in renal-transplanted patients: a single-center case-control study (LECoRT study). Int J Color Dis. 2021;36(6):1209–19.
14. Parker ME, Mathis KL, Kelley SR. Severity of diverticulitis in patients with polycystic kidney disease without transplantation. Int J Color Dis. 2017;32(12):1767–70.
15. Qasabian RA, Meagher AP, Lee R, et al. Severe diverticulitis after heart, lung and heart-lung transplantation. J Heart Lung Transplant. 2004;23:845–9.
16. Rencuzogullari A, Ozuner G, Binboga S, et al. Colonic diverticulosis and diverticulitis in renal transplant recipients: management and long-term outcomes. Am Surg. 2017;83(3):303–7.

17. Perrone G, Giuffrida M, Abu-Zidan F, et al. Goodbye Hartmann trial: a prospective, international, multicenter, observational study on the current use of a surgical procedure developed a century ago. World J Emerg Surg. 2024;19(1):14.
18. Pourfarziani V, Mousavi-Nayeeni SM, Ghaheri H, et al. The outcome of diverticulosis in kidney recipients with polycystic kidney disease. Transplant Proc. 2007;39(4):1054–6.
19. Iglesias C, Torres V, Offord K, et al. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980. Am J Kidney Dis. 1983;2:630–9.
20. Zeier M, Geberth S, Ritz E, et al. Adult dominant polycystic kidney disease – clinical problems. Nephron. 1998;49:177–83.
21. Sharp CK, Zeligman BE, Johnson AM, et al. Evaluation of colonic diverticular disease in autosomal dominant polycystic kidney disease without end-stage renal disease. Am J Kidney Dis. 1999;34:863–8.
22. Duarte-Chavez R, Stoltzfus J, Yellapu V, et al. Colonic diverticular disease in autosomal dominant polycystic kidney disease: is there really an association? A nationwide analysis. Int J Color Dis. 2021;36(1):83–91.
23. Scotti A, Santangelo M, Federico S, et al. Complicated diverticulitis in kidney transplanted patients: analysis of 717 cases. Transplant Proc. 2014;46(7):2247–50.
24. Gomez D, Acuna S, Joseph Kim S, et al. Incidence and mortality of emergency general surgery conditions among solid organ transplant recipients in Ontario, Canada: a population-based analysis. Transplantation. 2023;107(3):753–61.
25. Nantais J, Baxter NN, Saskin R, et al. Short- and long-term outcomes of acute diverticulitis in patients with transplanted kidneys. Color Dis. 2024;26(4):734–44.
26. Schultz JK, Azhar N, Binda GA, et al. European Society of Coloproctology: guidelines for the management of diverticular disease of the colon. Color Dis. 2020;22(Suppl 2):5–28.
27. Pittman ME, Jessurun J, Yantiss RK. Differentiating post-transplant inflammatory bowel disease and other colitides in renal transplant patients. Am J Surg Pathol. 2017;41:1666–74.
28. Salgueiro P, Lago P, Pedroto I. Natural history of inflammatory bowel disease patients submitted to solid organ transplantation. J Crohns Colitis. 2013;7:e196.



Lower Gastrointestinal Oncologic Surgery

9

Gerardo Sarno, Enrico Russo, and Paride De Rosa

9.1 Colorectal Cancer

Colorectal cancer (CRC) is the third most common cause of cancer death in kidney transplant recipients and among the top six causes of cancer death in patients on dialysis [1, 2]. Chronic dialysis patients have a higher incidence rate of colon cancer than the general population [3]. To reduce the burden of CRC, screening programs have been established to identify and treat precancerous and early cancer lesions, before their progression to invasive CRC [1, 2, 4]. Transplant candidates are evaluated extensively for factors that may adversely affect their post-transplant outcome. Early detection of cancer may benefit and reduce morbidity in transplant candidates, as post-transplant patients must undergo chronic immunosuppressive therapies. Colonoscopy is a useful tool for detecting colonic pathology before patients undergo transplant and subsequent immunosuppression. If end-stage renal disease (ESRD) patients have a higher incidence of CRC, pre-transplant screening colonoscopies should be performed to enhance post-transplant outcomes and reduce morbidities [5].

In patients with ESRD, including those receiving dialysis, reduced kidney function and uremic environment are associated with chronic inflammation, oxidative stress, and dendritic cell dysfunction, which may contribute to reduced cancer immune surveillance and the development of cancer [6, 7]. Transplant-specific factors, such as time on dialysis before transplant and peak panel reactive antibody (PRA) score, have been identified as risk factors for developing *de novo* cancer after transplantation [8–10]. In the ESRD spectrum (stages 3–5 not receiving renal replacement therapy [RRT], patients on dialysis, patients with a functioning kidney

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transplant), it was found that older age, male sex, azathioprine use, and erythropoiesis-stimulating agent (ESA) use are factors associated with advanced CRC, with the use of azathioprine and ESA as factors that are specific to patients with kidney disease. ESA use was found to be associated with a nearly twofold greater risk of advanced CRC [1] while, as a result of the widespread use of antiproliferative agents (everolimus) in immunosuppressive regimens, the risk of cancer onset has decreased in more recent years. Outcomes appear to be poorer in ESRD patients who develop CRC. In comparison with the age- and sex-matched general population, patients on dialysis and kidney transplant recipients have double the mortality from CRC [6, 8]. A number of studies have assessed the survival patterns of solid organ transplant recipients with *de novo* CRC compared with the general population. Papaconstantinou et al. [11] assessed 150 transplant recipients with *de novo* CRC and compared them with CRC patients in the National Cancer Institute Survival, Epidemiology and End Result (SEER) database. Transplant recipients with Dukes' A to C stage disease were noted to experience a significant decrease in 5-year survival. Johnson et al. [12] also showed a reduced 5-year survival in 40 transplant recipients with *de novo* CRC when compared with matched controls from the SEER database (30.7% vs 63.5%, respectively). The authors hypothesized that the worse prognosis in solid organ transplant recipients with *de novo* CRC may be related to increased tumor biological aggressiveness or reduced immunological response or a combination of both.

ESRD represents a challenge for the surgeon when faced with a patient in need of emergency or elective surgery. While the overall mortality after colorectal surgery in the general population ranges from 1% to 6% [13], the reported postoperative mortality and morbidity for ESRD patients undergoing elective colorectal surgery is around 6–10% and 12–15%, respectively, rising to 47–50% and 62–70% in emergency situations [14]. In view of this, we recommend a surgical approach based on a Hartmann procedure where stoma creation is always preferred to anastomosis, in order to minimize intra- and postoperative complications, with recanalization performed only after a careful oncologic workup and follow-up. Although ESRD patients are more and more frequent, they still represent a small proportion of the general population and series of patients on dialysis undergoing colorectal surgery remain small and scarce [14, 15]. Patients on RRT for chronic renal failure are fragile patients, often with a history of cardiac events as well as diabetes mellitus, which put them at high risk of complications after surgery, making them poorer candidates for surgery. In view of this, ESRD patients who need colorectal surgical resection should be carefully selected, prepared and closely managed in the postoperative period. A few case series on chronic dialysis patients undergoing colorectal surgery have been reported. Krysa et al. [14] presented a series of 73 colorectal procedures, including 38 patients on RRT and 35 with a renal transplant. They reported a much-increased risk of postoperative complications and mortality in the case of emergent surgery (81% and 26% vs 19% and 5%, respectively) [14]. Therefore, elective and (when possible) emergency surgeries should be carefully prepared and performed, and close postoperative management is paramount in such fragile patients very sensitive to hemodynamic changes and with delayed healing.

Anastomotic leak is a complication feared by the surgeons. Risk factors known to be associated with anastomotic leak are male gender, tobacco use, immunosuppression and emergency situations [16, 17]. A laparoscopic approach could help to decrease the risk of postoperative morbidity and mortality. Such an approach, due to its low invasiveness may be extremely useful in performing segmental colorectal resection for pre-neoplastic lesions not suitable for endoscopic radical excision; nevertheless, the imbalance between oncologic outcomes and postoperative complications has always to be evaluated when planning an extended colorectal resection, because the choice between an open and a laparoscopic approach has to be carefully pondered [18, 19]. Laparoscopy in peritoneal dialysis patients decreases the risk of shift to hemodialysis owing to better preservation of peritoneal integrity and earlier resumption of peritoneal dialysis [20], but there is a risk of hernias at the port-site incisions as well as an increased risk of peritonitis even for minimal anastomotic leaks. The impact of chronic dialysis on the outcomes of patients undergoing laparoscopic CRC resection, compared with a non-dialysis population (including non-ESRD patients) has been investigated, demonstrating comparable outcomes in the dialyzed patients' group, which suggests that the minimally invasive approach could be preferred [21, 22].

Although the oncologic outcomes and treatment plans for colorectal malignancy are an important issue in patients with ESRD, the randomized controlled studies that investigated colorectal malignancy either enrolled very few ESRD patients or excluded them completely [23, 24]. The oncologic outcomes between the ESRD-CRC group and the non-ESRD-CRC group were examined using a large-scale database [25]. Among 219,550 patients who received surgeries for CRC between 2002 and 2019, 6181 patients were diagnosed with ESRD at the time of the operation. The mean follow-up duration was 5.7 years for all patients. After 1:4 propensity matching and adjustment of risk factors, the median survival time was 8.71 years (IQR, 8.37–8.93 years) in the non-ESRD-CRC group and 5.63 years (IQR, 5.26–5.91 years) in the ESRD-CRC group, indicating that ESRD itself is a significant risk factor for survival. Furthermore, the subgroup analysis within the ESRD group showed that dialysis is a significant risk factor for survival [25].

9.2 Anal Cancer

Anal cancer is a rare malignancy of the gastrointestinal tract, which accounts for less than 1.5% of gastrointestinal tumors [26] and has an age-adjusted incidence rate of 1.4–2 per 100,000 [27]. It is, however, a significant disease in high-risk populations such as immunosuppressed patients, including HIV patients and transplant recipients [26, 28]. Anal human papillomavirus (HPV) infection is associated with anal intraepithelial neoplasia (AIN) and anal cancer. High-risk subtypes of HPV (16, 18, 31, 33, 35, 39, 45, 50, 51, 53, 55, 56, 58, 59 and 68) are commonly found in high-grade AIN and anal squamous cell carcinomas. AIN, the precursor of anal cancer, is graded from I to III according to the depth of nuclear abnormalities in the squamous epithelium. Patients who are systemically immunosuppressed may be at

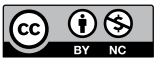
a higher risk of malignant progression [29]. Ogunbiyi et al. [30] investigated the prevalence of anal HPV 16 infection and associated AIN in 76 renal transplant recipients and compared it with age-matched controls. All patients underwent anoscopy and then targeted biopsies of any abnormal epithelium; in the presence of normal epithelium, random biopsies were taken. The prevalence of HPV 16 in the study group was 47% compared with 12% in the control group. AIN was present in 20% in the study group compared with 1% in the control group. Another study assessed the prevalence of anal HPV in 43 patients within 24 h of renal transplant (prior to significant immunosuppression) [31]. HPV infection was present in 21% of patients (high risk in 14% of patients). Only one study has assessed the prevalence of anal cancer among patients with ESRD on dialysis compared with the general population [32]. Data were collected from the ANZDATA registry. Of the 24,926 patients with ESRD, two developed anal cancer. Several population-based studies have concentrated on excess cancer risk in solid organ transplant patients. True interpretation of anal cancer prevalence in renal transplant patients was difficult because studies analyzed gastrointestinal cancers, rectal and anal cancers together, or anogenital cancers, or data were collected for solid organ transplants rather than renal transplants specifically. A number of studies have reported a 30- to 100-fold increase in rates of anogenital cancer in solid organ transplant recipients [29]. The Swedish and ANZDATA registries demonstrated a tenfold increase in anal cancer in solid organ transplant recipients and nearly a threefold increase in anal cancer for renal transplant recipients. Renal transplant patients accounted for 84% of the Swedish Solid Organ Transplant Registry, with the remainder being liver, heart, lung, pancreas or combined transplantation. For affected renal transplant patients in the ANZDATA registry, the mean time to anal cancer was 13 years. From available population-based studies, renal transplant was associated with a three to tenfold increase in anal cancer. In a single case-control study, the prevalence of anal HPV and AIN in patients with established renal transplants was significantly increased. The effectiveness of screening for HPV, AIN and anal cancer in renal transplant recipients remains unclear. Difficulty arises as the natural history, malignant potential and effective treatment modalities for AIN remain uncertain. Therefore, based on this evidence all renal transplant patients should undergo yearly assessment of the perianal area and biopsy of any suspicious lesions [29, 33].

References

1. Au EH, Wong G, Howard K, et al. Factors associated with advanced colorectal neoplasia in patients with CKD. Am J Kidney Dis. 2022;79(4):549–60.
2. Wong G, Hope RL, Howard K, et al. One-time fecal immunochemical screening for advanced colorectal neoplasia in patients with CKD (DETECT study). J Am Soc Nephrol. 2019;30(6):1061–72.
3. Iseki K, Osawa A, Fukiyama K. Evidence for increased cancer deaths in chronic dialysis patients. Am J Kidney Dis. 1993;22(2):308–13.
4. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112(2):594–642.

5. Lee S, Wasserberg N, Petrone P, et al. The prevalence of colorectal neoplasia in patients with end-stage renal disease: a case-control study. Int J Color Dis. 2008;23(1):47–51.
6. Safaeian M, Robbins HA, Berndt SI, et al. Risk of colorectal cancer after solid organ transplantation in the United States. Am J Transplant. 2016;16(3):960–7.
7. Lim WH, Kireta S, Russ GR, Coates PT. Uremia impairs blood dendritic cell function in hemodialysis patients. Kidney Int. 2007;71(11):1122–31.
8. Au E, Wong G, Chapman JR. Cancer in kidney transplant recipients. Nat Rev Nephrol. 2018;14(8):508–20.
9. Lim WH, Chapman JR, Wong G. Peak panel reactive antibody, cancer, graft, and patient outcomes in kidney transplant recipients. Transplantation. 2015;99(5):1043–50.
10. Wong G, Turner RM, Chapman JR, et al. Time on dialysis and cancer risk after kidney transplantation. Transplantation. 2013;95(1):114–21.
11. Papaconstantinou HT, Sklow B, Hanaway MJ, et al. Characteristics and survival patterns of solid organ transplant patients developing de novo colon and rectal cancer. Dis Colon Rectum. 2004;47(11):1898–903.
12. Johnson EE, Leverson GE, Pirsch JD, Heise CP. A 30-year analysis of colorectal adenocarcinoma in transplant recipients and proposal for altered screening. J Gastrointest Surg. 2007;11(3):272–9.
13. Drolet S, Maclean AR, Myers RP, et al. Morbidity and mortality following colorectal surgery in patients with end-stage renal failure: a population-based study. Dis Colon Rectum. 2010;53(11):1508–16.
14. Krysa J, Patel V, Taylor J, et al. Outcome of patients on renal replacement therapy after colorectal surgery. Dis Colon Rectum. 2008;51(6):961–5.
15. Nozawa H, Kitayama J, Sunami E, Watanabe T. Impact of chronic kidney disease on outcomes of surgical resection for primary colorectal cancer: a retrospective cohort review. Dis Colon Rectum. 2012;55(9):948–56.
16. Nikolian VC, Kamdar NS, Regenbogen SE, et al. Anastomotic leak after colorectal resection: a population-based study of risk factors and hospital variation. Surgery. 2017;161(6):1619–27.
17. McKenna NP, Bews KA, Cima RR, et al. Development of a risk score to predict anastomotic leak after left-sided colectomy: which patients warrant diversion? J Gastrointest Surg. 2020;24(1):132–43.
18. Kang CY, Halabi WJ, Chaudhry OO, et al. A nationwide analysis of laparoscopy in high-risk colorectal surgery patients. J Gastrointest Surg. 2013;17(2):382–91.
19. Hemandas AK, Abdelrahman T, Flashman KG, et al. Laparoscopic colorectal surgery produces better outcomes for high risk cancer patients compared to open surgery. Ann Surg. 2010;252(1):84–9.
20. Mari G, Scanziani R, Auricchio S, et al. Laparoscopic surgery in patients on peritoneal dialysis: a review of the literature. Surg Innov. 2017;24(4):397–401.
21. Higashino N, Matsuda T, Hasegawa H, et al. Outcomes of laparoscopic surgery in colorectal cancer patients with dialysis. Anticancer Res. 2020;40(4):2165–70.
22. Frezin J, Navez J, Johnson P, et al. Colorectal resection in end-stage renal disease (ESRD) patients: experience from a single tertiary center. Acta Chir Belg. 2022;122(2):92–8.
23. Kitchlu A, Shapiro J, Amir E, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. JAMA. 2018;319(23):2437–9.
24. Shin N, Han EC, Won S, et al. The prognoses and postoperative outcomes of patients with both colorectal cancer and liver cirrhosis based on a nationwide cohort in Korea. Ann Surg Treat Res. 2020;99(2):82–9.
25. Song I, Nam H, Lee B, et al. Real-world survival after colorectal surgery for malignancy in Korean patients with chronic kidney disease: an analysis of Korean healthcare big data, 2002–2019. Ann Surg Treat Res. 2023;105(5):281–9.
26. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. N Engl J Med. 2000;342(11):792–800.
27. Johnson LG, Madeleine MM, Newcomer LM, et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. Cancer. 2004;101(2):281–8.

28. Patel HS, Silver AR, Northover JM. Anal cancer in renal transplant patients. Int J Color Dis. 2007;22(1):1–5.
29. Parnaby CN, Barrow EJ, Edirimanne SB, et al. Colorectal complications of end-stage renal failure and renal transplantation: a review. Color Dis. 2012;14(4):403–15.
30. Ogunbiyi OA, Scholefield JH, Raftery AT, et al. Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. Br J Surg. 1994;81(3):365–7.
31. Roka S, Rasoul-Rockenschaub S, Roka J, et al. Prevalence of anal HPV infection in solid-organ transplant patients prior to immunosuppression. Transpl Int. 2004;17(7):366–9.
32. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006;296(23):2823–31.
33. Sillman FH, Sentovich S, Shaffer D. Ano-genital neoplasia in renal transplant patients. Ann Transplant. 1997;2(4):59–66.



Hepatobiliary Non-oncologic Surgery

10

Jacopo Romagnoli, Alessandra De Iacob, and Sergio Alfieri

10.1 Introduction

Uremia increases the hazards of most surgical procedures and enhances the risks of anesthesia [1] particularly in patients undergoing hepatobiliary surgery. Uremic patients receiving hemodialysis (HD) tend to have a higher American Society of Anesthesiologists (ASA) score due to frequent concomitant diseases which can affect the rates of perioperative complications. The impaired ability of the kidneys to regulate fluid and electrolyte balance and to excrete metabolic waste products is indeed at the basis of the majority of problems. HD may be required to prepare the uremic patient for elective surgery and special precautions are also necessary to manage uremia and its typical consequences, such as coagulation defects, malnutrition, impaired immune function and wound healing [2–5]. Residual glomerular filtration rate is an important risk factor and its preservation is of paramount importance [6]. Perioperative correction of fluid balance and maintenance of urine flow are essential. Knowledge of all the potential sequelae of renal failure and their appropriate management will result in optimal perioperative care of these patients, reducing morbidity and mortality [6, 7].

10.2 Hepatic Cysts

Simple hepatic cysts usually arise from aberrant bile duct cells that develop during embryonic development and occur in 2–5% to 5–8% of the population in studies utilizing ultrasound (US) [8]. They must be differentiated from abscesses, hemangiomas, and malignancies and, in the case of irregular walls, septations,

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calcifications, or daughter cysts, contrast-enhanced CT or MRI should be preferred to US. Complications include infection, spontaneous hemorrhage, rupture, and external compression of the biliary tree or major vessels. Rarely, jaundice occurs as a result of cystic compression of the biliary system. Relief of this obstruction is accomplished by surgical decompression or resection of the dilated cysts. Asymptomatic cysts do not usually require treatment. Conversely, infected hepatic cysts that do not respond to conventional antibiotic therapy may require surgical drainage. This procedure is usually performed with US- or CT- guided puncture, although identifying the source of infection in uremic patients can be difficult due to the reduced sensitivity of imaging consequent to low permeability of cyst epithelium, impaired native renal function and alterations in anatomy [9]. In doubtful cases fluorodeoxyglucose-positron emission tomography can be used to identify the infected cyst. Treatment techniques for symptomatic simple hepatic cysts in uremic patients are not different from those in use for non-uremic patients and include percutaneous aspiration, aspiration followed by sclerotherapy, and surgery [10, 11]. The percutaneous approach is usually indicated for immediate palliation of symptoms; however, it is burdened by a high recurrence rate. To improve its effect and achieve permanent ablation, aspiration of intracystic fluid may be followed by intracystic instillation of sclerosing agents, such as ethanol, tetracycline, and minocycline [12], to reduce cyst volume and destroy the inner epithelium with excellent outcomes and recurrence rates <1% [13]. Results are excellent in terms of efficacy and safety for both aspiration and sclerotherapy: cyst volume reduction ranges between 76% and 100%, symptom reduction between 72% and 100%, and symptom disappearance between 56% and 100% [14]. It is very likely that these results also apply to uremic patients. Surgical treatment, including open or laparoscopic fenestration and hepatic resection, is effective in the long term in up to 90% of patients [15–17]. Laparoscopic fenestration [18] is today the preferred method because of its success rate and the reduction in morbidity and length of hospital stay, as compared with open procedures [11, 19, 20]. The anatomical suitability of hepatic cysts for laparoscopic fenestration depends on operator experience and confidence. For very large cysts or those difficult to locate laparoscopically, open fenestration is the alternative [19]. Recurrence rates vary from 0% to 36% after laparoscopic fenestration [21, 22]. To prevent recurrence, wide fenestration of the hepatic cyst, omental transposition flap [23] or electrocoagulation ablation of the remnant hepatic cyst epithelium [20] have been proposed. When the diagnosis of a hepatic cystic lesion is uncertain, surgical intervention becomes necessary. Resective liver surgery in uremic patients carries a higher risk of infection-related complications requiring invasive interventions, as well as life-threatening cardiac complications, compared to non-uremic patients [24–26]. Complete excision of the hepatic cyst, segmentectomy, or lobectomy are associated with higher morbidity and mortality risk, as compared with fenestration [16]. Uremic patients on HD have an approximately twofold greater risk of postoperative complications and a more than fourfold greater risk of in-hospital mortality after hepatic resection compared with non-HD patients [26]. For this reason, hepatic resection should be reserved for patients with recurrence after deroofing, diffuse hepatic involvement, and multiple

hepatic cysts [27]. Uremic patients on HD undergoing hepatic surgery should be dialyzed either the day before or on the day of the procedure [28], in which case it is important to make sure that the patient is at or close to dry weight prior to surgery. Heparin use should also be avoided or minimized. Discussion among the surgeon, anesthesiologist, nephrologist and hepatologist is crucial to avoid perioperative hypervolemia and pulmonary edema, on the one hand, or hypotension due to anesthesia-induced systemic vasodilatation in a relatively hypovolemic patient on the other, which may finally result in thrombosis and additional complications. Postoperatively, patients should be closely monitored for the development of hyperkalemia and acidosis. Nonetheless, the results of elective surgery are relatively good, and recurrence rates of 0% have been reported for total excision and lobe resection [19].

10.3 Polycystic Liver Disease

Polycystic liver disease (PLD) is a rare genetic disorder characterized by replacement of normal liver tissue with fluid-filled cysts, and its prevalence in the general population is 1–10 cases per 1,000,000 [29]. Although of biliary epithelial origin, the cysts have no connection to the bile ducts. Most PLD patients are asymptomatic, and no treatment is indicated. However, the natural history of PLD is characterized by a continuous growth in the number and size of cysts, which may cause compression of adjacent organs and abdominal wall herniation. The most common complications are infection, hemorrhage or rupture of a cyst, compression of the inferior vena cava, hepatic veins and, rarely, bile ducts [13]. For symptomatic patients, the principal aim of all interventional procedures is to reduce symptoms by decreasing cyst volume and liver size [13]. The choice of treatment is based on the size, location and number of the liver cysts, and on total liver volume [30]. Percutaneous cyst aspiration and sclerotherapy is mainly indicated for large symptomatic liver cysts, with a diameter >5 cm. Fenestration is usually indicated when there are few large dominant cysts in the anterior segments of the right lobe or in the left lateral segments. The main complications include post-procedure drainage, ascites, pleural effusion, arterial or venous bleeding, and bile leak [30]. Clinical response after laparoscopic fenestration of symptomatic cysts can reach 90.2%, complications 10.8%, mortality 1.0% [30]. Segmental hepatic resection is indicated when the cysts are clustered to individual segments, provided that at least 25–30% residual normal liver parenchyma is left to avoid dysfunction [31]. The main complications include venous bleed or bile leak, due to distortion of the intrahepatic vasculature and biliary system by cysts and adhesions that can complicate liver transplantation, if required in the future [31, 32].

10.4 Lithiasis

Hepatobiliary lithiasis (HBL) is characterized by the formation of stones within the gallbladder or the intra- and extrahepatic bile ducts. The prevalence is higher in populations of European and North American descent compared to those of Asian or African origin [33]. Well-known risk factors include obesity, a diet rich in fat and poor in fiber, physical inactivity, pregnancy, and genetic predisposition. Data regarding end-stage renal disease (ESRD) patients is less systematic. Kazama et al. argue that the risk of hepatobiliary stone formation is higher in the ESRD population except for stage 5 patients, compared to the non-ESRD population [34]. Hahm et al. in their study focusing on the Korean population found a prevalence for stones of 18.2% in patients with ESRD treated with HD, which was significantly higher than 5.3% in the non-uremic controls [35]. The treatment of HBL depends on the severity of the symptoms and the presence of complications (e.g., cholecystitis, cholangitis, pancreatitis). Treatment options may range from observation if there are no symptoms, to resective surgery. Intrahepatic lithiasis is a very difficult-to-treat condition that is characterized by frequent recurrence and often requires multiple operative interventions [36]. Repeated infection episodes can lead to formation of micro-abscesses, portal thrombophlebitis, fistulae into surrounding structures, biliary strictures, and severe destruction of liver parenchyma [36]. Biliary cirrhosis, portal hypertension and bleeding varices are the terminal manifestations. Wu et al. examined the efficacy and safety of three endoscopic techniques, sphincterotomy (EST), papillary balloon dilatation (EPBD), and sphincterotomy plus balloon dilation (ESBD), in managing choledocholithiasis among patients with ESRD undergoing HD and needing endoscopic retrograde cholangiopancreatography (ERCP) [37]. All three techniques showed comparable effectiveness in clearing stones, EST was associated with the highest complication rate, particularly post-ERCP bleeding. In contrast, ESBD had significantly lower bleeding rates compared to EST. EPBD's bleeding risk was similar to that of EST and ESBD but required longer balloon dilation time. Patients on HD are at increased risk of post-ERCP complications, and particularly a three times higher risk of bleeding, due to impaired platelet function [37]. While all techniques bear some risk for inducing pancreatitis, ESBD showed a lower occurrence compared to EPBD. Although all three techniques can effectively manage choledocholithiasis, the authors recommend ESBD as the preferred method for ESRD patients on HD due to its efficacy, reduced bleeding risk, and time efficiency in the context of balloon dilation [37]. Unfortunately, the scarcity of data in the literature and the lack of randomized controlled trials for the management of HBL in uremic patients makes it difficult to establish evidence-based recommendations.

10.5 Rare Situations

HBL in the context of cystic liver disease is rare, and only one case in association with Caroli's disease has been reported [38]. The association with autosomal dominant polycystic kidney (ADPKD) without Caroli's disease is also very rare; biliary malformations or HD are possible pathophysiologic mechanisms [35, 39]. There are some reports that kidney stones in ADPKD can be safely and effectively treated by extracorporeal shock wave lithotripsy (ESWL) [40], and for optimal outcome ESWL should be performed several times to better fragment stones, before ERCP.

10.6 Conclusions

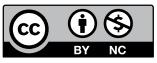
Special precautions are necessary for the management of the uremic patient undergoing hepatobiliary surgery. Treatment strategies should be personalized, based on individual patient risk, with special attention to the stage of chronic kidney disease and associated comorbidities. In all cases, endoscopic and minimally invasive techniques are preferred to reduce the risk of complications, emphasizing the need for tailored therapeutic choices. A multidisciplinary team approach, involving health professionals across all disciplines, is essential to lower the risk of complications and improve patient outcomes.

References

1. Trainor D, Borthwick E, Ferguson A. Perioperative management of the hemodialysis patient. Semin Dial. 2011;24:314.
2. Pinson CW, Schuman ES, Gross GF, et al. Surgery in long-term dialysis patients. Experience with more than 300 cases. Am J Surg. 1986;151:567.
3. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost. 2010;36(1):34–40.
4. Muscaritoli M, Molfino A, Bollea MR, et al. Malnutrition and wasting in renal disease. Curr Opin Clin Nutr Metab Care. 2009;12(4):378–83.
5. Cohen G, Vanholder R. Special issue: immune dysfunction in uremia. Toxins (Basel). 2021;13(1):70.
6. Cywinski JB, Mascha EJ, Kurz A, et al. Estimated glomerular filtration rate better predicts 30-day mortality after non-cardiac surgery than serum creatinine: a retrospective analysis of 92,888 patients. Can J Anesth. 2015;62:745–52.
7. Hansen LS, Hjortdal VE, Andreasen JJ, et al. 30-day mortality after coronary artery bypass grafting and valve surgery has greatly improved over the last decade, but the 1-year mortality remains constant. Ann Card Anaesth. 2015;18(2):138–42.
8. Gaines PA, Sampson MA. The prevalence and characterization of simple hepatic cysts by ultrasound examination. Br J Radiol. 1989;62(736):335–7.
9. Muther RS, Bennett WM. Cyst fluid antibiotic concentrations in polycystic kidney disease: difference between proximal and distal cysts. Kidney Int. 1981;20:519.
10. Doty JE, Tompkins RK. Management of cystic disease of the liver. Surg Clin North Am. 1989;69:285–95.
11. Marrero JA, Ahn J, Rajender Reddy K. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014;109:1328–47.

12. Drenth JP, Chrispijn M, Nagorney DM, et al. Medical and surgical treatment options for polycystic liver disease. Hepatology. 2010;52(6):2223–30.
13. Furumaya A, van Rosmalen BV, de Graeff JJ, et al. Systematic review on percutaneous aspiration and sclerotherapy versus surgery in symptomatic simple hepatic cysts. HPB (Oxford). 2020;23:11–24.
14. Wijnands TF, Görtjes AP, Gevers TJ, et al. Efficacy and safety of aspiration sclerotherapy of simple hepatic cysts: a systematic review. AJR Am J Roentgenol. 2017;208(1):201–7.
15. Lin TY, Chen CC, Wang SM. Treatment of non-parasitic cystic disease of the liver: a new approach to therapy with polycystic liver. Ann Surg. 1968;168:921–7.
16. Gall TM, Oniscu GC, Madhavan K, et al. Surgical management and longterm follow-up of nonparasitic hepatic cysts. HPB (Oxford). 2009;11:235–41.
17. Moorthy K, Mihssin N, Houghton PW. The management of simple hepatic cysts: sclerotherapy or laparoscopic fenestration. Ann R Coll Surg Engl. 2001;83:409–14.
18. Fabiani P, Katkhouda N, Iovine L, et al. Laparoscopic fenestration of biliary cysts. Surg Laparosc Endosc. 1991;1:162–5.
19. Garcea G, Pattenden CJ, Stephenson J, et al. Nine-year single-center experience with nonparasitic liver cysts: diagnosis and management. Dig Dis Sci. 2007;52:185–91.
20. Krâhenbühl L, Baer HU, Renzulli P, et al. Laparoscopic management of nonparasitic symptom-producing solitary hepatic cysts. J Am Coll Surg. 1996;183:493–8.
21. Yamada T, Furukawa K, Yokoi K, et al. Liver cyst with biliary communication successfully treated with laparoscopic deroofing: a case report. J Nippon Med Sch. 2009;76:103–8.
22. Tagaya N, Nemoto T, Kubota K. Long-term results of laparoscopic unroofing of symptomatic solitary nonparasitic hepatic cysts. Surg Laparosc Endosc Percutan Tech. 2003;13:76–9.
23. Emmermann A, Zornig C, Lloyd DM, et al. Laparoscopic treatment of nonparasitic cysts of the liver with omental transposition flap. Surg Endosc. 1997;11:734–6.
24. Barbas AS, Speicher PJ, Clary BM. Hepatic and pancreatic resection in patients with end-stage renal disease: a propensity analysis. HPB (Oxford). 2014;16:1016–22.
25. Chun-Chieh Y, Jaw-Town L, Long-Bin J. Hepatic resection for hepatocellular carcinoma patients on hemodialysis for uremia: a nationwide cohort study. World J Surg. 2013;37(10):2402–9.
26. Shinkawaa H, Yasunagab H, Hasegawaa K, et al. Mortality and morbidity after hepatic resection in patients undergoing hemodialysis: analysis of a national inpatient database in Japan. Surgery. 2018;163:1234–7.
27. Kaul V, Friedenberg F, Rothstein KD. Hepatic cysts. Curr Treat Options Gastroenterol. 2000;3:439–44.
28. Fielding-Singh V, Vanneman MW, Grogan T, et al. Association between preoperative hemodialysis timing and postoperative mortality in patients with end-stage kidney disease. JAMA. 2022;328(18):1837.
29. Masyuk TV, Masyuk AI, LaRusso NF. Therapeutic targets in polycystic liver disease. Curr Drug Targets. 2017;18(8):950–7.
30. Bernts LHP, Echternach SG, Kievit W, et al. Clinical response after laparoscopic fenestration of symptomatic hepatic cysts: a systematic review and meta-analysis. Surg Endosc. 2019;33(3):691–704.
31. Schindl MJ, Redhead DN, Fearon KC, et al. Edinburgh liver surgery and transplantation experimental research group (eLISTER). The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut. 2005;54(2):289–96.
32. Van Keipema L, Hockerstedt K. Treatment of polycystic liver disease. Br J Surg. 2009;96(12):1379–80.
33. Pak M, Lindseth G. Risk factors for cholelithiasis. Gastroenterol Nurs. 2016;39(4):297–309.
34. Kazama JJ, Kazama S, Koda R, et al. The risk of gallbladder stone formation is increased in patients with predialysis chronic kidney disease but not those undergoing chronic hemodialysis therapy. Nephron Clin Pract. 2009;111(3):c167–72.
35. Hahm JS, Lee HL, Park JY, et al. Prevalence of gallstone disease in patients with end-stage renal disease treated with hemodialysis in Korea. Hepato-Gastroenterology. 2003;50(54):1792–5.
36. Cha SW. Management of Intrahepatic Duct Stone. Korean J Gastroenterol. 2018;71(5):247–52.

37. Wu JH, Kang JW, Wang YS, et al. Comparison of different endoscopic methods used for managing choledocholithiasis in patients with end-stage renal disease undergoing hemodialysis. Dig Dis Sci. 2022;67(11):5239–47.
38. Lee JY, Dong SH, Woo YS, et al. Hepatolithiasis in a patient with autosomal dominant polycystic kidney disease treated by extracorporeal shock wave lithotripsy (ESWL). Dig Liver Dis. 2009;41(8):609.
39. Nakanuma Y, Terada T, Nagakawa T, et al. Pathology of hepatolithiasis associated with biliary malformation in Japan. Liver. 1988;8:287–92.
40. Martínez Sarmiento M, Broseta Rico E, Sanz Chinesta S, et al. Extracorporeal shock-wave lithotripsy in polycystic kidneys. Actas Urol Esp. 1994;18:35–8.



Hepatobiliary Oncologic Surgery

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Andrea Marchini, Enrico Gringeri, and Umberto Cillo

11.1 Introduction

Hepatobiliary cancers can occur in uremic patients. They include primary tumors such as hepatocellular carcinoma (HCC), cholangiocarcinoma (perihilar [pCCA], intrahepatic [iCCA] and distal [dCCA]), gallbladder cancer, and other rare primary liver cancers, and liver metastases.

These patients may have pre-existing chronic kidney disease (CKD) with uremia (end-stage renal disease [ESRD]) or can develop an acute kidney injury (AKI) with uremia. CKD is in itself a risk factor for cancer. AKI with uremia can also be caused by some cancers, such as pCCA or dCCA, which can cause obstructive jaundice with renal impairment [1]. In these patients, jaundice palliation and surgery for jaundice relief can reverse the AKI caused by hyperbilirubinemia.

In patients on long-term dialysis, the standardized incidence ratio for liver cancer is 1.41 [2].

Many hepatobiliary cancers occur in the setting of chronic liver disease, which independently increases the risk of both AKI and CKD.

HCC is the most common primary liver cancer and much of the existing literature focuses on HCC in uremic patients, whereas evidence for other hepatobiliary cancers in this population is scarce.

The population of patients with HCC highly overlaps with those for CKD and ESRD [3]. Renal dysfunction occurs in about 25% of HCC patients [3].

The risk factors that could lead to both HCC and CKD can be grouped into four categories: environmental toxins, viral hepatitis, metabolic syndrome, and vasoactive factors [3].

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HCC mostly occurs in cirrhotic patients. The prevalence of CKD in patients with cirrhosis has increased over the years, likely due to increased recognition and greater prevalence of metabolic risk factors. In-hospital renal replacement therapy (RRT) is required in 5–47% of patients, with mortality rates between 60% and 80% [4].

