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Acute Kidney Injury (AKI) and Management of Renal Tumors

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1. Introduction

Acute kidney injury (AKI) is characterized by a rapid decline in kidney function within a few hours or a few days. AKI is an independent risk factor for mortality in critically ill patients. Determination of the prevalence of AKI depends on the definition employed and on methods used for definite diagnosis. The incidence and prevalence of AKI vary with the clinical setting, based on separately addressed community-based, hospital-based or intensive care unit (ICU)-based AKI [Himmelfaub, Ikizler 2007]. The epidemiology of AKI has been made unclear in the past because of the use of different definitions across various studies. The lack of a uniform definition may results in many differences in the reported incidences and outcomes of AKI in the literature.

2. Definition of AKI

2.1 RIFLE criteria

In 2004, a group of experts on acute renal failure (Acute Dialysis Initiative, ADQI) stated that the name should be changed from “acute renal failure” to “acute kidney injury (AKI)” [Bellomo, Ronco, Kellum et al. 2004]. This group developed criteria for standardizing and staging AKI, which consist of Risk, Injury, Loss and End-stage Renal Failure (RIFLE). The aim of this classification was to standardize the definition of AKI in the same way as the two other common ICU syndromes (sepsis and ARDS). In the RIFLE criteria, serum creatinine and urine output were adopted as clinical parameters to formulate three severity categories (Risk, Injury and Renal Failure) of AKI and two clinical outcome categories (Loss and Renal Failure) (Table 1). At present, RIFLE criteria have been validated in more than 550,000 patients around the world [Srisawat, Hoste, Kellum et al. 2010]. The problems in adopting the criteria were using 1) very small alterations in serum creatinine and urine output, 2) an acronym instead of numerical stages such as with chronic kidney disease (CKD) and 3) a 50% increase of serum creatinine for categorizing as Risk. Recent investigations revealed that an alteration of less than 50% of serum creatinine was important [Chertow, Burdick, Honour 2005].

2.2 AKIN criteria

In 2007, the RIFLE criteria were revised by members of the Acute Kidney Injury Network (AKIN), a multi-disciplinary international group to increase their sensitivity [Mehta,

Kellum, Shah et al. 2007]. These modifications are summarized as follows: 1) broadening of the 'risk' category of RIFLE to include an increase in serum creatinine of at least 0.3mg/dL even if this does not reach the 50% of the basal creatinine level; 2) setting a 48-hour window on the first documentation of any criteria; 3) categorizing all patients as 'failure' if they are undergoing renal replacement therapy (RRT) regardless of what their serum creatinine or urine output is at the point of initiation and 4) using stages 1, 2 and 3 were used instead of R, I and F (Table 1).

3. Etiology of AKI in patients with neoplasms

The etiology of AKIs is classified into three types: pre-renal, intrinsic renal injury and post-renal causes [Denker, Robles-Osorio, Sabath 2011]. AKI in patients with neoplasms is most often multifactorial. Clinicians may experience each type or combinations of AKI during treatment of these patients.

3.1 Pre-renal causes

Pre-renal causes are common in patients with malignancies because these patients suffer from anorexia, nausea and vomiting or diarrhea as malignancy-related symptoms together with side effects of treatments. It is often difficult to diagnose in the pre-renal phase during which recovery of kidney function is possible with adequate fluid supplementation and also difficult to differentiate from the intrinsic renal phase during which AKI has been established [Lameire, Van Biesen, Vanholder 2010]. Moreover, electrolyte disturbances are frequently observed in patients with malignancies and they can aggravate AKI. Electrolyte and acid base disturbances are consequences of neoplastic spread, anticancer treatment or paraneoplastic phenomena of tumors.

3.2 Intrinsic renal causes

Most intrinsic renal injury is classified as acute tubular necrosis (ATN), acute interstitial nephritis, vasculopathy and glomerulopathy.

