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Abstract

Introduction: The incidence of acute kidney injury (AKI) in the oncology population remains unknown. However, the impact is strong on morbidity, mortality, and hospitalization costs. Sepsis and hypoperfusion are very common etiologies of AKI in cancer patients; they converge on prerenal and intrinsic causes.

Objective of the review: The aim was to describe the main pathophysiological aspects and establish diagnosis and treatment criteria in patients with acute kidney injury and sepsis in cancer patients.

Essential points of the review: A significant group of cancer patients on immunosuppressants develop viral infections with sepsis and acute kidney failure. Although AKI in patients with sepsis is multifactorial, the primary mechanism is acute tubular necrosis after renal hypoperfusion due to circulatory failure. Early administration of antibiotics and control of the etiological basis of sepsis are usually the cornerstones of prevention.

Conclusion: The prognosis of ICU patients with severe sepsis-related AKI is poor, reaching an in-hospital mortality rate of 70%. Furthermore, the presence of leukemia or lymphoma has been shown to be an independent predictor of mortality in the ICU. Unfortunately, no agent has proven effective in preventing severe sepsis.

Keywords:

Acute kidney injury, Sepsis, Cancer.
Cancer patients account for approximately 20% of all intensive care unit (ICU) admissions. The precise incidence of acute kidney injury (AKI) in the oncology population remains unknown; data from several sources suggest a high incidence with a substantial impact on morbidity, mortality, and hospitalization costs. According to the case series studied, AKI develops in 13% to 42% of critically ill patients with cancer, and 8% to 60% of these patients will require renal replacement therapy. The need for dialysis is more common in critically ill patients with cancer than in those without cancer. The incidence of dialysis therapy for AKI in cancer patients admitted to the ICU ranges between 9% and 33% and is associated with a short-term mortality of more than 66%. This is likely an underestimate of the actual severity of AKI in this population, given that many cancer patients choose to forgo life-sustaining treatments. Limited clinical experience and existing data suggest that the incidence rate of AKI might be more significant in oncology patients than in the rest of the population [1, 2].

Cancer is associated with many risk factors for AKI in addition to traditional factors, such as older age, female sex, diabetes mellitus, congestive heart failure, chronic kidney disease, and the use of nephrotoxic medications other than antineoplastics (analgesics, bisphosphonates, and contrast media). These patients are predisposed to hemodynamic and total practical volume compromise due to their immunosuppression, and cancer itself can directly affect the kidney (nephrectomy, postrenal causes due to compression or obstruction, concomitant diseases of the renal parenchyma such as paraneoplastic glomerulopathies, thrombotic microangiopathy, immune-mediated nephropathy) as well as many chemotherapeutic agents. AKI can lead to decreased functional status, reduced quality of life, and exclusion from other cancer treatments [3].

There is a reciprocal relationship between AKI and chronic kidney disease (CKD) since patients with CKD have a greater risk of developing AKI. On the other hand, AKI increases the risk of CKD since patients with CKD have a greater risk of developing AKI. On the other hand, AKI increases the risk of progressive CKD [1, 2].

The etiological context of AKI in cancer patients is similar to that in the rest of the population, with the causes being classified as prerenal, renal, or intrinsic and postrenal, but the etiology is often multifactorial.

Sepsis-associated acute kidney injury is a common complication in hospitalized and critically ill patients that increases the risk of developing chronic comorbidities and is associated with extremely high mortality. Individual syndromes, sepsis, and acute kidney injury make the host susceptible to each other. While sepsis is the most common risk factor for developing AKI, AKI of any origin is associated with an increased risk of developing sepsis. Sepsis has a complex and unique pathophysiology, making sepsis-associated acute kidney injury a syndrome distinct from any other AKI phenotype. Sepsis and hypoperfusion are very common etiologies of AKI in oncology patients; they have both prerenal and intrinsic causes since they have multiple effects on tubular and endothelial epithelial cells, in addition to being common causes of hypovolemia due to capillary leakage [1, 2].

**Etiology**

Patients receiving chemotherapy frequently develop hematological complications such as neutropenia, which, if prolonged, especially for periods longer than seven days, increases the risk of infection. Sepsis is the second most common cause of AKI in the general population of patients not admitted to the ICU. According to several studies, it is the most common etiology in patients requiring the ICU. Specific data on oncology patients are scarce, but hematologic malignancies appear to be a risk factor for the development of AKI in the ICU.

Furthermore, a retrospective study of 232 patients revealed that sepsis was independently associated with a greater incidence of severe AKI in breast cancer patients receiving high-dose chemotherapy [4].