11.2 Complexities in Surgical Management

Surgical management must consider the fragility of these patients, especially the cirrhotic ones. To the uremia-related complications we must add the other cirrhotic impairments which worsen the patients' prognosis. Thus, an accurate selection of patients candidate to surgery is necessary, evaluating the increased anesthesiological risk which will focus on platelet dysfunction, fluid overload risk, electrolyte imbalances, augmented risk of bleeding and infections.

Liver resection with complete tumor excision with free margins is still considered the most radical treatment. Locoregional therapies, such as radiofrequency (RFA) or microwave ablation (MWA), using a minimally invasive approach can be valid alternatives in selected cases. Liver transplant or combined sequential liver-kidney transplant is another option in selected patients.

The risk of bleeding, already high in hepatic surgery, is further increased in cirrhotic patients with uremia, due to platelet dysfunction and altered interaction of the platelets with vascular endothelium in addition to thrombocytopenia [5].

Therefore, an extended evaluation of hemostasis using rotational thromboelastometry (ROTEM) as well as of platelet function by platelet function analyzer (PFA) and multiple electrode aggregometry (Multiplate) should be considered in these patients [6].

Liver resection in ESRD is associated with increased mortality and morbidity. A propensity score study involving more than 50,000 eligible patients, of whom 498 (0.93%) were on hemodialysis, demonstrated that these patients had more postoperative major complications (18.1% vs 7.4%) and in-hospital mortality: OR 2.36 in limited resection, 4.61 in segmentectomy or sectoriectomy and 5.58 in bisectoriectomy or trisectoriectomy [7].

Oncologic hepatobiliary surgery should be performed by experienced surgeons, with a preference for minimally invasive approaches to reduce bleeding risk. Enhanced recovery after surgery (ERAS) protocols, including preoperative nutritional support, early mobilization, and minimization of opioid use, are recommended. Postoperative strategies to prevent renal failure should include: careful monitoring of renal function, avoidance of nephrotoxic medications, and early postoperative dialysis when necessary. A multidisciplinary approach is strongly recommended [8].

11.3 Surgical Treatment of Hepatocellular Carcinoma

CKD is a negative prognostic predictor in HCC patients receiving surgical resection and transarterial chemoembolization [9].

According to a recent meta-analysis considering liver resection for HCC in CKD patients, the CKD group experienced greater blood loss, need for blood transfusion (OR = 2.47), overall complications (OR = 2.1), grade III or higher complications (OR = 2.04) and worse overall survival (OS) (HR = 1.28), though disease free survival (DFS) was not significantly different (HR = 1.11, p = 0.16) [10]. Among the complications, postoperative bleeding and surgical site infection were higher in CKD [11].

Cumulative survival seems to be lower in HCC patients on regular hemodialysis. The major studies of resected uremic patients reported one 1-, 5-, and 10-year OS rates of 86%, 52%, and 38%, and DFS rates of 77%, 27%, and 18% [12]. Another study found that 1-, 3-, and 5- year survival rates were 78%, 67.9%, and 54.4% for patients with HCC on hemodialysis, compared to 88.3%, 74.5% and 64.8% for those without hemodialysis. Hemodialysis, older age and advanced tumor stages were independent predictors for mortality, with the risk of death 2.03 higher in hemodialysis patients compared to non-hemodialysis patients [13].

In conclusion, ESRD on dialysis does not seem to significantly affect the survival outcomes of patients undergoing liver resection for HCC. With meticulous operative techniques and perioperative care, comparable OS and DFS can be achieved in selected patients with ESRD and HCC undergoing liver resection. ESRD on dialysis is not expected to be an obstacle to hepatectomy in selected patients [3].

Given the high complication rates associated with resection, locoregional therapies might be a valid alternative. Notably, there appear to be no significant differences in OS and DFS in patients with *naïve* HCC treated with liver resection or RFA [14].

A significant study evaluating the safety and efficacy of percutaneous RFA in hemodialysis patients (enrolling 437 patients on regular hemodialysis and 1345 matched non-dialyzed patients) found that in-hospital mortality was higher in the dialysis group (1.1% vs 0.15%). Mortality was significantly lower in patients ≤70 years compared to older patients. Hemorrhagic complications were also more common in dialysis than non-dialysis patients (3.4% vs 0.87%) [15]. While most studies focus on the percutaneous approach, laparoscopic MWA should also be considered due to its advantages [16].

Liver transplant for early-stage HCC is effective even in patients with advanced CKD, and combined liver-kidney transplant is recommended in selected individuals [17].

11.4 Surgical Treatment of Cholangiocarcinoma and Liver Metastasis

There is limited literature on other primary liver cancers and metastatic disease in uremic patients. One important consideration is the renal impairment caused by prolonged chemotherapy, particularly for colorectal liver metastases and other metastatic diseases. Careful patient selection is critical for surgery. It is unlikely that these patients will undergo elective surgery while in a uremic state; however, they should be considered for surgery at an appropriate time. Repeated surgeries using minimally invasive approaches may also serve as a strategy to reduce chemotherapy-related renal impairment.

An emerging frontier in this field is transplant oncology, where liver transplantation is considered for patients with cholangiocarcinoma and colorectal liver metastases under specific protocols. Many of these patients have received chemotherapy, which can lead to renal impairment. However, no literature currently addresses uremic patients in this context.

For dCCA, the standard surgical treatment is duodenopancreatectomy.

11.5 Conclusion

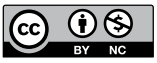
In conclusion, a uremic state has to be considered a severe comorbidity, in particular in the setting of hepatobiliary malignancies where the high technical complexity of the interventions required significantly increases the risk of postoperative morbidity and mortality. Moreover, the transitory liver impairment frequently occurring in the postoperative course of such interventions may *per se* induce further renal function impairment in the context of the pathophysiologic derangements typical of a hepatorenal syndrome.

On these bases, the timing, extent of parenchymal resection, access route, surgical expertise and other converging comorbidities should be carefully considered before planning an hepatobiliary operation in uremic patients.

References

1. Mairiang P, Bhudhisawasdi V, Borirakchanyavat V, Sitprija V. Acute renal failure in obstructive jaundice in cholangiocarcinoma. Arch Intern Med. 1990;150(11):2357–60.
2. Xie X, Li F, Xie L, et al. Meta-analysis of cancer risk among end stage renal disease undergoing maintenance dialysis. Open Life Sci. 2023;18(1):20220553.
3. Yeh H, Chiang CC, Yen TH. Hepatocellular carcinoma in patients with renal dysfunction: pathophysiology, prognosis, and treatment challenges. World J Gastroenterol. 2021;27(26):4104–42.
4. Nadim MK, Kellum JA, Forni L, et al. Acute kidney injury in patients with cirrhosis: acute disease quality initiative (ADQI) and international club of ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol. 2024;81(1):163–83.
5. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? Blood. 1999;94(8):2569–74.

6. Gäckler A, Rohn H, Lisman T, et al. Evaluation of hemostasis in patients with end-stage renal disease. PLoS One. 2019;14(2):e0212237.
7. Shinkawa H, Yasunaga H, Hasegawa K, et al. Mortality and morbidity after hepatic resection in patients undergoing hemodialysis: analysis of a national inpatient database in Japan. Surgery. 2018;163(6):1234–7.
8. Ruff SM, Cloyd JM, Pawlik TM. Annals of Surgical Oncology practice guidelines series: management of primary liver and biliary tract cancers. Ann Surg Oncol. 2023;30(13):7935–49.
9. Ho SY, Liu PH, Hsu CY, et al. ALBI grade in dialysis patients with hepatocellular carcinoma: prognostic impact and staging strategy. J Gastrointest Oncol. 2021;12(2):722–34.
10. Liu XY, Zhao ZQ, Cheng YX, et al. Does chronic kidney disease really affect the complications and prognosis after liver resection for hepatocellular carcinoma? A meta-analysis. Front Surg. 2022;9:870946.
11. Sakamoto Y, Shimada S, Kamiyama T, et al. Impact of comorbid renal dysfunction in patients with hepatocellular carcinoma on long-term outcomes after curative resection. World J Gastrointest Surg. 2022;14(7):670–84.
12. Yeh CC, Lin JT, Jeng LB, et al. Hepatic resection for hepatocellular carcinoma patients on hemodialysis for uremia: a nationwide cohort study. World J Surg. 2013;37(10):2402–9.
13. Lee CH, Hsieh SY, Chang CC, et al. Hepatocellular carcinoma in hemodialysis patients. Oncotarget. 2017;8(42):73154–61.
14. Hiraoka A, Kumada T, Michitaka K, et al. Clinical features of hemodialysis patients treated for hepatocellular carcinoma: comparison between resection and radiofrequency ablation. Mol Clin Oncol. 2017;6(4):455–61.
15. Sato M, Tateishi R, Yasunaga H, et al. Mortality and hemorrhagic complications associated with radiofrequency ablation for treatment of hepatocellular carcinoma in patients on hemodialysis for end-stage renal disease: a nationwide survey. J Gastroenterol Hepatol. 2017;32(11):1873–8.
16. Cillo U, Bertacco A, Fasolo E, et al. Videolaparoscopic microwave ablation in patients with HCC at a European high-volume center: results of 815 procedures. J Surg Oncol. 2019;120(6):956–65.
17. Fabrizi F, Cerutti R, Alfieri CM, Ridruejo E. An update on hepatocellular carcinoma in chronic kidney disease. Cancers. 2021;13(14):3617.



Non-oncologic Pancreatic Surgery

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12.1 Introduction

Advancements in renal replacement therapy and the management of diabetes and cardiovascular conditions have improved life expectancy among patients with chronic renal failure [1]. However, surgical outcomes in these patients remain a challenge, given their increased vulnerability to complications and mortality. Uremic patients undergoing general, vascular, and cardiac surgeries frequently experience higher rates of pulmonary complications, reoperations, and infections [2–7]. While significant literature exists for oncologic pancreatic surgeries, data on non-oncologic pancreatic surgeries for uremic patients are sparse [1].

12.2 Complications and Considerations in Uremic Patients

Uremic patients undergoing surgery often face complications related to pulmonary function, cardiovascular stability, and infection risks. Pulmonary problems are particularly common and may stem from dialysis-induced hypoxemia and resultant hypoventilation [8]. These complications result from impaired gas exchange,

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alveolar-capillary barrier damage, and possible microvascular pathology related to chronic dialysis. Prolonged hospital stays, higher reintubation rates and delayed wound healing further underscore their complexity [9]. Preoperative, perioperative, and postoperative management tailored to renal dysfunction is critical in mitigating these risks. The intricacies of managing these patients demand careful attention at every phase of care:

- Preoperative care: Comprehensive preoperative evaluation is critical. This includes a detailed cardiovascular assessment using echocardiography or stress testing, given the high prevalence of cardiovascular disease among uremic patients. Correcting anemia with erythropoiesis-stimulating agents and optimizing hemoglobin levels minimizes perioperative hypoxia and enhances wound healing. Stabilizing electrolyte imbalances, particularly potassium and calcium, is vital for reducing perioperative cardiac arrhythmia risks [10]. Timely scheduling of dialysis before surgery prevents fluid overload and maintains electrolyte balance.
- Perioperative considerations: Close monitoring of intravascular volume is imperative. Uremic patients are prone to fluid shifts, which can exacerbate pulmonary edema or precipitate hypovolemic shock. Anesthetic agents need adjustments based on altered pharmacokinetics and renal clearance. Anticoagulation therapy must balance the risks of bleeding due to uremic platelet dysfunction and the thrombotic risk associated with dialysis catheters. Fluid and electrolyte management demand precise control to prevent exacerbation of renal damage. Coagulation disorders require careful monitoring and potential preemptive interventions [3].
- Postoperative phase: Aggressive infection control strategies are paramount, given the immune dysfunction associated with uremia. Regular pain assessments should guide analgesic administration, avoiding nephrotoxic agents wherever possible. Dialysis may require modifications to accommodate nutritional and electrolyte losses exacerbated by surgery [1].

12.3 Indications for Non-oncologic Pancreatic Surgery

While complication and mortality rates of dialysis patients have been a subject of several articles in cardiac surgery [11], there is a relative paucity of data on the complication and mortality rates of uremic patients undergoing general surgery [7]; in addition, most of them deal with topics related to neoplastic pathology. Non-oncologic pancreatic surgery in uremic patients is typically indicated for conditions such as pancreatic trauma, chronic pancreatitis, and severe acute pancreatitis. Uremic patients are uniquely vulnerable due to the impact of end-stage renal disease (ESRD) on pancreatic physiology, with prolonged peritoneal dialysis potentially exacerbating exocrine insufficiency [12–14].

In chronic pancreatitis, indications for surgery typically revolve around alleviating pain or managing complications such as pseudocysts and bile duct stenoses or obstructions. Surgical techniques, such as lateral pancreaticojejunostomy (Puestow

procedure), aim to decompress dilated ducts, while preserving endocrine and exocrine function. Endoscopic drainage remains preferable in fragile uremic populations, given its minimally invasive nature and reduced perioperative risk [15, 16].

Management of severe acute pancreatitis in uremic patients exhibits unique challenges and involves a multidisciplinary approach- Surgical interventions should be reserved for:

1. Infected necrotizing pancreatitis with clinical deterioration, unresponsive to percutaneous or endoscopic interventions [16].
2. Persistent organ failure after infection resolution [17].
3. Sterile necrotizing pancreatitis with significant mass effect, including biliary or intestinal obstruction, represents another clear surgical indication [15].

Minimally invasive approaches, such as percutaneous drainage, endoscopic necrosectomy and laparoscopic or robotic debridement, are increasingly favored due to shorter recovery times and reduced systemic inflammation, and should precede surgical approaches whenever feasible [12, 15].

12.4 Surgical Techniques and Outcomes

Surgical strategies for pancreatic diseases vary based on the pathology and patient profile. Surgical options include drainage procedures, pancreatic debridement, and resections. Drainage procedures target localized fluid collections and can be performed using percutaneous, endoscopic, or open methods. In uremic patients, non-surgical drainage is highly recommended when feasible. Although effective for specific indications, pancreatic resections carry significant risks, including anastomotic leaks and infection, with mortality rates heightened in renal-compromised individuals, emphasizing the need for a multidisciplinary approach [1].

The involvement of an integrated team of nephrologists, intensivists, anesthesiologists, and surgeons is vital for developing personalized care plans. This collaborative approach enhances outcomes by providing personalized perioperative plans, optimizing preoperative preparation, intraoperative management, and postoperative recovery, mitigating the risks inherent to this population [1].

The evidence-based analysis of pancreatic resections highlights a consistent theme: patients with renal insufficiency undergoing pancreatic surgery face greater risks compared to non-uremic patients with increased mortality and complications rates. Analysis of perioperative outcomes for pancreatic resections revealed increased mortality associated with delayed interventions, emphasizing the importance of timeliness and multidisciplinary planning [17]. A systematic review confirming a significant association between hemodialysis and incidence of acute pancreatitis underscores the need for proactive screening in ESRD populations [13]. A retrospective study detailed the clinical course of acute pancreatitis in dialysis patients, noting increased rates of necrotizing forms and longer hospitalizations [12]. Factors contributing to these poor outcomes include prolonged surgical

durations, infection risks, and inadequate preoperative dialysis [17]. Conversely, studies emphasize the importance of preoperative stabilization and multidisciplinary planning in achieving acceptable outcomes [1, 10].

Radiological and endoscopic emerging technologies and techniques have transformed the management of pancreatic diseases offering safer alternatives to traditional surgery. Endoscopic interventions, including endoscopic retrograde cholangiopancreatography (ERCP)-guided drainage and stent placement, have proven particularly advantageous. These minimally invasive methods avoid large incisions, reduce pain, and enable quicker recovery, crucial for uremic patients with limited physiological reserves [15, 16].

12.5 Challenges and Future Directions

Key challenges include limited high-quality research data on non-oncologic pancreatic surgery specific to uremic populations, necessitating reliance on broader studies and the adaptation of guidelines from general surgical populations. Future directions should focus on: expanded use of robotic-assisted pancreatic surgeries to optimize precision and reduce morbidity; advanced imaging modalities, such as endoscopic ultrasound (EUS), for early detection of pancreatic abnormalities; prospective multicenter trials to generate robust evidence tailored to the unique physiology of uremic patients [17].

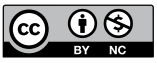
12.6 Conclusion

Non-oncologic pancreatic surgery in uremic patients is complex, requiring a highly nuanced and tailored approach accounting for their increased vulnerability and complex pathophysiology. Success depends on multidisciplinary collaboration, careful surgical selection, and integration of minimally invasive techniques. Continuous research is essential to optimize outcomes and develop evidence-based guidelines for managing this high-risk group.

References

1. Norman KS, Domingo SR, Wong LL. Pancreatic resections in renal failure patients: is it worth the risk? HPB Surg. 2014;2014:938251.
2. Ozel L, Krand O, Ozel MS, et al. Elective and emergency surgery in chronic hemodialysis patients. Ren Fail. 2011;33(7):672–6.
3. Schneider CR, Cobb W, Patel S, et al. Elective surgery in patients with end stage renal disease: what's the risk? Am Surg. 2009;75(9):790–3.
4. 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(4):766–73.

5. Labrousse L, de Vincentiis C, Madonna F, et al. Early and long term results of coronary artery bypass grafts in patients with dialysis dependant renal failure. Eur J Cardiothorac Surg. 1999;15(5):691–6.
6. Bechtel JFM, Detter C, Fischlein T, et al. Cardiac surgery in patients on dialysis: decreased 30-day mortality, unchanged overall survival. Ann Thorac Surg. 2008;85(1):147–53.
7. Gajdos C, Hawn MT, Kile D, et al. Risk of major nonemergent inpatient general surgical procedures in patients on long-term dialysis. JAMA Surg. 2013;148(2):137–43.
8. Pierson DJ. Respiratory considerations in the patient with renal failure. Respir Care. 2006;51(4):413–22.
9. Drolet S, MacLean AR, Myers RP, et al. Morbidity and mortality following colorectal surgery in patients with end-stage renal failure: a population-based study. Dis Colon Rectum. 2010;53(11):1508–16.
10. Yasuda K, Tahara K, Kume M, et al. Risk factors for morbidity and mortality following abdominal surgery in patients on maintenance hemodialysis. Hepato-Gastroenterology. 2007;54(80):2282–4.
11. 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(7):2275–83.
12. Bruno MJ, van Westerloo DJ, van Dorp WT, et al. Acute pancreatitis in peritoneal dialysis and haemodialysis: risk, clinical course, outcome, and possible aetiology. Gut. 2000;46(3):385–9.
13. Wang H, Rong J, Song C, et al. Hemodialysis and risk of acute pancreatitis: a systematic review and meta-analysis. Pancreatology. 2021;21(1):89–94.
14. Avram MM. High prevalence of pancreatic disease in chronic renal failure. Nephron. 1977;18(1):68–71.
15. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–16.
16. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13(4 Suppl 2):e1–e15.
17. Teh SH, Diggs BS, Deveney CW, Sheppard BC. Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines. Arch Surg. 2009;144(8):713–21.



Oncologic Pancreatic Surgery

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13.1 Introduction

Patients with chronic kidney disease (CKD) are at increased risk of developing cancers compared to the general population, and their number is expected to rise in the future [1, 2]. Specifically, patients receiving chronic hemodialysis are at significant risk for all cancers, which are the third leading cause of death among these patients with higher incidence and mortality rates of cancer than the general population [2–4].

A recent nationwide cohort study of hemodialysis patients with cancer in Japan was conducted at 20 centers to evaluate the long-term prognosis of hemodialysis patients with cancer compared with cancer patients in general [5]. Patients with

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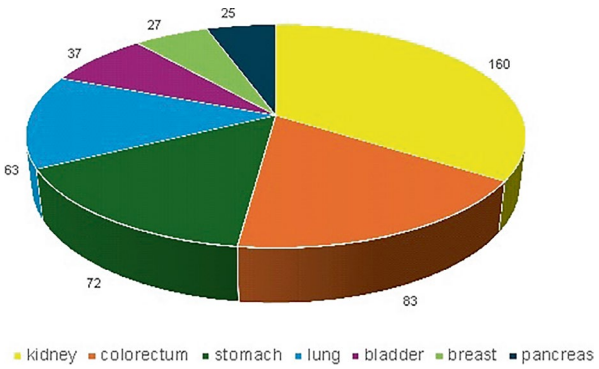

Fig. 13.1 Cancer occurrence in uremic patients on hemodialysis in a nationwide multicenter study in Japan. (Original graph obtained from the results of the study [5])

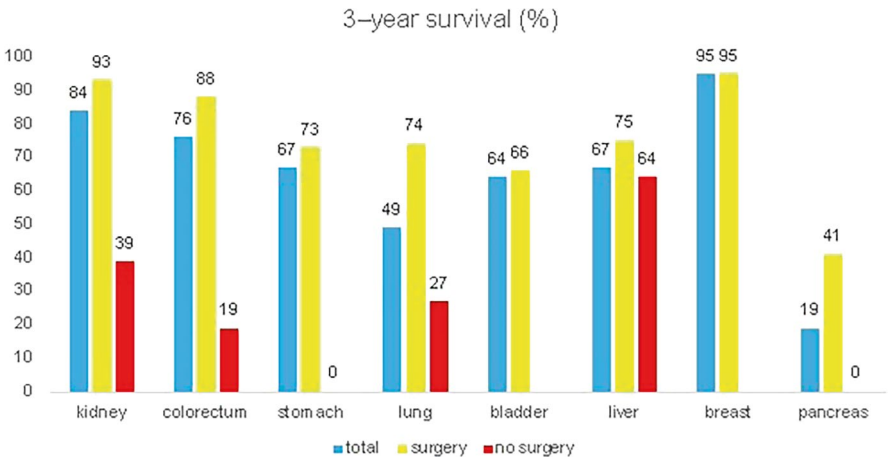

Fig. 13.2 3-year survival rates (%) among operated uremic patients on hemodialysis (surgery) and non-operated uremic patients on hemodialysis (no surgery). (Original graph obtained from the results of the study [5])

uremia had a higher cancer incidence (Fig. 13.1) and a worse prognosis (Fig. 13.2) than those not receiving hemodialysis [5]. Overall, 3-year survival was 83% in patients who underwent surgery and 32% in those who did not [5]. In the surgical group, patients with kidney and breast cancer had 3-year survival rates greater than 90%, while those with pancreatic cancer (PC) had the worst 3-year survival rates (40%) [5]. In contrast, in the non-surgical group, while patients with liver cancer had a 3-year survival rate of 64%, those with stomach or PC had a 3-year survival rate of 0% [5]. The causes of death were different in the surgical group compared with the non-surgical group [5]. Non-cancer-related mortality (80%) was more common in the surgical group, while cancer-related mortality (70%) was predominant in the non-surgical group [5].

Among tumors, we focused on PC in uremic patients, trying to analyze whether in these subjects PC has peculiar characteristics in terms of incidence, resectability, and prognosis.

PC is one of the deadliest malignancies worldwide and the one with the lowest survival rates after diagnosis [1, 3]. Its incidence has been gradually increasing over the years, probably owing to the aging of the population and for the improvement of diagnostic imaging [3, 4]. Pancreatic adenocarcinoma has the highest incidence (85%) and is much more frequent than neuroendocrine forms such as gastrinoma, insulinoma, somatostatinoma, glucagonoma and non-functional islet cell tumors [4]. The most common site of onset is in the pancreatic head [1, 4].

Several factors, both genetic and environmental, have been recognized as being responsible for PC, but among them no correlation has been demonstrated between uremia and increased development of PC [1, 3, 4]. However, uremic patients present very high complication and mortality rates after pancreatectomy, with postoperative complications reported to range from 30.6% up to 100% [1, 2, 4]. The number of patients with uremia is expected to rise in the future and, consequently, the number of pancreatectomies performed in this category of patients [1, 4].

Currently, the results of pancreatectomy in uremia are not well understood. Therefore, it is necessary to explore the current state of the art of pancreatectomy results in these patients.

13.2 Perioperative Management

Uremic patients undergoing pancreatectomy have a peculiar peri- and postoperative complexity [1, 2, 6]. In fact, these patients often have altered cardiovascular and respiratory function [2, 6]. Chronic dialysis can induce hypoxic damage with consequent hypoventilation and can generate damage to the microcirculation [2, 6]. This results in prolonged postoperative hospital stay, which increases the risk of nosocomial infections [2, 6]. For these reasons, the perioperative management of uremic patients undergoing pancreatectomy must be particularly careful [6].

The preoperative phase of these patients is characterized by a detailed cardiorespiratory evaluation [2, 6]. In fact, the main comorbidities of uremic patients are anemia, often with associated hypoxia, cardiac pathologies and electrolyte imbalances induced by renal malfunction [2, 6]. Consequently, the preoperative phase includes blood tests, electrocardiogram and echocardiogram, dialysis programming and the potential use of erythropoiesis-stimulating agents to correct the anemia [2, 6]. Furthermore, since these patients are at risk for platelet dysfunction, adjustments of anticoagulant therapy should be considered to reduce the risks of intra- and postoperative bleeding [2, 6, 7].

Uremic patients have an increased risk of developing hypovolemia and hypovolemic shock intraoperatively [6, 7]. Therefore, during pancreatectomy, special attention should be paid to monitoring fluid intake and urine output to reduce the risk of acute renal failure or renal damage [6, 7].

The usually longer postoperative hospitalization of uremic patients requires careful monitoring for the appearance of nosocomial infections [6, 7], as they are in fact often immunosuppressed and more easily incur bacterial, viral and fungal infections [6, 7]. Furthermore, their nephropathy requires not to administer nephrotoxic anti-inflammatory drugs, except in cases of extreme necessity [6, 7].

In the postoperative evaluation, the surgeon should consider that a uremic patient who has undergone pancreatectomy more often has underlying comorbidities such as ischemic heart disease, diabetes mellitus, and hypertension than the general population [2]. In a retrospective analysis of 307 patients, the most common complication was peritonitis, followed by sepsis, disseminated intravascular coagulation, intra-abdominal bleeding, and acute coronary event [2]. Furthermore, these patients had higher 30-day mortality (OR 7.45; 95% CI 3.26–17.0; $p < 0.001$) and 90-day mortality (OR 10.9; 95% CI, 6.58–18.2; $p < 0.001$) than those who did not undergo hemodialysis [2]. The highest postoperative mortality in uremic patients occurs after any abdominal surgery in addition to pancreatectomy, and renal dysfunction is one of the main causes of mortality [2]. A lack of statistically significant evidence of increased mortality in these patients has been reported in only one paper, but this study was based on small numbers and did not differentiate uremic patients based on CKD stage [2]. The same authors note that severe CDK in uremic patients is associated with an increased risk of postoperative complications, so they conclude that only few patients with uremia can undergo pancreatectomy (pancreaticoduodenectomy [Whipple], distal pancreatectomy, central pancreatectomy, or total pancreatectomy) [2], as also reported by other authors [8]. When drawing these conclusions, it should still be considered that, given that pancreatectomies in themselves carry a significant risk of morbidity and mortality, the influence of preoperative renal function on the surgical outcomes of such procedures has a statistically significant role.

In the J-CANDY study, the authors analyzed 374 hemodialysis patients undergoing surgery for renal, colorectal, gastric, pancreatic, liver, lung, bladder, and breast cancer [5]. The study divided patients into two groups: surgical and non-surgical. The main causes of death in the surgical group were heart failure and cerebrovascular accident because, in this series, the oncologic uremic patients in the surgical group tended to have less advanced cancers, and therefore surgery could give curative results [5]. In contrast, the oncologic uremic patients in the non-surgical group were more likely to die from cancer because of advanced cancer [5]. Uremia with pancreatic cancer and anemia was characterized by unfavorable prognosis in the surgical group [5]. This study underscored that the treatment of comorbidities in hemodialysis is important to improve the survival of cancer patients with uremia [5] and that early diagnosis could positively influence the prognosis also in those oncologic uremic patients to be subjected to surgery [5].

13.3 Oncologic Treatment

Since 2020, gemcitabine (GEM) and S-1 have been used as neoadjuvant chemotherapy for resectable pancreatic cancer [9–11]. Neoadjuvant chemotherapy with S-1, GEM and nab-paclitaxel is performed in patients with borderline resectable tumors, which can be combined with neoadjuvant radiotherapy [9, 10]. In cases of patients with initially unresectable tumors and subsequent successful chemotherapy, it is considered whether to perform pancreatectomy [9–11].

Adjuvant therapy does not present pharmacological differences between uremic patients and the general population [6]. In addition to chemotherapy based on S-1 or GEM, in cases of positive resection margins, radiotherapy should be requested [6]. However, the difference between the two groups of patients concerns the dosage of adjuvant chemotherapy: uremic patients receive a reduced dose of S-1 or GEM, due to their reduced GFR [10–12]. Blood tests and CT scan are performed every 3 months for the first 3 years after resection, both in uremic and non-uremic patients [10–13]. After the first 3 years, patients without recurrence are usually followed up every 4–6 months [11, 13]. The authors who performed the follow-up of these patients defined recurrence on radiological or biopsy findings [10, 12]. In the literature, uremia is a statistically significant risk factor for any complication after pancreatectomy but not for the onset of serious complications (Clavien-Dindo class ≥IIIa) [14].

The results of the JASPAC-01 study show that S-1 is better than GEM alone for adjuvant therapy in terms of both the time from the date of surgery to the date of confirmed cancer recurrence (recurrence-free survival) and the time from the date of surgery to the date of death from any cause (overall survival) and that these patients have a better prognosis [10]. Uremic patients tend to discontinue neoadjuvant chemotherapy earlier than non-uremic patients, mainly due to creatinine clearance <60 mL/min, anemia [10, 15], or immunodeficiency, [8] and they have a reduced ability to complete adjuvant chemotherapy compared to non-uremic patients [8].

For metastatic pancreatic ductal adenocarcinoma (PDAC), GEM-based therapy has been the oncologic treatment of choice [16, 17]. Recently, the combined chemotherapy regimen of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) has been adopted to improve the median survival of non-uremic patients [16, 17]. Uremic patients with PDAC receiving GEM tolerated chemotherapy without unexpected side effects, like patients without renal insufficiency [18]. However, there are currently few studies of uremic patients with PDAC treated with GEM and even fewer with FOLFIRINOX [16–18]. Only one study has examined the effects of GEM with nab-paclitaxel in uremic patients [16]. Considering that paclitaxel pharmacokinetics in these patients is similar to that in patients with normal renal function, as demonstrated by Janus et al., it was hypothesized that nab-paclitaxel would not require any dose reduction even in uremic patients [16, 19]. The outcome was not encouraging as the patient undergoing this chemotherapy

regimen developed pneumonitis and grade 3 neutropenia during the first cycle and again in the second cycle, even after the dose of both drugs was reduced by 80% [16]. Subsequently, this patient continued combination chemotherapy for 7 months, with efficacy equal to that of patients with normal renal function [16]. These results confirm the need to adjust the dosage of chemotherapy in uremic patients [16]. Usually, patients with impaired renal function are not enrolled in studies to evaluate the efficacy of chemotherapy [17, 18]. Therefore, the limited case reports present in the literature do not allow one to draw statistically significant conclusions in uremic patients with pancreatic cancer [16–18]. The lower survival of these patients compared to non-uremic patients with pancreatic cancer depends on the greater underlying comorbidities [16, 17, 20].

13.4 Surgical Techniques and Outcomes

There is no difference in the surgical approach between uremic patients and non-uremic patients [6, 7, 12, 21–23]. In fact, for both groups of patients, the surgical approach to pancreatic head carcinoma is pancreaticoduodenectomy (PD) together with lymphadenectomy of the anterior and posterior pancreatic region, pyloric region, hepatoduodenal ligament, common and superior hepatic artery [6]. Resection and reconstruction of portal vein and/or superior mesenteric vein is performed in the case of tumor adherence to these vessels [6, 24], as per the REDISCOVER guidelines [25, 26]. Finally, the extrapancreatic nerve plexus surrounding the superior mesenteric artery, common hepatic artery, and celiac trunk must be cleared to minimize the risk of local recurrence [6]. PD accounts for the highest number of pancreatectomies in uremic patients, followed by distal pancreatectomy and, finally, central or total pancreatectomy [6].

The short-term results after pancreatic resection in uremic patients may be acceptable, while the medium- and long-term results may be poor [12, 20]. According to Shinkawa et al., in a retrospective analysis of 307 uremic patients undergoing PD for cancer, the main postoperative complications were post-pancreatectomy hemorrhage, acute coronary event, peritonitis, sepsis, and disseminated intravascular coagulation. The 30-day mortality rate was 5.2%, and the 90-day mortality rate was 17.3%, which was 10.9 times higher in dialyzed uremic patients [2, 12]. According to Feyko et al. and Norman et al., the 30-day mortality rates were 5.1% and 21.4%, respectively [20, 23]. In addition, both authors reported septic shock and reintubation as main postoperative complications [20, 23, 26]. Different authors have reported several different complications arising in uremic patients: cholangitis (100%) [22]; ascites (100%) [21]; postoperative pancreatic fistula, surgical site infection, cholangitis and bile leakage [6]. However, most authors reported on the short-term outcomes after pancreatectomy, while the long-term outcomes often are not available, because uremic patients have shorter survival due to overall compromised general health [4, 6, 20–23]. Therefore, the latter are currently not well defined, and no definitive conclusions can be drawn.

13.5 Future Directions

Many studies have common limitations that currently hinder the drawing of definitive conclusions. Series of uremic patients with CKD undergoing neoadjuvant therapy are often small compared to the non-uremic oncologic population, so it is difficult to assess in detail both the safety and efficacy of neoadjuvant chemoradiotherapy. Furthermore, the studies are retrospective, single-center, with a selection bias, and statistical analysis is not available due to the small number of patients undergoing pancreatectomy. However, the current results indicate that pancreatectomy can be performed safely in uremic patients, while the rate of completion of adjuvant therapy is significantly low. Therefore, large-scale multicenter and prospective studies are needed in the future to properly identify how CKD and its associated comorbidities may influence the postoperative outcomes of pancreatectomy in patients with uremia. Further advances in safer chemotherapy and radiotherapy to reduce perioperative comorbidities are expected.

13.6 Conclusion

In uremic patients, pancreatectomies—particularly PD and total pancreatectomy—should be carefully considered due to the high burden of comorbidities and the increased risk of postoperative complications. Treatment should be individualized, and a multidisciplinary approach is essential. While the short-term outcomes after PD are promising, this procedure should be performed in specialized centers to minimize postoperative morbidity and mortality. In the future, large-scale studies and the development of standardized guidelines for the peri- and postoperative surgical management of patients with uremia will be crucial.

References

1. Saad AM, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades. BMC Cancer. 2018;18:688.
2. Shinkawa H, Yasunaga H, Hasegawa K, et al. Mortality and morbidity after pancreatoduodenectomy in patients undergoing hemodialysis: analysis using a national inpatient database. Surgery. 2019;165:747–50.
3. Pearce N. Epidemiology as a population science. Int J Epidemiol. 1999;28(5):S1015–S8.
4. Lau MK, Davila JA, Shaib YH. Incidence and survival of pancreatic head and body and tail cancers: a population-based study in the United States. Pancreas. 2010;39:458–62.
5. Toriu N, Yamamoto S, Matsubara T, et al. Cancer diagnosis and prognosis after initiation of hemodialysis: multicenter Japan CANcer and DialYsis (J-CANDY) study. Clin Kidney J. 2024;18(2):sfae430.
6. Tamura S, Kanemoto H, Fujita A, et al. The impact of preoperative renal insufficiency on the outcomes of patients with pancreatic cancer undergoing pancreaticoduodenectomy. Langenbeck's Arch Surg. 2024;409(1):338.

7. Yamada S, Shimada M, Morine Y, et al. Significance of frailty in prognosis after surgery in patients with pancreatic ductal adenocarcinoma. World J Surg Oncol. 2021;19(1):94.
8. Squires MH, Mehta VV, Fisher SB, et al. Effect of preoperative renal insufficiency on postoperative outcomes after pancreatic resection: a single institution experience of 1,061 consecutive patients. J Am Coll Surg. 2014;218:92–101.
9. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.
10. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388:248–57.
11. Motoi F, Satoi S, Honda G, et al. A single-arm, phase II trial of neoadjuvant gemcitabine and S1 in patients with resectable and borderline resectable pancreatic adenocarcinoma: PREP-01 study. J Gastroenterol. 2019;54:194–203.
12. Teraoku H, Morine Y, Ikemoto T, et al. Short- and long-term outcomes of pancreatectomy in patients with hemodialysis. J Med Investig. 2023;70:105–9.
13. Motoi F, Kosuge T, Ueno H, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). Jpn J Clin Oncol. 2019;49:190–4.
14. Bolliger M, Kroehnert JA, Molineus F, et al. Experiences with the standardized classification of surgical complications (Clavien-Dindo) in general surgery patients. Eur Surg. 2018;50:256–61.
15. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310:1473–81.
16. Kaneko T, Sugimori K, Tozuka Y, et al. Combination chemotherapy with gemcitabine and nab-paclitaxel for a metastatic pancreatic ductal adenocarcinoma patient undergoing hemodialysis. Clin J Gastroenterol. 2019;12:484–9.
17. Takakura K, Koido S, Takahara A, et al. Long-term management of gemcitabine in a patient with advanced pancreatic cancer undergoing haemodialysis. J Chemother. 2014;26:369–72.
18. Kiani A, Köhne CH, Franz T, et al. Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard hemodialysis treatment. Cancer Chemother Pharmacol. 2003;51:266–70.
19. Janus N, Thariat J, Boulanger H, et al. Proposal dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol. 2010;21:1395–403.
20. Feyko J, Hazard H, Cardinal J, et al. Pancreatectomy in patients with impaired renal function: how risky is it? Am Surg. 2016;82:16–21.
21. Otani T, Yamamoto H, Bandai Y, et al. Pancreaticoduodenectomy for bile duct carcinoma of a patient undergoing hemodialysis. Hepato-Gastroenterology. 2008;55:24–6.
22. Uchida H, Shibata K, Kai S, et al. Pylorus-preserving pancreaticoduodenectomy in patients undergoing chronic hemodialysis. Surg Today. 2008;38:1152–4.
23. Norman KS, Domingo SR, Wong LL. Pancreatic resections in renal failure patients: is it worth the risk? HPB Surg. 2014;2014:938251.
24. Santangelo M, Esposito A, Tammaro V, et al. What indication, morbidity and mortality for central pancreatectomy in oncological surgery? A systematic review. Int J Surg. 2016;28(Suppl 1):S172–6.
25. Boggi U, Kauffmann E, Napoli N, et al. REDISCOVER international guidelines on the perioperative care of surgical patients with borderline-resectable and locally advanced pancreatic cancer. Ann Surg. 2024;280(1):56–65.
26. Boggi U, Kauffmann EF, Napoli N, et al. REDISCOVER guidelines for borderline-resectable and locally advanced pancreatic cancer: management algorithm, unanswered questions, and future perspectives. Updat Surg. 2024;76(5):1573–91.