3.2.1 Acute tubular necrosis (ATN)

ATN is defined by AKI and tubular damage in the absence of significant glomerular or vascular pathology [John, Herzenberg 2009]. The presentation of ATN is a sudden rise of serum creatinine, sometimes with microscopic hematuria and small amounts of proteinuria. The presence of tubular epithelial enzymes in the urine is a valuable indicator of detect damage. Microscopically, ATN is recognized by a combination of degenerative tubular changes. The mildest change is apical blebbing and the most severe is cellular necrosis, which is rare. The presence of sloughed epithelium and casts is a common finding. Mild interstitial inflammatory cell infiltration is commonly observed around the damaged tubular segments. Tamm-Horsfall mucoprotein can elicit an exuberant inflammatory reaction. Isometric vacuolization is a form of tubular injury characterized by numerous small vacuoles filling the cytoplasm. The pathogenetic mechanism of ATN is still unclear. The two major causes of ATN are ischemic and toxic factors. Both lead to ATN via tubular epithelial cell damage. Prolonged renal ischemia is the most common cause of ATN. While sepsis, commonly observed in critically ill patients with malignancy, is a cause of hypotension and renal ischemia, a recent investigation using sepsis models suggested that reactions between Gram-negative toxins and toll-like receptors including their effector

Category	RIFLE			AKIN		
	Creatinine/GFR	Urine output (UO)	Stage	Creatinine	Urine output (UO)	
Risk	Cr increase by 1.5 times or GFR decrease by $\geq 25\%$	$UO \leq 0.5 \text{ mL/kg/hr}$ for 6hrs	Stage 1	Cr increase by $\times 1.5$ times or $\geq 26 \mu\text{mol/L}$	$UO \leq 0.5 \text{ mL/kg/hr}$ for 6hrs	
Injury	Cr increase by $\times 2$ times or GFR decrease by $\geq 50\%$	$UO \leq 0.5 \text{ mL/kg/hr}$ for 12hrs	Stage 2	Cr increase by $\times 2$	$UO \leq 0.5 \text{ mL/kg/hr}$ for 12hrs	
Failure	Cr increase by $\times 3$ times or GFR decrease by 75% or $Cr \geq 354 \mu\text{mol/L}$ (with acute rise $\geq 44 \mu\text{mol/L}$)		Stage 3	Cr increases by $\times 3$ or $Cr \geq 354 \mu\text{mol/L}$ (with acute rise $44 \mu\text{mol/L}$) or RRT	$UO \leq 0.3 \text{ mL/kg/hr}$ for 24hrs or anuria for 12hrs	
Loss (outcome)	Persistent ARF = complete loss of renal function > 4 weeks (but > 3 months	N/A	Nil			
ESRD (outcome)		N/A	Nil			

Table 1. RIFLE and AKIN criteria
Patients requiring RRT are automatically classified as Stage 3 AKIN regardless of stage at time of RRT initiation.

proteins such as MyD88 were also involved in ATN [Goncalves, Zamboni, Camara 2010, Li, Khan, Maderdrut et al. 2010].

3.2.2 Tubulointerstitial nephritis

Tubulointerstitial nephritis is defined as inflammation of the renal interstitium and tubules either with interstitial edema and acute tubular damage or with interstitial fibrosis and tubular atrophy. Acute interstitial nephritis (AIN) is clinically similar to ATN. Signs suggesting systemic hypersensitivity such as rash or eosinophilia are sometimes present. The major causes of AIN include drugs, infection, autoimmune diseases and cancer infiltration. The most frequent cause is drugs, which account for two thirds of all AIN [Baker, Pusey 2004]. The onset of symptom after administration of a drug that can induce AIN is on average 2-3 weeks, but this interval varies widely [Rossert 2000]. While eosinophilia has been suggested to predict drug-induced AIN, good evidence is lacking for diagnosis of AIN based on the presence or absence of eosinophilia [Nolan, Anger, Kelleher 1986]. AIN shows interstitial edema, tubular damage and mixed infiltration of mononuclear cells. Eosinophilic infiltration is common drug-induced AIN, but it shows low sensitivity. An immunological basis for drug-induced AIN is apparent in most cases. Drugs act as haptens and create antigenicity after binding to tubular basement membrane or interstitial matrices [Rossert 2000].

3.2.3 Thrombotic microangiopathy

The association between thrombotic microangiopathy (TMA) and cancer was first described in 1973. TMA may be associated with cancer itself, with cancer chemotherapy or with allogeneic bone marrow transplantation (BMT) [Kwaan, Gordon 2001]. Thrombocytopenia with microangiopathic hemolytic anemia (peripheral non-autoimmune anemia with schizocytes) and no alternative diagnosis is sufficient to establish a presumptive diagnosis of TMA [Darmon, Cioldi, Thiery et al. 2006]. Intravascular coagulation (DIC) must be ruled out in this setting. Most TMA occurs in patients with solid tumors, the most common type being adenocarcinoma (stomach, breast and lungs) although TMA has been reported in patients with other solid tumors or hematological malignancies [Gordon, Kwaan 1997]. While the pathophysiology of malignancy-related TMA remains controversial, recent studies have shown that disseminated cancer is associated with decreased ADAMTS 13 activity, without anti-ADAMTS 13 antibodies [Oleksowicz, Bhagwati, DeLeon-Fernandez 1999].