Viral infections are an emerging cause of AKI in bone marrow transplant patients. Several studies have confirmed that AKI is associated with adenovirus, polyomavirus (BK or JC), and simian polyomavirus. The well-documented association between BK virus and hemorrhagic cystitis may explain the high incidence of hemorrhagic cystitis after bone marrow transplantation (20% to 25%) and the development of nephropathy. Simian virus-40 was recently found to be associated with AKI and hemorrhagic cystitis. It has also been determined that adenovirus is associated with disseminated infections such as encephalitis, pneumonitis, and AKI [2, 3, 6].

**Pathophysiology of sepsis and acute kidney failure**

The pathophysiology of sepsis is complex and still needs to be fully understood. Sepsis includes the simultaneous presence of invasive infection and systemic host inflammatory response syndrome (SIRS), which is characterized by a hyperinflammatory state in which pathogen-associated molecular patterns (PAMPs) and molecular patterns damage-associated proteins (DAMPs) are released into the intravascular compartment and bind to membrane-bound pattern recognition receptors such as Toll-like receptors present on the surface of immune cells, initiating a signaling cascade that results in the synthesis and release of proinflammatory molecules and a massive and deregulated activation of innate and adaptive immunity, generally followed by an equally vast and harmful counterregulatory response, leading to so-called “immune paralysis.” Renal tubular epithelial cells also
express Toll receptors, especially types 2 and 4; when exposed to DAMPs or PAMPs filtered through the glomerulus or neighboring peritubular capillaries, they exhibit increased oxidative stress, reactive oxygen species production, and mitochondrial damage. Therefore, in septic patients, the first early phase results from SIRS, and the second late phase is caused by immunosuppression and lymphocyte depletion.

Severe AKI is currently considered to be the consequence of several concomitant factors, such as dysfunction of the renal microvascular system, the direct interaction of pathogen fragments with renal resident cells, the cytotoxic effect of the so-called “cytokine storm,” and the crossing of harmful effects. However, it is generally accepted that circulating inflammatory mediators can directly affect the renal parenchyma and are associated with an increased risk of mortality in patients with AKI. These soluble mediators include eicosanoids, leukotrienes, complement components, cytokines, chemokines, coagulation factors, other small peptides, and potentially critical vasogenic substances.

Although AKI in patients with sepsis is multifactorial, the primary mechanism is acute tubular necrosis after renal hypoperfusion due to circulatory failure. A clinical picture characterized by renal hypoperfusion and acute tubular necrosis is typically observed in septic patients with cancer, especially those affected by hematological malignancies and neutropenia, considering the aggravation of ischemic lesions by the administration of nephrotoxic antibiotics [2-4, 6, 7].

**Diagnosis of acute kidney injury in cancer patients**

Uniform definitions of AKI, according to the RIFLE, AKIN, and KDIGO classifications, have established AKI staging by (1) relative increases in serum creatinine compared to baseline or (2) progressive decreases in urine production. It should be noted that the KDIGO classification, developed to develop a common terminology and, above all, to diagnose AKI earlier, is currently the most widely accepted classification [8].

Several endogenous markers can be used to determine the glomerular filtration rate: inulin, which has a molecular mass of 5000 daltons, meets many criteria to be an ideal marker of the glomerular filtration rate. However, it is not readily available. Other markers, such as i125-iothalamate or Cr-EDTA (Chromium Edetate), and radiocontrast, such as iohexol and meglumine diatrizoate, which are often determined by high-performance liquid chromatography, are also not widely available, and can be associated with adverse effects from radiation exposure and the risk of anaphylaxis. Its role in oncology may be to confirm glomerular filtration rate values obtained through other techniques to determine the glomerular filtration rate in situations of clinical uncertainty, such as extreme body mass or clinical research [9, 10].

Regarding endogenous markers, we can speak of the first instance of serum creatinine, which has been used to estimate GFR considering that it is freely filtered in the glomerulus and, therefore, excreted by glomerular filtration, in addition to the fact that the production and excretion of creatinine are constant in the basal state. However, using an arbitrary cutoff value of serum creatinine for AKI is discouraged because it can be affected by many factors: muscle mass, protein intake, volume expansion, liver diseases, and medications that affect its levels independently of kidney function. Launay-Vacher et al. [11] reported that abnormal serum creatinine levels were detected in less than 10% of cancer patients, while an abnormal glomerular filtration rate was detected in approximately 50%. Indeed, some cancer patients who have recovered from AKI may have “normal” serum creatinine but decreased renal functional reserve. This reserve may predict the future risk of AKI in patients with stomach cancer [12] and offers an opportunity to stratify the risk of patients at high risk of AKI before future cancer treatments and maintain closer monitoring of kidney function [9, 10].