Kidney Surgery

14

Alberto Briganti and Alfonso Santangelo

14.1 Introduction

Uremia is a characteristic condition found in patients affected by chronic kidney disease (CKD) and end-stage renal disease (ESRD), which can also be a consequence of acute kidney injury (AKI) [1]. Overall surgical mortality rates in patients with CKD and ESRD are major concerns in modern surgery as the prevalence of these conditions is rising and ESRD is estimated to be associated with a significantly increased 30-day mortality after surgery [2]. The main causes of death in these surgical patients are to be found in cardiovascular and infectious conditions [3]. Indeed, common features of renal failure include:

- Electrolyte disorders (e.g., hyperkalemia)
- Immunological disorders
- Bleeding and anemia.

Those conditions are of vital importance when surgery, and especially kidney surgery, is performed since surgical renal impairment can only worsen them, exposing the patient to further perioperative complications.

14.2 Hyperkalemia

A patient with renal failure may suffer from electrolyte imbalances such as hyperkalemia. Surgical and anesthesiologic factors like intraoperative tissue damage, extensive tissue dissection, blood transfusion and suxamethonium may sustain and

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enhance the imbalance by elevating the levels of blood potassium during surgery and heighten the putting risk of serious arrhythmias [4]. For these reasons, surgery should be postponed in patients at high risk of developing hyperkalemia. In particular, although there is no clear serum potassium cut-off level to aid decisions in this setting, it has been observed that patients with a serum potassium level >5.5 mEq/L in the preoperative period are twice as likely to require intraoperative management for hyperkalemia as compared to those with a preoperative serum potassium level <5.5 mEq/L [4]. Strict monitoring of electrolytes during and after surgery is a key point for the management of these patients. Treatment options include loop diuretics and/or polystyrene-binding resins (for mild disease), insulin in combination with dextrose i.v. and bicarbonate i.v. (for severe disease). In the acute setting, also calcium gluconate i.v. can be considered [4–6].

14.3 Immunological Disorders

Patients with uremia develop severe metabolic and immunological disorders. In ESRD, neutrophils tend to undergo apoptosis because of the uremic plasma conditions, thus leading to lymphocytopenia and T lymphocyte function impairment [3]. Moreover, uremia leads to impaired neutrophilic phagocytosis and monocyte alterations, and enhances oxidative stress with reactive oxygen species production and complement dysregulation [1]. In this setting, the probability of developing sepsis and septic shock rises dramatically, especially in patients undergoing procedures like percutaneous nephrolithotomy (PCNL) [7]. Renal surgery exposes the patient to the risk of developing urosepsis, most frequently determined by *E. coli* infection; furthermore, any kind of renal manipulation (whether endoscopic or not) is associated with increased inflammation, augmented risk of stenosis and hydroureteronephrosis, leading to higher susceptibility to infectious disease. Both the European Association of Urology (EAU) and the American Urological Association (AUA) suggest a <24 h antibiotic prophylaxis before a PCNL; prophylaxis can be either performed with fluoroquinolones or cephalosporines depending on the guidelines chosen [7]. However, once the infection has developed, initial empiric antimicrobial therapy should be started against all likely causative pathogens and should be adapted based on culture results, once available [8].

14.4 Bleeding and Anemia

Bleeding in CKD is a multifactorial condition, related to factors such as platelet dysfunction, anemia, concomitant antiplatelet/anticoagulation drugs, and dialysis independently increasing the bleeding risk [9]. In CKD patients, platelet function is impaired on many levels. First, uremic toxins severely affect von Willebrand factor's functionality; in addition, uremic patients have increased levels of prostacyclin and nitric oxide (NO), which are both platelet inhibitors. Platelet granule contents are dysfunctional as well, enabling reduced release of ADP, serotonin and

thromboxane A2. The activity of the IIb/IIIa surface receptors can also be altered by uremic toxins [10].

Patients with CKD also exhibit prothrombotic changes with increased factor VIII activity which, along with other comorbid conditions commonly affecting these patients, often implies the need for anticoagulant/antiplatelet therapy [9, 10]. This usually results in increased bleeding risk after surgery. Nevertheless, anemia is not only the result of an increased bleeding risk but it could be also its cause. In fact, kidney injury usually results in a reduced production of erythropoietin and consequently low levels of red cell mass, dispersion of circulating platelets, difficulty in adhesion to the vascular wall and formation of the platelet thrombus [9, 10]. Preoperative anemia is also associated with higher rates of acute renal injury [11] and therefore CKD patients with these conditions have a higher risk of developing acute or chronic kidney injury. The need for blood transfusion after renal surgery is not only a driver of hyperkalemia, but it is also associated with disease recurrence and mortality from any cause [12]. Therefore, it is important to ensure that a CKD patient, especially when candidate for elective renal surgery, reaches the operating room with an adequate hemoglobin/hematocrit level. To this end, patients with CKD and anemia usually have their own tailored erythropoiesis-stimulating therapy but, when urgent surgery is required, transfusion may also be considered. The hemoglobin (Hb) threshold for transfusion in this situation is uncertain but the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on anemia suggest proceeding with transfusion when the Hb value is ≤7 g/dL (or 70 g/L) [13].

14.5 Surgical Approaches and Nephron-Sparing Surgery in Uremic Patients

14.5.1 Renal Cancer

Kidney cancer is the 14th cancer for incidence overall for both sexes combined [14]. Although much of the epidemiologic data pertain to kidney cancer overall, histologically, renal cell carcinoma (RCC) accounts for almost 90% of the cases, mainly including clear cell RCC (ccRCC; 70%), papillary RCC (pRCC; 10–15%), and chromophobe RCC (5%). The remaining subtypes represent around 1% of the cases [15]. Among the risk factors for developing kidney cancer, CKD and ESRD must be considered. CKD and ESRD increase the risk of two- to threefold, particularly among African American patients [15]. The increased risk of cancer in patients with CKD is well known since kidney dysfunction creates an inflammatory microenvironment and oxidative stress, which can establish the ideal setting for cancer development [16]. Therefore, surgery for renal masses is not uncommon in CKD patients. Renal surgery can heavily impact on glomerular filtration rate (GFR), modifying perioperative outcomes and patients' quality of life. CKD in patients with cancer also markedly reduces the survival rates [16]. Lane et al. demonstrated that renal surgery impacts estimated GFR (eGFR) loss in kidney cancer patients with or without pre-existing CKD. They showed that patients with a baseline CKD prior to

surgery had a more rapid postoperative disease progression compared to patients who only developed CKD (defined by an eGFR <60 mL/min) after surgery. Moreover, there was a strong relationship between the grade of preoperative CKD and the postoperative stability of renal function, with particularly adverse outcomes in the subgroups with stages 3b and 4 CKD prior to surgery. A similar association was noted when considering all-cause and non-renal cancer mortality [17].

14.5.2 Radical Nephrectomy or Partial Nephrectomy?

Owing to the preservation of a variable amount of the glomerular mass, partial nephrectomy has always been appealing to approach a CKD patient with a renal mass. In a retrospective cohort study of 662 patients with both healthy kidneys and RCC undergoing partial or radical nephrectomy, partial nephrectomy was associated with a decreased risk of CKD (80% vs 35% probability of freedom from eGFR <60 mL/min/1.73 m^2 at the 3-year follow-up, $p < 0.001$) [18]. However, when considering patients with CKD prior to surgery, the scenario changes. It seems that adverse overall survival in patients with a pre-existing eGFR reduction does not result from further impairment of renal function following surgery, but rather from other medical comorbidities causing pre-surgical CKD [17].

The EAU guidelines on RCC advise to choose partial over radical nephrectomy in patients with T1–T2 tumors and pre-existing CKD so as to limit the risk of ESRD which requires hemodialysis [19]. However, patients with CKD are also at risk of rapid progression to ESRD; in this case the morbidity that can be associated with partial rather than radical nephrectomy would not be justified. Understanding the main predictors of progression to ESRD would be helpful to correctly evaluate the adequate surgical approach. One retrospective review revealed that, in African Americans, a minimally invasive approach and a preoperative eGFR <25 mL/min/1.73 m^2 were the main predictors of progression to ESRD [20]. Conversely, another study on kidney cancer patients reported that both in patients with conserved or reduced eGFR (> or <90 mL/min/1.73 m^2) the main factors influencing postoperative renal function were age, baseline GFR, RENAL score, diabetes and ischemia time [21].

When planning renal surgery, the CKD patient's diagnostic workup should include sequential renal scintigraphy to evaluate split renal function [19] in order to predict the possible postoperative functional outcome. This topic is now regaining interest and further steps have been made in this direction, as reported by Rathi et al. [22]. Clearly, in patients already undergoing dialysis and/or with a kidney affected by a tumor which is functionally excluded (e.g., by staghorn calculi), considering a partial nephrectomy does not add any benefit.

14.5.3 Off-Clamp vs On-Clamp Techniques

In order to minimize or avoid warm ischemia time and improve functional outcomes, off-clamp techniques have raised growing interest for partial nephrectomy. One randomized control trial known as the CLOCK study [23] showed a comparable safety profile of off-clamp vs on-clamp partial nephrectomy in terms of intra- and perioperative complications as well as comparable absolute eGFR variation and split renal function at 6 months from surgery in patients with regular baseline function and two kidneys. However, the selective inclusion criteria of this trial exclude CKD patients, for whom off-clamp techniques may still be indicated [19].

14.5.4 Upper Tract Urothelial Carcinoma

Surgical excision of the kidney may also be needed for tumors not originating from the renal parenchyma, but which derive from the urothelium; this is the case of the upper tract urothelial carcinoma (UTUC).

UTUCs are tumors which account for almost 5–10% of urothelial carcinomas with an annual incidence reaching almost two cases per 100,000 inhabitants in Western countries. UTUC's aggressiveness deeply influences the choice of surgical approach. Based on the risk of progression to pT2/non organ-confined disease, we can identify low- and high-risk UTUC. The current EAU guidelines state that open radical nephroureterectomy with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumor location, while, for low-risk tumors, kidney-sparing surgery is preferred since it reduces the morbidity associated with radical nephroureterectomy (e.g., loss of kidney function), without compromising oncologic outcomes [24]. Kidney-sparing surgery includes:

- Ureteroscopy and endoscopic ablation. A systematic review shows comparable survival outcomes when this technique is compared to radical nephroureterectomy. However, the patient is exposed to higher local recurrence rates and the long-term renal preservation outcomes are still uncertain after endoscopic treatment [25].
- Percutaneous access and endoscopic ablation. This is usually offered for low-risk tumors in the lower calyceal system that are inaccessible or difficult to manage by flexible ureterorenoscopy.
- Ureteral resection. Distal ureterectomy with ureteroneocystostomy is indicated for low-risk tumors in the distal ureter that cannot be completely removed endoscopically. However, despite the low level of evidence, also high-risk patients can be treated with this technique [26].

When dealing with a CKD patient, the difference between high and low risk, and subsequently between the choice of aggressive or conservative treatment, becomes a game-changer for the patient's quality of life. In this setting, also high-risk patients can be treated with nephron-sparing surgery, at the cost of higher recurrence and progression rates and with a direct impact on survival. The need to perform kidney-sparing surgery in a CKD patient whose ureter is involved by tumor paves the way for either total ureterectomy with ileal-ureteral replacement or renal autotransplantation with pyelocystostomy [24].

14.5.5 Stones

The relationship between kidney function and the development of nephrolithiasis has always been a topic of interest; in 2004, Vupputuri et al. [27] conducted a case-control study which demonstrated that patients with a history of stone formation were twice as likely to develop CKD. In 2005, Gillen et al. [28] stated that the association between a history of stones and eGFR depended on BMI; in particular, a BMI >27 kg/m^2 was associated with a decrease of 3.4 mL/min/1.73 m^2 of eGFR. Similar results were found in two other prospective cohort studies [29, 30]. However, both CKD and urolithiasis represent a risk factor for each other's development, and suffering from CKD puts patients at high risk of stone formation [31].

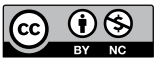
Surgical intervention on these patients is a fundamental approach. In particular, renal insufficiency (renal failure, bilateral obstruction, or single kidney) represents a main indication for the treatment of ureterolithiasis, while belonging to the high-risk class for stone formation (e.g., every patient with CKD) is an indication for the removal of renal stones. It is evident that uremic patients need surgery when affected by stone disease. The choice of surgical approach is mainly dependent on stone localization and dimensions. For proximal or distal ureteral stones larger than 10 mm flexible ureterorenoscopy is preferred over shock wave lithotripsy. If the stone is localized in the renal pelvis, the first choice is percutaneous nephrolithotripsy for stones >20 mm, shock wave lithotripsy, PCNL or retrograde intrarenal surgery for stones 10–20 mm, and shock wave lithotripsy or retrograde intrarenal surgery for stones <10 mm [31].

References

1. Cohen G. Immune dysfunction in uremia 2020. Toxins (Basel). 2020;12(7):439.
2. 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(2):395–8.
3. Song S, Cho C, Park SY, et al. Cause of postoperative mortality in patients with end-stage renal disease. Anesth Pain Med (Seoul). 2022;17(2):206–12.
4. Lema GF, Tesema HG, Fentie DY, Arefayne NR. Evidence-based perioperative management of patients with high serum potassium level in resource-limited areas: a systematic review. Int J Surg Open. 2019;21:21–9.

5. Krishnan M. Preoperative care of patients with kidney disease. Am Fam Physician. 2002;66(8):1471–6, 1379.
6. Joyce H, Hollander-Rodriguez C, Calvert JF. Hyperkalemia. Am Fam Physician. 2006;73(2):283–90.
7. Kreydin EI, Eisner BH. Risk factors for sepsis after percutaneous renal stone surgery. Nat Rev Urol. 2013;10(10):598–605.
8. Bonkat G, et al. EAU Guidelines on urological infections. Edn. Presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.
9. Jones A, Swan D, Lisman T, et al. Anticoagulation in chronic kidney disease: current status and future perspectives. J Thromb Haemost. 2024;22(2):323–36.
10. Heras Benito M, Sánchez Hernández R, Fernández-Reyes MJ, Isabel Díez Lobo A. Management of perioperative bleeding in renal patients. Nefrologia. 2008;28(6):593–6.
11. Fowler AJ, Ahmad T, Phull MK, et al. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J of Surg. 2015;102(11):1314–24.
12. Arcaniolo D, Manfredi C, Cindolo L, et al. Impact of perioperative blood transfusions on the outcomes of patients undergoing kidney cancer surgery: a systematic review and pooled analysis. Clin Genitourin Cancer. 2019;17(1):e72–9.
13. KDIGO. Clinical practice guideline for anemia in chronic kidney disease [Internet]. 2012 [cited 2024 Dec 9]. Available from: https://kdigo.org/guidelines/anemia-in-ckd/.
14. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
15. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of renal cell carcinoma: 2022 update. Eur Urol. 2022;82(5):529–42.
16. Malyszko J, Tesarova P, Capasso G, Capasso A. The link between kidney disease and cancer: complications and treatment. Lancet. 2020;396(10246):277–87.
17. Lane BR, Demirjian S, Derweesh IH, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. Eur Urol. 2015;68(6):996–1003.
18. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol. 2006;7(9):735–40.
19. Ljungberg B et al. EAU Guidelines on renal cell carcinoma. Edn. Presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.
20. Aguilar Palacios D, Li J, Mahmood F, et al. Partial nephrectomy for patients with severe chronic kidney disease – is it worthwhile? J Urol. 2020;204(3):434–41.
21. Liu X, Jin D, Zhang Y, Zhang S. Limited non-linear impact of warm ischemia time on renal functional decline after partial nephrectomy: a propensity score-matched study. Int Urol Nephrol. 2023;55(7):1699–708.
22. Rathi N, Palacios DA, Abramczyk E, et al. Predicting GFR after radical nephrectomy: the importance of split renal function. World J Urol. 2022;40(4):1011–8.
23. Antonelli A, Cindolo L, Sandri M, et al. Is off-clamp robot-assisted partial nephrectomy beneficial for renal function? Data from the CLOCK trial. BJU Int. 2022;129(2):217–24.
24. EAU. Upper urinary tract urothelial carcinoma guideline [Internet]. 2024 [cited 2024 Dec 9]. Available from: https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma.
25. Kawada T, Laukhtina E, Quhal F, et al. Oncologic and safety outcomes for endoscopic surgery versus radical nephroureterectomy for upper tract urothelial carcinoma: an updated systematic review and meta-analysis. Eur Urol Focus. 2023;9(2):236–40.
26. Seisen T, Peyronnet B, Dominguez-Escrig JL, et al. Oncologic outcomes of kidney-sparing surgery versus radical nephroureterectomy for upper tract urothelial carcinoma: a systematic review by the EAU non-muscle invasive bladder cancer guidelines panel. Eur Urol. 2016;70(6):1052–68.
27. Vupputuri S. History of kidney stones as a possible risk factor for chronic kidney disease. Ann Epidemiol. 2004;14(3):222–8.

28. Gillen DL, Worcester EM, Coe FL. Decreased renal function among adults with a history of nephrolithiasis: a study of NHANES III. Kidney Int. 2005;67(2):685–90.
29. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. BMJ. 2012;345:e5287.
30. Rule AD, Bergstralh EJ, Melton LJ, et al. Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(4):804–11.
31. Skolarikos A et al. EAU Guidelines on urolithiasis. Edn. Presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.



Kidney Transplant Surgery

15

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15.1 Introduction

Kidney transplantation is the optimal therapeutic approach for end-stage renal disease (ESRD), offering a superior quality of life [1]. The first kidney transplant in Italy was successfully performed on 2 May 1966 at Policlinico Umberto I by Dr. Paride Stefanini, assisted by Dr. Raffaello Cortesini and Dr. Carlo Umberto Casciani. The donor kidney was obtained from a young woman with a ptotic kidney at San Salvatore Hospital in L'Aquila. Since then, progress in immunosuppressive therapies and advances in immunological understanding have significantly improved both graft and recipient survival. Over the past three decades, donation rates have quadrupled in Italy, but the number of donors is still insufficient to meet the needs of those on the waiting list. As a result, innovative strategies have been developed to expand the donor pool. In 2023, Italy reported 1667 donors with an average age of

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62.1 years—a significant increase from the average age of 48 years in 2002. In the same year, 1898 kidney transplants were performed to meet the needs of nearly 6000 patients on the kidney transplant waiting list [2].

15.2 Indications and Contraindications

Kidney transplantation is indicated in cases of chronic ESRD (stage 5: GFR less than 15 mL/min), with superior patient and graft survival rates observed when the procedure is performed pre-emptively. Currently, diabetes mellitus is the primary cause of ESRD in numerous developed and developing countries [3]. Other etiologies include hypertension, glomerular disease (primary or secondary), and cystic kidney diseases (Fig. 15.1).

Contraindications are primarily associated with immunosuppressive therapies that have been demonstrated to facilitate the growth of tumors and infections. Accordingly, absolute contraindications include neoplasms in the active phase or with a follow-up period of less than five years. Nevertheless, in selected cases where the tumor type and stage are appropriate, a shorter follow-up period may be feasible. Furthermore, the presence of chronic infections in the active phase or severe cardiorespiratory conditions represents an additional absolute contraindication. Relative contraindications are conditions that may impair the patient's capacity to adhere to immunosuppressive therapy. These include alcoholism, drug addiction and severe psychiatric illnesses.

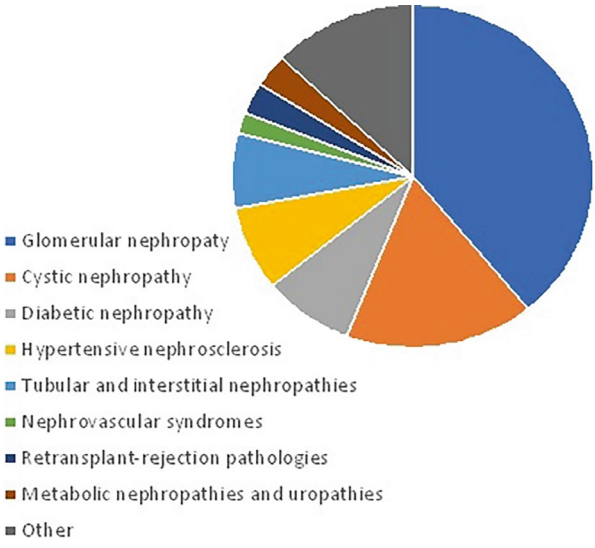


Fig. 15.1 The underlying conditions that result in end-stage renal disease in patients on the kidney transplant waiting list. (Data derived from the SIT database 2002–2019)

15.3 Deceased-Donor Kidney

The possibility of transplantation is conditioned upon the availability of an organ donor, who may be either living or deceased (donors after brain death or after circulatory death). In the latter case, if the deceased donor has consented to donation during their lifetime or if there is no objection from the donor's relatives following the donor's death, organ procurement is permitted.

15.3.1 Donation After Brain Death

In donation after brain death (DBD) the procurement of organs is conducted in subjects who have succumbed to brain death as a consequence of irreparable damage to the brain, precipitated by trauma, hemorrhage, ischemia or the presence of brain tumors (regulated by Italian Law N. 578 of 29 December 1993 and the associated Decree N. 582 of 22 August 1994). The certification of brain death is conducted through specific tests designed to assess the absence of all cranial nerve reflexes and the death of the brain stem by a committee comprising a medical examiner (or, in their absence, a chief medical officer, or otherwise an anatomopathologist); an anesthetist; a neurologist or neurosurgeon with expertise in electroencephalography. A neurologist or neurosurgeon with expertise in electroencephalography must also be present at the inception and conclusion of an observation period, which spans 6 h for adults, 12 h for children under five years of age and 24 h under one year of age.

15.3.2 Donation After Circulatory Death

In Italy, in order to verify donation after circulatory death (DCD), an electrocardiogram must be recorded for a minimum of 20 min (no-touch period). This is to demonstrate the irreversibility of the cardiac arrest (in accordance with Law No. 578 of 29 December 1993). This period is considerably longer than that required by law in the majority of other Western countries, where the required duration ranges between 5 and 10 min. DCD can be classified into two principal categories: controlled and uncontrolled.

15.3.2.1 Uncontrolled Donation After Circulatory Death

An uncontrolled DCD is defined as a patient who has experienced a sudden cardiac arrest. In particular, the Maastricht classification differentiates between three categories of uncontrolled cardiac arrest: uncontrolled and unwitnessed (category 1), uncontrolled and witnessed (category 2), or heart suddenly stopped after the criteria for declaring brain death have been met (category 4). In the case of the first two categories of patients, death is declared when all attempts at cardiopulmonary resuscitation have been unsuccessful.

15.3.2.2 Controlled Donation After Circulatory Death

A controlled DCD (Maastricht category 3) is defined as a patient who experiences an expected cardiac arrest following the suspension of life-support treatments. A considerable number of kidneys, lungs, and livers (and, in selected cases, hearts) that are successfully used for transplantation today originate from DCD donations in the United States, Australia, and certain European countries. The 20 min no-touch period presents a challenge for Italy in terms of the quality of the organs to be transplanted, resulting in a delay in the implementation of DCD programs. Nevertheless, DCD programs have been established in numerous hospitals across various Italian regions since 2015, representing approximately 20–25% of the transplanted kidneys today. The long-term results are highly favorable and, on the whole, comparable to those observed following the procurement of organs from DBD [4, 5].

15.3.3 Expanded Criteria Donors

An expanded criteria donor (ECD) is defined as any individual aged 60 years or above, or a donor aged 50 years or above with two or more of the following characteristics: a history of elevated blood pressure, serum creatinine levels exceeding 1.5 mg/dL, and a cause of death related to stroke. The utilization of ECD has the potential to reduce waiting list times. It is anticipated that the outcomes will be inferior to those achieved with a standard donor, although the precise level of risk is currently unknown. At the 5-year follow-up, 50% of kidneys from ECD were still functioning. Furthermore, transplant recipients exhibited higher survival rates compared to patients who remained on the waiting list [6].

15.3.4 Dual Kidney Transplant

In some instances, the function of a single kidney from an ECD is deemed insufficient. In this instance, it is feasible to transplant both kidneys into the same recipient. This dual transplant option offers outcomes that are comparable to those of a single-kidney transplant with normal function and can effectively address the shortage of donor organs [6].

15.4 Hypothermic and Normothermic Machine Perfusion

The preservation of marginal kidney grafts, including those from DCD or ECD, through hypothermic machine perfusion has been demonstrated to result in superior clinical outcomes [7]. The system comprises a circuit to which the kidney transplant is connected. A preservation solution is circulated within the kidney transplant at a pulsatile or continuous flow, with the assistance of a pump. The temperature is set at 4–8 °C, which results in a reduction in cellular metabolism to between 5% and 10% [8]. Experimental studies have indicated that the addition of oxygen to the

perfusion solution may prove beneficial in the hypothermic machine perfusion of kidney transplants. Normothermic machine perfusion represents an emerging alternative technique that employs cardiopulmonary bypass technology with extracorporeal membrane oxygenation to perfuse kidneys with a warmed and oxygenated red-cell-based plasma-free solution [9, 10].

15.5 Living-Donor Kidney

The outcomes of transplants from living donors are superior to those from deceased donors due to a reduction in ischemia time, an enhancement in organ quality, and, in the case of blood relatives, an elevated level of genetic compatibility. In Italy, living kidney donation is subject to strict regulation in accordance with the provisions set forth in Law 26 June 1967 n.458. It is permitted in the context of blood relatives, emotionally related subjects, and in cases of so-called "Samaritan donation", whereby an individual donates to an unknown recipient. The donation must be a free, voluntary, and informed act, revocable at any time and without any undue influence.

15.5.1 Living Donor Nephrectomy

The initial surgical techniques developed for living donor nephrectomy were performed using the open technique, with incisions made on the side (lombotomy) or on the anterior abdominal wall (transperitoneal). These two approaches have been superseded by the video-assisted laparoscopic kidney approach via the transperitoneal or retroperitoneal route. In the literature, the mortality rate reported for all living donor procurements is 0.03% [11]. Furthermore, it is possible to perform the nephrectomy procedure with a robot-assisted laparoscopic approach, which yields the same esthetic and clinical results.

15.5.2 Immunological Incompatibility

It is estimated that 55% of cases where couples are unable to proceed with direct transplantation are attributable to immunological causes: blood group incompatibility or positive cross-match.

15.5.2.1 AB0 Incompatible Transplant

Group incompatibility occurs when the donor and recipient have different blood groups and are not both group 0. In such cases, specific desensitizing treatment can be performed before the transplant in the recipient. This may include plasmapheresis, anti-B cell drugs and enhanced induction and maintenance immunosuppression. The results of this treatment are comparable to those achieved in standard AB0-compatible pairs [12].

15.5.2.2 HLA Incompatible Transplant (Positive Flow Cross-Match)

HLA-incompatible transplants, such as those with a positive flow cross-match, occur when a recipient has pre-formed donor-specific anti-HLA antibodies (DSA), leading to a higher risk of graft rejection. In such cases, the recipient's immune system is primed to recognize and attack the donor tissue, resulting in acute or hyperacute rejection. Despite these challenges, advances in immunosuppressive therapies and desensitization protocols, including plasmapheresis, intravenous immunoglobulin, and rituximab, have improved outcomes for these patients. These strategies help reduce DSA levels and suppress immune activation, allowing successful transplantation. However, HLA-incompatible transplants remain associated with increased risks of graft dysfunction, antibody-mediated rejection, and infection due to intensified immunosuppression. Careful patient selection, meticulous monitoring, and tailored therapeutic approaches are crucial for optimizing outcomes and minimizing complications in this high-risk transplant population [12].

15.5.3 Kidney Paired Donation Programs

In cases of blood group incompatibility with a high antibody titer and, consequently, an elevated risk of transplant failure, or in instances of high-level HLA incompatibility accompanied by a positive cytotoxic cross-match, the donor and recipient may be presented with the option of joining the national kidney paired donation (KPD) protocols. These programs facilitate the formation of compatible combinations among pairs of patients who are candidates for a kidney transplant from a living donor but who are immunologically incompatible with each other. These programs comprise the standard KPD protocol, transplant chains initiated from a Samaritan donor and the DEC-K transplant program, which commences from a standard deceased donor.

Since September 2007, Italy has been part of the South Alliance for Transplant, an international organization that oversees the KPD program at an international level between three countries of the Mediterranean area, together with Spain and Portugal.

15.6 Transplant Surgery

Kidney transplantation is a heterotopic transplant, meaning the donor kidney is placed in a location different from that of the native kidneys. Typically, the transplanted kidney (graft) is positioned in an extraperitoneal location within the iliac fossa. Importantly, the native kidneys are generally left in place unless specific conditions necessitate their removal. These conditions include significantly enlarged polycystic kidneys, which might occupy the space required for the graft, or the presence of complications such as neoplasms or recurrent infections like

pyelonephritis. The surgery is performed under general anesthesia with the patient in the supine position. A commonly used incision is the pelvic Gibson incision, an oblique or curvilinear cut providing optimal access to the iliac vessels. The decision to operate on the right or left side depends on the surgeon's preference and specific circumstances, such as the anatomical condition of the recipient's iliac vessels. For example, the right side often allows simpler vessel preparation, but factors like atherosclerosis or prior transplants may affect the choice. Vascular anastomoses are critical steps in the procedure. The donor renal vein is connected to the recipient's external iliac vein, and the donor renal artery is connected to the recipient's external iliac artery. These connections are made using precise end-to-end anastomosis techniques with a non-absorbable monofilament suture (6/0 or 5/0) to ensure secure and efficient blood flow. Following vascular anastomoses, the kidney is reperfused, restoring blood flow to the graft. After the graft is reperfused, the donor ureter is surgically connected to the recipient's bladder. This step involves an anti-reflux technique, often performed using the Lich-Gregoire method, to reduce the risk of urinary reflux, which can lead to infections and other complications. Kidney transplant surgery is intricate and requires meticulous planning and execution to ensure graft functionality and minimize postoperative risks. The success of the surgery depends on precise vascular and urinary reconstructions, careful patient preparation, and individualized surgical strategies.

15.7 Laparoscopic Kidney Transplant

Laparoscopic kidney transplantation is a minimally invasive surgical technique that offers potential benefits, including reduced postoperative pain, faster recovery, and improved cosmetic outcomes. However, it presents unique technical challenges, particularly in performing precise vascular anastomoses. These challenges can lead to an increase in warm ischemia time—the period during which the transplanted kidney remains without blood flow at body temperature—which may impact early graft function if prolonged. While initial studies suggest that laparoscopic kidney transplantation achieves outcomes comparable to traditional open procedures regarding graft and patient survival, the existing data should be interpreted with caution. The majority of studies to date are single-center investigations with small sample sizes, which may not provide the statistical power needed for generalized conclusions [13].

15.8 Robot-Assisted Kidney Transplantation

Robot-assisted kidney transplantation (RAKT) represents an evolution of minimally invasive techniques, particularly advantageous for obese patients and those at higher risk for complications. Obese patients often face challenges with traditional

surgical approaches, such as increased risk of wound infections and difficulty in surgical access. Robotic systems, equipped with enhanced visualization, precision, and dexterity, enable surgeons to perform intricate procedures, such as vascular and ureteral anastomoses, with greater accuracy and control. Current literature supports the use of robotic assistance for achieving improved clinical outcomes in selected patient groups. Despite this promise, the success of RAKT heavily depends on the surgeon's expertise and training. Robotic technology has a steep learning curve, and centers with significant experience in robotic surgery report the best outcomes. Broader adoption of RAKT may require standardization of training protocols and improved accessibility to robotic systems.

While robotic and laparoscopic techniques are advancing the field of kidney transplantation, further high-quality multicenter randomized controlled trials are needed to assess their long-term impact on graft function, survival, and overall cost-effectiveness compared to open surgical methods across diverse patient populations and surgical teams [14].

15.9 Kidney Transplant Complications

Kidney transplantation is a life-saving treatment for ESRD but is associated with a range of complications that can impact patient outcomes. These complications can be broadly categorized into surgical, medical, immunological, and non-immunological types, reflecting the complexity of the procedure and post-transplant care [15–17] (Table 15.1).

Table 15.1 Kidney transplant complications

Surgical complications		
Vascular complications	Bleeding	
	Renal artery stenosis	
	Renal artery thrombosis	
	Renal vein thrombosis	
Urological complications	Ureteral stenosis	
	Urinary fistula	
General complications	Lymphocele	
	Wound infection	
Medical complications		
Immunological complications	Hyperacute rejection	
	Acute rejection	Antibody-mediated
	Chronic rejection	Cell-mediated
Non-immunological complications	Infections	Viral
		Bacterial
		Parasitic
	Neoplasms (long-term)	Lymphomas
		Skin tumor

15.9.1 Surgical Complications

Surgical complications include issues related to the technical aspects of transplantation.

- Vascular complications (range between 0.1% and 23%):
  - Renal artery stenosis: The most common vascular complication, occurring in 1–23% of cases, often diagnosed during routine ultrasound surveillance. Causes include intimal trauma, hyperplasia, and minimal surgical errors, leading to hypertension, graft dysfunction, and fluid retention. Treatment involves angioplasty and stenting; surgical intervention is reserved for refractory cases [18].
  - Renal artery thrombosis: Caused by technical issues like vessel torsion or underlying conditions such as hypercoagulable states or rejection. Clinically, cessation of diuresis is observed. Diagnosis relies on duplex ultrasound and CT angiography. Immediate surgical intervention is critical, and in cases of irreversible ischemia, transplantectomy is required.
  - Renal vein thrombosis: Rare (0.1–4.2%), it may result from factors like surgical technique, immunosuppression, or donor-recipient mismatch. High clinical suspicion is necessary for diagnosis, and treatment options include thrombolytic therapy or thrombectomy and in cases of irreversibility, transplantectomy is required [19].
- Urological complications (range between 1.7% and 15%):
  - Ureteral stenosis: Often linked to ischemia or fibrosis, ureteral stenosis is marked by hydronephrosis seen on ultrasound. Management ranges from stent placement to reconstructive surgery.
  - Urinary fistulae: These can occur at the ureter, pelvis, or bladder and present as fluid collections identified by ultrasound. Management includes drainage, catheterization, and potentially surgical re-anastomosis.
- Other complications:
  - Lymphocele (ranges between 0.6% and 18%): Commonly caused by lymphatic vessel disruption, it is diagnosed by ultrasound and fluid analysis to differentiate it from urinoma. Treatments range from drainage to laparoscopic fenestration.
  - Wound infection (ranges between 8% and 10%): This requires prompt treatment to prevent further complications. A robot-assisted laparoscopic approach is promising in reducing its incidence.

15.9.2 Medical Complications

Medical complications arise from immunosuppression or the underlying health conditions of the recipient.

- Immunological complications:
- Diagnosed by ultrasound-guided graft biopsy and categorized according to the Banff Classification of Allograft Pathology, an international consensus classification of renal transplant pathology that has been continuously refined since 1991 and is reflected in the relevant Banff meeting reports [20].
  - Hyperacute rejection: This now very rare event, occurring within 48 h, results from pre-existing antibodies to donor antigens. Stringent cross-matching protocols have significantly reduced its incidence.
  - Acute rejection: A common event within three months, but possible throughout the life of the graft, caused by cell-mediated or antibody-mediated immune responses. It is diagnosed by biopsy, and treatment involves intensification of immunosuppression.
  - Chronic rejection: This insidious form of rejection evolves over years, characterized by gradual graft dysfunction. Chronic rejection is managed through optimization of immunosuppression but may ultimately necessitate re-transplantation.
- Non-immunological complications:
  - Infections: Opportunistic infections (viral, bacterial, fungal, or parasitic) are common due to immunosuppressive therapy. Careful monitoring and prophylaxis reduce these risks.
  - Neoplasms: Immunosuppressed patients face an elevated risk of malignancies, particularly lymphomas and skin cancers. Long-term monitoring for early detection and treatment is critical [21].

15.9.3 Management and Prevention Strategies

Proper surgical techniques, advanced imaging for early diagnosis, and multidisciplinary care are essential in managing complications.