The link between TMA and cancer chemotherapy was first described for mitomycin C. Subsequently, TMA has been reported in connection with many anti-cancer agents, including gemcitabine, bleomycin, cisplatin, cytosine arabinoside, daunorubicin, deoxycoformycin, 5-FU, azathioprine and interferon α [Kwaan, Gordon 2001]. The association between TMA and bone marrow transplantation (BMT) has been reported since the 1980s. Typically, TMA starts from 2 to 12 months after BMT and is unresponsive to plasma exchange. BMT associated TMA has been reported to be related to total body irradiation, graft-vs-host disease and cytomegalovirus infection. Treatment of TMA has not been established. Although plasma exchange has been shown to improve patients without malignancies [Rock, Shumak, Buskard et al. 1991], it is possible that plasmapheresis harms TMA patients with malignancies [Penne, Vignau, Auburtin et al. 2005].

3.3 Toxicity related to cancer treatment

3.3.1 Contrast-induced AKI (CI-AKI)

CI-AKI accounts for approximately 10% of all cases of hospital-acquired AKI. CI-AKI may lead to increased morbidity and mortality rates in the selected at-risk population including

critically ill patients with cancer [Briguori, Tavano, Colombo 2003]. Hemodynamic changes in renal blood flow, which lead to hypoxia of the renal medulla and direct toxic effects of contrast media on renal cells are thought to contribute to the pathogenesis of CI-AKI [Briguori, Quintavalle, De Micco et al. 2011].

3.3.2 Cisplatin-induced renal toxicity

Metastatic renal pelvic cancers, like those of the bladder, are generally highly chemosensitive diseases. At present, a combination of cisplatin, methotrexate, doxorubicin and vincristine (M-VAC) is most widely used for the treatment of metastatic urothelial carcinoma [Sternberg, Yagoda, Scher et al. 1989, Tannock, Gospodarowicz, Connolly. 1989]. The dismal results obtained with M-VAC have prompted efforts to determine new regimens against urothelial carcinoma. Combined chemotherapy with gemcitabine and cisplatin is now widely considered to be first-line chemotherapy against metastatic renal pelvic cancer [von der Maase, Hansen, Roberts et al. 2000, Tanji, Ozawa, Miura et al. 2010].

Cisplatin has direct toxicity and causes AKI. Cisplatin is also associated with chronic dose-dependent reduction of the glomerular filtration rate (GFR) [Arany, Safirstein 2003]. The most widely used protective measurement is saline infusion to induce solute diuresis. Since amifostine (an inorganic thiophosphate) has been found to be effective for prevention of AKI, the American Society of Clinical Oncology recommended use of amifostine for the prevention of AKI in patients receiving cisplatin-based chemotherapy (grade A recommendation) [Schuchter, Hensley, Meropol et al. 2002].

Metastatic renal cell carcinoma (RCC) is highly resistant to both conventional chemotherapy and radiotherapy. During the last decade, several new targeted drugs (sorafenib, sunitinib, everolimus and temsirolimus) have been used for the treatment of advanced RCC [Tanji, Yokoyama 2011]. Molecular targeted drugs are associated with adverse events different from those of classical anticancer agents. AKI has been reported in patients with advanced RCC administered anti-vascular endothelial growth factor (VEGF) agents, including sorafenib and sunitinib. Proteinuria and hypertension are often observed in the patients treated with these agents and pathologically, various kidney lesions, including thrombotic microangiopathy, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, cryoglobulinemic glomerulonephritis, immune complex glomerulonephritis, glomerular endotheliosis and AIN, are detected [Gurevich, Parazella 2009]. A patient contracting AKI after using temsirolimus has been reported [Kwitkowski, Prowell, Ibrahim 2010].