Cystatin C, a cysteine protease inhibitor produced by all nucleated cells, is freely filtered by the glomerulus and is not secreted or reabsorbed by the tubules. Therefore, the serum cystatin C concentration depends on the glomerular filtration rate and can be used to measure renal function. However, there appear to be independent effects of both malignancy and chemotherapy on cystatin C levels, which confound its usefulness [13]; the significant increase in the cost of measuring cystatin C versus creatinine has limited its use in clinical practice.

Several formulas have been used to estimate creatinine clearance: Modifying Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Compared to the Cockcroft and Gault equations, the MDRD and CKD-EPI equations estimate the glomerular filtration rate and incorporate race (black versus other) and sex but not weight. The CKD-EPI and MDRD study equations are designed for use with a standardized serum creatinine assay and have been validated in cohort studies of cancer patients; the CKD-EPI equation is more accurate than the MDRD study equation, especially at higher glomerular filtration rates (>60 ml/min/1.73 m²), which explains the preference for its use over the MDRD equation.

Various CKD-EPI equations can be used with serum creatinine, serum cystatin C, or a combination of both values. It should be noted that cancer patients were not well represented in the patient cohorts from which these estimated glomerular filtration rate equations were derived. Therefore, caution should be taken when extrapolating these equations to this patient population. However, in recent years, several publications have demonstrated the superior performance of the CKD-EPI equation in the cancer patient population compared to other methodologies. In addition, the MDRD equation is superior to the Cockcroft and Gault equations when applied to patients receiving chemotherapy. More recent studies compared the
CKD-EPI equation with the MDRD and the Cockcroft and Gault equations. They found that using the CKD-EPI equation adjusted for body surface area was more accurate, demonstrated less bias, and may describe a higher estimated GFR [9].

Due to the potential errors in GFR estimation in cancer patients described previously, cancer-specific estimated GFR formulas and drug dosing equations have been developed from small cohorts of cancer patients, one of which is Martin's formula, which was evaluated in 123 patients with different mixed tumor types. This study used plasma clearance concentrations of Cr-EDTA, and then the formula was validated in a group of 45 cancer patients. Similar to the formulas by Martin, the Wright formula was also developed through a Cr-EDTA population pharmacokinetic method. An example of a dose determination formula based on the GFR is the Calvert formula, which uses the drug elimination (clearance) rate and the overall systemic plasma concentration of the drug over time (AUC) to prevent drug toxicity. This formulation uses the GFR as a measure of clearance to achieve a target AUC.

This approach has been well documented for carboplatin dosing, especially in patients with ovarian cancer or seminoma, so a target AUC of 4–6 mg/mL per minute was determined to be the most appropriate therapeutic range. Significantly, increasing the AUC above this range increases the risk of myelotoxicity without improving drug efficacy, and doses below this range may result in increased relapse rates. The National Comprehensive Cancer Network recommends using the Calvert calculation for carboplatin dosing based on specific area under the curve (AUC) targets (such as 4–6 mg/mL per minute). However, as a whole, cancer-specific equations underperform the aforementioned conventional equations, such as the CKD-EPI equation, and have not gained widespread acceptance or use [9, 10].

Finally, new urinary biomarkers of kidney injury, which potentially have a better ability to detect the onset and severity of AKI, are being investigated. Possible markers include inflammatory biomarkers (NGAL and interleukins 6 and 18), cellular injury biomarkers (KIM-1, L-FABP, NHE-3, and netrin 1), and cell cycle markers (TIMP-2 and IGFBP-7). Although some studies have demonstrated the benefit of urinary biomarkers for the early detection of AKI after chemotherapy, other studies have demonstrated poor diagnostic yield. Additionally, no study has shown better outcomes for patients with earlier detection. Currently, the routine use of these new biomarkers of kidney damage cannot be recommended [1].

Prevention

Early administration of appropriate antibiotics and control of the etiological basis of sepsis are usually the cornerstones of prevention. Late administration of antibiotics in septic shock patients was associated with the early development of AKI. However, specific nephrotoxic agents involved in treatment, such as aminoglycosides and vancomycin, particularly in combination with piperacillin-tazobactam and amphotericin B, should be used with caution to prevent AKI and monitoring of plasma concentrations of certain potentially nephrotoxic medications should be considered.