- Routine ultrasound surveillance plays a key role in identifying vascular and urological issues.
- Protocols for immunosuppressive therapy aim to balance rejection prevention and the risk of secondary complications like infections or malignancies.
- Cancer screening: A significant focus in long-term care, with research highlighting increased cancer mortality in transplant recipients.

Understanding and mitigating these complications are critical to improving survival and quality of life in kidney transplant recipients.

15.10 Immunosuppressive Treatment

Immunosuppressive therapy is a cornerstone of care for kidney transplant recipients to prevent immune-mediated rejection of the transplanted organ. These regimens are tailored to factors such as the time since transplantation, the recipient's immunological risk, the underlying cause of renal failure, and the condition and function of the graft.

15.10.1 Types of Immunosuppressive Drugs

Immunosuppressive medications are broadly classified into induction therapy and maintenance therapy, with distinct goals and mechanisms of action.

- Induction Therapy: Induction therapy is administered during the immediate perioperative period to prevent and suppress immune activation to minimize the risk of acute rejection. Biological agents such as monoclonal and polyclonal antibodies, including anti-thymocyte globulin (ATG), basiliximab (IL-2 receptor antagonist), and alemtuzumab (anti-CD52 antibody), are common choices. These drugs deplete or inhibit T-cell activity, reducing the recipient's immune response to the graft.
  - Basiliximab is a chimeric monoclonal antibody directed against the alpha chain of the interleukin-2 receptor (IL-2R). It is involved in binding to and blocking this chain, thereby preventing IL-2R activation.
  - Anti-thymocyte globulin (ATG) is an infusion of horse or rabbit-derived antibodies against human T cells and their precursors (thymocytes), which is used in the prevention and treatment of acute rejection.
  - Polyclonal antibodies (immunoglobulins)—the polyclonal immunoglobulin (Ig) is an Ig extract pooled from thousands of plasma donors to create a product that is rich in IgG [22].
- Maintenance Therapy: Maintenance therapy is required lifelong to maintain graft acceptance and prevent chronic rejection.
  - Triple-drug regimen: The most common protocol includes:
    - Glucocorticosteroids (e.g., methylprednisolone and prednisone): In the early 1960s, corticosteroids were first used. These drugs provide rapid, broad immunosuppression and immunomodulatory effects by suppressing inflammatory cytokine production and lymphocyte immunosuppressive activity. They bind to glucocorticoid receptors in the cell cytoplasm and inhibit the production of various pro-inflammatory and immunomodulatory cytokines, such as IL-1, IL 2, IL-6, and TNF-α, through the blockage or competition for the function of transcription factors, such as nuclear factor-kappa-B (NF-kB) and activator protein-1 (AP-1), which are necessary for transcription of pro-inflammatory mediators. Side effects include increased risk of infections, osteoporosis, edema, alkalosis, metabolic and gastrointestinal disorders.

- Calcineurin inhibitors (CNIs) (e.g., cyclosporine and tacrolimus): Cyclosporine (CsA) and tacrolimus (FK506) inhibit cellular activity and the humoral immune response by calcineurin inhibition. This inhibition occurs through the formation of a complex with the immunophilin FK506, preventing NF-AT translocation, which promotes T helper cell proliferation mediated by IL-2. They are pivotal for preventing acute rejection but carry risks of side effects, including nephrotoxicity, hepatotoxicity, cardiovascular disease, increased incidence of neoplasms, post-transplant lymphoproliferative disease related to the activation of Epstein-Barr virus (EBV). Tacrolimus seems to have an immunosuppressive effect one hundred times stronger than CsA. For this reason, tacrolimus has replaced cyclosporine in new transplants. The target concentrations of both CsA and FK506 are influenced by several factors and by interactions with other drugs. For this reason, periodic determination of their blood level is necessary.
- Antiproliferative drugs: Azathioprine in the 1960s was the first immunosuppressive drug used on a large scale in organ transplantation. Today it has been replaced by mycophenolate mofetil (MMF), and mycophenolic acid (MPA), which inhibit lymphocyte proliferation by disrupting purine base synthesis required for T- and B-cell proliferation. Side effects are gastrointestinal disturbances, leukopenia and increased risk of cytomegalovirus infection. Sodium mycophenolate is an enteric-coated formulation developed to minimize MPA-related gastrointestinal symptoms through release and absorption after the passage through the stomach.

– Other currently available drugs
  - Mammalian target of rapamycin inhibitors (mTOR-i) (e.g., sirolimus and everolimus): mTOR-i are inhibitors of mTOR, inhibiting T- and B-cell proliferation and differentiation, antibody production, and the proliferation of non-immune cells (fibroblasts, endothelial cells, hepatocytes, and smooth muscle cells). The most common side effects of mTOR-i are pneumonitis, surgical scar infection or late healing, lymphocele, post-transplant diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, proteinuria and edemas.
  - Belatacept is a CTLA-4 molecule fused to the Fc domain of human IgG1 produced by recombinant DNA technology in Chinese hamster ovary cells. This protein binds to the CD80 and CD86 molecules on APCs and prevents their interaction with the CD28 molecule of T lymphocytes, blocking co-stimulation, the second signal of lymphocyte activation; thus, belatacept is a selective blocker of T lymphocyte co-stimulation.

15.10.2 Evolving Therapies and Considerations

Biological agents also play a role in treating rejection episodes and minimizing the need for high-dose corticosteroids, thereby reducing steroid-related complications.

Research is ongoing into agents like belatacept, a co-stimulation blocker, which offers an alternative to calcineurin inhibitors for maintenance therapy, reducing nephrotoxicity risks.

15.10.3 Tailoring Therapy

Immunosuppressive regimens are individualized based on:

- Immunological risk: High-risk patients (e.g., with pre-existing donor-specific antibodies) may require intensified induction therapy and careful monitoring.
- Underlying pathology: Certain causes of ESRD, such as autoimmune diseases, may warrant modified protocols.
- Graft condition: If the graft shows signs of dysfunction, regimens may be adjusted to improve efficacy while minimizing side effects.

15.10.4 Challenges and Risks

- Side effects: Long-term use of immunosuppressive drugs can lead to complications such as infections, cardiovascular disease, diabetes, hypertension, and malignancies.
- Therapeutic monitoring: Many drugs, particularly CNIs, require frequent monitoring of blood levels to balance efficacy and toxicity.

15.10.5 Future Directions

Advancements in immunosuppressive therapies aim to improve long-term graft survival while minimizing adverse effects. Innovations such as precision medicine, tolerance induction strategies, and the use of biologics with targeted mechanisms are areas of active research. Improved immunosuppressive protocols will enhance patient outcomes and quality of life, highlighting the need for continued exploration and optimization.

15.11 Combined Transplantation

Combined organ transplantation is a life-saving option for patients with multi-organ dysfunction, offering better survival, improved quality of life, and enhanced metabolic control. This approach is particularly relevant for individuals with coexisting kidney and other organ failures, such as those associated with diabetes or liver disease. Two primary types of combined transplantation are pancreas-kidney transplantation and simultaneous liver-kidney transplantation.

15.11.1 Pancreas-Kidney Transplantation

Pancreas-kidney transplantation is most commonly performed in patients with type 1 diabetes mellitus and ESRD. Pancreas-kidney transplantation restores renal function, eliminates insulin dependence and alleviates progressive diabetes-related complications. Recipients often report significantly improved quality of life and a reduced risk of cardiovascular events [23].

- Simultaneous pancreas-kidney transplant (SPKTx): SPKTx accounts for approximately 75% of pancreas transplants and involves transplanting both organs from a single deceased donor. SPKTx is indicated for patients with severe metabolic complications of diabetes and ESRD, offering both insulin independence and renal function restoration. SPKTx improves survival by addressing both kidney failure and metabolic complications of diabetes. It prevents the progression of diabetic complications such as retinopathy and neuropathy, reducing morbidity, and it prevents recurrence of diabetic nephropathy on the kidney allograft.
- Pancreas after kidney transplant (PAKTx): In about 15–20% of cases, the pancreas transplant follows a successful kidney transplant (mainly from a living donor). PAKTx is typically indicated for patients whose kidney transplant has stabilized renal function, allowing them to focus on resolving diabetes-related metabolic challenges and preventing diabetic nephropathy on the graft.
- Pancreas transplant alone (PTA): In a smaller subset of patients (5–10%), PTA is performed for individuals with diabetes but without diabetic nephropathy. These patients often experience severe and potentially life-threatening complications like hypoglycemia unawareness, frequent diabetic ketoacidosis, and poor metabolic control despite advanced insulin therapies.

15.11.2 Liver-Kidney Transplantation

Simultaneous liver-kidney transplantation (SLKTx) is a critical intervention for patients with dual organ failure, particularly end-stage liver disease (ESLD) combined with ESRD, a common complication in patients with severe liver disease, often exacerbated by conditions such as hepatorenal syndrome or systemic complications of liver disease. Mortality in such cases is significantly reduced by combined transplantation. SLKTx is primarily indicated for HCV liver disease with associated glomerulonephritis; hepatorenal polycystic disease, a genetic disorder affecting both the liver and kidneys; and primary hyperoxaluria type I, a rare metabolic disorder that leads to systemic oxalate deposition and severe organ damage. Since the first SLKTx in 1983, its use has increased dramatically, especially after the introduction of the MELD (Model for End-Stage Liver Disease) scoring system in 2002 [24]. MELD prioritizes transplantation based on liver and kidney function giving preference to patients with co-existing ESRD, and its introduction has increased the number of SLKTx procedures by over 300%. SLKTx improves survival and quality of life in patients with dual organ failure. By treating both liver and

kidney dysfunction at the same time, it reduces the risks associated with staged procedures and improves the success of organ transplantation.

Combined transplantation represents a critical option for patients with complex medical needs, offering improved outcomes when performed in centers with extensive expertise. Ongoing advancements in immunosuppression, organ procurement, and patient management are set to further enhance the success rates and accessibility of these procedures.

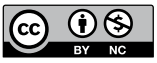
15.12 Conclusions

Kidney transplantation remains the gold standard for treating ESRD, significantly improving quality of life and survival rates. Progress in donor availability, such as expanded criteria donors and donation after circulatory death, and innovative preservation techniques like machine perfusion have broadened the transplant landscape. Advances in immunosuppressive therapy and strategies to overcome immunological barriers, including AB0-incompatible transplants, have enhanced graft and patient outcomes. Surgical innovations, such as robotic-assisted procedures, offer additional benefits for selected patient groups, despite their technical complexities. Living donor programs continue to provide superior outcomes due to reduced ischemia and better organ compatibility. Comprehensive management of surgical, immunological, and non-immunological complications is pivotal to patient success. Multidisciplinary approaches and continuous research into new immunosuppressive and regenerative therapies hold promise for further reducing complications. As donor numbers strive to meet rising demands, bioartificial organs and xenotransplantation are emerging as future directions. Kidney transplantation exemplifies the integration of surgical precision, medical advancements, and innovative science to address the growing global need for effective renal replacement therapies.

References

1. Sitjar-Suñer M, Suñer-Soler R, Bertran-Noguer C, et al. Mortality and quality of life with chronic kidney disease: a five-year cohort study with a sample initially receiving peritoneal dialysis. Healthcare (Basel). 2022;10(11):2144.
2. Rete azionale trapianti. Donazioni, trapianti, liste di attesa in Italia al 31 dicembre 2023 [Internet]. 2024 [cited 2024 Dec 9]. Available from: https://trapianti.sanita.it/statistiche/attivita/2023_D_ATTIVITA_ORGANI_DX-TX.pdf.
3. Ghaderian SB, Hayati F, Shayanpour S, et al. Diabetes and end-stage renal disease; a review article on new concepts. J Renal Inj Prev. 2015;4(2):28–33.
4. De Carlis R, Di Sandro S, Lauterio A, et al. Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. Liver Transpl. 2017;23(2):166–73.
5. Geraci P, Sepe V. Non-heart-beating organ donation in Italy. Minerva Anestesiol. 2011;77(6):613–23.
6. Argani H. Expanded criteria donors. Exp Clin Transplant. 2022;20(Suppl 4):13–9.

7. Tatsisa V, Dounousib M. Hypothermic machine perfusion of kidney transplant: a mini-review. Transplant Proc. 2021;53(9):2793–6.
8. Catena F, Coccolini F, Montori G, et al. Kidney preservation: review of present and future perspective. Transplant Proc. 2013;45:3170–7.
9. Rogers N, Wyburn K. COMPARE trial: new hope for organ preservation. Lancet. 2020;396(10263):1609–11.
10. Hosgood SA, Callaghan CJ, Wilson CH, et al. Normothermic machine perfusion versus static cold storage in donation after circulatory death kidney transplantation: a randomized controlled trial. Nat Med. 2023;29(6):1511–9.
11. Ghods AJ. Living kidney donation: the outcomes for donors. Int J Organ Transplant Med. 2010;1(2):63–71.
12. Parolo A, Silvestre C, Neri F, et al. Therapeutic apheresis in kidney AB0 incompatible transplantation. Transfus Apher Sci. 2017;56(4):506–9.
13. Modi P, Pal B, Modi J, et al. Retroperitoneoscopic living donor nephrectomy and laparoscopic kidney transplantation: experience of initial 72 cases. Transplantation. 2013;95:100–5.
14. Spiers HVM, Sharma V, Woywodt A, et al. Robot-assisted kidney transplantation: an update. Clin Kidney J. 2022;15(4):635–43.
15. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012;12(2):388–99.
16. Ciancio G, Tabbara MM, Gonzalez J, et al. Surgical modifications to the conventional kidney transplant technique: the Miami transplant institute approach in a retrospective cohort study. Int J Surg. 2024;110:4839–49.
17. Fathi P, Golriz M. Impact of surgeon's experience on vascular and haemorrhagic complications after kidney transplantation. Eur J Vasc Endovasc Surg. 2019;57:139–49.
18. Gunawardena T, Sharma H. Transplant renal artery stenosis: current concepts. Exp Clin Transplant. 2022;20(12):1049–57.
19. Zorkany KE, Bridson JM, Sharma A, et al. Transplant renal vein thrombosis. Exp Clin Transplant. 2017;15(2):123–9.
20. Naesens M, Roufosse C, Haas M, et al. The Banff 2022 kidney meeting report: reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. Am J Transplant. 2024;24(3):338–49.
21. Taborelli M, Serraino D, Cimaglia C, et al. Cancer mortality after kidney transplantation: a multicenter cohort study in Italy. Int J Cancer. 2024;154(5):842–51.
22. Szumilas K, Wilk A, Kipp M, et al. Current status regarding immunosuppressive treatment in patients after renal transplantation. Int J Mol Sci. 2023;24:10301.
23. Espinoza-Loyola PS, Fernández-López LJ, Mogrovejo-Vázquez PS, et al. Pancreas transplantation: review. Cir Cir. 2024;92(4):547–56.
24. Nair G, Nair V. Simultaneous liver–kidney transplantation. Clin Liver Dis. 2022;26:313–22.



General Surgery and Kidney Transplantation

16

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16.1 Introduction

The pathological features that can modify the outcome of a transplant and impact the patients' quality of life must always be evaluated. The surgical treatments for these diseases, regardless of the affected organ, are described in the other chapters of this monograph. In this chapter we will focus specifically on two common conditions that may require a nephrectomy: polycystic kidney diseases (PKDs) and the removal of a non-functioning kidney graft.

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16.2 Polycystic Kidney Diseases

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent form of PKD, and it leads to end-stage renal disease (ESRD). It is a multisystem disease characterized by the bilateral formation of renal cysts. It has adult onset and a genetic basis: the two most commonly involved genes are *PKD1* and *PKD2*, which encode for the proteins polycistin-1 and -2, respectively [1–4]. Clinical features such as hypertension, abdominal pain and fullness, hematuria and urinary tract infections are common and manifest years before the renal failure. Hypertension is the first manifestation of ADPKD and it occurs in nearly all patients with ESRD [5–8]. It has a progressive course towards ESRD: the expanding cysts secrete cytokines with the development of fibrosis and this process determines the impairment of the renal parenchyma [9]. Management is mainly aimed at slowing down the renal failure and mitigating its symptoms by using standard therapies, but also at controlling the cysts' growth with common drugs such as octreotide LAR, mTOR inhibitors (e.g., sirolimus, everolimus), or the newer vasopressin V2 receptor inhibitors (e.g., tolvaptan). Unfortunately, despite these therapies almost all patients will need renal replacement therapy (RRT), that is, hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation (KTx). The RRT gold standard should be KTx, especially in patients receiving pre-emptive transplantation after living donation [10, 11].

Native nephrectomy (NN) is not routinely recommended before the KTx, but it is performed in selected circumstances, such as cyst infection, recurrent or severe bleeding, pain not responsive to medical therapy or in the case of lack of space for the graft [3, 10, 12] (Fig. 16.1).

Polycystic kidney nephrectomy is often performed at highly specialized centers. However, it is not uncommon for the procedure to be done also in general surgery units, for a variety of circumstances (i.e., emergency conditions). The ideal timing is an ongoing topic of discussion in the literature. In fact, while polycystic kidneys are always at risk of septic or bleeding complications, their removal causes a decrease of erythropoietin and a worsening quality of life due to a reduced quantity of residual diuresis. Avoiding the anuric state allows the patients to better handle the dialysis treatment and, in the pre-dialysis ESRD phase, to receive a preventive transplant [2, 12].

A PubMed database search using the key words "polycystic kidney disease", "native nephrectomy" and "kidney/renal transplantation" was carried out to retrieve the latest published research regarding the optimal timing for NN.

Veroux et al. conducted a retrospective study on 145 patients, divided into three groups. They analyzed post-transplant outcomes and patient and graft survival rates at 5 years and found no differences between patients who did not undergo nephrectomy and those who underwent simultaneous nephrectomy and transplantation. The patients subjected to pre-transplant NN had longer time on the waiting list, severe anuria and anemia. The study results showed the superiority of concurrent nephrectomy, when the size of the polycystic kidney prevents correct graft positioning [2].

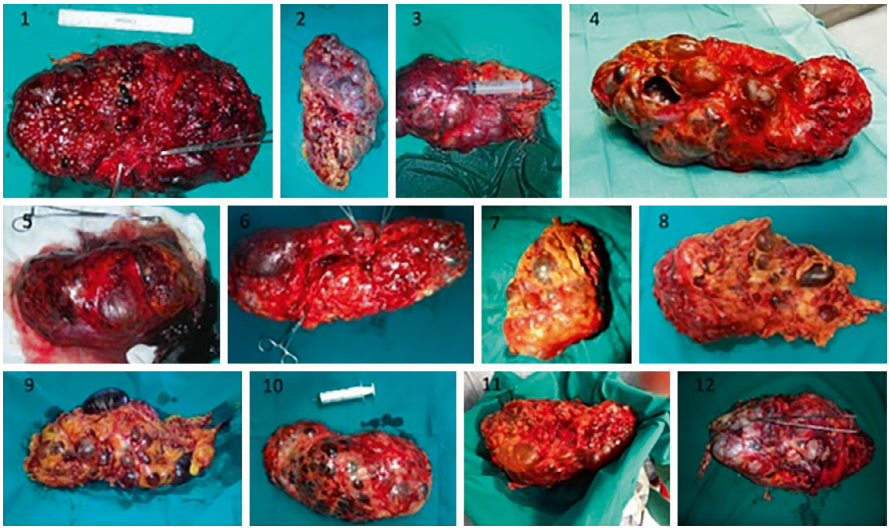


Fig. 16.1 Polycystic kidneys. Surgical specimens from nephrectomies performed because of: lack of space (1, 4, 6, 11), hematuria and pain (2, 3, 5, 9), recurrent infections and pain (7, 8, 10, 12)

Accordingly, many authors support the feasibility of concurrent NN during transplantation.

In 2013, in an observational study on 100 patients who received simultaneous ipsilateral nephrectomy and KTx, Neeff et al., noted high rates of patient survival and graft function at 1 and 5 years, with low rates of complications [13]. Lucas et al. compared the safety of NN during transplantation with transplantation alone, and they did not find significant differences regarding operative time, blood loss, creatinine levels and post-operative complications [14]. Król et al. performed concurrent bilateral nephrectomies in potential transplant recipients and reported a moderate risk of perioperative complications, but with the advantage of a single surgical operation in symptomatic patients [15]. Simultaneous nephrectomy has been carried out without negative effects also in cases of living-donor KTx. Wagner et al. presented a study of symptomatic ADPKD patients who underwent either simultaneous laparoscopic nephrectomy and living-donor transplantation or staged pre-transplant NN if the patients were on the waiting list. They found no significant difference in patient survival or graft function, supporting the role of concurrent NN in living-donor transplant recipients [16]. Similarly, Kramer et al. published their results with concurrent bilateral nephrectomy and living-donor transplant, reporting successful outcomes for both donor and recipient and manageable complications [17].

However, a number of authors support the decision to perform NN before or after the KTx in selected cases. Kirkman et al. studied 35 patients identifying higher rates of perioperative complications and mortality in the pre-transplant group and suggesting that the optimal timing for nephrectomy, in the absence of complications, is after the transplant. In three patients, they carried out the so-called "sandwich technique", whereby the worse affected kidney is removed prior to transplantation and

the second in the following months. These patients showed no adverse effects but the sample was too small to draw useful conclusions [18]. Likewise, Maxeiner et al. in their study of 121 patients noted an increased complication rate and longer hospital stays in the pre-transplant group, confirming that the NN can be performed only when needed. Patel et al.'s study of 157 transplanted ADPKD patients over 10 years, 20% of them requiring nephrectomy for acute renal complications, demonstrated that the majority of ADPKD patients do not require a routine NN. Furthermore, Fuller et al. found no statistically significant differences in outcomes when comparing pre-, post-transplant and concomitant NN, whilst Jankowska et al. noted longer waiting list times for patients receiving a pre-transplant nephrectomy [19–22].

Prophylactic nephrectomy is still endorsed by some authors. Sulikowski et al. published a retrospective study of 50 transplanted patients who received pre- or post-transplant NN (group I and II) or no nephrectomy (group III). They found a greater rate of urological or infectious complications in group III and few adverse effects linked to the NN. Their conclusions show the positive results of preventive nephrectomy [23]. Bellini et al. performed NN in 33 cases, either ESRD or transplanted patients, without any consequence on graft function or donor-specific antibody (DSA) status. They suggest postponing the surgery until after three months of dialysis to avoid the consequences of anemia [24]. Moreover, Garcia- Rubio et al., in a 2015 study comparing 27 patients who underwent pre-transplant NN to patients who did not, found a that pre-transplant NN was not associated with a higher incidence of complications or graft dysfunction. The authors therefore support pre-transplant nephrectomy in selected cases. Similarly, Anselmo et al. suggests performing the NN before the transplant to reduce to minimize the risks associated with the procedure [25, 26]. Ismail et al. found fewer early and late complications in patients who received staged bilateral laparoscopic nephrectomy prior to the KTx. Nevertheless, they recommend the procedure only in selected patients [27].

In recent years, increasing importance has been given to minimally invasive techniques and various studies support the use of laparoscopic and robotic surgery to perform the nephrectomy before and after the transplant, reporting good outcomes and a reduced timeframe between the two surgeries [28–34]. Minimally invasive surgery is a safe technique even in ESRD or transplanted patients, without effects on graft function [35, 36], Furthermore, El-Galley showed that bilateral laparoscopic hand-assisted nephrectomy is a safe and effective procedure either before or after KTx and can be a useful procedure in the event of complications or when space for the graft is needed [37].

In conclusion, there is currently no consensus on the timing of NN in patients with ADPKD and the choice should be tailored to each patient. However, the majority of authors support the possibility of performing KTx and NN at the same time, when the indication is lack of space, while in other circumstances (e.g., bleeding, infections or pain—generally the clinical manifestation of the former two), it seems that most authors do not prefer simultaneous nephrectomy. Moreover, even if the minimally invasive approach is gaining ground, it is generally used in uncomplicated cases and with relatively small kidneys. In any case, polycystic kidneys should

always be considered a resource for the patient with renal failure and their excision must be performed only when really necessary in order to avoid a prolonged state of anuria.

16.3 Removal of a Non-functioning Kidney Graft

Graft failure is a fearsome complication of KTx and in some cases it can require an allograft nephrectomy (AN). It is often subsequent to complication following graft rejection, whose origins are immunological [38]. There is still no consensus on whether or not the graft should be routinely removed, because AN has high rates of mortality and morbidity. However, the compromised allograft left *in situ* causes a chronic inflammatory response whose treatment, not always effective, requires long-term administration of low-dose immunosuppressive therapy. Recent meta-analyses have nevertheless reported that AN is associated with a greater risk of primary non-function (PNF) and delayed graft function (DGF) after a second transplant [38–40].

Transplantectomy is mandatory and urgent in early failures secondary to hyperacute or acute rejection, vascular thrombosis, hemorrhage or sepsis and kidney rupture. In cases of chronic rejection, the procedure should be reserved only for specific conditions (e.g., recurrent infections, abdominal pain, hematuria and intolerance of immunosuppressive therapy) or in the case of graft intolerance syndrome, which manifests in about 40% of patients with fever, anemia, pain, graft swelling, weight loss and hematuria [41, 42].

As stated, AN has high rates of mortality and morbidity and may be carried out with different surgical techniques: with an extracapsular or intracapsular excision, through an extraperitoneal or intraperitoneal approach. Every technique is associated with various risks and the choice is made considering the graft implantation, the time since the transplant, the possibility of a concurrent intraperitoneal disease and the surgeon's inclination [38, 42, 43] (Fig. 16.2).

When the graft is transplanted with an extraperitoneal approach, after a short time its capsule adheres to extraperitoneal organs and tissues. Thus, extracapsular nephrectomy is a safe procedure when performed in early transplantectomy: it consists of removal of the graft with its capsule and allows good control of the iliac vessels. In late transplantectomy, it is associated with an increased risk of lymphocele or collection formation [41, 43].

If AN is performed more than one month after transplantation, the intracapsular approach, carried out through an extraperitoneal incision, is usually the technique of choice. In fact, from a technical point of view, dissection of the renal capsule from its parenchyma is easier than identifying an appropriate plane between the native tissues and the renal capsule, as in the extracapsular approach. However, with this approach, the capsule—and so more allogeneic tissue—is left *in situ* and the patient may be at higher risk of allosensitization, which could potentially compromise the outcome of a second transplant. Furthermore, control of the vessels and ureter is

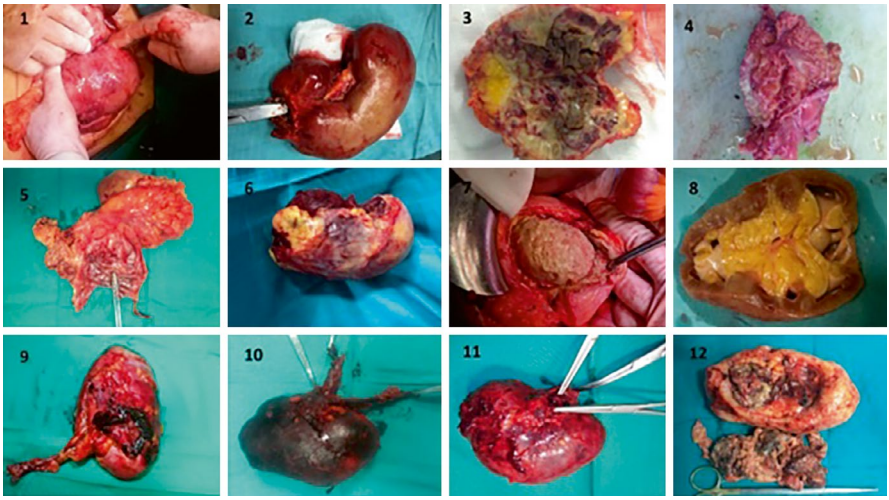


Fig. 16.2 Surgical specimens from allograft nephrectomies performed for: graft intolerance syndrome (1, 3, 4, 11); inferior pole necrosis (2); hematuria (6); recurrent infections (5, 7); renal lipomatosis with recurrent infections (8); arterial thrombosis (9); venous thrombosis with kidney rupture (10); renal mycetoma (12). Surgical technique: intracapsular (1, 2, 7, 8); extracapsular (3, 4, 9, 10, 11); mixed (5, 6, 12)

more challenging and blunt dissection of the capsule from the renal parenchyma may cause significant blood loss [43, 44].

The intraperitoneal approach is usually reserved for intraperitoneal grafts, when greater control of the iliac vessels is necessary, but it carries a risk of causing damage to the intraperitoneal structures [42, 43]. Several authors have found that extracapsular AN, compared to intracapsular AN, has shorter hospital stays despite being associated with significant blood loss and longer operating times [38, 44].

In recent years, percutaneous embolization of the graft has been proposed as a valid alternative to AN. It consists of the injection of ethanol and subsequently of steel coils in the graft's renal artery. It can also be performed before the AN to minimize the hemorrhagic complications. A systematic review comparing transplantectomy and embolization showed lower morbidity rates with the latter. On the other hand, the incidence of post-embolization syndrome, characterized by fever, abdominal pain and vomiting, was high and 20% of patients underwent AN after the embolization [45, 46].

With the aim of achieving better control of the surgical site and iliac vessels, reducing blood loss and the risk of vascular injury as well as removing more allogeneic tissues, over the last few years we have developed an intraperitoneal AN technique that uses an extracapsular approach for the medial surface and intracapsular access for the lateral surface.

After intraperitoneal laparotomy and exposure of the medial surface of the transplanted kidney, located in its retroperitoneal position, we proceed to open the parietal peritoneum at the level of the kidney's concave surface and poles; then we

continue with the isolation of these poles from the iliac vessels so the surgeon can carry out the so-called "hanging maneuver" by placing two fingers of the left hand above and below the renal hilum and pulling up the graft. This renal suspension allows better access to the hilum through its detachment from the iliac vessels and firm control of the graft's vessels. After isolation and ligation of the graft's vessels and ureter, the renal capsule is incised along the convex edge and the kidney is excised along with the capsule and peritoneum which covers its medial aspect. The posterior capsule is instead left *in situ*. In our experience, this technique has proven to be safe and valid. We are still studying to compare its effectiveness with that of other techniques.

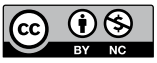
In conclusion, AN is a demanding procedure for the patients. Indeed, they are generally in a fragile state with severe comorbidities and the present an adhesional fibrosis between the graft and the surrounding tissues as a result of chronic rejection and other pathological processes involving the graft. Therefore, this procedure is associated with higher mortality and morbidity rates than renal transplantation itself and must be performed respecting the correct indications and only in the case of real necessity.

References

1. Bergmann C, Guay-Woodford LM, Harris PC, et al. Polycystic kidney disease. Nat Rev Dis Primers. 2018;4(1):50.
2. Veroux M, Zerbo D, Basile G, et al. Simultaneous native nephrectomy and kidney transplantation in patients with autosomal dominant polycystic kidney disease. PLoS One. 2016;11(6):e0155481.
3. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. J Am Soc Nephrol. 2018;29(1):13–23.
4. Grantham JJ, Torres VE. The importance of total kidney volume in evaluating progression of polycystic kidney disease. Nat Rev Nephrol. 2016;12(11):667–77.
5. Rahbari-Oskoui F, Williams O, Chapman A. Mechanisms and management of hypertension in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2014;29(12):2194–201.
6. Geertsema P, Stellema R, Casteleijn NF. The importance of recognizing pain in patients with autosomal dominant polycystic kidney disease. Kidney Med. 2024;6(5):100821.
7. Kalatharan V, Grewal G, Nash DM, et al. Stone prevalence in autosomal dominant polycystic kidney disease: a systematic review and meta-analysis. Can J Kidney Health Dis. 2020;7:2054358120934628.
8. Akoh JA. Current management of autosomal dominant polycystic kidney disease. World J Nephrol. 2015;4(4):468–79.
9. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007;369(9569):1287–301.
10. Spithoven EM, Kramer A, Meijer E, et al. Analysis of data from the ERA-EDTA registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. Kidney Int. 2014;86(6):1244–52.
11. Argyrou C, Moris D, Vernadakis S. Tailoring the "perfect fit" for renal transplant recipients with end-stage polycystic kidney disease: indications and timing of native nephrectomy. In Vivo. 2017;31(3):307–12.

12. Copur S, Ozbek L, Guldan M, et al. Native nephrectomy in polycystic kidney disease patients on transplant lists: how and when? J Nephrol. 2024;37(6):1463–75.
13. Neeff HP, Pisarski P, Tittelbach-Helmrich D, et al. One hundred consecutive kidney transplantations with simultaneous ipsilateral nephrectomy in patients with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2013;28:466–71.
14. Lucas SM, Mofunanya TC, Goggins WC, Sundaram CP. Staged nephrectomy versus bilateral laparoscopic nephrectomy in patients with autosomal dominant polycystic kidney disease. J Urol. 2010;184:2054–9.
15. Król R, Ziaja J, Cierniak T, et al. Simultaneous transabdominal bilateral nephrectomy in potential kidney transplant recipients. Transplant Proc. 2006;38:28–30.
16. Wagner MD, Prather JC, Barry JM. Selective, concurrent bilateral nephrectomies at renal transplantation for autosomal dominant polycystic kidney disease. J Urol. 2007;177(6):2250–4; discussion 2254.
17. Kramer A, Sausville J, Haririan A, et al. Simultaneous bilateral native nephrectomy and living donor renal transplantation are successful for polycystic kidney disease: the University of Maryland experience. J Urol. 2009;181(2):724–8.
18. Kirkman MA, van Dellen D, Mehra S, et al. Native nephrectomy for autosomal dominant polycystic kidney disease: before or after kidney transplantation? BJU Int. 2011;108(4):590–4.
19. Maxeiner A, Bichmann A, Oberländer N, et al. Native nephrectomy before and after renal transplantation in patients with autosomal dominant polycystic kidney disease (ADPKD). J Clin Med. 2019;8(10):1622.
20. Patel P, Horsfield C, Compton F, et al. Native nephrectomy in transplant patients with autosomal dominant polycystic kidney disease. Ann R Coll Surg Engl. 2011;93(5):391–5.
21. Fuller TF, Brennan TV, Feng S, et al. End stage polycystic kidney disease: indications and timing of native nephrectomy relative to kidney transplantation. J Urol. 2005;174:2284–8.
22. Jankowska M, Kuźmiuk-Glembin I, Skonieczny P, Dębska-Ślizień A. Native nephrectomy in renal transplant recipients with autosomal dominant polycystic kidney disease. Transplant Proc. 2018;50:1863–7.
23. Sulikowski T, Tejchman K, Zietek Z, et al. Experience with autosomal dominant polycystic kidney disease in patients before and after renal transplantation: a 7-year observation. Transplant Proc. 2009;41(1):177–80.
24. Bellini MI, Charalmpidis S, Brookes P, et al. Bilateral nephrectomy for adult polycystic kidney disease does not affect the graft function of transplant patients and does not result in sensitisation. Biomed Res Int. 2019;2019:7423158.
25. García-Rubio JH, Carrasco Valiente J, Campos Hernández JP, et al. Graft survival in patients with polycystic kidney disease with nephrectomy of native kidney pretransplant. Transplant Proc. 2015;47:2615–7.
26. Anselmo A, Iaria G, Pellicciaro M, et al. Native nephrectomy in patients with autosomal dominant polycystic kidney disease evaluated for kidney transplantation. Transplant Proc. 2019;51:2914–6.
27. Ismail HR, Flechner SM, Kaouk JH, et al. Simultaneous vs. sequential laparoscopic bilateral native nephrectomy and renal transplantation. Transplantation. 2005;80:1124–7.
28. Bansal RK, Kapoor A. Laparoscopic nephrectomy for massive polycystic kidney disease: updated technique and outcomes. Can Urol Assoc J. 2014;8:341–5.
29. Verhoest G, Delreux A, Mathieu R, et al. Transperitoneal laparoscopic nephrectomy for autosomal dominant polycystic kidney disease. JSLS. 2012;16:437–42.
30. Bendavid Y, Moloo H, Klein L, et al. Laparoscopic nephrectomy for autosomal dominant polycystic kidney disease. Surg Endosc. 2004;18:751–4.
31. Asimakopoulos AD, Gaston R, Miano R, et al. Laparoscopic pretransplant nephrectomy with morcellation in autosomic-dominant polycystic kidney disease patients with end-stage renal disease. Surg Endosc. 2015;29:236–44.