3.4 Intra- or extra-renal obstruction

3.4.1 Acute tumor lysis syndrome

Tumor lysis syndrome (TLS) is a potentially life-threatening complication of cancer treatments in patients with extensive growing and chemosensitive malignancies. TLS results from degenerated cells, which rapidly release intracellular electrolytes, proteins and metabolites into the extracellular space. TLS often causes AKI by renal tubular occlusion resulting from uric acid crystal formation secondary to hyperuricemia [Jasek, Day 1994]. Another cause is calcium phosphate deposition by hyperphosphatemia [Darmon, Ciroidi, Thiery et al. 2006]. Although TLS typically occurs in patients with hematological malignancies, it has been reported in patients with RCC and pelvic cancer [Lin, Lim, Chen 2007, Persons, Garst, Vollmer et al. 1998]. Volume expansion and recombinant urate oxidase (rasburicase), which reduce uric acid levels, diminish the risk of uric acid deposition

nephropathy. Urine alkalization, which was previously recommended to prevent uric acid precipitation within renal tubules, is controversial since urine alkalization induces calcium phosphate deposition [Baeksgaard, Sorensen 2003].

3.5 Post-renal causes

Post-renal causes of AKI are based on obstruction of the outflow tracts of the kidneys. Causes include prostatic hypertrophy, catheters, tumors, strictures and crystals. Neurogenic bladder also causes an obstruction. Clinical manifestations of post-renal obstructive uropathy vary with the site, degree and rapidity of obstruction [Kapoor, Chan 2001].

B-mode ultrasonography is a very useful imaging tool to rule out the possibility of urinary tract obstruction as a cause of AKI [Kalantarinia 2009]. Early detection of urinary tract obstruction may prevent patients from progressing to established AKI by early release of urinary obstruction [Choudhury 2010].

Release of obstruction, either by percutaneous nephrostomy or through a ureteral stent, is the fundamental treatment. Recovery of renal function depends on the severity and duration of the obstruction [Kapoor and Chan 2001]. Thus, early discovery and treatment are crucial.

4. Biomarkers of AKI

Although serum creatinine and blood urea nitrogen have been used as standard biomarkers, they are not sufficiently specific and sensitive to detect AKI in the early phase [Choudhury 2010]. Moreover, the resultant inability to meaningfully segregate critical aspects of injury such as type, onset, propagation and recovery from ongoing renal function has hindered successful translation of promising therapeutics. Recently, efforts to identify novel plasma or urine biomarkers for AKI have resulted in discovery about 20 potential candidates. Promising markers include urine or plasma neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), IL-18, cystatin C and liver fatty-acid binding protein (L-FABP) [Malyszko 2010].

4.1 NGAL

Human NGAL is a 25-kDa protein expressed by neutrophils and various epithelial cells including cells of the proximal convoluted tubules [Goetz, Holmes, Borregaard et al. 2002]. Urinary NGAL is up-regulated within 2 hours after acute renal cellular injury. Microarray analysis identified NGAL as one of the earliest and most prominently induced genes in the kidneys after ischemic or nephrotoxic renal injury in mouse models and humans [Schmidt-Ott, Mori, Kalandadze 2006, Cowland, Borregaard 1997]. In one study, patients in an intensive care unit with AKI had more than 10-fold increases in plasma NGAL and more than 100-fold increases in urine NGAL levels, when compared with controls [Mori, Lee, Rapoport et al. 2005]. Other studies demonstrated the ability of serum and/or urine NGAL to predict the development of postsurgical AKI before elevation of serum creatinine [Mishra, Dent, Tarabishi et al. 2005, Dent, Ma, Dastrala et al. 2007].

4.2 KIM-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein overexpressed in proximal tubule cells of the kidneys in response to ischemic or nephrotoxic injury and has a

potential role as a predictive marker of AKI [Ichimura, Bonventre, Bailly et al. 1998]. In a cross-sectional study, the area under the curve (AUC) of KIM-1 for differentiating patients with AKI from controls was 0.9 [Han, Waikar, Johnson et al. 2008]. A prospective study of 90 adult patients undergoing cardiac surgery indicated that the AUC of urinary KIM-1 was higher than those of NGAL and NAG. Several studies demonstrated that urinary KIM-1 can differentiate ischemic AKI from pre-renal azotemia and CKD and may be useful for differentiating among various subtypes of AKI [Han, Waikar, Johnson 2008].

4.3 Cystatin C

Cystatin C is a low molecular weight cysteine protease inhibitor. The serum level of cystatin C is determined by the glomerular filtration rate (GFR), indicating that serum and urine levels of cystatin C reflect changes in the GFR [Villa, Jimenez, Soriano et al. 2005]. Although serum creatinine levels do not rise until GFR drops to under 50 ml/min (creatinine blind area), serum cystatin C increases at a GFR of around 70ml/min [Shimizu-Tokiwa, Kobata, Io et al. 2002]. This means that serum cystatin C is superior to serum creatinine in detecting impaired GFR.