Fluid resuscitation followed by vasopressors is the cornerstone of shock treatment. Isotonic crystalloids have been recommended for patients at risk of AKI; observational studies have shown a reduction in the incidence of AKI and lower mortality when crystalloid solutions with more physiological chloride concentrations (lactated Ringer’s solution) are used. The SPLIT trial revealed no difference in the rate of AKI or incidence of renal replacement therapy with the use of “balanced” saline and crystalloid (chloride concentrations < 110 mmol/L) in ICU patients, even in the subgroup with sepsis. Other more extensive trials, such as the SALT-ED and SMART, reported fewer composite adverse renal events, such as death, dialysis, and persistent renal dysfunction, in the balanced crystalloid group than in the saline group [14].

Norepinephrine is recommended as the agent of choice for the treatment of septic shock. Compared with norepinephrine, dopamine is not recommended for renal protection and is associated with more adverse effects. Vasopressin did not appear to increase the risk of AKI and was even associated with lower rates of renal replacement therapy in an open trial [15]. Another trial in septic shock patients showed that a higher mean arterial pressure target of 80 to 85 mmHg was associated with a lower requirement for renal replacement therapy in a subgroup of patients with chronic hypertension compared with a target of 65 to 70 mmHg. However, no survival benefit was observed [16].

Despite the extensive literature on the benefits of early protocolized resuscitation, there are three clinical trials in patients with septic shock (ProCESS, ARISE, and ProMISE) that did not demonstrate any improvement in mortality or the need for renal replacement therapy. A secondary ProCESS study focused on renal outcomes found no significant differences with protocolized resuscitation or usual care on the development of AKI, severity of AKI, fluid overload, requirement for renal replacement therapy, or renal recovery [14].

Treatment

Conservative Management in Oncology Patients with AKI-CKD

The decision to start renal replacement therapy in oncology patients and AKI patients represents a challenge for the treatment team since these patients are generally elderly and have multiple comorbidities, which is why an interdisciplinary care approach is necessary. In high-risk populations such as cancer patients, deciding to start dialysis involves weighing both the risks and benefits and their potential impact on quality of life.

Although cancer itself is not a contraindication to the initiation of renal replacement therapy, when evaluating the long-term benefits of this treatment, it is imperative to take into account factors such as age, functional status, severity of concomitant organ failure, and medical status, of the underlying cancer.

Ample scientific evidence suggests that conservative management should be considered for this type of patient based on the
minimal improvement in survival and quality of life achieved with dialysis treatment.

The care of patients with cancer and chronic kidney disease can be optimized by involving the Palliative Care service and communicating with nephrology, oncology, and intensive care [2].

Triazole antifungal agents may reduce the incidence of Candida infection in neutropenic allogeneic bone marrow transplant recipients. However, their routine use in all neutropenic cancer patients remains controversial because they may also increase the risk of bacteremia [17, 18].

Renal Replacement Therapies

The use of dialysis circuits for patients with chronic renal failure is the basis of renal replacement therapy (RRT) modalities available in the ICU. RRT modalities have generally been classified according to (1) their duration and (2) clearance technique. Intermittent therapy is applied for less than 12 hours per session, continuous therapy (CRRT) is prescribed to work for 24 hours a day, and hybrid therapies are prescribed for between 8 and 12 hours.

Intermittent techniques generally rely on more significant extracorporeal blood flows and lead to more rapid correction of metabolic disorders; this mode uses dialysate and replacement fluid from tap water with added electrolyte solution. However, intermittent hemodialysis may be poorly tolerated in hemodynamically unstable septic patients and in those who require a slower restoration of metabolic balance, for example, those with cerebral edema.

In contrast, continuous therapies (continuous veno-venous hemofiltration, continuous veno-venous hemodialysis, and continuous veno-venous hemodiafiltration with pre- or postdilutional modalities) can be administered with lower blood flow. They can be adjusted to the patient's hemodynamic status. Because patients with septic AKI often receive a catecholamine infusion to maintain mean arterial pressure, CRRT is frequently preferred in these circumstances. Some limitations of this type of therapy include the need for trained medical and nursing staff; lower blood flow demands a greater need for anticoagulation, which can cause hemorrhagic complications, as well as a longer duration in a circuit. Extracorporeal therapy may limit patient mobility, lead to better elimination of medications and micronutrients, and have more significant costs than intermittent treatments [17].