32. Dunn MD, Portis AJ, Elbahnasy AM, et al. Laparoscopic nephrectomy in patients with end-stage renal disease and autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2000;35:720–5.
33. Collini A, Benigni R, Ruggieri G, Carmellini PM. Laparoscopic nephrectomy for massive kidneys in polycystic kidney disease. JSLS. 2021;25:e2020.00107.
34. Chen K, Tan YG, Tan D, et al. Predictors and outcomes of laparoscopic nephrectomy in autosomal dominant polycystic kidney disease. Investig Clin Urol. 2018;59:238–45.
35. Whitten MG, Van der Werf W, Belnap L. A novel approach to bilateral hand-assisted laparoscopic nephrectomy for autosomal dominant polycystic kidney disease. Surg Endosc. 2006;20:679–84.
36. Desai PJ, Castle EP, Daley SM, et al. Bilateral laparoscopic nephrectomy for significantly enlarged polycystic kidneys: a technique to optimize outcome in the largest of specimens. BJU Int. 2008;101:1019–23.
37. El-Galley R, Safavy S, Busby JE, Colli J. Outcome of hand assisted laparoscopic bilateral native nephrectomy in transplant recipients. J Urol. 2011;185(3):1021–5.
38. Vavallo A, Lucarelli G, Bettocchi C, et al. Allograft nephrectomy: what is the best surgical technique? Transplant Proc. 2012;44(7):1922–5.
39. Gavriilidis P, O'Callaghan JM, Hunter J, et al. Allograft nephrectomy versus non-allograft nephrectomy after failed renal transplantation: a systematic review by updated meta-analysis. Transpl Int. 2021;34(8):1374–85.
40. Ghyselen L, Naesens M. Indications, risks and impact of failed allograft nephrectomy. Transplant Rev (Orlando). 2019;33(1):48–54.
41. Figueiredo A, editor. European textbook on kidney transplantation. European Association of Urology, The EAU Section of Transplantation Urology; 2017.
42. Gómez-Dos-Santos L-ÁJ, Hevia-Palacios V, et al. The failing kidney transplant allograft. Transplant nephrectomy: current state-of-the-art. Curr Urol Rep. 2020;21(1):4.
43. Phillips BL, Callaghan CJ. Graft nephrectomy in children. Pediatr Nephrol. 2018;33(6):947–55.
44. Touma NJ, Sener A, Caumartin Y, et al. Extracapsular versus intracapsular allograft nephrectomy: impact on allosensitization and surgical outcomes. Can Urol Assoc J. 2011;5(1):49–52.
45. McDonald M. Allograft nephrectomy vs. no nephrectomy for failed renal transplants. Front Nephrol. 2023;3:1169181.
46. Takase HM, Contti MM, Nga HS, et al. Nephrectomy versus embolization of non-functioning renal graft: a systematic review with a proportional meta-analysis. Ann Transplant. 2018;23:207–17.



Endocrine Surgery: Thyroid and Parathyroid

17

Livia Palmieri, Roberta Lucchini, Daniela Angelucci, and Nicola Avenia

17.1 Parathyroid Surgery in Uremic Patients

17.1.1 Definition

Secondary hyperparathyroidism (SHPT) is common in patients affected by chronic kidney disease (CKD). As the incidence of CKD is rapidly growing, the prevalence of SHPT is also increasing: with a prevalence from 30% to 50% [1]. SHPT occurs in 40% of patients with grade 3 CKD, 82% of patients with grade 4 and almost 100% of patients with grade 5 [2]. In SHPT the excessive secretion of parathyroid hormone (PTH) is a response to the reduction in serum calcium concentration, which is why the PTH level is elevated while the serum calcium is normal. The mechanisms leading to an elevated PTH are varied: phosphate retention due to the low glomerular filtration rate (GFR) which reduces the serum calcium level, hyperphosphatemia which increases PTH secretion, and a reduced intestinal absorption of calcium. Most CKD patients who are initially normocalcemic frequently develop hypercalcemia, and all patients develop bone and cardiovascular complications. In patients on long-term dialysis or who have undergone kidney transplantation, the parathyroid glands become hypertrophic with autonomous function and inappropriately increased levels of PTH associated with hypercalcemia: this condition is defined tertiary hyperparathyroidism (THPT).

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17.1.2 Pathogenesis

In normal kidney function, three hormones contribute to maintain calcium and phosphorus homeostasis: PTH, 1,25-dihydroxycholecalciferol (or calcitriol) and fibroblast growth factor 23 (FGF23). Normal physiology involves multiple factors:

- Calcium and phosphate concentration, regulated by intestinal absorption.
- PTH increases bone dissolution, releasing calcium and phosphate into the circulation and increasing calcitriol conversion by 25-hydroxyvitamin D.
- Calcitriol blocks PTH production by vitamin D receptors (VDRs) in the parathyroid glands. The parathyroid expresses calcium-sensing receptors (CaSR)—which regulate PTH secretion based on serum calcium concentration—and FGF receptors.
- FGF23, secreted by osteocytes and osteoblasts, reduces intestinal and renal phosphate absorption and reabsorption, and inhibits PTH secretion with calcitriol reduction.

In patients with CKD, this homeostasis is already unregulated when GFR falls to <70 mL/min/1.73 m^2, and with disease progression it gradually worsens. Early on, FGF23 increases, with increasing urinary phosphate excretion, reducing calcitriol synthesis and suppressing PTH secretion [3]. When GFR falls to <60 mL/min/1.73 m^2, PTH secretion increases, but multifactorial compensation is still maintained and serum calcium and phosphorus concentration remain within normal ranges [4]. This precarious balance collapses when GFR falls to <20 mL/min/1.73 m^2, with the persistent increase of PHT, the increase in serum phosphorus, the rise of FGF23 and the reduction of calcitriol [4]. Continuous PTH stimulation leads to proliferation of the parathyroid cells and parathyroid hyperplasia, with reduced numbers of VDRs and FGF receptors and a consequent increase in PTH secretion [5].

17.1.3 Clinical Presentation and Diagnosis

The first laboratory abnormality is increased FGF23, followed by a calcitriol reduction and PTH increase, with normal or high levels of calcium and phosphate. The most important changes occur in bone and the vascular system. Initially, patients may report pruritus, thirst and headaches; later on, fatigue, muscle weakness, bone pain, depression, fragility fractures, and vascular calcification develop [4]. Vascular calcification can include several organs: solid organs (heart, kidneys, pancreas), soft tissues, valvular calcification, calcific arteriolopathy. Vascular calcification increases morbidity and mortality: the increase in FGF23 promotes left ventricular hypertrophy and worsens the ejection fraction [6]. Calciphylaxis, i.e., calcific uremic arteriolopathy, manifests with painful violaceous subcutaneous nodules that can ulcerate and become infected or even septic, potentially leading the patient to death.

Biochemical abnormalities (elevated PTH with low vitamin D, phosphate and calcium) are often sufficient for diagnosis, but the KDIGO (Kidney Disease Global Outcome) guidelines recommend monitoring the evolution of bone disease in these patients by using dual-energy X-ray absorptiometry (DEXA) [7].

17.1.4 Medical Treatment

Most dialysis patients manage to control the disease with medical treatment, with only a fraction of them requiring surgery.

The first recommended supplementation for these patients is vitamin D, which led to decreased PTH, stable levels of calcium and improvement in vascular function [8]. The main target in medical treatment is to control serum levels of calcium and phosphorus and manage the abnormal PTH levels. Initially, restricted nutritional phosphorus intake is recommended [7]. However, because adherence to a low-protein diet could be difficult, phosphate-binding agents are necessary, and the latest molecules are effective and safe [9]. An increase in phosphate removal through dialysis should be considered in patients who are unable to obtain satisfactory plasma levels of phosphorus.

The updated KDIGO guidelines [7] suggest maintaining the PTH levels between 2 and 9 times the upper limit of normal. For this purpose, calcitriol analogs have been developed to control the intestinal absorption of calcium and phosphorus and maximize parathyroid suppression [10]. In 2004, cinacalcet, a calcimimetic agent that mimics increased extracellular calcium on the CaSR to increase intracellular calcium and reduce PTH release, was approved for use in dialysis patients.

17.1.5 Surgical Treatment

17.1.5.1 Indications for Parathyroidectomy

Precise indications for parathyroidectomy for SHPT are not easy to define, and a multidisciplinary approach involving a nephrologist, surgeon and anesthesiologist is essential. The KDIGO guidelines [7] suggest that patients with PTH more than 9 times the normal range, hypercalcemia and/or hyperphosphatemia refractory to medical treatment should be considered for parathyroidectomy. Other possible indications can be: patients with the opportunity for kidney transplantation in the next 6 months [11], presence of symptoms, and pathologic radiography or DEXA [7].

The introduction of new pharmacological treatments have reduced the rate of parathyroidectomy: from 30% between 1995 and 1999 to 5.4/1000 patients between 2002 and 2011 [12]. Parathyroidectomy, leading to a reduction of PTH, serum calcium and phosphorus, correlates with the improvement of cardiovascular and bone morbidity. A better quality of life in CKD patients after parathyroidectomy was shown, with improvement of all symptoms. Much debated is the potential influence of parathyroidectomy on renal transplantation: some studies show better outcomes

for transplantation if it is preceded by parathyroidectomy [13], but in other studies the outcomes are controversial [14].

The main surgical risk in these patients is due to the comorbidities and postoperative complications, especially the hungry bone syndrome with severe postoperative hypocalcemia [7]. A total 30-day postoperative mortality rate of 3.1%, and a lower mortality rate (10–15%) have been demonstrated in patients undergoing parathyroidectomy compared to patients not treated with surgery [15]. Parathyroidectomy has been shown to be more cost-effective when compared to life-long calcimimetic therapy [16].

17.1.5.2 Perioperative Strategy

Perioperative optimization is strongly recommended as CKD increases the risk of postoperative cardiac events, acute kidney injury (AKI) and overall mortality. A detailed preoperative risk assessment of cardiac function, coagulopathy, management of hypertension are needed. Correct timing of dialysis relative to surgery must be assessed.

Preoperatively, all AKI predictors should be used to stratify the risk: serum creatinine, eGFR and prediction tools. Timing of dialysis in relation to surgery is fundamental: an excessively long interdialytic period must be avoided and patients should be dialyzed the day before surgery [7]. In all patients preoperative electrocardiogram and echocardiogram are recommended, and in selected patients a stress test is necessary [17]. In patients with uncontrolled hypertension, surgery should be delayed until stabilization [18]. Iron anemia, erythropoietin deficiency and platelet dysfunction can increase the risk of postoperative bleeding. The KDIGO guidelines recommend erythropoietin-stimulating agents and iron supplementation to reach a hemoglobin value $\geq$10 g/dL [7]. Vitamin D supplementation is recommended in all patients to prevent postoperative hungry bone syndrome. Calcimimetics should be stopped 14 days before surgery, even though there are no concordant data on the optimal timing [19].

17.1.5.3 Surgical Approaches

A bilateral four-gland exploration should be conducted in all patients. However three different surgical approaches have been described. There is no recommended approach, and the choice depends on the surgeon's preference and the patient's characteristics. In kidney transplant candidates subtotal parathyroidectomy should be preferred, to prevent the risk of hypoparathyroidism associated with total parathyroidectomy [20]. Total parathyroidectomy can be performed in patients ineligible for kidney transplantation [21].

1. Total parathyroidectomy without autotransplantation. All identified parathyroid glands are removed and no parathyroid tissue is reimplanted, to avoid the risk of persistent or recurrent disease. The main risk of this approach is postoperative hypocalcemia, and a variable proportion of patients from 0% to 75% will require oral calcium supplementation [22]. A strong recommendation is to avoid this approach in patients who may undergo kidney transplantation [7].

2. Total parathyroidectomy with autotransplantation. After identification and resection of all identified glands, the surgeon chooses a site for the graft and prepares the parathyroid tissue for the autograft (several millimetric fragments of the chosen gland). Most surgeons choose the visually smallest gland; however, real-time histologic examination is recommended [23]. The choice of the optimal site for autotransplantation is based on patient factors, but all autograft sites should be marked with non-absorbable suture [7]. Several graft sites are reported:
   - The brachioradialis site in non-dominant/non-shunt arm is the most common: the advantage is the possibility of demonstrating a PTH gradient in blood tests between the grafted arm and the ungrafted arm in recurrent disease.
   - The sternocleidomastoid site has the advantage of not requiring any additional skin incisions.
   - Other sites (trapezius, presternal site, abdominal adipose tissue).

   Postoperative complications: the graft could require time to recruit a blood supply and parathyroid function could be delayed; graft failure is possible due to local ischemia; the graft could become hyperplastic with recurrence of disease [24].
3. Subtotal parathyroidectomy. 3.5 of the glands are removed and a remnant of parathyroid tissue with its vascular pedicle is preserved to reduce postoperative hypocalcemia. Firstly, all four glands are visually inspected and one is selected to remain *in situ* (the smallest one or the most normal-appearing); then, this gland is partially resected, and the remnant (1/2 or 1/3 of the total gland) is marked with a non-absorbable suture; finally, the other three glands are removed.

17.1.6 Postoperative Outcomes

The rate of postoperative complications after surgery is higher than that of surgery for primary HPT, varying from 3.8% to 15%, with a 30-day readmission rate of 17% [25].

The most common postoperative complication is hypocalcemia, due both to the hungry bone syndrome (the bone uptake of calcium after the fall of PTH) and to the metabolic rearrangements after surgery. Patients must be monitored after surgery and treated aggressively to avoid life-threatening consequences of hypocalcemia; this explains the longer postoperative hospital stay and higher readmission rate (4–17%) compared to surgery for primary HPT [26]. In 9% of patients affected by CKD, permanent hypoparathyroidism after surgery is reported [21]. Another cause for the longer postoperative hospital stay is the higher risk of postoperative hematoma, which occurs in 0.1–2% of patients and reaches 5.7% in patients receiving anticoagulation therapy [25]. Cardiovascular and cerebrovascular events in the immediate postoperative period are more frequent in patients affected by CKD compared to patients with primary HPT, with a reported cardiac-related death rate ranging from 1.8% to 7% [25].

Recurrent or persistent HPT is common after surgery. Persistent HPT is a failure of PTH to decrease after surgery, with a PTH level above the upper normal limit

immediately after surgery. Recurrent HPT is when, after an initial decrease to normal levels, PTH increases within 6 months after surgery. Causes of recurrent or persistent hyperparathyroidism can be ectopic localizations of glands, regrowth of the remnant gland/graft, and parathyromatosis (spread of parathyroid cells in the surgical field).

17.2 Thyroid Pathology in Uremic Patients

Several studies show an increased prevalence of hypothyroidism, nodular goiter and thyroid carcinoma in patients affected by CKD [27] when compared with the general population.

In patients with CKD, thyroid hormone metabolism is impaired due to CKD-induced modification of the hypothalamic-pituitary-thyroid axis [28]: 20% of dialysis patients have reduced serum levels of free triiodothyronine (FT3) and free thyroxine (FT4) hormones [29]. These anomalies can be explained by the hormonal removal during dialysis, the altered hormonal catabolism, the increased thyroid autoantibodies and the decreased peripheral conversion [28]; also the chronic metabolic acidosis can contribute to the reduction of FT3 [30]. The prevalence of hypothyroidism increases with the reduction of GFR: from 7% for a value <90 mL/min/1.73 m^2 up to 18% for a value <60 mL/min/1.73 m^2 [31].

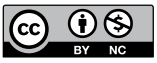
Metabolic changes in prolonged dialysis patients could also contribute to the increased incidence of thyroid nodules, especially malignant ones. The prevalence of thyroid cancer is also correlated with years of dialysis, with a higher rate of multifocal carcinomas compared to the general population [32]. Higher genomic instability, impaired antigen recognition and altered T-cell and B-cell function may explain the higher incidence of malignancies in CKD patients [33]. Another stimulatory effect on thyroid malignancies might result from the action of SHPT: dialysis patients with SHPT showed a 10.2 higher risk of developing thyroid carcinoma compared to dialysis patients without SHPT [34]. An issue that remains debated is radioiodine treatment in these patients, due to the renal excretion of iodine. Radioiodine treatment could cause hematological toxicity (anemia, leukopenia, thrombocytopenia or, extremely rarely, leukemia), which would add to the already higher risk of these patients for hematological events [35]. Thus, a lower than standard dose of radioiodine might be a more cautious approach in patients with CKD and thyroid carcinoma [36].

References

1. Hedgeman E, Lipworth L, Lowe K, et al. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. Int J Nephrol. 2015;2015:184321.
2. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71(1):31–8.

3. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. 2011;79(12):1370–8.
4. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol. 2011;6(4):913–21.
5. Tokumoto M, Tsuruya K, Fukuda K, et al. Reduced p21, p27 and vitamin D receptor in the nodular hyperplasia in patients with advanced secondary hyperparathyroidism. Kidney Int. 2002;62(4):1196–207.
6. Nielsen TL, Plesner LL, Warming PE, et al. FGF23 in hemodialysis patients is associated with left ventricular hypertrophy and reduced ejection fraction. Nefrologia (Engl Ed). 2019;39(3):258–68.
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7(1):1–59.
8. Kumar V, Yadav AK, Lal A, et al. A randomized trial of vitamin D supplementation on vascular function in CKD. J Am Soc Nephrol. 2017;28(10):3100–8.
9. Goldsmith DR, Scott LJ, Cvetković RS, Plosker GL. Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. Drugs. 2008;68(1):85–104.
10. Tarrass F, Yazidi A, Sif H, et al. A randomized trial of intermittent versus continuous oral alfacalcidol treatment of hyperparathyroidism in end-stage renal disease. Clin Nephrol. 2006;65(6):415–8.
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2009;113:S1–S130.
12. Fligor SC, Li C, Hamaguchi R, et al. Decreasing surgical management of secondary hyperparathyroidism in the United States. J Surg Res. 2021;264:444–53.
13. Schwarz A, Rustien G, Merkel S, et al. Decreased renal transplant function after parathyroidectomy. Nephrol Dial Transplant. 2007;22(2):584–91.
14. van der Plas WY, El Moumni M, von Forstner PJ, et al. Timing of parathyroidectomy does not influence renal function after kidney transplantation. World J Surg. 2019;43(8):1972–80.
15. Kestenbaum B, Andress DL, Schwartz SM, et al. Survival following parathyroidectomy among United States dialysis patients. Kidney Int. 2004;66(5):2010–6.
16. Narayan R, Perkins RM, Berbano EP, et al. Parathyroidectomy versus cinacalcet hydrochloride-based medical therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. Am J Kidney Dis. 2007;49(6):801–13.
17. Weiner DE, Tighiouart H, Amin MG, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol. 2004;15(5):1307–15.
18. Sear JW. Perioperative control of hypertension: when will it adversely affect perioperative outcome? Curr Hypertens Rep. 2008;10(6):480–7.
19. Dream S, Kuo LE, Kuo JH, et al. The American Association of Endocrine Surgeons Guidelines for the definitive surgical management of secondary and tertiary renal hyperparathyroidism. Ann Surg. 2022;276(3):e141–76.
20. Pitt SC, Sippel RS, Chen H. Secondary and tertiary hyperparathyroidism, state of the art surgical management. Surg Clin North Am. 2009;89(5):1227–39.
21. Puccini M, Carpi A, Cupisti A, et al. Total parathyroidectomy without autotransplantation for the treatment of secondary hyperparathyroidism associated with chronic kidney disease: clinical and laboratory long-term follow-up. Biomed Pharmacother. 2010;64(5):359–62.
22. Coulston JE, Egan R, Willis E, Morgan JD. Total parathyroidectomy without autotransplantation for renal hyperparathyroidism. Br J Surg. 2010;97(11):1674–9.
23. Li C, Lv L, Wang H, et al. Total parathyroidectomy versus total parathyroidectomy with autotransplantation for secondary hyperparathyroidism: systematic review and meta-analysis. Ren Fail. 2017;39(1):678–87.

24. Puccini M, Ceccarelli C, Meniconi O, et al. Near total parathyroidectomy for the treatment of renal hyperparathyroidism. Gland Surg. 2017;6(6):638–43.
25. Schneider R, Slater EP, Karakas E, et al. Initial parathyroid surgery in 606 patients with renal hyperparathyroidism. World J Surg. 2012;36(2):318–26.
26. Cheng SP, Liu CL, Chen HH, et al. Prolonged hospital stay after parathyroidectomy for secondary hyperparathyroidism. World J Surg. 2009;33(1):72–9.
27. Rhee CM, Chen Y, You AS, et al. Thyroid status, quality of life, and mental health in patients on hemodialysis. Clin J Am Soc Nephrol. 2017;12(8):1274–83.
28. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol. 2009;160(4):503–15.
29. Rhee CM. Thyroid disease in end-stage renal disease. Curr Opin Nephrol Hypertens. 2019;28(6):621–30.
30. Wiederkehr MR, Kalogiros J, Krapf R. Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients. Nephrol Dial Transplant. 2004;19(5):1190–7.
31. Da Costa ABBA, Pellizzari C, Carvalho GA, et al. High prevalence of subclinical hypothyroidism and nodular thyroid disease in patients on hemodialysis. Hemodial Int. 2016;20(1):31–7.
32. Demirer AN, Kemal Y, Gursoy A, et al. Clinicopathological characteristics of thyroid cancer in patients on dialysis for end-stage renal disease. Thyroid. 2008;18(1):45–50.
33. Sandoval SB, Pastor S, Stoyanova E, et al. Genomic instability in chronic renal failure patients. Environ Mol Mutagen. 2012;53(5):343–9.
34. Lin SY, Lin WM, Lin CL, et al. The relationship between secondary hyperparathyroidism and thyroid cancer in end stage renal disease: a population based cohort study. Eur J Intern Med. 2014;25(3):276–80.
35. Ortega AJM, Vázquez RG, Cuenca JIC, et al. (131)I treatment in differentiated thyroid cancer and end-stage renal disease. Rev Esp Med Nucl Imagen Mol. 2016;35(1):29–33.
36. Pahlka RB, Sonnad JR. The effects of dialysis on (131)I kinetics and dosimetry in thyroid cancer patients – a pharmacokinetic model. Health Phys. 2006;91(3):227–37.



Endocrine Surgery: Adrenal and Breast Surgery

18

Angela Gurrado, Francesco Prete, Elisabetta Poli, and Mario Testini

18.1 Adrenal Surgery

The identification of adrenal gland disease (AD) in uremic patients is challenging. Resistant and refractory hypertension is very common in chronic kidney disease (CKD) [1] and may dissimulate symptoms of AD [2], while conventional blood and urinary tests for adrenal hormone excess are not reliable [3]. Hypertension from AD in CKD is most commonly due to primary aldosteronism (PA), less commonly to pheochromocytoma (PH) and Cushing's syndrome (CS) [4].

18.1.1 Indications for Adrenal Surgery

Adrenal surgery (AS) is indicated in CKD for malignancy or excessive hormone secretion.

Functioning adrenal masses are aldosteronoma, cortisol- or androgen-secreting tumors, and pheochromocytoma (PH). Of the adrenal masses found incidentally on imaging (incidentaloma), 85% is non-functioning. Approximately 2% of tumors <4 cm diameter, 6% of those 4–6 cm, and up to 25% >6 cm are known to be malignant [5]. Primary adrenal cancer is rare. Malignant PH occurs more frequently in familial syndromes such as MEN 2A, 2B and von Hippel-Lindau disease [6]. Adrenal tumors secreting more than one hormone are often malignant [7]. Adrenal metastasis from the lung, kidney, breast, melanoma and gastrointestinal tract may be considered for AS [5].

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Higher surgical risks from renal failure and associated comorbidities make the indication for AS more complex; multidisciplinary teams including nephrologists, endocrinologists and surgeons are key to assessing individual risks and benefits [5, 6].

18.1.2 Incidence

In CKD, hypertension from AD is most commonly due to PA, although PA in CKD is underdiagnosed and undertreated [1]. PH occurs in approximately 0.1% to 0.6% of patients with hypertension [8, 9]. PHs are rare in HD patients, with only 22 cases described in the English literature [10]. Incidence data of Cushing's disease in patients with CKD are limited.

18.1.3 Symptoms

Hypertension is a common symptom of AD, but it is easily attributed to underlying renal disease:

- excessive mineralocorticoid receptor activation in PA results in kidney and cardiac fibrosis and progression of CKD [11, 12];
- PH in CKD patients is usually suspected based on symptoms from catecholamine (CA) overload, such as hypertension unresponsive to therapy or hemodynamic instability. Hypertension is present in >90% of patients and it is paroxysmal in 25–50% of cases. Other paroxysmal symptoms are: episodic headaches, sweating, and tachycardia [8].
- manifestations of Cushing's syndrome considerably overlap with hypertension, elevated cardiovascular risk, insulin resistance, dyslipidemia, sarcopenia, osteoporosis, immune dysfunction or mood disturbance observed in CKD [11]; altered biochemical tests and equivocal radiology also render the diagnosis challenging [13].

18.1.4 Work-Up

18.1.4.1 Imaging

CT with adrenal protocol gives information about size, density, contrast uptake and washout, and extra-adrenal invasion; MRI may add better determination of invasion into surrounding organs in selected cases [6]. Imaging in PA, while useful, cannot suggest laterality of hypersecretion [6]. Metaiodobenzylguanidine (MIBG) scan shows higher rates of PH detection (88%) than 18-fluorodeoxyglucose (FDG)-PET (77%), and is useful for excluding PH in HD with high CA levels and an adrenal mass; 10% of PHs that are not detectable by MIBG should be confirmed by FDG-PET. FDG-PET cannot reliably differentiate benign from malignant PH while it has a role in the evaluation of adrenal metastasis [14].

18.1.4.2 Laboratory Tests

Symptoms guide the choice of hormone tests.

Conventional CA tests for PH in CKD are not reliable, as CA metabolite excretion is tied to creatinine clearance. Compared to controls, in HD patients plasma epinephrine and norepinephrine levels are 3 times higher and dopamine is doubled, so only CA concentrations >three-fold are suspicious for PH [14, 15]; plasma deconjugated metanephrines, chromogranine A and vanillymandelic acid levels are unreliable for diagnosing PH [3]. Free plasma metanephrine (FM) levels are relatively independent of renal function, less frequently elevated, and any increases mostly depend on sympathetic nervous system activation in end-stage renal disease (ESRD); plasma normetanephrine >410 pg/mL or metanephrine >142 pg/mL are highly likely indicative of PH [4].

Labetalol, sotalol, tricyclic antidepressants, benzodiazepines, buspirone, amphetamines, ethanol, methyldopa, levodopa, CA-based decongestants, physical stress and obstructive sleep apnea can cause false-positive results [8].

In CKD, the absence of circadian rhythms of cortisol and ACTH is a more sensitive indicator of Cushing's disease than low-dose dexamethasone suppression testing; 24-h urinary free cortisol is not recommended due to its impaired clearance [16]. Late-night salivary cortisol measurement is preferred in CKD, although stage-specific cutoffs for diagnosis are not well established [17].

18.1.4.3 Biopsy

Needle biopsy is not reliable for differentiating functional from non-functional adenoma, or adenoma from adrenocortical carcinoma. Violating an adrenal cortical carcinoma is oncologically unfavorable; in PH it may result in hemorrhage or potentially fatal hypertensive crisis [6].

18.1.4.4 Adrenalectomy

Since 1992, laparoscopic adrenalectomy (LA) has been the gold standard for excision of the majority of benign adrenal lesions [5, 6].

Adrenalectomy for PA in CKD has been associated with fewer antihypertensive requirements [1, 4] and improved outcomes regarding progression to ESRD and mortality [2].

LA for PH is feasible in CKD [10]. Preoperative antihypertensive treatment is recommended. HD patients may suffer severe volume depletion despite high arterial blood pressure; therefore, increasing intravascular volume before AS appears to make perioperative management safer [18].

18.1.4.5 Open vs Laparoscopic Adrenalectomy

When planning the approach we should consider:

- Patient characteristics:
  - prior AS or trauma;
  - comorbidities: coagulopathy, chronic obstructive pulmonary disease, cardiac disease [5];

- Tumor characteristics:
  - size >6 cm is not a contraindication, in the absence of local invasion [19];
  - local invasion suggests an open approach to facilitate lymph node dissection and *en bloc* resection, tumor thrombectomy or vascular reconstruction [20];
- Surgeon experience, crucial in large tumors
- Reasons for conversion during LA: intraoperative hemorrhage, difficult anatomy, suspicion of malignancy and difficulty to perform a radical resection [5];

Minimally invasive approaches (LA or robotic-assisted) are:

- Lateral (left-flank, right-flank);
- Anterior transabdominal;
- Posterior retroperitoneoscopic.

Open adrenalectomy access can be:

- Transabdominal;
- Extrapleural-extraperitoneal (incision in the X-XI intercostal space);
- Transpleural-transdiaphragmatic [5, 6].

18.2 Breast Surgery

Many studies have confirmed that patients with CKD (GFR <60 mL/min/1.73 m^2 or markers of kidney damage for >3 months) have a higher incidence of malignancy and mortality [21].

Breast cancer (BC) is the most diagnosed cancer worldwide among women and the second most common cause of cancer death [22]. BC is a highly heterogeneous neoplasm with a variety of histologic and molecular subtypes: luminal-like (A/B; 60–70%), HER2-enriched (12–20%), and basal-like (15%). The molecular subtypes are categorized based on tumor biomarkers expression status: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu overexpression [22].

Some studies have shown an increased risk of BC and higher mortality in HD patients [23]. This increase in mortality was attributed to a few different reasons. First, adjusting the dose of cytotoxic agents for patients with reduced kidney function can be challenging, and therefore treatment can be suboptimal. Second, patients with ESRD may have more aggressive BC, given the state of chronic inflammation induced by continuous exposure to oxidative stress and uremia (accentuating mitogenesis).

Although the occurrence of combined CKD among these patients is even rarer, it poses a significant challenge for BC treatment. Surgery, radiation, and systemic therapies are the mainstay of the treatment of BC.

Patients with early-stage operable BC initially undergo upfront surgery (BCS or mastectomy and sentinel lymph node biopsy/axillary lymph node dissection), and adjuvant systemic therapy if indicated, based on primary tumor characteristics and

molecular subtypes. Radiation is typically sequenced after definitive surgery and after systemic chemotherapy (if delivered).

Systemic therapies can be administered as adjuvant, neoadjuvant, or palliative. The primary categories include chemotherapy, hormone therapy, anti-HER2 therapy, CDK4/6 and PARP inhibitors. In patients with operable tumors, neoadjuvant therapy (NAC) is the preferred approach in cases of triple negative (TNBC) or HER2+ BC that is clinical stage T2N0 and higher or is clinically node-positive.

When treating BC patients with ESRD, HD does not limit the utility of surgical treatment and radiotherapy. Treating such patients often requires both targeted and endocrine therapies.

In the literature, there are few studies [24] on the treatment of BC in patients with ESRD, and these patients rarely successfully complete the standard regimens of surgery and systemic therapy.

This stems mainly from the altered pharmacokinetics in these patients. The decision-making process is further complicated by the need for potential dose adjustments and the impact of renal function on drug efficacy and toxicity. While hormone therapies and other systemic treatments offer additional options, their use in the ESRD population also requires a nuanced understanding of their interaction with renal dysfunction.

18.2.1 Hormone Therapies

Tamoxifen is a selective ER modulator and is often used for premenopausal women. The study by Langenegger et al. [25] reported that the use of tamoxifen in HD does not need any dose adjustments. However, concomitant medications used in HD may inhibit these enzyme systems, leading to reduced efficacy of tamoxifen.

18.2.2 Aromatase Inhibitors

Aromatase inhibitors (Ais) include anastrozole, letrozole, and exemestane, and are preferred over tamoxifen for treating postmenopausal women with HR+ BC [22]. The study by Langenegger et al. [25] mentioned that the serum concentrations of anastrozole in HD patients are similar to those seen in patients with normal renal function. Therefore, no dose adjustment is needed. There are no specific guidelines on the administration and safety of exemestane for patients with a GFR below 30 mL/min/1.73 m^2, including patients on HD. It is preferable to avoid the drug and use other alternative options if available [26].

18.2.3 CDK 4/6 Inhibitors

More recently, CDK 4/6 inhibitor drugs (palbociclib, ribociclib, and abemaciclib) have been introduced for HR+ and metastatic BCs [27]. Although no studies are

available yet, according to the drug pharmacokinetics, there is no need to reduce the dose in CKD/ESRD patients on HD.

18.2.4 Cyclophosphamide

Cyclophosphamide (CTX) is utilized with following regimens: AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel; TC (+ docetaxel); EC (+ epirubicin) and TAC (+ docetaxel/doxorubicin). The exploration of CTX in patients undergoing HD has been limited [28]. Based on the findings, it is evident that CTX is dialyzable. In another study, the AUC was increased in HD patients. Thus, it is necessary to reduce the dose of CTX by 25% in HD patients.

18.2.5 Two-Drug Regimen: AC/EC

Anthracyclines have renal clearance. For HD patients, there are specific guidelines for the anthracycline regimen. A reduction in the doxorubicin dose of 20–25% is considered safe for patients with CKD/ESRD, including those receiving HD treatment [29].

18.2.6 Paclitaxel and Docetaxel (Taxane)

Studies indicate that the pharmacokinetics of a standard dose of paclitaxel in patients on HD mirrors that in subjects with normal renal function [30].

18.2.7 Platinum Compounds

Basal-type BCs like BRCA1/2 mutation and TNBC are uniquely susceptible to platinum compounds. Carboplatin has less protein binding than cisplatin with greater elimination in the kidney and it is a choice when CKD limits the use of cisplatin [31]. The AIOM (Italian Association of Medical Oncology) guidelines recommend adjusting an AUC × 25 mg dosage for HD patients [29].

18.2.8 Anti-Her2 Monoclonal Antibodies

For patients with HER2+ BC, candidates for NAC, chemotherapy and trastuzumab-based therapy are recommended. After surgery, trastuzumab and chemotherapy regimens, followed by 1 year of HER2-targeted therapy, are a backbone of adjuvant therapy. To our knowledge, there are no reports of trastuzumab/pertuzumab-induced nephrotoxicity.

18.2.9 PARP Inhibitors (Olaparib, Talazoparib)

PARP inhibitor drugs have been approved as monotherapies for metastatic or locally advanced HER2- BC like BRCA1/2 mutation.

The substantially higher olaparib exposure levels associated with CKD could potentially lead to heightened toxicity risks, especially hematologic side effects, over time [32]. Consequently, dose reductions are recommended, but there are no solid guidelines.

18.2.10 Conclusion

The approach to BC treatment in individuals with CKD/ESRD undergoing HD demands a comprehension of the pharmacokinetic changes resulting from renal dysfunction. In BC patients with CKD, drug metabolism and dosage selection are issues that must be considered to avoid aggravation of systemic toxicity caused by renal failure. Considering the clearance of drugs during dialysis, appropriate timing of medication should be selected for HD patients. More research is advised given the scarcity of data in literature.

References

1. Cohen DL, Wachtel H, Vaidya A, et al. Primary aldosteronism in chronic kidney disease: blood pressure control and kidney and cardiovascular outcomes after surgical versus medical management. Hypertension. 2023;80:2187–95.
2. Chen Y-Y, Lin Y-HH, Huang W-C, et al. Adrenalectomy improves the long-term risk of end-stage renal disease and mortality of primary aldosteronism. J Endocr Soc. 2019;3:1110–26.
3. Eisenhofer G, Huysmans F, Pacak K, et al. Plasma metanephrines in renal failure. Kidney Int. 2005;67:668–77.
4. Salman LA, Cohen DL. Chronic kidney disease in adrenal disorders. Curr Opin Endocrinol Diabetes Obes. 2021;28:312–7.
5. Valeri A, Bergamini C, Bellantone R, Lombardi CP, editors. Surgery of the adrenal gland. Milan: Springer; 2013.
6. Smith PW, Hanks JB. Adrenal surgery. In: Jameson L, De Groot LJ, editors. Endocrinology: adult and pediatric. 7th ed. Elsevier; 2016. p. 1931–50.
7. Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376:1451–9.
8. Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. Lancet. 2005;366:665–75.
9. Young WF. Adrenal causes of hypertension: pheochromocytoma and primary aldosteronism. Rev Endocr Metab Disord. 2007;8:309–20.
10. Tatarano S, Mitsuke A, Sakaguchi T, et al. Laparoscopic surgery for pheochromocytoma in hemodialysis patients. Int J Nephrol. 2022;2022:3060647–5.
11. Sagmeister MS, Harper L, Hardy RS. Cortisol excess in chronic kidney disease – a review of changes and impact on mortality. Front Endocrinol (Lausanne). 2023;13:1075809.
12. Ogata H, Yamazaki Y, Tezuka Y, et al. Renal injuries in primary aldosteronism: quantitative histopathological analysis of 19 patients with primary aldosteronism. Hypertension. 2021;78:411–21.