4.4 IL-18

IL-18 is a proinflammatory cytokine and powerful mediator of ischemia induced AKI in animal models [Melnikov, Ecdar, Fantuzzi et al. 2001]. IL-18 is induced and cleaved in the proximal tubules and is detected in urine following experimental AKI [Melnikov, Faubel, Sigmund et al. 2002]. In a cross-sectional study, IL-18 levels were significantly higher in patients with established AKI but not in those with urinary tract infections. The AUC for diagnosis of established AKI is 0.95 [Parikh, Jani, Melnikov et al. 2004]. In general, it is considered that IL-18 is specific for ischemic AKI but may also be a non-specific marker of inflammation and has shown inconsistent results [Moore, Bellomo, Nichol 2010].

4.5 L-FABP

L-FABP is expressed in various organs including the liver and kidneys. The function of L-FABP is cellular uptake of fatty acids from plasma and promotion of intracellular fatty acid metabolism. Since free fatty acids can be easily oxidized, they can lead to oxidative stress and cellular injury. L-FABP inhibits the accumulation of intracellular fatty acids and prevents oxidation of free fatty acids. L-FABP is an important cellular antioxidant during oxidative stress [Noiri, Doi, Negishi et al. 2009].

L-FABP is filtered by glomeruli and reabsorbed in the proximal tubules. This partly explains the increase of L-FABP in injury of the proximal tubules. Renal L-FABP expression is up-regulated and urinary L-FABP excretion is accelerated by accumulation of free fatty acids in proximal tubule injury [Kamijo, Sugaya, Hikawa et al. 2004,].

In a clinical study, urine L-FABP appeared to be a more sensitive predictor of AKI than serum creatinine, and differentiated patients with septic shock from those with severe sepsis [Nakamura, Sugaya, Koide 2009]. Urine L-FABP can predict AKI in pediatric cardiopulmonary bypass surgery with AUC of 0.81 at 4-hours post-surgery [Portilla, Dent, Sugaya et al. 2008]. Although urine L-FABP is an early, accurate biomarker of AKI, it appears later than NGAL [Moore E, Bellomo R, Nichol. 2010].

5. Treatment

People who have risk factors of AKI (eg, past history of AKI, CKD or diabetes mellitus) should be treated as carefully as possible [Lamaire, Adam, Becker et al. 1999]. The best method for preventing contrast media induced AKI is to avoid use of contrast media. If contrast media must be used, the most effective prevention is to avoid volume depletion and to assure adequate volume [Davidson, Hlatky, Morris et al. 1989, Cigarroa, Lange, Williams et al. 1989]. The effect of administration of *N*-acetylcysteine (NAC) is controversial [Fishbane 2008] and there is no convincing evidence of benefits in periprocedural blood purification [Frank H, Werner D, Lorusso V et al. (2003), Vogt B, Ferrari P, Schonholzer C et al. (2001)]. Since renal autoregulatory capacity maintains renal blood flow, several vasopressors including dopamine, norepinephrine, vasopressin and terlipressin, have been used or tested for prevention of renal ischemia. There is no clear convincing evidence on the beneficial effects of these agents for treating AKI [Rudnik MR, Kesselheim A, Goldfarb S (2006)].

There are currently no specific pharmacological interventions for patients with established AKI but renal replacement therapy (RRT) is a key component of supportive care. AKI associated with cancer shows substantial morbidity and mortality. Among critically ill cancer patients, 12-49% experience AKI and 9-32% need RRT [Lanore JJ, Brunet F, Pchard et al. 1991, Benoit, Hoste, Depuydt et al. 2005, Azoulay, Recher, Alberti C et al. 1999, Azoulay, Moreau, Alberti et al. 2000, Darmon, Thiery, Cioldi et al. 2005]. These figures are much higher than those for critically ill patients without cancer. Most of the studies on AKI in cancer patients focus on patients with hematological malignancies whose mortality is over 80% when RRT is necessary [Zager, O'Quigley, Zager et al. 1989]. Studies focusing on AKI in renal tumor patients have not been reported. In a cohort study, the benefits of early organ support including RRT was shown in the patients with non-hematological cancers associated with AKI [Darmon, Thiery, Cioldi et al. 2007]. AKI, which has multiple causes and shows higher mortality in cancer patients, allows physicians to perform reluctant RRT, but there are no adequate treatment guidelines for AKI in patients with malignancies.