However, evidence supporting an optimal modality for renal replacement therapy is limited. Most studies comparing outcomes after intermittent and continuous modes have been observational, with various forms of AKI and different disease severities, excluded hemodynamically unstable patients, had small cohorts and did not consider concomitant interventions. Furthermore, other RRT variables were not controlled, such as clearance mode, choice of dialysis/replacement fluids, anticoagulation, onset time, and filter membrane type. Over the last decade, controlled studies that have evaluated different modalities have reached the same conclusion: there is no apparent benefit in terms of mortality, with no statistically significant differences in length of hospital stay, recovery of kidney function, or need for chronic dialysis.

Blood purification therapies for sepsis

The use of RRT in septic patients has been evaluated for renal support and immunomodulation. Although the modulation of inflammatory mediators appears to be the primary goal of blood purification in sepsis patients, this therapy may also offer additional physiological benefits, including temperature control, acid-base control, fluid balance control, protective support at the kidney, heart, lung, brain, liver and bone marrow levels, and blood detoxification.

Extracorporeal circulation may potently modulate body temperature and general thermal balance. A negative thermal balance may be obtained depending on the length of the bloodlines, the ambient temperature, and the temperature of the replacement fluid.

Cardiac support can be achieved by optimizing fluid balance, reducing organ edema, and restoring preload and afterload to desirable levels. Optimizing the patient's volume status and removing interstitial fluid through extracorporeal therapy may support lung failure. Blood purification can improve the encephalopathy of sepsis by removing uremic toxins and amino acid derivatives and correcting acidemia. By eliminating uremic toxins, blood purification also supports the bone marrow.

Blood purification therapies designed to remove substances from the circulation include diffusion-based hemodialysis, convection-based hemofiltration (including high-volume hemofiltration), mixed diffusion-convection strategies (hemodiafiltration), plasmapheresis, hemoperfusion, or some combination of the following. Themselves. Despite considerable advances in knowledge and technical capacity in recent years, there still needs to be a consensus on the optimal method and conditions for using these therapies.

Hemoadsorption

It is a technique in which a sorbent is placed in direct contact with blood in an extracorporeal circuit. Adsorbents, typically carbon and resins, attract solutes through various forces, including hydrophobic interactions, ionic (or electrostatic) attraction, and hydrogen bonding.

The adsorption capacity of resins and carbons is usually high. Therefore, targeting larger molecules that exceed the molecular weight limit of synthetic high-flux dialysis membranes is possible. Adsorption membranes such as polymethylmethacrylate (PMMA) and AN69ST have been used to enhance the removal of endotoxins and cytokines; this makes these adsorbents potentially ideal for intervention in sepsis.

The biocompatibility of these devices is the main limitation of their use, and thrombocytopenia and the risk of bleeding are the most relevant possible side effects.

Recently, highly adsorbent and biocompatible sorbents such as CytoSorb and Oxiris have been used to eliminate multiple inflammatory mediators from the bloodstream.

Plasma Therapy
It is a treatment modality that includes plasmapheresis and plasma exchange. Plasmapheresis is a two-step process in which blood is first separated into its components (cells and plasma) using a centrifugal pump or filter. Then, the separated plasma flows along the column(s), containing different adsorbents, allowing selective removal of the components, and the processed plasma is rein infused into the patient. Instead, plasma exchange occurs in a single step in which blood is similarly separated into plasma and cells using centrifugation pumps or a filter. The cells are returned to the patient, while the plasma is replaced with albumin or fresh frozen plasma to replenish any factors (immunoglobulins) necessary to restore homeostasis and often to correct the underlying disorder.

It has been shown that plasma therapy is more effective in patients with sepsis-associated thrombotic microangiopathy [18].

Conclusion

The prognosis of ICU patients with severe sepsis-related ARF is poor, reaching an in-hospital mortality rate of 70%. Furthermore, the presence of leukemia or lymphoma is an independent predictor of mortality in the ICU. Unfortunately, no agent has proven effective in preventing severe sepsis.

Abbreviations

CKD: Chronic kidney disease.
AKI: acute kidney injury.
ICU: intensive care unit.

Supplementary information

The supplementary materials have not been provided.

Acknowledgments

Does not apply.

Contributions of _ authors

Jorge Quinchuela Hidalgo: Project administration, Resources, Software, Writing – original draft.

Financing

The study was self-financed by the author.

Availability of data or materials

The datasets generated and analyzed during the current study are not publicly available but can be shared with an academic request.

References


DOI: Digital Object Identifier. PMID: PubMed Identifier.

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