13. Garg R, Memon SS, Lila A, et al. Overnight 1-mg DST serum cortisol in various stages of chronic kidney disease – normative data and underlying mechanisms. J Endoc Soc. 2024;8(3):bvae002.
14. Ozawa N, Okamura T, Koyama K, et al. Usefulness of F-18 FDG-PET in a long-term hemodialysis patient with renal cell carcinoma and pheochromocytoma. Ann Nucl Med. 2007;21:239–43.
15. Stumvoll M, Radjaipour M, Seif F. Diagnostic considerations in pheochromocytoma and chronic hemodialysis: case report and review of the literature. Am J Nephrol. 1995;15:147–51.
16. Stroud A, Zhang J, McCormack A. Diagnosing Cushing's disease in the context of chronic kidney disease: a case report and literature review. Eur J Endocrinol. 2019;181:K29–35.
17. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021;9:847–75.
18. Kamranmanesh M, Gharaei B, Soltani MH, et al. Central venous pressure guided fluid management during anaesthesia of a phaeochromocytoma patient with end stage renal disease. Arch Anesth Crit Care. 2017;3(4):398–9.
19. Henry J, Sebag F, Iacobone M, et al. Results of laparoscopic adrenalectomy for large and potentially malignant tumors. World J Surg. 2002;26:1043–7.
20. Crucitti F, Bellantone R, Ferrante A, et al. The Italian registry for adrenal cortical carcinoma: analysis of a multi-institutional series of 129 patients. Surgery. 1996;119:161–70.
21. Malyszko J, Tesarova P, Capasso G, et al. The link between kidney disease and cancer: complications and treatment. Lancet. 2020;396:277–87.
22. Gradishar WJ, Moran MS, Abraham J, et al. Breast cancer, version 3.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2024;22(5):331–57.
23. Khan S, Araji G, Yetiskul E, et al. Systemic oncological therapy in BC patients on dialysis. World J Clin Oncol. 2024;15(6):730–44.
24. Cai JH, Zheng JH, Lin XQ, et al. Individualized treatment of breast cancer with chronic renal failure: a case report and review of literature. World J Clin Cases. 2021;9(33):10345–54.
25. Langenegger T, Wahl P, Schiesser D, et al. Plasma levels of tamoxifen, N-desmethyl tamoxifen and anastrozole in a patient with metastatic breast cancer and chronic hemodialysis. Breast Cancer Res Treat. 2006;100:177–81.
26. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. PubChem Compound Summary for CID 3902, Letrozole; [cited 2025 Feb. 20]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Letrozole
27. Wekking D, Lambertini M, Dessì M, et al. CDK4/6 inhibitors in the treatment of metastatic breast cancer: focus on toxicity and safety. Semin Oncol. 2023;50(6):131–9.
28. Yang L, Zhang XC, Yu SF, et al. Pharmacokinetics and safety of cyclophosphamide and docetaxel in a hemodialysis patient with early-stage breast cancer: a case report. BMC Cancer. 2015;15:917.
29. Pedrazzoli P, Silvestris N, Santoro A, et al. Management of patients with end-stage renal disease undergoing chemotherapy: recommendations of the Associazione Italiana di Oncologia Medica (AIOM) and the Società Italiana di Nefrologia (SIN). ESMO Open. 2017;2:e000167.
30. Watanabe M, Aoki Y, Tomita M, et al. Paclitaxel and carboplatin combination chemotherapy in a hemodialysis patient with advanced ovarian cancer. Gynecol Oncol. 2002;84:335–8.
31. Nallathambi N, Chinnadurai A, Yogesh S. Carboplatin-induced hematuria with obstructive acute kidney injury. Cureus. 2024;16(4):e58931.
32. Rolfo C, de Vos-Geelen J, Isambert N, et al. Pharmacokinetics and safety of olaparib in patients with advanced solid tumours and renal impairment. Clin Pharmacokinet. 2019;58:1165–74.

Bariatric Surgery

19

Armando Di Dato, Silvana Nardi, and Carlo Socci

19.1 Introduction

Obesity is a chronic disease that stems from excessive fat deposits in the body and impairs health. The World Health Organization defines obesity as a body mass index (BMI) >30 kg/m^2, severe obesity as a BMI >35 kg/m^2, and extreme obesity as a BMI >40 kg/m^2 [1].

In 2022, one in eight individuals worldwide were obese [1]. The obesity prevalence is constantly rising also in the chronic kidney disease (CKD) population [2]. This increased prevalence has become a major barrier to the best medical treatment (transplantation) and has increased the patients' morbidity [3–6].

Obesity is associated with a lower arteriovenous fistula survival in patients receiving hemodialysis (HD), and patients on peritoneal dialysis (PD) are more susceptible to catheter insertion site infections. In kidney transplant recipients, obesity is associated with a greater risk of onset of diabetes, acute rejection or delayed graft function (DGF) [4–8]. A direct correlation has been demonstrated between obesity severity and increased postoperative complication rate [6, 9]. Obesity is an emergent cause of inactive status on waitlists for kidney transplant, immediately after cardiovascular diseases and suspected malignancies [9].

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19.2 How Obesity Influences Chronic Kidney Disease in the Pre-transplant Setting

There is evidence that obesity impairs the treatment of the CKD patients and delays or precludes renal transplant. Obesity poses challenges to both HD and PD patients.

In the HD group, the survival of arteriovenous fistulae (AVF) is lower than in normal BMI patients. The 3-year AVF survival among obese patients was shown to be significantly lower than in non-obese patients (47% vs 70%, p = 0.04) [10], and these findings were supported by later studies on obese CKD patients [10, 11]. It has also been reported that obese patients need a prolonged dialysis time to achieve dry weight status [12]. Moreover, obesity is associated with a higher frequency of cardiovascular disease, so an intensive dialytic treatment increases the risk of hypotension and failure to achieve the goal of desired creatinine levels.

In the PD setting, on the other hand, catheter malfunction, site infection, peritonitis and abdominal wall hernias are more frequently reported. Visceral fat wraps around the catheter and blocks the drain holes. There is no evidence in support of omentectomy or omentopexy during first catheter insertion [13, 14]. Finally, an obese patient on PD treatment has also metabolic complications. Indeed, the dialysate contains glucose that is absorbed during dialysis and provides extra calories and thus weight gain [15]. Abdominal wall hernias are more common in obese PD patients owing to the increased intra-abdominal pressure. Despite all these problems PD is recommended and used in obese patients [16, 17].

19.3 How Obesity Influences Renal Transplant Outcomes

In the recent past, obesity was considered a contraindication for kidney transplantation, with intervention being postponed indefinitely in obese patients, particularly those with a BMI >35 kg/m^2 [18]. Obesity is a relative contraindication for renal transplant and obese transplant recipients have been shown to be more susceptible to DGF, wound infection, and new-onset diabetes as a result of immunosuppressive therapy, compared to normal BMI patients [19].

Moreover, patients with a BMI >35 kg/m^2 are almost 30% less likely to receive a kidney transplant if compared to normal BMI patients [18]. Obesity is detrimental to kidney function (both native or grafted kidney) owing to its pro-inflammatory action that leads to proteinuria and obesity-related kidney damage. Leptin and interleukin-6 pathway modifications have been studied and reported [20–22]. Additionally, obesity impairs the metabolism of immunosuppressive drugs [23].

A systematic review has demonstrated how obesity negatively impacts the postoperative outcomes of renal transplant, and specifically: A) biopsy-proven acute rejection (BPAR); B) postoperative death; C) allograft loss; D) diabetes after transplant; E) DGF. After multivariate analysis obese patients were significantly more susceptible to BPAR, allograft loss and DGF (respectively, hazard ratio$_{\text{BPAR}}$ 1.51, hazard ratio$_{\text{allograft loss}}$ 1.54, odds ratio$_{\text{DGF}}$ 1.81, confidence interval > 95%) [24].

19.4 Medical Therapies

To reduce patient weight, and give patients access to transplant, different therapies have been experimented. For example, a low-calorie diet with physical activity [25] is considered a cost-effective therapy but results in a modest weight loss, up to 10% [26]. Other disadvantages are that this strategy needs to be strictly followed by the patient, dietary restrictions and high protein intake are not recommended in dialysis patients, and the weight loss is not durable [25].

There is no clear evidence that deferring transplantation for weight improvement leads to better outcomes, and it is no coincidence that CKD patients living with obesity have worse survival rates compared to non-obese patients waiting for a kidney transplant [8, 26, 27].

Finally, most drugs used for weight loss in the past are contraindicated in dialysis patients [28].

In July 2024, the New England Journal of Medicine published a paper in which patients living with both CKD and diabetes were randomly assigned to receive semaglutide, a GLP-1 receptor agonist, or placebo. The primary outcome was major kidney disease events, such as a reduction of at least 50% of eGFR or initiation of dialysis and transplantation. The secondary outcomes were death from kidney-related causes or cardiovascular causes [29]. Among above 3000 patients recruited, the risk of a primary outcome was 24% lower in the semaglutide group than in the placebo group, and the result was statistically significant ($p = 0.0003$). Comparable results were reported for mean annual eGFR decrease in the semaglutide group ($p < 0.001$), risk of major cardiovascular events (18%, hazard ratio 0.82; $p = 0.029$). The investigators assume that semaglutide has a protective effect on renal function thanks to its anti-inflammatory and antioxidative stress effect [29].

19.5 Surgical Therapies

In CKD and obese patients, bariatric surgery is currently the best medical treatment for weight loss. According to the recommendations issued by the DECARTES group (European Renal Association Developing Education Science and Care for Renal Transplantation in European States) on behalf of the European Renal Association, bariatric surgery should be considered in a possible kidney transplant candidate with a BMI $\geq$40 kg/m^2 or BMI $\geq$35 kg/m^2 with a major obesity-related condition (diabetes, fatty liver disease, heart disease, obstructive sleep apnea syndrome) improved by weight loss [30].

Essentially there are two types of bariatric surgery strategies: (A) restrictive intervention, with reduction of stomach volume, such as laparoscopic sleeve gastrectomy (LSG); (B) malabsorptive intervention with restriction, prototypically represented by the Roux-en-Y gastric bypass (RYGB), in which a segment of small intestine is excluded from alimentary absorption, thereby reducing the calorie intake and nutrients absorbed plus reducing the stomach volume to a little pouch of almost 50–60 mL of volume. Alexander et al. already in 2004 proved that metabolic

surgery could be safely performed in the dialysis and kidney transplant population by using open RYGB [31, 32].

Today the best way to achieve weight loss with bariatric surgery is still unclear.

Comparable short-term weight loss has been shown in randomized clinical trials in the general population between LSG and L-RYGB at 3 and 12 months [33, 34]. Furthermore, the long-term efficacy of estimated weight loss for LSG and L-RYGB at 3 years was comparable (68% vs 62%) [35]. A randomized clinical trial in diabetic patients without renal disease compared intensive medical weight loss with LSG and L-RYGB. Glycemic control at 1 year was significantly better in the two surgical groups compared to the group receiving medical therapy alone, and this result was clear also for weight loss [36]. Also, insulin use was significantly reduced in the surgical groups (4% in the RYGB group and 8% in the LSG group, $p < 0.01$). Bariatric surgery was associated with a resolution of diabetes in over 60% of patients in the general population [36].

Data published by Sheetz reported that LSG is the preferred bariatric surgical option owing to the reduced rate of complications compared to RYGB, and the lack of potential malabsorptive effect on immunosuppressive drug pharmacokinetics [37].

Freeman et al. reported that, of 52 patients with end-stage renal disease (ESRD) who underwent LSG, 40% had resolution of diabetes and 50% reduced or eliminated antihypertensive medications [38]. Another study reported a mortality rate of 3.8%, which is higher than the mortality rate among the non-CKD population, whose value is 0.08% [39], but lower than the mortality rate among patients on the wait list, which is 7%.

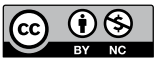
Over the years LSG has become the mainstay of bariatric surgery for CKD patients living with obesity, with an increase from <1% in 2006 to 84% in 2016 [37]. This result can be explained firstly by the fact that LSG is simpler but equally efficient to RYGB and, secondly, there is a chance that RYGB may alter the serum levels of immunosuppressive drugs [40]. As reported by one of the authors in a retrospective study, there is no immunosuppressive change after LSG bariatric surgery [41]. The importance of avoiding malabsorptive procedures is still unknown. LSG has recently been described as the procedure of choice in pre-transplantation candidates [42], and in patients who have undergone kidney transplantation [43].

References

1. World Health Organization. Obesity and overweight. World Health Organization; 2024. [cited 2024 Dec 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Wang Y, Beydoun MA, Liang L, et al. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity. 2008;16(10):2323–30.
3. Friedman AN, Miskulin DC, Rosenberg IH, et al. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. Am J Kidney Dis. 2003;41(2):480–7.
4. Howard RJ, Thai VB, Patton PR, et al. Obesity does not portend a bad outcome for kidney transplant recipients. Transplantation. 2002;73(1):53–5.

5. Modlin CS, Flechner SM, Goormastic M, et al. Should obese patients lose weight before receiving a kidney transplant? Transplantation. 1997;64(4):599–604.
6. Orofino L, Pascual J, Quereda C, et al. Influence of overweight on survival of kidney transplant. Nephrol Dial Transplant. 1997;12(4):855.
7. Gore JL, Pham PT, Danovitch GM, et al. Obesity and outcome following renal transplantation. Am J Transplant. 2006;6(2):357–63.
8. Beddhu S, Pappas LM, Ramkumar N, et al. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol. 2003;14(9):2366–72.
9. Shafi S, Zimmerman B, Kalil R. Temporary inactive status on renal transplant waiting list: causes, risk factors, and outcomes. Transplant Proc. 2012;44(5):1236–40.
10. Kats M, Hawxby AM, Barker J, et al. Impact of obesity on arteriovenous fistula outcomes in dialysis patients. Kidney Int. 2007;71(1):39–43.
11. Celebi-Onder S, Schmidt RJ, Holley JL. Treating the obese dialysis patient: challenges and paradoxes. Semin Dial. 2012;25(3):311–9.
12. Turgut F, Abdel-Rahman EM. Challenges associated with managing end-stage renal disease in extremely morbid obese patients: case series and literature review. Nephron. 2017;137(3):172–7.
13. Reissman P, Lyass S, Shiloni E, et al. Placement of a peritoneal dialysis catheter with routine omentectomy—does it prevent obstruction of the catheter? Eur J Surg. 1998;164(9):703–7.
14. Krezalek MA, Bonamici N, Kuchta K, et al. Peritoneal dialysis catheter function and survival are not adversely affected by obesity regardless of the operative technique used. Surg Endosc. 2018;32(4):1714–23.
15. Diaz-Buxo JA, Burgess WP. Is weight gain inevitable in most chronic peritoneal dialysis patients? Adv Perit Dial. 1992;8:334–9.
16. McDonald SP, Collins JF, Johnson DW. Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. J Am Soc Nephrol. 2003;14(11):2894–901.
17. Shetty A. Logistics of peritoneal dialysis in the obese population. Dial Transplant. 2011;40(8):364–6.
18. Chapman JR. The recipient of a renal transplant. In: Morris PJ, Knechtle SJ, editors. Kidney transplantation principles and practice. 6th ed. Philadelphia: Saunders/Elsevier; 2008.
19. Shi B, Ying T, Xu J, et al. Obesity is associated with delayed graft function in kidney transplant recipients: a paired kidney analysis. Transpl Int. 2023;36:11107.
20. Praga M, Hernandez E, Morales E, et al. Clinical features and longterm outcome of obesity-associated focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2001;16(9):1790–8.
21. Verani RR. Obesity-associated focal segmental glomerulosclerosis: pathological features of the lesion and relationship with cardiomegaly and hyperlipidemia. Am J Kidney Dis. 1992;20(6):629–34.
22. Adelman RD, Restaino IG, Alon US, et al. Proteinuria and focal segmental glomerulosclerosis in severely obese adolescents. J Pediatr. 2001;138(4):481–5.
23. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004;351(26):2715–29.
24. Sood A, Hakim DN, Hakim NS. Consequences of recipient obesity on postoperative outcomes in a renal transplant: a systematic review and meta-analysis. Exp Clin Transplant. 2016;14(2):121–8.
25. Position of the American Dietetic Association. Very-low-calorie weight loss diets. J Am Diet Assoc. 1990;90(5):722–6.
26. Kraschnewski JL, Boan J, Esposito J, et al. Long-term weight loss maintenance in the United States. Int J Obes. 2010;34(11):1644–54.
27. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med. 2017;5(7):161.
28. Kramer H, Tuttle KR, Leehey D, et al. Obesity management in adults with CKD. Am J Kidney Dis. 2009;53(1):151–65.

29. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391(2):109–21.
30. Oniscu GC, Abramowicz D, Bolignano D, et al. Management of obesity in kidney transplant candidates and recipients: a clinical practice guideline by the DESCARTES Working Group of ERA. Nephrol Dial Transplant. 2021;37(Suppl 1):i1–i15.
31. Alexander JW, Goodman HR, Hawver LR, et al. Improvement and stabilization of chronic kidney disease after gastric bypass. Surg Obes Relat Dis. 2009;5(2):237–41.
32. Alexander JW, Goodman HR, Gersin K, et al. Gastric bypass in morbidly obese patients with chronic renal failure and kidney transplant. Transplantation. 2004;78(3):469–74.
33. Peterli R, Wölnerhanssen B, Peters T, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg. 2009;250(2):234–41.
34. Lee W-J, Ser K-H, Chong K, et al. Laparoscopic sleeve gastrectomy for diabetes treatment in nonmorbidly obese patients: efficacy and change of insulin secretion. Surgery. 2010;147(5):664–9.
35. Kehagias I, Karamanakos SN, Argentou M, et al. Randomized clinical trial of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for the management of patients with BMI < 50 kg/m2. Obes Surg. 2011;21(11):1650–6.
36. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
37. Sheetz KH, Woodside KJ, Shahinian VB, et al. Trends in bariatric surgery procedures among patients with ESKD in the United States. Clin J Am Soc Nephrol. 2019;14(8):1193–9.
38. Freeman CM, Woodle ES, Shi J, et al. Addressing morbid obesity as a barrier to renal transplantation with laparoscopic sleeve gastrectomy. Am J Transplant. 2015;15(5):1360–8.
39. Robertson AGN, Wiggins T, Robertson FP, et al. Perioperative mortality in bariatric surgery: meta-analysis. Br J Surg. 2021;108(8):892–7.
40. Currie A, Chetwood A, Ahmed AR. Bariatric surgery and renal function. Obes Surg. 2011;21(4):528–39.
41. Gazzetta PG, Bissolati M, Saibene A, et al. Bariatric surgery to target obesity in the renal transplant population: preliminary experience in a single center. Transplant Proc. 2017;49(4):646–9.
42. Lin MY, Tavakol MM, Sarin A, et al. Laparoscopic sleeve gastrectomy is safe and efficacious for pretransplant candidates. Surg Obes Relat Dis. 2013;9(5):653–8.
43. Adani GL, Righi E, Baccarani U, et al. Laparoscopic sleeve gastrectomy as a weight reduction strategy in obese patients after kidney transplantation. Am J Transplant. 2015;15(4):1126–7.



Geriatric Surgery

20

Alessandro Tropea, Duilio Pagano,
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20.1 Introduction

The aging of the global population is rising due to a sustained decline in birth rates alongside increased longevity, a result of advancements in both preventive and curative medical interventions [1].

Comorbidities in the elderly often present as a pathological bundle that requires multidisciplinary assessment and combined therapeutic strategies tailored to the stage of the disease, and assessment of the status of the individual's overall health is often required to manage these complexities.

Estimates of GFR in humans support hyperfiltration as a relevant pathophysiologic mechanism. Elevated GFR is combined with risk factors for disease progression, which include obesity, a family history of end-stage renal disease (ESRD), and increased glomerulosclerosis and atherosclerosis. These factors indicate a compensatory mechanism in the remaining neurons to maintain total GFR [2, 3]. The decline in kidney function in chronic kidney disease (CKD) is initially typically asymptomatic. However, as renal function deteriorates, patients may exhibit symptoms of advanced kidney failure, including volume overload, hyperkalemia, metabolic acidosis, hypertension, anemia, and mineral and bone disorders. The onset of ESRD presents with a constellation of signs and symptoms collectively referred to as uremia. Following progression to ESRD, kidney transplantation becomes the

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treatment of choice, and is the most widely performed solid organ transplant. Compared to maintenance dialysis, transplantation improves the quality of life and reduces the risk of mortality for most patients. The complexity of managing elderly surgical patients is compounded by a longer recovery period and an increased risk of complications, which can have a significant impact on prognosis. Postoperative complications can lead to prolonged hospital stays, readmissions, and a decline in patient quality of life [4].

This chapter delves into the specialized field of geriatric surgery, focusing on the unique challenges and considerations when operating on elderly uremic patients. It explores the intricacies of surgical care in this demographic, highlighting age-related factors and perioperative challenges that must be addressed for optimal outcomes.

20.2 Surgical Care for Elderly Uremic Patients

Considering the many different conditions that can affect kidney function, a complete evaluation is imperative in patients with renal dysfunction undergoing surgery.

The National Kidney Foundation recommends the following assessments for uremic patients:

- Diagnosis (specific kidney disease)
- Comorbidities
- Severity, estimated by renal function level
- Complications associated with renal function level
- Risk of loss of kidney function
- Risk of cardiovascular disease.

These are the most important evaluations for accurate preoperative assessment, but it is mandatory that a complete multidisciplinary surgical risk work-up be performed to tailor surgery.

Uremic patients often have multiple major comorbidities, and the primary purpose of the preoperative evaluation must be to optimize the variable risk factor status before surgery [5].

Cardiac complications are the most common cause of perioperative complications and death in surgical patients of all ages, but especially in the elderly. This is because patients often have concurrent cardiac impairment, combined with poor functional reserve. The combined effects of intravascular volume depletion, age-related impairment of catecholamine responsiveness, and prolongation of myocardial relaxation time adversely affect cardiac function in an elderly patient under stress in the perioperative period [6]. Pulmonary complications account for up to 50% of postoperative complications and 20% of preventable deaths. Risk factors for pulmonary complications include a positive smoking history, the presence of shortness of breath, or clinical evidence of chronic obstructive pulmonary disease [7]. There is also an increased incidence of renal complications in the perioperative

period in elderly surgical patients. Renal size and volume decrease with age, accompanied by intrarenal vascular changes. The number of glomeruli and nephron mass is reduced, resulting in a decreased filtering area. However, serum creatinine concentration is an insensitive indicator of renal function in the elderly.

Functional assessment is an important part of the preoperative evaluation of elderly surgical candidates, including an assessment of cognitive function. This will ensure that surgery will not have a significant impact on the quality of life of an elderly surgical candidate. An elderly patient's functional status directly and inversely correlates with pulmonary and cardiac complications that can follow surgery [8]. Performing surgery in elderly patients must be a considered compromise of surgical strategies in order to minimize perioperative complications.

Laparoscopic surgery has become an attractive option in elderly patients in all abdominal specialties due to advances in surgical techniques. A comprehensive multidisciplinary preoperative evaluation is essential to identify appropriate surgical candidates. Morbidity and comorbidity factors must be considered. Elderly patients are particularly susceptible to adverse surgical outcomes due to more severe primary disease, higher comorbidity burden, and reduced functional reserve. Some technical problems must also be considered, as well as prolonged operative times, increased pulmonary and systemic vascular resistance due to pneumoperitoneum, and potential heart failure, which leads many surgeons to limit the use of laparoscopic techniques in elderly patients. However, the benefits of reduced operative time and blood loss, earlier postoperative mobilization, and improved enteral tolerance have become apparent in all age groups as surgical techniques have been perfected. It is now becoming accepted that the laparoscopic approach may have special advantages for the elderly patient [9].

A wider range of conditions, both cancerous and benign, may require surgery in older patients. The impact of age-related impairments in immune function can be exacerbated by coexisting medical issues and changes in mental status as a result of dementia, medications, infection, or nutritional deficiencies. Biliary diseases, including acute cholecystitis, intestinal obstruction, and incarcerated hernia, are the most common benign surgical emergencies in the elderly. Often these are conditions that are delayed or misdiagnosed in the elderly. This frequently results in higher rates of perforation and complications that have a negative impact on morbidity and mortality. This is perhaps due to age-related changes in the biliary system, such as an alteration in the lithogenicity of bile, and an associated increase in the prevalence of cholelithiasis. Complications such as ascending cholangitis, gallbladder perforation or gallstone ileus can result from delayed diagnosis due to atypical or misleading symptoms. Because of a suppressed immune response, elderly patients with acute peritonitis may not present with the typical symptoms of acute abdominal pain, fever, or leukocytosis [10].

Most cancers are age-related, and a growing elderly population is rapidly resulting in an increasing number of older patients requiring multidrug therapy for a variety of cancers, including lung, breast, hepatobiliopancreatic (HPB), gastric, and colorectal cancers. The development of a multimodal treatment plan for an elderly patient with a surgically resectable malignancy is based on careful consideration of

the expectation of the patient's life expectancy. The major potential risk associated with major HPB surgery in elderly patients is the expected higher risk; therefore, a better understanding of the surgical risk is critical in optimizing management in these patients.

Liver resection (Fig. 20.1) and pancreatic surgery (Fig. 20.2) are the treatment of choice for a variety of primary and secondary cancers. Primary tumors of the liver are one of the most common solid tumors in the world, and the incidence of hepatocellular carcinoma (HCC) is the fourth highest of all tumors. HCC is often associated with cirrhosis, and can occur 20–30 years after exposure to the injury. Nevertheless, 25% of patients show no risk factors for developing cirrhosis. Extensive liver dysfunction limits treatment options, and many patients die from liver failure due to tumor progression. The incidence of HCC is most common in the sixth decade of life, and the number of elderly HCC patients being referred for liver surgery is growing due to the aging of the world's population [11].

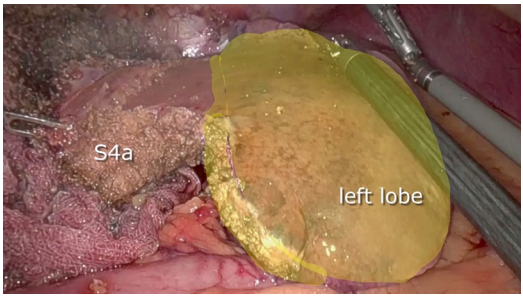


Fig. 20.1 Robotic liver resection in geriatric uremic patient. Major open surgeries often require large fluid shifts, prolonged anesthesia, and increased stress response, all of which can worsen renal function in uremic patients. Robotic surgery minimizes these risks by reducing operative time, hemodynamic fluctuations, and fluid requirements, preserving residual renal function. Advanced robotic technology allows for safe resection of tumors in difficult liver segments (e.g., posterior or caudate lobe) without the need for large incisions

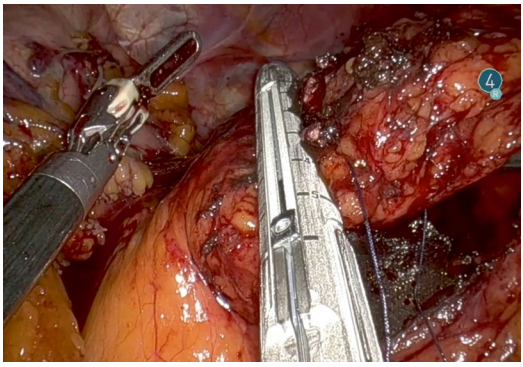


Fig. 20.2 Robotic pancreatic resection in geriatric uremic patient. Enhanced 3D visualization and instrument dexterity allow precise dissection of the pancreas and spleen, reducing trauma to surrounding structures. Geriatric uremic patients often have multiple comorbidities, making open surgery riskier, whereas robotic surgery offers a safer, less invasive alternative

20.3 Age-Related Considerations and Perioperative Challenges

In frail patients, surgery can be particularly dangerous and lead to irreversible functional decline. Quality care for elderly surgical patients should achieve patient-centered outcomes and requires clear communication and coordination among many health care professionals. Enhanced recovery after surgery (ERAS) and prevention are an interesting combination that can improve the health status of the elderly frail patient. These pathways could potentially increase the ability of these patients to tolerate the stresses of surgery. ERAS programs are treatment regimens that combine evidence-based changes in perioperative care with the goal of reducing organ dysfunction and optimizing patient performance status. This program involves an evaluation by a multidisciplinary medical team, including surgeons, anesthesiologists, physical therapists, and nurses with the goal of optimizing the perioperative course of elderly patients [12].

20.4 Conclusions

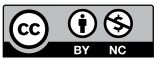
Surgical decisions in the elderly should be individualized. Potential benefits should be weighed against predicted risks. Preoperative assessment that evaluates medical, functional, and psychosocial problems can improve surgical outcomes in older patients by highlighting medical conditions that may adversely affect outcome, especially when associated with age-related physiologic changes. Specific interventions to minimize complications such as functional decline and malnutrition are included in postoperative management. Planning for discharge begins with preoperative assessment.

A comprehensive assessment and interdisciplinary collaboration can improve the outcomes of the elderly patient while at the same time mitigating the potential adverse effects of hospitalization. Therefore, careful preoperative assessment, including screening for and addressing modifiable health concerns, is paramount in preventing adverse outcomes. Surgeons, anesthesiologists, and the entire surgical team must be aware of the unique needs of the aging population in order to implement appropriate measures to ensure patient safety and optimize surgical outcomes.

References

1. United Nations Department of Economic and Social Affairs. World population ageing 2023 [Internet]. United Nations Department of Economic and Social Affairs; 2023 [cited 2024 Dec 9]. Available from: https://www.un.org/development/desa/pd/content/launch-World-Population-Ageing-2023.
2. Cesari M, Pérez-Zepeda MU, Marzetti E. Frailty and multimorbidity: different ways of thinking about geriatrics. J Am Med Dir Assoc. 2017;18(4):361–4.
3. Aggarwal P, Woolford SJ, Patel HP. Multi-morbidity and polypharmacy in older people: challenges and opportunities for clinical practice. Geriatrics (Basel). 2020;5(4):85.

4. Rubin DS, Huisingh-Scheetz M, Ferguson MK, et al. U.S. trends in elective and emergent major abdominal surgical procedures from 2002 to 2014 in older adults. J Am Geriatr Soc. 2021;69(8):2220–30.
5. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis. 2020;76(3 Suppl 1):S1–S107.
6. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2014;64(22):e77–137.
7. Odor PM, Bampoe S, Gilhooly D, et al. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. BMJ. 2020;368:m540.
8. Aceto P, Antonelli Incalzi R, Bettelli G, et al. Perioperative management of elderly patients (PriME): recommendations from an Italian intersociety consensus. Aging Clin Exp Res. 2020;32(9):1647–73.
9. Theodorakis N, Nikolaou M, Hitas C, et al. Comprehensive peri-operative risk assessment and management of geriatric patients. Diagnostics (Basel). 2024;14(19):2153.
10. Zhang ZM, Liu Z, Liu LM, et al. Therapeutic experience of 289 elderly patients with biliary diseases. World J Gastroenterol. 2017;23(13):2424–34.
11. Shehta A, Medhat M, Farouk A, et al. Liver resection for hepatocellular carcinoma in elderly patients: does age matter? BMC Surg. 2024;24(1):248.
12. Li Y, Pederson JL, Churchill TA, et al. Impact of frailty on outcomes after discharge in older surgical patients: a prospective cohort study. CMAJ. 2018;190(7):E184–90.



Abdominal Emergency Surgery

21

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21.1 Introduction

Surgical risk is fundamentally linked to two main factors: the surgical procedures and the patient's condition, which interact with each other.

Emergency abdominal surgery (EAS) is associated with high complication rates and postoperative mortality in the general population, and these risks are further elevated in patients with organ dysfunction or pre-existing conditions, with chronic kidney disease (CKD) being a recognized significant prognostic factor. The relationship between EAS and CKD exemplifies this interaction.

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This chapter aims to assess the prognostic impact of CKD on EAS and to explore specific situations that may arise in uremic patients undergoing such surgeries.

21.2 Relevance of Emergency Abdominal Surgery and Chronic Kidney Disease

EAS is an independent risk factor for postoperative complications and mortality, with a 5–8 times higher mortality rate compared to elective surgery [1–4]. Postoperative complications following emergency general surgery occur in 21% to 58% of cases, and 80–92.6% of patients who develop a serious complication (classified as Clavien-Dindo class >III) may die within 30 days [5, 6].

In Italy, it is estimated that 1 in 7 individuals has moderate CKD [7], defined as a halved GFR, with an annual increase of 6%–8% [8]. The CARHES study by the Italian Society of Nephrology indicates a CKD (stage 1–5) prevalence of 8.1% in men and 7.8% in women, suggesting that 2.5–3.0 million individuals in Italy have CKD [9].

Clinically, various preoperative and intraoperative factors are linked to severe postoperative outcomes. CKD is a recognized independent risk factor, alongside American Society of Anesthesiologists (ASA) grade ≥ IV, chronic heart failure, a Barthel index (BI) <35, general anesthesia, emergency, and major surgery [10].

CKD increases the risk of postoperative morbidity and mortality after major abdominal surgery [11]. Moreover, acute kidney failure (AKI) alone, AKI on top of CKD, and end-stage renal disease (ESRD) are independent mortality risk factors, whereas CKD alone is not [12]. AKI and CKD are interrelated syndromes, with the presence of CKD being a significant risk factor for developing AKI [13].

21.3 Strategies for Rapid Assessment and Intervention

Patients facing EAS are critically ill and often lack the luxury of time for thorough preparation. Those with CKD suffer from a condition that is not curable but can sometimes be stabilized. It is crucial to evaluate the timing of surgery, prepare patients to the best of our ability, and ensure vigilant care throughout the perioperative period. EAS must be performed swiftly to address life-threatening conditions like hemorrhagic shock, while in other cases, correcting metabolic imbalances is the priority.

The adverse effects of comorbidities can be mitigated through proper preoperative assessment and management. Coordinated perioperative care involving physicians, anesthesiologists, and surgeons is essential. Factors such as ASA grade, body mass index (BMI), emergency surgery, intraoperative blood loss, extended surgical time, intraoperative complications, and contaminated wounds are linked to postoperative complications but can be modified to lower risks.

During the perioperative phase, fluid management in CKD patients must be carefully balanced; appropriate fluid therapy positively affects surgical outcomes. Preventing organ hypoperfusion due to hypovolemia and avoiding tissue edema from excessive fluid volume are critical. Excessive fluids can lead to heart failure in those with compromised cardiac function, and fluid overload is a known risk factor

for AKI [14, 15]. Conversely, a restrictive fluid approach has been associated with a higher incidence of AKI following major abdominal surgeries [16]. Therefore, a goal-directed fluid therapy (GDFT) approach is advocated. Some studies have shown that GDFT reduces morbidity within 30–180 days post-surgery and shortens hospital stays [17]. However, another study found no reduction in complications or mortality within 30 days post-surgery with GDFT [18]; patients with postoperative complications exhibited higher fluid inputs and total input excesses, yet the ratio of over-input per unit of time was lower [18]. Currently, numerous controversial issues surround fluid therapy, including the debate over liberal versus restrictive fluid strategies and the use of crystalloid versus colloid solutions in fluid resuscitation, all in the absence of definitive data.

For patients assigned a color code other than "red", the decision-making time for further diagnostic investigations or treatments may be prolonged. Therefore, it is crucial for a surgeon to be involved early in the clinical pathway if any of the following conditions are present [19]:

- Clinical instability or signs of hypoperfusion.
- A NEWS score >7, indicating a severe risk that necessitates "prompt emergency assessment by a clinical team with critical care competencies" [20].
- Clinical stability with a quick SOFA score >2 and lactate levels >2, as per "The Third International Consensus Definitions for Sepsis and Septic Shock" [21].
- A yellow or green code with risk indicators and a waiting time exceeding twice the expected duration.

The promptness of diagnostic imaging is vital for time-sensitive pathways, both due to the complexity of accumulating tests and the need for 24-h staff availability in high-volume facilities. This aligns with the guidelines set forth by the diagnostic and therapeutic care pathways (PDTA) of the Società Italiana di Chirurgia d'Urgenza e Trauma (SICUT) (Table 21.1) [19].

Surgeons must be aware of the risk of iodinated contrast media-induced nephropathy (CIN) following an enhanced CT scan. Both iodine-based and gadolinium-based agents can be cleared from the bloodstream through hemodialysis or peritoneal dialysis (PD). However, there is no evidence to suggest that hemodialysis can prevent kidney damage. The risk of CIN is significantly higher in patients with CKD, increasing the risk by 20-fold, and when combined with diabetes, the risk of developing CIN is 50% [22, 23]. It is recommended to adhere to the Società Italiana di Radiologia Medica e Interventistica (SIRM) guidelines for the use of radiological contrast media as much as possible (Table 21.2).

In EAS appropriate antibiotic therapy is vital, yet it poses a dual challenge in CKD: renal function affects drug pharmacokinetics, and many antibiotics are nephrotoxic. Before prescribing an antibiotic and determining the correct dosage, an accurate assessment of renal function is essential, with creatinine clearance (CrCl) being the most reliable indicator. To maintain effective blood levels of antibiotics in CKD, dosages can be reduced while keeping the administration frequency the same, or the interval between doses can be extended [24–26]. Typically, dose reduction is preferred for antibiotics that require steady blood levels, whereas extending the

Table 21.1 Patients' conditions and diagnostic approach

Patient's condition	Timing	Procedure
Unstable or hypoperfused patient or NEWS >7	Within 1 h	E-FAST Contrast-enhanced CT if condition has stabilized.
Stable with diffuse abdominal pain	Within 1 h	Possible US Contrast-enhanced CT as first choice in the presence of: history of abdominal aneurysm; quick SOFA >2 and lactate values >2; significant increase in biological markers C-reactive protein and/or procalcitonin.
Stable with obstipation	Within 2 h	Plain abdominal radiography Depending on history and clinical review, choice between the use of prokinetic drugs with subsequent radiological check or proceed directly to contrast-enhanced CT.
Stable with pain in the right quadrants or with renal colic	Within 2 h	US of anatomical region CT scan if indicated by US findings.

E-FAST Extended Focused Assessment with Sonography in Trauma, *NEWS* National Early Warning Score, *SOFA* Sequential (sepsis-related) Organ Failure Assessment

Table 21.2 Protocols for at-risk patients

GFR mL/min/1.73 m^2	
>60	No prophylaxis
>30	Consider an alternative investigation if possible Otherwise proceed without prophylaxis
<30	Before the examination: (a) Hydration with sodium bicarbonate 1.4% (or 154 mmol/L in dextrose 5%) i.v.: 3 mL/kg/h for 1 h before contrast medium administration Or (b) Hydration with saline solution 0.9% i.v.: 1 mL/kg/h for 3–4 h before contrast medium administration and for 4–6 h after
<15	Personalized prophylaxis with multidisciplinary decision

dosing interval is used for those with a prolonged half-life. Additionally, it is important to remember that certain antibiotics can induce renal damage through direct toxicity or an immuno-allergic mechanism, leading to acute interstitial nephritis (Table 21.3).