5.1 Dosage in renal replacement therapy (RRT)

The effectiveness of RRT can be adjusted by the rate of solute clearance (duration of the session) and/or the frequency of RRT sessions. The assessment of RRT dose is traditionally performed by single-pooled Kt/V urea. This refers to fractional clearance of urea (K), which takes into consideration therapy duration (t) and volume of distribution of urea in the body (V). In contrast to end stage kidney disease (ESKD) patients, critically ill patients with AKI have an unstable metabolic status (eg. hypercatabolism and fluid expansion). When continuous RRT (CRRT) is performed, ultrafiltration volume acts as a surrogate for clearance, based on with sieving coefficient of most small solutes such as urea. Therefore, application of Kt/V urea in critically ill patients has its limitations [Schiffl, Lang, Fischer 2002]. The RRT adequacy is more complex than small-solute removal. Fluid overload has been independently associated with increased mortality of AKI [Payen, de Pont, Sakr et al. 2008, Bouchard J, Soroko S, Chertow G et al. 2009].

5.2 Intensity of RRT and outcome

Renal replacement therapy (RRT) is usually performed in critically ill patients by intermittent hemodialysis or continuous RRT (CRRT). CRRT is performed together with hemofiltration, dialysis or a combination of them. The efficacy of CRRT for critically

ill patients is not superior to that of intermittent hemodialysis [Himmelfarb 2007]. Studies on the dose of intermittent hemodialysis (IHD) or CRRT and their outcomes have shown conflicting results although some clinical trials suggested an improvement in survival with higher doses of RRT [Ronco, Bellomo, Homel et al. 2000, Palvesky, Zhang, O'Connor et al. 2008, Bellomo, Cass, Cole et al. 2009, Tolwani, Cruz, Fumagalli et al. 2008, Boumann, Oudemans-Van Straaten, Tijssen et al. 2002, Saudan, Niederberger, Seigneux et al. 2006]. One of the reasons for this phenomenon is that there is considered to be an inflection point separating the dose-response portion and dose-independent portion between RRT dose and survival. Recent multicenter randomized trials showed that higher intensity of CRRT or IHD did not reduce mortality of critically ill patients with AKI [Palvesky, Zhang, O'Connor et al. 2008, Bellomo, Cass, Cole et al.]. If a critically ill patient with AKI is given RRT, the mortality is expected to be over 90%. Under-dialysis for critically ill patients with AKI results in higher mortality because of uremic complications. The correct dose is around the inflection point, at which the RRT dose is not too small but not excessive.

5.3 Recommendation of RRT for critically ill patients with AKI

The balance of current evidence suggests that CRRT should be performed with an effluent flow rate higher than 20-25ml/kg/h in hemodynamically unstable patients with AKI. Alternative-day IHD is acceptable in more stable patients and minimum single pool Kt/V urea of 1.2-1.4 is recommended [Schiffl 2010]. Clinicians should check whether patients actually receive the current optimal doses of RRT. Higher doses and more intensive therapy can be considered if patients become extremely hypercatabolic or have a volume overload.

6. Conclusion

Although a large number of studies have been performed on AKI, little is known about its pathophysiology, appropriate diagnosis or treatment. It is hoped that further studies will improve the prognosis of patients with AKI. It appears that suitable treatments should be selected for AKI especially in patients with malignancies.

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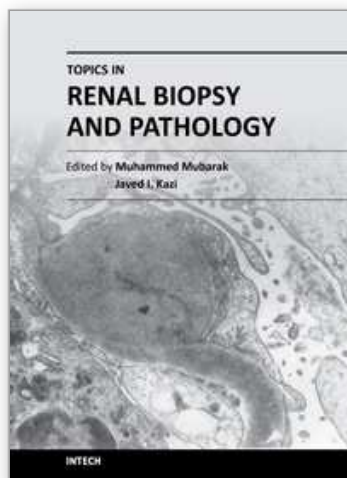
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There is no dearth of high-quality books on renal biopsy and pathology in the market. These are either single author or multi-author books, written by world authorities in their respective areas, mostly from the developed world. The vast scholarly potential of authors in the developing countries remains underutilized. Most of the books share the classical monotony of the topics or subjects covered in the book. The current book is a unique adventure in that it bears a truly international outlook and incorporates a variety of topics, which make the book a very interesting project. The authors of the present book hail not only from the developed world, but also many developing countries. The authors belong not only to US but also to Europe as well as to Pakistan and Japan. The scientific content of the book is equally varied, spanning the spectrum of technical issues of biopsy procurement, to pathological examination, to individual disease entities, renal graft pathology, pathophysiology of renal disorders, to practice guidelines.

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