21.4 Management of Acute Abdomen in Uremic Patient

During surgery, operative time, intraoperative blood loss, and complications must be managed with proper control strategies. Intraoperative hypotension is closely associated with postoperative adverse events. Prolonged perioperative hypotension can lead to hypoperfusion in vital tissues and organs, resulting in postoperative complications. It has been reported that intraoperative hypotension lasting over 20 min significantly increases the risk of postoperative complications. A decrease in

Table 21.3 Antibiotics and renal damage [26]

Direct toxicity	Immuno-allergic mechanism
Aminoglycosides	Penicillins (ampicillin, amoxicillin, piperacillin)
Amphotericin b	Cephalosporins (ceftazidime, cefotaxime)
Vancomycin	Macrolides (erythromycin, azithromycin)
Tetracyclines	Quinolones (ciprofloxacin, norfloxacin)
Sulfamides	Vancomycine
Pentamidine	Tetracyclines

intraoperative systolic blood pressure by more than 20% for over 20 min can notably raise the risk of postoperative complications. Thus, for patients undergoing emergency surgery, it is crucial to keep the decrease in intraoperative systolic blood pressure within 20% of the baseline to minimize the risk of a poor prognosis.

Furthermore, longer surgical durations and greater blood loss during surgery contribute to an increased risk of postoperative complications. Studies on adverse events in hospitalized patients have shown that postoperative complications in longer surgeries are linked to increased blood loss, extended anesthesia duration, and the nature of the surgery itself [27].

Occlusion, perforation, ischemia, peritonitis and bleeding require EAS in the general population as well as in the uremic patient, although in the latter they may present different frequency and severity. In uremic patients, however, there are peculiar aspects that must be known and promptly detected.

21.4.1 Bleeding

Gastrointestinal bleeding (GIB) is a prevalent yet often underappreciated condition that leads to increased morbidity and mortality in patients with CKD [28]. Numerous studies have highlighted the escalating issue of GIB in CKD patients [29–31]. GIB is a leading cause of death in those with CKD and ESRD, responsible for 3–7% of mortalities [32–35]. GIB in individuals on hemodialysis typically stems from peptic ulcers (20–30%), gastritis (20%), and telangiectasia in the stomach, duodenum, jejunum, and colon (20–30%) [36]. Research has identified risk factors for GIB in hemodialysis patients, including the use of anticoagulants, platelet dysfunction, and anticoagulation during dialysis [35, 37–39]. In uremic patients, addressing bleeding is a delicate matter. Red blood cell (RBC) transfusion should be judiciously used and avoided, if possible, as it may trigger anti-HLA antibody formation, reducing kidney transplantation success and causing hypervolemia and congestive heart failure symptoms, especially in older patients. The risks and benefits of transfusion therapy must be weighed on a case-by-case basis. In emergencies like severe bleeding or urgent surgery, RBC transfusion can stabilize the patient. For stable CKD patients, transfusion is an option when erythropoiesis-stimulating agent (ESA) treatment fails (due to hemoglobinopathies, bone marrow failure, or ESA resistance). While the hemoglobin threshold for transfusion is not definitive, it is generally considered when hemoglobin falls below 7 g/dL [40].

21.4.2 Occlusion

Encapsulating peritoneal sclerosis (EPS) is specific complication of prolonged PD therapy, with its major risk factor being closely linked to episodes of peritonitis [41–43]. EPS is commonly used interchangeably with terms such as "peritoneal sclerosis", "peritoneal fibrosis", "peritoneal sclerosing syndrome", and "sclerosing encapsulating peritonitis". In 1998, the International Society for Peritoneal Dialysis Ad Hoc Committee defined EPS as a syndrome that manifests with symptoms of intestinal obstruction due to adhesions from a diffusely thickened peritoneum, making it a clinical diagnosis. It represents an advanced stage of disease with considerable morbidity and mortality [44, 45]. Peritoneal thickening and fibrosis in EPS can lead to a fibrous cocoon enveloping the bowel, causing intestinal obstruction, ischemia, and perforation. These occlusions stem from bowel adhesions, which are common in EPS patients. Radiological tests for diagnosing EPS are non-specific and challenging, often necessitating confirmation through laparoscopy or laparotomy [43, 46].

21.4.3 Perforation and Peritonitis

Global surveys of dialysis patients indicate that 11% were receiving PD in 2004 [45, 47], and this figure rose to 15.8% in 2009 [47]. Peritonitis is the primary complication of PD, contributing to increased morbidity and mortality rates, and is also the leading cause of technique failure. Severe or recurrent peritonitis episodes can result in ultrafiltration failure. The goal of peritonitis treatment is to quickly reduce inflammation to maintain the functional integrity of the peritoneal membrane. PD peritonitis treatment primarily involves antibiotic therapy, with surgical intervention usually not required.

PD patients most commonly experience PD-related peritonitis, whereas endogenous peritonitis is rarer but has a mortality rate of 46.3% [48]. The causes of infection vary, with gastrointestinal perforation being one source of endogenous peritonitis, which is a significant reason for emergency laparotomy and often presents with severe abdominal signs and symptoms like muscular guarding and colicky pain. Perforations may be due to peptic ulcers, diverticulitis, cholecystitis, ischemic colitis, appendicitis, malignancy, ingestion of foreign objects like fish or chicken bones and, more rarely, bamboo slivers or indwelling catheters [49–54].

It is crucial to distinguish "catheter-related" peritonitis from secondary peritonitis caused by visceral lesions, where surgical treatment is prioritized. Confusing secondary with "catheter-related" peritonitis can lead to grave mistakes in treatment selection, putting the patient's life at risk. Diagnosing whether a PD patient has refractory or secondary peritonitis can be challenging. In cases of refractory PD peritonitis, it is imperative not to delay surgical exploration.

Peritonitis in PD patients has distinct characteristics that differentiate it from the "classical" scenarios (Table 21.4).

Table 21.4 Diagnosis of PD peritonitis (presence of at least 2)

Cloudy dialysis effluent with white blood cell count of more than 100 cells/mm^3 (usually more than 50% polymorphonuclear neutrophils)—present in 98% of the cases
Abdominal pain (present in approximately 75% of the cases)
Positive cultures from dialysate [55, 56]

Persistent effluent turbidity after 5 days of appropriate antibiotic treatment indicates refractory peritonitis, which necessitates catheter removal to safeguard the peritoneal membrane [56, 57].

Prompt surgical evaluation and continuous monitoring are crucial to differentiate PD-related peritonitis from surgical peritonitis in PD patients [56, 58]. This issue requires swift resolution. A thorough clinical multidisciplinary assessment, including laboratory and imaging studies for encapsulated collections and associated digestive and genital pathologies, is imperative. Misdiagnosis and delays in etiological treatment can significantly impact the patient's prognosis [56].

Three CT scan indicators are predictive of perforation sites: localized extraluminal air bubbles adjacent to the bowel wall; a distinct defect in the bowel wall; and localized bowel wall thickening [59]. Meanwhile, CT scans show intraperitoneal free air in 30% of PD patients without perforative peritonitis [60, 61].

For all patients whose peritonitis symptoms persist beyond 5 days of proper antibiotic treatment, exploratory laparotomy or laparoscopy should be considered [56, 62]. However, confirming a diagnosis of perforated peritonitis is challenging without an exploratory laparotomy. Studies have reported diagnostic delays of over 10 days and increased mortality rates (16–50%) [54, 63–65] in PD patients compared to non-PD patients with appendicitis (4%) [54, 63, 66] or cholecystitis (9.5–15.2%) [67–71].

Finally, in uremic patients, specific perforative events are observed:

- Delayed perforation, a rare and specific complication of PD [72], involves erosion or perforation of hollow viscera [73], primarily due to the peritoneal catheter and, on rare occasions, from direct exposure to hot dialysate or hot water [74].
- EPS, accounting for about 20% of small intestinal perforations [43, 64].

21.4.4 Ischemia

Colitis is commonly associated with CKD, though severe colitis remains rare, as indicated by an autopsy study of 78 patients with end-stage renal disease (ESRD) on hemodialysis [75, 76]. Ischemic colitis may occur in up to 3% of cases [77] (Figs. 21.1 and 21.2). Intestinal necrosis in patients with uremia was first reported decades ago [78, 79]. The risk factors for colon necrosis apply to both uremic and non-uremic patients [80] (Table 21.5). The combination of sorbitol and sodium polystyrene sulfonate has been linked to intestinal necrosis in uremic patients [81]. Ischemic colitis can also occur without any identifiable trigger.

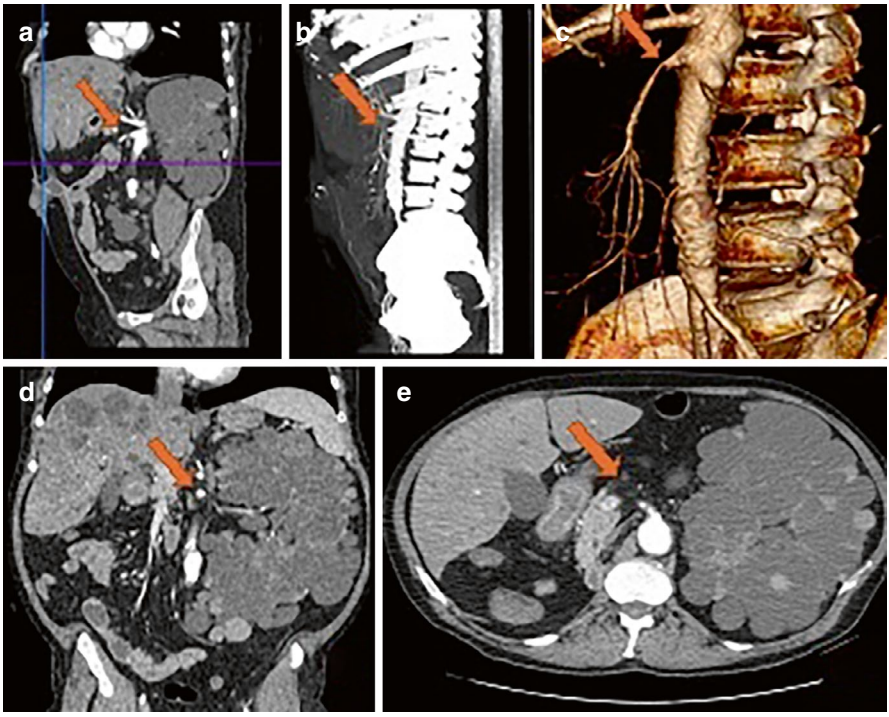


Fig. 21.1 Superior mesenteric artery stenosis in an autosomal dominant polycystic kidney (ADPKD) patient affected by angina abdominis who underwent previous right nephrectomy (Angio CT scan: (**a**, **b**, **c**) sagittal reconstruction; (**d**) coronal reconstruction; (**e**) axial section). (Courtesy Prof. U.M. Bracale)

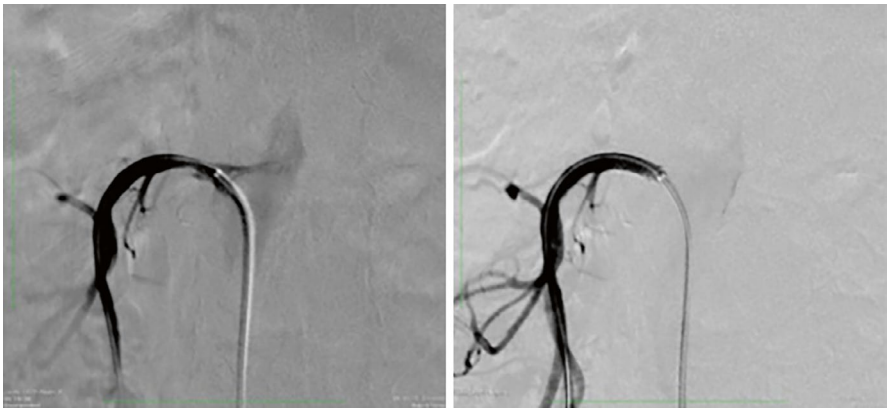


Fig. 21.2 Previous case. Endovascular treatment: superior mesenteric artery stenting and reperfusion. (Courtesy Prof. U.M. Bracale)

Table 21.5 Risk factors for ischemic colitis [82–87]

Low cardiac output	Intrinsic cardiac causes	Heart failure, myocardial infarction, arrhythmia
	Extrinsic factors	Sepsis, hypovolemia, shock
Vascular risk factors		Atherosclerosis, vasculitis, and microembolism
Drugs		Digoxin, vasopressors, diuretics, and estrogens
Constipation and colonic distension		

An enhanced abdominal CT scan can help to point to the cause of ischemia. Colonoscopy is a sensitive and specific way to assess colon ischemia but does not always allow a doctor to make a definitive diagnosis and should be performed as early as possible, preferably within the first 3 days after symptom onset [77, 82, 88–90].

21.5 Conclusion

The improved longevity of patients with CKD has led to an increased incidence of surgical issues.

Prompt diagnosis and proper perioperative management are critical for a positive outcome. Whenever feasible, uremic patients should be stabilized before surgery, necessitating a multidisciplinary approach, particularly in coordination with a nephrologist for fluid infusion, accurate drug dosing, and potential hemodialysis.

The surgeon must be meticulous in selecting the most suitable surgical method, aiming to minimize operation duration, bleeding, ischemia, leaks, or any other complications that could arise in a patient as vulnerable as one with uremia.

References

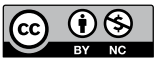
1. Havens JM, Peetz AB, Do WS, et al. The excess morbidity and mortality of emergency general surgery. J Trauma Acute Care Surg. 2015;78(2):306–11.
2. Bijker JB, van Klei WA, Kappen TH, et al. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology. 2007;107(2):213–20.
3. McGillicuddy EA, Schuster KM, Davis KA, et al. Factors predicting morbidity and mortality in emergency colorectal procedures in elderly patients. Arch Surg. 2009;144(12):1157–62.
4. Sun M, Xu M, Sun J. Risk factor analysis of postoperative complications in patients undergoing emergency abdominal surgery. Heliyon. 2023;9(3):e13971.
5. Portinari M, Bianchi L, De Troia A, et al. Non-traumatic emergency abdominal surgery in nonagenarian patients: a retrospective study. Eur J Trauma Emerg Surg. 2022;48(2):1205–16.
6. Perregaard H, Tenma J, Antonsen J, et al. Mortality after abdominal emergency surgery in nonagenarians. Eur J Trauma Emerg Surg. 2021;47(2):485–92.
7. A. A. V. V. Identificazione, prevenzione e gestione della malattia renale cronica nell'adulto [Internet]. Sistema Nazionale delle Linee Guida; 2015 [cited 2024 Dec 9]. Available from:

https://www.fadoi.org/wp-content/uploads/2017/05/linee-guida-Malattia-renale-cronica-adulto.pdf.
8. Buccianti G, Baragetti I, Alberghini E, et al. La presa in carico precoce nell'insufficienza renale cronica: un nuovo approccio. G Ital Nefrol. 2005;22:134–9.
9. De Nicola L, Donfrancesco C, Minutolo R, et al. Epidemiologia della malattia renale cronica in Italia: stato dell'arte e contributo dello studio CARHES. G Ital Nefrol. 2011;28(4):401–7.
10. Fu H, Zheng J, Lai J, et al. Risk factors of serious postoperative outcomes in patients aged ≥90 years undergoing surgical intervention. Heliyon. 2023;9(2):e13117.
11. Cloyd JM, Ma Y, Morton JM, et al. Does chronic kidney disease affect outcomes after major abdominal surgery? Results from the National Surgical Quality Improvement Program. J Gastrointest Surg. 2014;18(3):605–12.
12. Miyake K, Iwagami M, Ohtake T, et al. Association of pre-operative chronic kidney disease and acute kidney injury with in-hospital outcomes of emergency colorectal surgery: a cohort study. World J Emerg Surg. 2020;15(1):22.
13. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66.
14. Solomon R. Improving intravenous fluid therapy for prevention of contrast-induced nephropathy: how to give more without causing heart failure. JACC Cardiovasc Interv. 2016;9(1):97–9.
15. Wang N, Jiang L, Zhu B, et al. Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. Crit Care. 2015;19:371.
16. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378(24):2263–74.
17. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). Br J Anaesth. 2018;120(4):734–44.
18. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA. 2014;311(21):2181–90.
19. Il percorso gestionale e clinico per gli interventi di urgenza. Consensus multidisciplinare sviluppata da: Associazione dei Chirurghi Ospedalieri ACOI, Società Italiana Anestesia, Analgesia, Rianimazione e Terapia Intensiva SIAARTI, Società Italiana di Chirurgia d'Urgenza e del Trauma SICUT, Società Italiana di Malattie Infettive e Tropicali SIMIT, Società Italiana di Radiologia Medica SIRM, World Society Emergency Surgery – Italian Chapter WSES, Gruppo di lavoro multidisciplinare di Medina Legale GMML. 2016.
20. The Royal College of Physicians. National Early Warning Score [Internet]. The Royal College of Physicians; 2015 [cited 2024 Dec 9]. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news
21. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
22. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med. 1989;320(3):143–9.
23. Weinrauch LA, Healy RW, Leland OS Jr, et al. Coronary angiography and acute renal failure in diabetic azotemic nephropathy. Ann Intern Med. 1977;86(1):56–9.
24. Bennett WM, Muther RS, Parker RA, et al. Drug therapy in renal failure: dosing guidelines for adults. Part I: antimicrobial agents, analgesics. Ann Intern Med. 1980;93(1):62–89.
25. Chennavasin P, Brater DC. Nomograms for drug use in renal disease. Clin Pharmacokinet. 1981;6(3):193–214.
26. Nardiello S, Catapano F, Galanti B. Antibiotics and kidney. Infez Med. 2000;8(2):74–81.
27. Dharap SB, Barbaniya P, Navgale S. Incidence and risk factors of postoperative complications in general surgery patients. Cureus. 2022;14(11):e30975.
28. Huang CH, Chao JY, Ling TC, et al. Effect of dialysis modalities on risk of hospitalization for gastrointestinal bleeding. Sci Rep. 2023;13(1):52.

29. Wuerth BA, Rockey DC. Changing epidemiology of upper gastrointestinal hemorrhage in the last decade: a nationwide analysis. Dig Dis Sci. 2018;63(5):1286–93.
30. Charilaou P, Devani K, Enjamuri D, et al. Epidemiology of lower GI bleed in the United States – an update from the National Inpatient Survey 2005–2014. Am J Gastroenterol. 2018;113(Suppl):S319.
31. Geyer M, Stamenic I, Bühler H, et al. Epidemiology of gastrointestinal bleeding in the elderly. Praxis. 2006;95(19):757–65.
32. Kuo CC, Kuo HW, Lee IM, et al. The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: a population-based cohort study. BMC Nephrol. 2013;14(1):15.
33. Spinelli G, Tomasello G, Damiani F, et al. Endoscopic findings in chronic renal failure: review of literature. Acta Med Mediterr. 2012;28:261–5.
34. Wasse H, Gillen DL, Ball AM, et al. Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients. Kidney Int. 2003;64(4):1455–61.
35. Lin Y, Li C, Waters D, Kwok CS. Gastrointestinal bleeding in chronic kidney disease patients: a systematic review and meta-analysis. Ren Fail. 2023;45(2):2276908.
36. Janssen MJ, van der Meulen J. The bleeding risk in chronic haemodialysis: preventive strategies in high-risk patients. Neth J Med. 1996;48(5):198–207.
37. Trivedi H, Yang J, Szabo A. Gastrointestinal bleeding in patients on long-term dialysis. J Nephrol. 2015;28(2):235–43.
38. Saeed F, Agrawal N, Greenberg E, et al. Lower gastrointestinal bleeding in chronic hemodialysis patients. Int J Nephrol. 2011;2011:272535.
39. Kringen MK, Narum S, Lygren I, et al. Reduced platelet function and role of drugs in acute gastrointestinal bleeding. Basic Clin Pharmacol Toxicol. 2011;108(3):194–201.
40. Rivera RF, Sciarrone Alibrandi MT, Di Lullo L, Fioccari F. Clinical management of anemia in patients with CKD. G Ital Nefrol. 2017;34(Suppl 69):20–35.
41. Moinuddin Z, Summers A, Van Dellen D, et al. Encapsulating peritoneal sclerosis-a rare but devastating peritoneal disease. Front Physiol. 2015;5:470.
42. Yamamoto R, Otsuka Y, Nakayama M, et al. Risk factors for encapsulating peritoneal sclerosis in patients who have experienced peritoneal dialysis treatment. Clin Exp Nephrol. 2005;9(2):148–52.
43. Fujii K, Washida N, Arai E, et al. Adhesive intestinal obstruction increases the risk of intestinal perforation in peritoneal dialysis patients: a case report. BMC Nephrol. 2018;19(1):153.
44. Kawaguchi Y, Kawanishi H, Mujais S, et al. Encapsulating peritoneal sclerosis: definition, etiology, diagnosis, and treatment. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit Dial Int. 2000;20(Suppl 4):S43–55.
45. Tu HY, Hsia CC, Chen T, et al. Extensive peritoneal calcification and small intestinal perforation in a peritoneal dialysis patient: a case report. Kaohsiung J Med Sci. 2011;27(5):199–202.
46. Nakamoto H. Encapsulating peritoneal sclerosis - a clinician's approach to diagnosis and medical treatment. Perit Dial Int. 2005;25(Suppl 4):S30–8.
47. Grassmann A, Gioberge S, Moeller S, et al. ESRD patients in 2004: global overview of patient number, treatment modalities and associated trends. Nephrol Dial Transplant. 2005;20:2587–93.
48. Kern EO, Newman LN, Cacho CP, et al. Abdominal catastrophe revisited: the risk and outcome of enteric peritoneal contamination. Perit Dial Int. 2002;22(3):323–34.
49. Vermeulen J, van der Harst E, Lange JF. Pathophysiology and prevention of diverticulits and perforation. Neth J Med. 2010;68:303–9.
50. Jhobta RS, Attri AK, Kaushik R, et al. Spectrum of perforation peritonitis in India – review of 504 consecutive cases. World J Emerg Surg. 2006;1:26.
51. Straube S, Tramér MR, Moore RA, et al. Mortality with upper gastrointestinal bleeding and perforation: effects of time and NSAID use. BMC Gastroenterol. 2009;9:41.
52. Suzuki Y, Mizuno M, Nakashima R, et al. A case of perforative peritonitis by a piece of bamboo in a patient on peritoneal dialysis. Clin Exp Nephrol. 2011;15:962–5.

53. Beinkley M, Wible BC, Hong K, et al. Colonic perforation by a percutaneously displaced biliary stent: report of a case and a review of current practice. J Vasc Interv Radiol. 2009;20:680–3.
54. Mizuno M, Suzuki Y, Nonaka K, et al. Perforative peritonitis caused by appendicitis in a patient on peritoneal dialysis. Intern Med. 2013;52(11):1177–81.
55. Teitelbaum I, Burkart J. Peritoneal dialysis. Am J Kidney Dis. 2003;42(5):1082–96.
56. Mihalache O, Bugă C, Doran H, et al. The time for surgery of peritonitis associated with peritoneal dialysis. J Med Life. 2016;9(3):284–7.
57. Choi P, Nemati E, Banerjee A, et al. Peritoneal dialysis catheter removal for acute peritonitis – a retrospective analysis of factors associated with catheter removal and prolonged postoperative hospitalization. Am J Kidney Dis. 2004;43:103–11.
58. Brook NR, White SA, Waller JR, et al. The surgical management of peritoneal dialysis catheters. Ann R Coll Surg Engl. 2004;86:190–5.
59. Hainaux B, Agneessens E, Bertinotti R, et al. Accuracy of MDCT in predicting site of gastrointestinal tract perforation. Am J Roentgenol. 2006;187:1179–83.
60. Lee FT Jr, Leahy-Gross KM, Hammond TG, et al. Pneumoperitoneum in peritoneal dialysis patients: significance of diagnosis by CT. J Comput Assist Tomogr. 1994;18(3):439–42.
61. Arata R, Banshodani M, Yamashita M, et al. Perforative peritonitis confused with peritoneal dialysis-related peritonitis: report of three cases. Int J Surg Case Rep. 2020;70:20–3.
62. Pătrașcu T, Bugă C, Popescu I. Peritoneal dialysis. In: Textbook of surgery. București: Ed. Academiei Române; 2008. p. 1044–56.
63. Carmeci C, Muldowney W, Mazbar SA, et al. Emergency laparotomy in patients on continuous ambulatory peritoneal dialysis. Am Surg. 2001;67:615–8.
64. Takagi A, Hatta T, Ueno R, et al. A patient with perforative peritonitis undergoing peritoneal dialysis: a case report. Toseki Igakukai Zasshi. 2011;44:1039–45.
65. Moffat FL, Deitel M, Thompson DA. Abdominal surgery in patients undergoing long-term peritoneal dialysis. Surgery. 1982;92:598–604.
66. Schwarz A, Bölke E, Peiper M, et al. Inflammatory peritoneal reaction after perforated appendicitis: continuous peritoneal lavage versus non lavage. Eur J Med Res. 2007;12:200–5.
67. Ausania F, Guzman Suarez S, Alvarez Garcia H, et al. Gallbladder perforation: morbidity, mortality and preoperative risk prediction. Surg Endosc. 2015;29:955–60.
68. Date RS, Thrumurthy SG, Whiteside S, et al. Gallbladder perforation: case series and systematic review. Int J Surg. 2012;10:63–8.
69. Stefanidis D, Sirinek KR, Bingener J. Gallbladder perforation: risk factors and outcome. J Surg Res. 2006;131:204–8.
70. Derici H, Kamer E, Kara C, et al. Gallbladder perforation: clinical presentation, predisposing factors, and surgical outcomes of 46 patients. Turk J Gastroenterol. 2011;22:505–12.
71. Wu YL, Lin YS, Hsueh TY, et al. Green dialysate and gallbladder perforation in a peritoneal dialysis patient: a case report and literature review. BMC Nephrol. 2018;19(1):165.
72. Wang RD, Chen ZM, Wang JX, et al. Delayed bowel perforation in a peritoneal dialysis patient: a case report and literature review. Perit Dial Int. 2014;34(4):460–6.
73. Bustos E, Rotellar C, Mauoni MJ, et al. Clinical aspects of bowel perforation in patients undergoing continuous ambulatory peritoneal dialysis. Semin Dial. 1994;7(5):355–9.
74. Lai X, Nie M, Xu X, et al. Delayed bowel perforation after instilling over warmed peritoneal dialysate. BMC Nephrol. 2021;22(1):139.
75. Vaziri ND, Dure-Smith B, Miller R, et al. Pathology of gastrointestinal tract in chronic hemodialysis patients: an autopsy study of 78 cases. Am J Gastroenterol. 1985;80(8):608–11.
76. Zhou J, Zeng Y, Zhou X, et al. Unexplained colonic necrosis in a patient with end-stage kidney disease on chronic hemodialysis: case report and review of uremic colitis. BMC Anesthesiol. 2024;24(1):249.
77. García Agudo R, Aoufi Rabih S, González Carro P, et al. Gastrointestinal lesions in chronic kidney disease patients with anaemia. Nefrologia (Engl Ed). 2019;39(1):50–7.
78. Diamond SM, Emmett M, Henrich WL. Bowel infarction as a cause of death in dialysis patients. JAMA. 1986;256:2545–7.

79. Zeier M, Wiesel M, Rambausek M, et al. Non-occlusive mesenteric infarction in dialysis patients: the importance of prevention and early intervention. Nephrol Dial Transpl. 1995;10:771–3.
80. Dahlberg PJ, Kisken WA, Newcomer KL, et al. Mesenteric ischemia in chronic dialysis patients. Am J Nephrol. 1985;5:327–32.
81. Joo M, Bae WK, Kim NH, et al. Colonic mucosal necrosis following administration of calcium polystyrene sulfonate (Kalimate) in a uremic patient. J Korean Med Sci. 2009;24:1207–11.
82. Dimitrijević I, Micev M, Dj S, et al. Ischaemic colitis–review. Acta Chir Iugosl. 2008;55:89–95.
83. Berk JL. Nonocclusive mesenteric vascular insufficiency. Arch Surg. 1976;111:829–30.
84. Byrd RL, Cunningham MW, Goldman LI. Nonocclusive ischemic colitis secondary to hemorrhagic shock. Dis Colon Rectum. 1987;30:116–8.
85. Miura S, Kurose I, Fukumura D, et al. Ischemic bowel necrosis induced by endothelin-1: an experimental model in rats. Digestion. 1991;48:163–72.
86. Sharefkin JB, Silen W. Diuretic agents: inciting factor in nonocclusive mesenteric infarction? JAMA. 1974;229:1451–3.
87. Saegesser F, Sandblom P. Ischemic lesions of the distended colon: a complication of obstructive colorectal cancer. Am J Surg. 1975;129:309–15.
88. Doulberis M, Panagopoulos P, Scherz S, et al. Update on ischemic colitis: from etiopathology to treatment including patients of intensive care unit. Scand J Gastroenterol. 2016;51:893–902.
89. Habu Y, Tahashi Y, Kiyota K, et al. Re-evaluation of clinical features of ischemic colitis. Analysis of 68 consecutive cases diagnosed by early colonoscopy. Scand J Gastroenterol. 1996;31:881–6.
90. Scowcroft CW, Sanowski RA, Kozarek RA. Colonoscopy in ischemic colitis. Gastrointest Endosc. 1981;27:156–61.



The Role of Interventional Radiology in Uremic Patients

22

Domenico Santangelo and Francesco De Cobelli

22.1 Percutaneous Nephrostomy

Recent diagnostic, interventional and technological advances (e.g., US, CT, cone-beam CT) currently allow multimodal and combined approaches for the treatment of renal pathology, optimizing outcomes. Percutaneous nephrostomy (PCN) is a widespread, minimally invasive procedure, mostly performed by interventional radiologists.

PCN is indicated for treatment of both intrinsic and extrinsic urinary obstruction (e.g., lithiasis, cancer, iatrogenic lesions). Hydronephrosis without infection may account for 72–97% of PCN, while infected cases account for 3–19% [1], with a high risk of evolution to sepsis, requiring urgent drainage. The onset of acute renal failure leading to hyperkalemia and cardiac conduction alterations also requires an emergent PCN. PCN is also indicated in urinary leaks/fistulae (urinary diversions) or to provide an access to the pelvicalyceal system for other procedures (e.g., anterograde ureteral stent placement, endoscopic procedure). The Society of Interventional Radiology classifies PCN as a level 3 procedure (significant bleeding risk/bleeding difficult to detect) requiring well-defined coagulation parameters (INR <1.5 and platelet count >50,000/cm^3 [2]). In renal transplant patients, PCN indications are the same as in the native kidney, yet the etiology may differ (e.g., ureterovesical

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anastomosis stenosis/fistula). The placement of a PCN is generally more challenging as the non-anatomical position of the kidney often forces a transperitoneal puncture, requiring this procedure to be performed by experienced interventional radiologists. In cases of anastomotic fistula, an anterograde ureteral stent may be placed to accelerate fistula healing (Fig. 22.1).

For native kidneys, the procedure is generally performed with the patient in the prone position under combined fluoroscopic-US guidance; a supine position may also be considered. Access to the collecting system should be performed through Brödel's avascular line, targeting the dorsolateral calyx. The best access site is the inferior third which presents less risk of complications. The calyx is punctured using a Chiba needle (22 gauge); urine is then collected to confirm correct position.

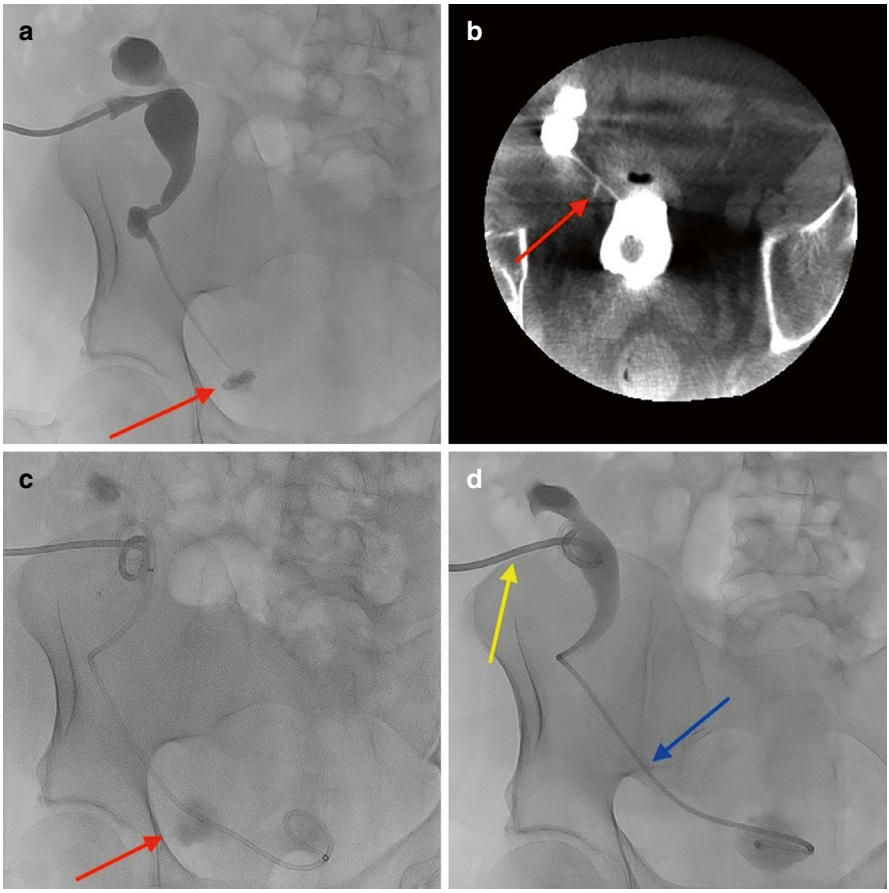

Fig. 22.1 Percutaneous descending pyelography of a right iliac fossa transplanted kidney showing distal urinary leakage (red arrow) (**a**). Cone-beam CT demonstrates urinary leakage at the ureterovesical anastomosis (**b**). A percutaneous nephrostomy tube and anterograde double-J ureteral stent were placed (**c**). 1-month follow-up showing complete healing of the fistula, with PCN (yellow arrow) and DJ stent (blue arrow) still in place (**d**)

A wire is advanced into the proximal ureter and a three-step introducer is advanced over this guide. The wire is then replaced with a stiffer guidewire and the nephrostomy drainage tube (8–12 Fr) is advanced. A post-procedural US scan is highly recommended to rule out acute complications (perirenal hemorrhages, subcapsular hematomas). Acute hemorrhage requiring blood transfusion is the most common serious complication after PCN placement (0.5–4% procedures) [3]. Hemorrhages more frequently occur in the renal parenchyma and are generally self-limiting as the drainage tube works as a hemostat. Delayed hemorrhage is observed in less than 1% of procedures, is mainly sustained by arteriovenous fistulae (AVF) and pseudoaneurysm, and is managed with endovascular techniques. Injuries to the collecting system are usually identified intraoperatively and managed by placing a larger caliber PCN tube or an additional urinary drainage system (ureteral stent) in severe cases. Colon perforation is an uncommon complication (0.2–0.5% [4]), especially in the US-guided procedure. Hydrothorax/pneumothorax development is strictly linked to the access site; the literature reports a frequency of 4.6% above the 12th rib and 26.7% above the 11th rib [5].

22.2 Dialysis Arteriovenous Fistula Management

The most frequent hemodialysis access is a surgically created AVF; 20–60% of these do not mature, prolonging dependence on the temporary dialysis system [6]. Endovascular AVFs represent a valid alternative procedure. Approved devices are the WavelinQ™ (BD, Franklin Lakes, New Jersey) and Ellipsys™ (Medtronic, Minneapolis, Minnesota), both relying on the presence of a perforator vein on the proximal forearm able to arterialize the deep venous system, directing the flow into the superficial veins. Ellipsys™ is a single-catheter system that uses thermal energy to create an autogenous fistula between the proximal radial artery and the perforator vein. The WavelinQ™ is a dual-catheter system embedded with magnets that allow device alignment under US and fluoroscopic guidance, delivering radiofrequency energy to create radio-radial/ulno-ulnar fistula, verified through contrast medium injection. Embolization of the deep brachial veins close to the elbow is recommended to redirect the flow to the superficial venous system and increase fistula flow. A recent metanalysis demonstrated an overall technical success rate of both systems of 97.5%, with a 90-day maturation rate of 89%, high patency rates at 6 and 12 months (92% and 86%), and a low rate of procedure-related adverse events (5.5%) [7].

Complications of AVF techniques are vascular stenosis and thrombosis. Maturation failure in surgical AVFs is often associated with underlying stenosis. A retrospective study [8] showed an 88% clinical success rate of balloon percutaneous angioplasty (PTA) for immature autogenous fistulas (80% of the stenoses were in the juxta-anastomotic zone) (Fig. 22.2).

US-guided PTA access avoids multiple puncture attempts with consequent vessel spasm and hematoma formation. PTA is performed using a high-pressure, semi-compliant or non-compliant balloon. Venous stenosis may also develop upstream

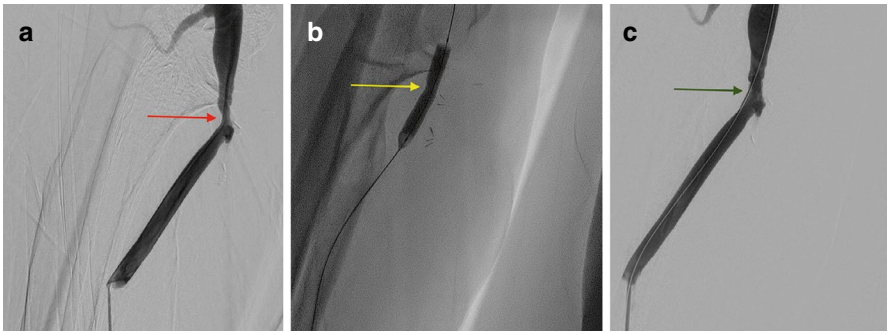

Fig. 22.2 Phlebography of a prosthetic humeral-cephalic arteriovenous fistula with distal prosthetic anastomosis stenosis (red arrow) (**a**). Percutaneous angioplasty with a 6 mm semi-compliant balloon, showing stenosis incision on the balloon (yellow arrow) (**b**). Post-procedural phlebography demonstrating stenosis resolution (green arrow) (**c**)

from the anastomosis; in these cases, PTA is indicated to improve fistula flow. Small caliber of the vein drainage tube is associated with poor outcomes after fistula creation [9]. Dilatations should be divided into different treatment sessions to prevent vessel trauma [10]. AVF thrombosis is nearly always linked to underlying stenoses. Endovascular intervention shows short- and long-term benefit compared to the conventional Fogarty technique [11]. The main complication of mechanical thrombectomy is arterial embolism (up to 7%); other complications include vessel rupture and pulmonary embolism. Thrombo-aspiration is a more rapid and less expensive option than mechanical thrombectomy and does not require thrombolytics, with the advantage of exposing patients to a lower risk of lung emboli [12].

22.3 Renal Artery Stenosis

Renal artery stenosis (RAS) has different etiologies which lead to different probabilities of developing renal failure. Treatment options available for RAS are medical therapy (antihypertensive therapy and therapies to limit atherosclerosis), percutaneous intervention (PTA and stenting), and surgery.

Atherosclerosis RAS (ARAS) is the most frequent etiology (90%), with a very high prevalence (50–60%) in elderly patients with hypertension and chronic kidney disease (CKD) [13]. CKD is the most common outcome with approximately half of the patients developing renal atrophy and GFR reduction within 3 years of diagnosis [14]. Stenosis progression is frequent, with 8–16% of ARAS evolving to complete occlusion within 5 years [15]. According to the guidelines [16], percutaneous revascularization is indicated in: (a) malignant hypertension leading to acute pulmonary edema (class I); (b) unstable angina, renal failure, and uncontrolled hypertension (class IIA); (c) unilateral ARAS with CKD (class IIB). Stenting is preferred over

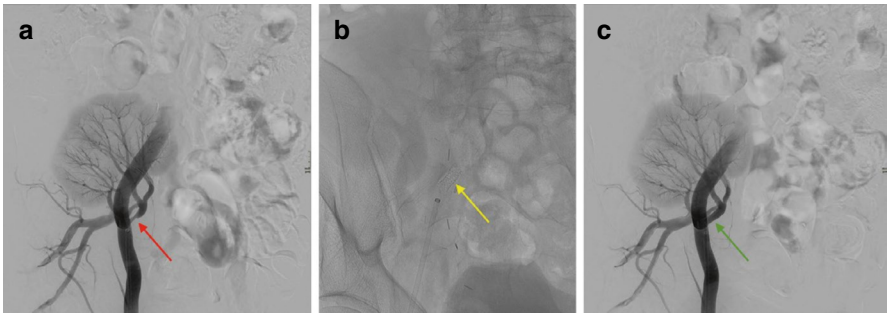

Fig. 22.3 Angiography of a right transplanted renal artery showing anastomotic stenosis (red arrow) (**a**). Percutaneous revascularization with balloon-expandable stent placement (6 × 18 mm) (yellow arrow) (**b**). Post-procedural angiogram showing resolution of stenosis (green arrow) (**c**)

PTA, and generally performed with balloon-expandable stents due to their high radial strength. Stenting revascularization has demonstrated to improve renal function with a significant increase of GFR [13]. Medical therapy should be optimized in all ARAS patients, regardless of revascularization [17].

Renal fibromuscular dysplasia (FMD), most common in young women (<50 years), accounts for 10% of RAS, often involving the right renal artery. FMD can be unifocal, which occurs in younger patients with severe hypertension, or multifocal and is often asymptomatic, although some patients develop severe hypertension. FMD does not generally lead to renal failure, unless associated with dissection or thrombosis [13]. Optimal candidates for treatment are patients <35 years with acute onset of hypertension, or patients with resistant/malignant hypertension regardless of age. PTA is generally sufficient, with stent placement being reserved for patients with artery dissection [18].

Vasculitis is a rare cause of large-vessel RAS (<1%), also affecting the renal microcirculation in patients with systemic lupus erythematosus, polyarteritis nodosa and Wegener's granulomatosis.

Transplant RAS (TRAS), usually diagnosed during the first year after transplantation, is defined as >50% reduction of the graft artery lumen, with increased systolic peak velocity at Doppler US, and it has a documented incidence of 1–12% [19]. Early-onset TRAS is associated with surgical procedure, while a late onset may indicate atherosclerosis apposition or aberrant immune response [19]. Treatment is required in cases of uncontrolled hypertension or deterioration of graft function. TRAS is usually localized at the anastomosis (25–75% [20]), but pre−/post-anastomotic or diffuse stenosis may also occur. PTA and stenting are the main effective treatment options, without high-evidence documented superiority [21] (Fig. 22.3). The complication rate ranges from 0–25%, with 3.2% puncture site hematoma/pseudoaneurysm, 1.8% artery dissection, 1% stent misplacement and 0.5% allograft loss [19].

References

1. Pabon-Ramos WM, Dariushnia SR, Walker TG, et al. Quality improvement guidelines for percutaneous nephrostomy. J Vasc Interv Radiol. 2016;27(3):410–4.
2. Patel IJ, Davidson JC, Nikolic B, et al. Addendum of newer anticoagulants to the SIR consensus guideline. J Vasc Interv Radiol. 2013;24(5):641–5.
3. Rana AM, Zaidi Z, El-Khalid S. Single-center review of fluoroscopy-guided percutaneous nephrostomy performed by urologic surgeons. J Endourol. 2007;21(7):688–91.
4. Barros PL, Oliveira B, Pereira R, et al. A possible novel approach to small iatrogenic colonic perforation during nephrostomy placement. Urol Case Rep. 2023;50:102495.
5. Dyer RB, Regan JD, Kavanagh PV, et al. Percutaneous nephrostomy with extensions of the technique: step by step. Radiographics. 2002;22(3):503–25.
6. Rajan DK, Ahmed O. Percutaneous hemodialysis fistula creation. J Vasc Interv Radiol. 2022;33(10):1135–1142.e2.
7. Yan Wee IJ, Yap HY, Tang TY, Chong TT. A systematic review, meta-analysis, and meta-regression of the efficacy and safety of endovascular arteriovenous fistula creation. J Vasc Surg. 2020;71(1):309–317.e5.
8. Clark TWI, Cohen RA, Kwak A, et al. Salvage of nonmaturing native fistulas by using angioplasty. Radiology. 2007;242(1):286–92.
9. Allon M, Lockhart ME, Lilly RZ, et al. Effect of preoperative sonographic mapping on vascular access outcomes in hemodialysis patients. Kidney Int. 2001;60(5):2013–20.
10. Kim J, Kwon Y, Choi TW, Won JH. Management of immature arteriovenous fistulas. Cardiovasc Intervent Radiol. 2023;46(9):1125–35.
11. Lundström UH, Welander G, Carrero JJ, et al. Surgical versus endovascular intervention for vascular access thrombosis: a nationwide observational cohort study. Nephrol Dial Transplant. 2022;37(9):1742–50.
12. Maleux G. Management of thrombosed dialysis access circuits. Cardiovasc Intervent Radiol. 2023;46(9):1162–7.
13. Safian RD. Renal artery stenosis. Prog Cardiovasc Dis. 2021;65:60–70.
14. Caps MT, Zierler RE, Polissar NL, et al. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int. 1998;53(3):735–42.
15. Caps MT, Perissinotto C, Zierler RE, et al. Prospective study of atherosclerotic disease progression in the renal artery. Circulation. 1998;98(25):2866–72.
16. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(13):1425–43.
17. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2014;370(1):13–22.
18. Gornik HL, Persu A, Adlam D, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. Vasc Med. 2019;24(2):164–89.
19. Pini A, Faggioli G, Pini R, et al. Assessment and management of transplant renal artery stenosis. A literature review. Ann Vasc Surg. 2022;82:13–29.
20. Su C, Lian J, Chang H, et al. Long-term outcomes of patients treated with primary stenting for transplant renal artery stenosis: a 10-year case cohort study. World J Surg. 2012;36(1):222–8.
21. Ngo AT, Markar SR, De Lijster MS, et al. A systematic review of outcomes following percutaneous transluminal angioplasty and stenting in the treatment of transplant renal artery stenosis. Cardiovasc Intervent Radiol. 2015;38(6):1573–88.

Additional Iconography to Some Chapters of the Monograph

23

Michele Santangelo and Fabio Vistoli

Regarding surgery in uremic patients, visual representation plays a crucial role in illustrating anatomical challenges, surgical strategies, and potential complications.

This chapter, entirely devoted to surgical illustrations and related visual material, is designed to complement and expand on the images already included in some specific sections of the monograph.

The images presented here (Figs. 23.1, 23.2, 23.3, 23.4, 23.5, 23.6, 23.7, 23.8, 23.9, 23.10, 23.11, 23.12 and 23.13) come from the authors' personal archives and constitute a valuable iconographic resource, documenting key moments of surgical practice. These moments range from the preoperative phase to the execution of the procedure, and include the management of complications and the analysis of excised surgical specimens.

Each image has been carefully selected for its educational value and its ability to provide a clear and immediate representation of the challenges and strategies involved in treating specific pathological conditions of uremic patients.

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This visual collection complements the textual content, offering the reader a direct and concrete perspective of the procedures described in the preceding chapters. The strength of iconography lies in its ability to overcome language barriers, offering an immediate and detailed representation of surgical reality.

We hope that this section will serve as a valuable teaching and reference tool for readers of this monograph and for all professionals involved in the surgical management of uremic patients.

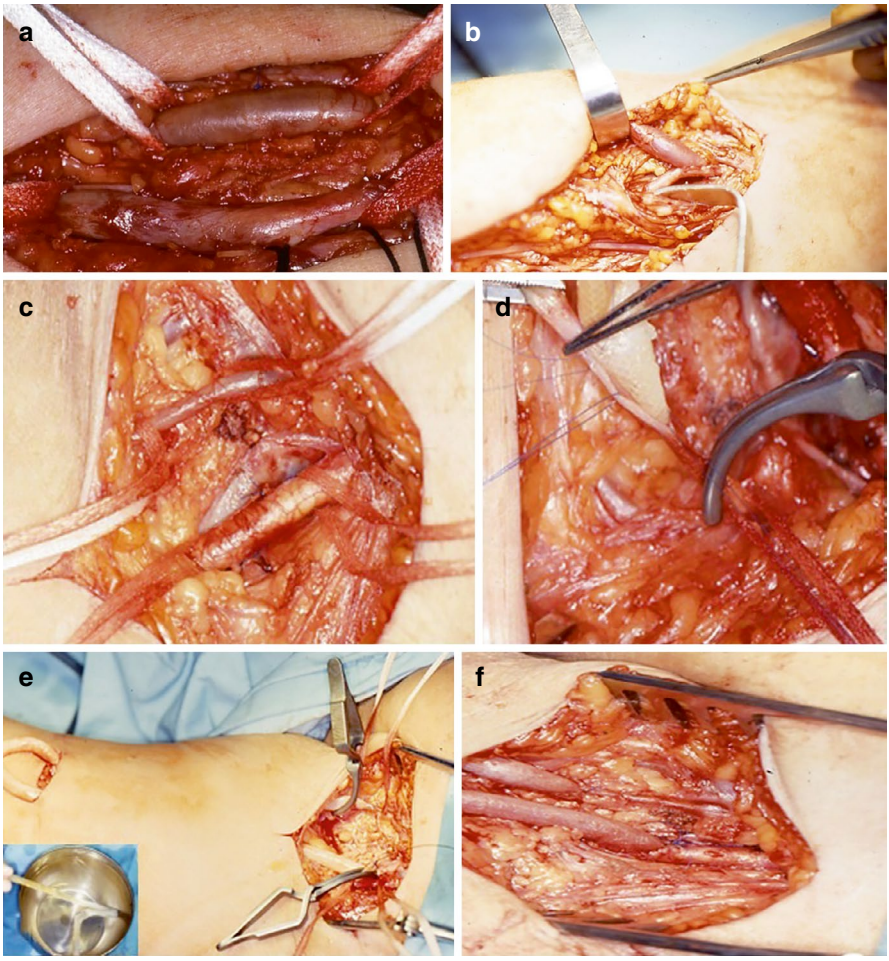

Fig. 23.1 Additional iconography to Chap. 3. Case 1: (**a**, **b**) Side-to-end arteriovenous fistula (AVF) (Courtesy Prof. Paride De Rosa/Prof. Michele Santangelo). Case 2: (**c**–**f**) Performance of femoral-femoral AVF with biological prosthesis (autologous saphenous vein). (Courtesy Prof. Paride De Rosa/Prof. Michele Santangelo)

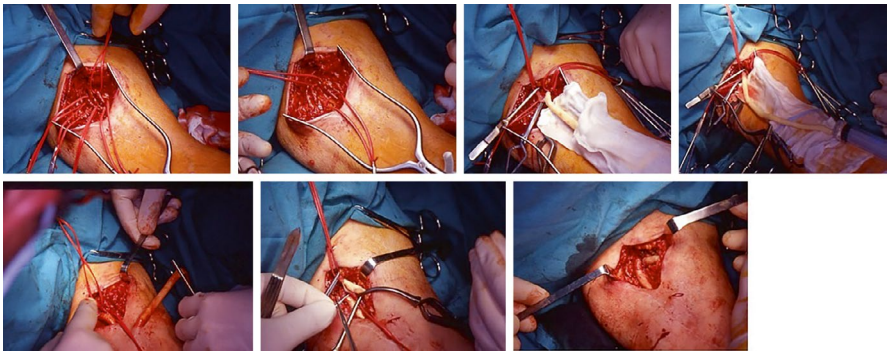

Fig. 23.2 Additional iconography to Chap. 3. Performance of axillary-axillary arteriovenous fistula with biological prosthesis (bovine ureter). (Courtesy Prof. Paride De Rosa/Prof. Michele Santangelo)

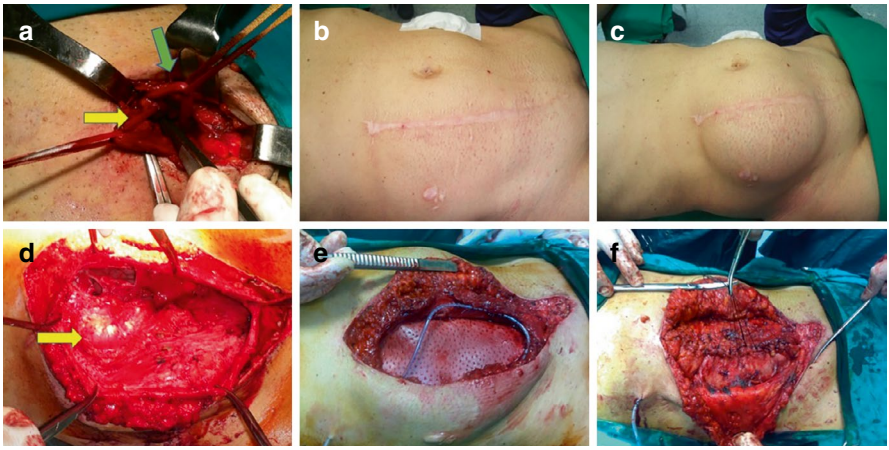

Fig. 23.3 Additional iconography to Chap. 4. Case 1: (**a**) Engagement of ureter of transplanted kidney (green arrow) in inguinal hernia. Spermatic funiculus is also visible (yellow arrow). (**b**–**f**) Laparocele after kidney transplantation. Performance of laparoplasty with biological prosthesis (porcine dermis) placed extraperitoneally. Yellow arrow indicates transplanted kidney. (Courtesy Prof. Michele Santangelo)

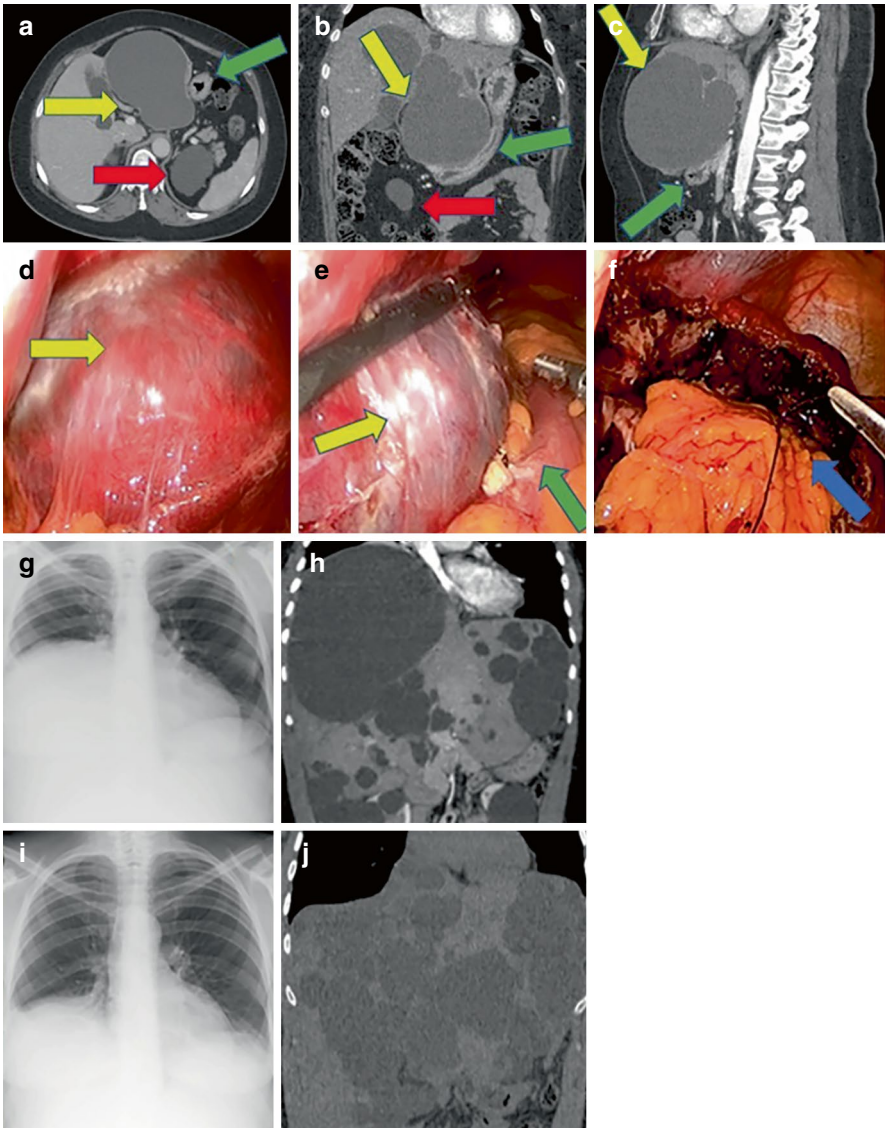

Fig. 23.4 Additional iconography to Chap. 10. Case 1: Compression of stomach by large cyst of hepatic segments II-III in a patient with autosomal dominant polycystic kidney (ADPKD): (**a**–**c**) CT scan of large cyst (arrowheads) arising from the liver (axial, coronal and sagittal sections). (**d**–**f**) Intraoperative laparoscopic images of cyst fenestration and omentoplasty. Yellow arrow > hepatic cyst; green arrow > compressed stomach; red arrow > kidney cysts; blu arrow > omentoplasty (Reproduced with permission from: Eleonora Riccio, Michele Santangelo, Alessandro Scotti, Antonio Pisani. A strange epigastric pain. Clin Kidney J. 2014 Oct;7(5):493–4, doi: 10.1093/ckj/sfu088. Epub 2014 Aug 21. This figure is excluded from the CC-BY-NC 4.0 licence under which this book is published. Any reuse requires permission from the publisher—see https://academic.oup.com/journals/pages/access_purchase/rights_and_permissions/). Case 2: Mediastinal deflection, T-wave inversion in v1–v3, dyspnea caused by giant cyst in right hepatic lobe in a patient with ADPKD, treated with percutaneous drainage. (**g**, **h**) X-ray and CT before percutaneous treatment. (**i**, **j**) X-ray and CT after percutaneous treatment. (Courtesy Prof. Michele Santangelo)

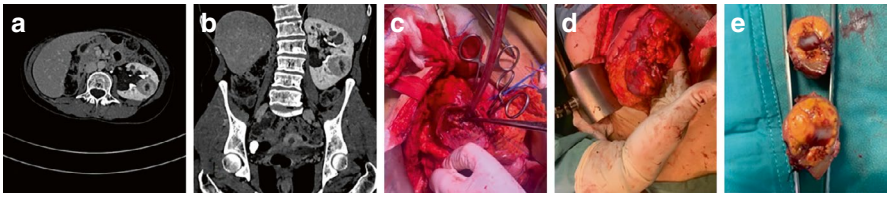

Fig. 23.5 Additional iconography to Chap. 14: Partial nephrectomy/enucleoresection for renal cell carcinoma (RCC) in a monorenal patient: (**a**) Axial section CT scan; (**b**) Coronal section CT scan; (**c**) Renal surgical bed after exeresis of RCC; (**d**) Completed surgery; (**e**) Open operative specimen with visible healthy perilesional tissue. (Courtesy Prof. Michele Santangelo)

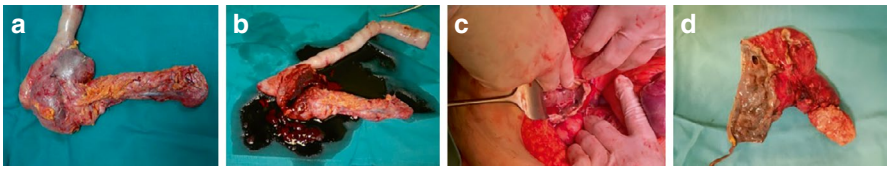

Fig. 23.6 Additional iconography to Chaps. 12 and 21: Graft pancreatectomy in patients undergoing combined kidney and pancreas transplantation. Case 1: (**a**, **b**) Graft pancreatectomy performed for severe hemorrhagic shock from bleeding from transplanted duodenum unresponsive to conservative and angioradiologic therapy. Case 2: (**c**, **d**) Graft pancreatectomy performed for peritonitis caused by necrosis of transplanted duodenum. (Courtesy Prof. Michele Santangelo)

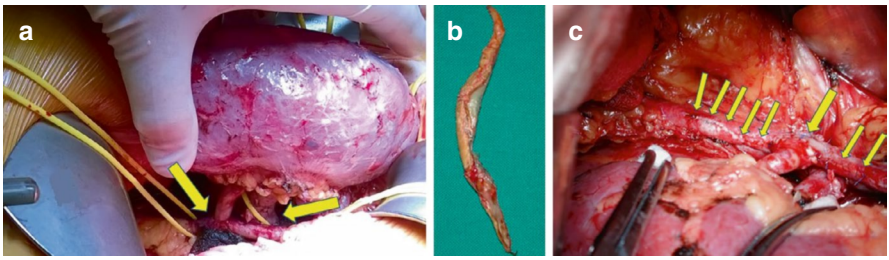

Fig. 23.7 Additional iconography to Chap. 15. Case 1: (**a**) Kidney transplantation. Arrows indicate arterial termino-lateral anastomosis without Carrel patch on the external iliac artery, and venous termino-lateral anastomosis on the external iliac vein (Courtesy Prof. Fabio Vistoli). Case 2: (**b**, **c**) Kidney transplantation with endarterectomy of the recipient's external iliac artery. (**b**) Atherosclerotic plaque removed from the recipient's external iliac artery via endarterectomy. (**c**) Kidney transplantation following endarterectomy of the recipient's external iliac artery. Arrows indicate the post-endarterectomy suture line and the termino-lateral arterial anastomosis between the renal artery (with Carrel patch) and the recipient's external iliac artery (Courtesy Prof. Fabio Vistoli)

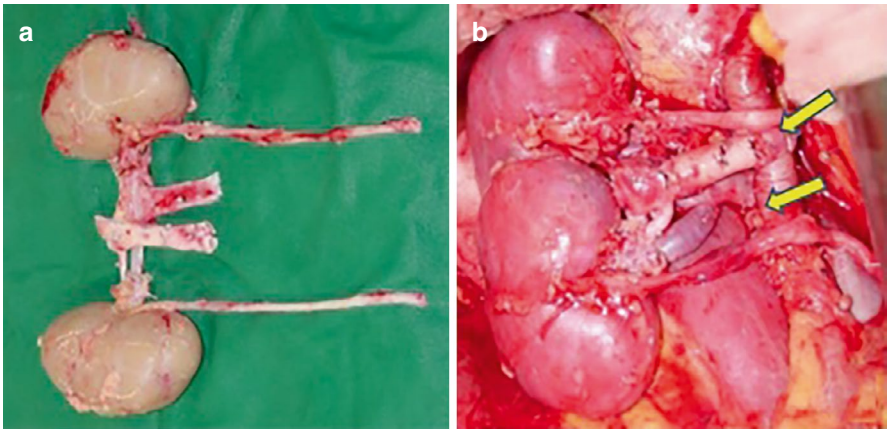

Fig. 23.8 Additional iconography to Chap. 15. Deceased-donor pediatric kidney transplantation in an adult recipient. (**a**) Deceased pediatric donor kidney graft harvested *en bloc* with aortic and caval stumps. (**b**) Deceased pediatric donor kidney graft transplanted *en bloc* into an adult recipient using aortic and caval stumps for arterial and venous anastomoses. Arrows indicate the termino-lateral arterial anastomosis between the distal stump of the aortic graft and the recipient's external iliac artery, and the termino-lateral venous anastomosis between the proximal stump of the caval graft and the recipient's external iliac vein. (Courtesy Prof. Fabio Vistoli)

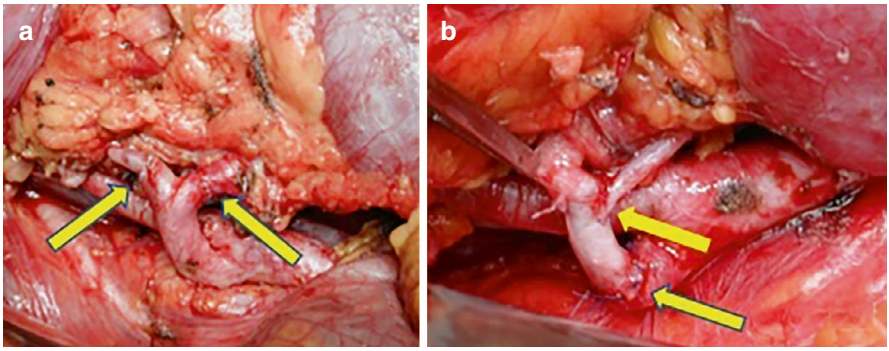

Fig. 23.9 Additional iconography to Chap. 15. Reconstruction options in cases of kidney graft with multiple arteries. (**a**) Arrows indicate arterial termino-terminal anastomosis of two renal arteries on the two bifurcation arms of the recipient's internal iliac artery. (**b**) Arrows indicate termino-lateral anastomosis of the polar renal artery on the main renal artery trunk, and arterial termino-terminal anastomosis of the main renal artery on the recipient's internal iliac artery. (Courtesy Prof. Fabio Vistoli)

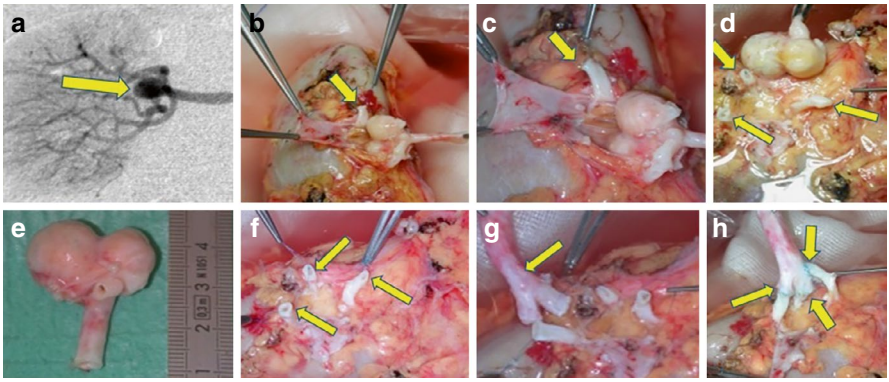

Fig. 23.10 Additional iconography to Chap. 15. Living-donor kidney with renal artery aneurysm. (**a**) Angiogram of the living donor kidney showing a double-chamber sacciform aneurysm (arrow) of the trifurcation of the main trunk of the renal artery. (**b**–**d**) Progressive isolation and excision of the double-chamber aneurysm of the trifurcation of the main trunk of the renal artery. Arrows indicate the isolated and resected arterial branches. (**e**) The removed double-chamber sacciform aneurysm of the renal artery trifurcation. (**f**) Arrows indicate the three branches to be reconstructed to maintain complete vascularization of the transplanted kidney. (**g**) Internal iliac artery graft (arrow) removed from the recipient and ready to be used to reconstruct renal graft vascularization. (**h**) Arrows indicate the termino-terminal anastomoses between the branches of the recipient internal iliac artery graft and two renal arteries; the other renal artery is anastomosed termino-laterally to the common branch of the recipient internal iliac artery graft, thus completing the arterial reconstruction. (Courtesy Prof. Ugo Boggi/Prof. Fabio Vistoli)

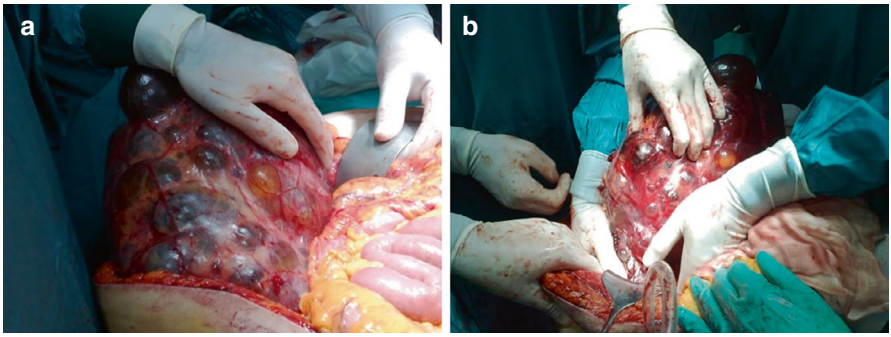

Fig. 23.11 Additional iconography to Chap. 16. (**a**, **b**) Intraoperative finding of right nephrectomy of a giant polycystic kidney, weighing over 10 kg. (Courtesy Prof. Michele Santangelo)

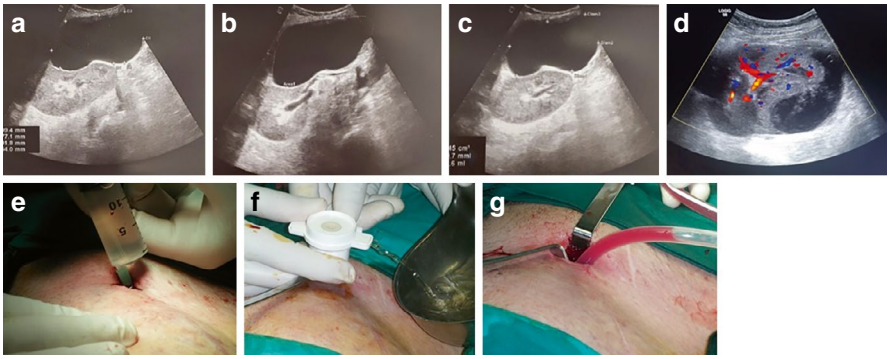

Fig. 23.12 Additional iconography to Chap. 21. Hypertensive lymphocele after kidney transplant. (**a**–**e**) Drainage performed with ultrasound-guided minimally invasive technique. (Courtesy Prof. Michele Santangelo)

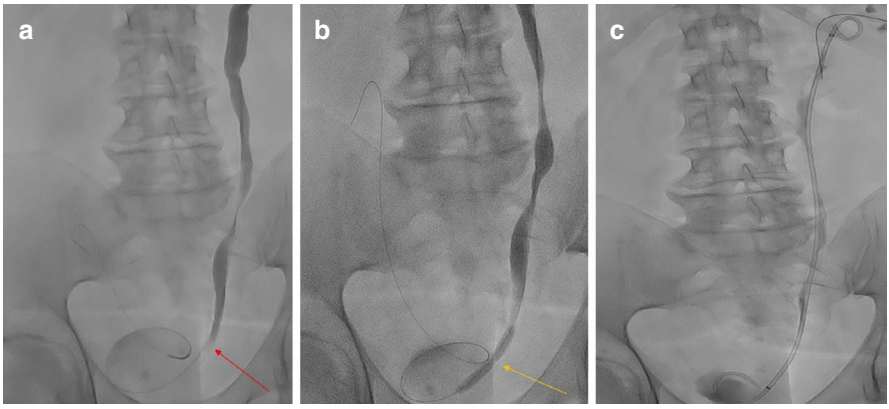

Fig. 23.13 Additional iconography to Chap. 22. Obstructive acute renal failure from left ureterovesical stricture (red arrow) arising after transurethral resection of bladder (TURB) in a patient with chronic renal failure. (**a**) Stricture crossing using a hydrophilic guidewire and an angiographic catheter. (**b**) Ureteroplasty with a 5 × 40 mm balloon, highlighting the stenosis (yellow arrow). (**c**) Anterograde placement of a double-J ureteral stent to protect the treated stricture. (Courtesy Prof. Francesco De Cobelli)

Surgery in Uremic Patients: Challenges, Innovations, Future Prospects and Concluding Remarks

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Michele Santangelo and Fabio Vistoli

The surgical management of uremic patients remains a complex challenge in clinical practice.

Chronic kidney disease (CKD) is responsible for numerous homeostatic alterations that impact every surgical procedure. Precisely because of the systemic effects of these alterations and their clinical implications, any surgical procedure in these patients involves not only the treatment of the local disease but also the comprehensive management of associated comorbidities, making a multidisciplinary approach mandatory.

Cardiovascular, metabolic, and immunologic dysfunction, common in patients with CKD, significantly increases the risk of perioperative and postoperative complications. Electrolyte imbalances, hypertension, bleeding, and susceptibility to infection require meticulous preoperative preparation, careful intraoperative management, and vigilant postoperative care.

As discussed in previous chapters—both general and disease-specific—the surgical approach to patients with CKD must be individualized, with an emphasis on risk stratification and optimization of systemic function prior to any intervention.

Different chapters of the monograph also underscore the role of minimally invasive techniques in the treatment of these patients. However, although laparoscopic

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and robotic surgeries have indeed proven valuable in reducing the surgical trauma associated with traditional open procedures—thereby facilitating faster recovery, shorter hospital stays, and potentially fewer complications—these techniques require careful consideration in the patient with CKD, where factors like compromised tissue healing and limited vascular supply may complicate the benefits of minimal-access surgery. In addition, the increased risk of bleeding of the patient with CKD must be carefully considered and managed when using these techniques.

Even today the creation of dialysis accesses, whether through arteriovenous fistulas or hemodialysis/peritoneal catheters, remains a cornerstone of the care of patients with CKD. As highlighted by the contributors to this monograph, the operative management of patients with CKD undergoing surgery is not easy due to the increased risk of infection, occlusion and thrombosis; therefore, optimal access placement and continuous monitoring are essential to prevent complications, especially in patients undergoing multiple operations.

Renal transplantation is another critical procedure for many CKD patients, offering the potential to significantly improve quality of life and long-term survival. However, patient selection remains a challenging process, since coexisting comorbidities, such as cardiovascular disease and diabetes, can adversely affect transplant survival. The chapters on renal transplant surgery offer valuable insights into both surgical technique and postoperative management of transplant recipients, emphasizing the importance of immunosuppressive therapy and careful monitoring of complications.

The complexity of managing patients with CKD requires a highly individualized approach to care. Each patient presents a unique set of challenges based on the degree of renal impairment, the presence of comorbidities, and his or her overall functional status. As emphasized by the experts who contributed to this monograph, collaboration among nephrologists, cardiologists, anesthesiologists, and surgeons is critical for optimal outcomes. In addition, it is crucial to address the nutritional and psychosocial status of patients with CKD, as the burden of CKD and uremia often involves considerable mental and emotional stress.

Looking ahead, advances in research and technology have the potential to further revolutionize the surgical management of patients with CKD. The use of new biomarkers for preoperative risk stratification, advanced imaging techniques for precise surgical planning, and new perioperative monitoring systems could help improve surgical outcomes. In addition, regenerative medicine may offer attractive alternatives to traditional surgical interventions, potentially reducing the need for invasive procedures and improving tissue repair.

In conclusion, although the surgical management of patients with CKD remains an unresolved challenge, the growing body of knowledge and technological advances offer new opportunities for more effective and safer treatment. Advances in surgical techniques, together with an increasingly integrated and personalized approach to care, offer not only more targeted intervention but also a real opportunity to improve the quality of life of this vulnerable patient population. Interdisciplinary collaboration and ongoing research will continue to be the cornerstones of the future of surgery in uremic patients, with the ultimate goal of optimizing both survival and well-being.