Available online on 15.07.2020 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

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Review Article

## Acute Renal Injury: Revisited

Kamel El-Reshaid\*, Shaikha Al-Bader\*\*

\* Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

\*\* Nephrology center, Al-Amiri Hospital, Ministry of health, Kuwait

### ABSTRACT

Acute kidney injury (AKI) indicates its abrupt deterioration and is defined as an increase in serum creatinine more than the baseline by  $\geq 26$   $\mu\text{mol/L}$  within 48 hours or  $\geq 50\%$  within 1 week. The latter since glomerular failure is the life-threatening one with: (a) uremic intoxication, (b) water and salt retention with fluid overload, and (c) potassium accumulation with cardiac arrest. The etiology can be pre-renal, post-renal or intrinsic. Diagnosis is established by history of new insults, physical examination for hydration status, systemic stability and manifestations of autoimmune diseases/infections as well as an initial laboratory testing for renal function (serum creatinine, electrolytes and urine routine) and kidney ultrasound. Additional specific tests are indicated to assess etiology of AKI and its associated co-morbid conditions that interacts with its management. Severity of AKI ranges from mild (stage 1) to advanced (stage 5) that requires dialytic support. Moreover, it depends on the type and duration of the insult. Prognosis depends on etiology of AKI, its co-morbid conditions and the timely interventions by the supportive medical team.

**Keywords:** acute, causes, epidemiology, injury, kidney, management.

**Article Info:** Received 11 April 2020; Review Completed 14 June 2020; Accepted 23 June 2020; Available online 15 July 2020



#### Cite this article as:

El-Reshaid K, Al-Bader S, Acute Renal Injury: Revisited, Journal of Drug Delivery and Therapeutics. 2020; 10(4):221-224  
<http://dx.doi.org/10.22270/jddt.v10i4.4154>

#### \*Address for Correspondence:

Dr. Kamel El-Reshaid, Professor, Dept. Of Medicine, Faculty of Medicine, Kuwait University, P O Box 24923, 13110 Safat, Kuwait

### INTRODUCTION

The kidneys are 2 bean-shaped, 10-12 cm organs, that lies posteriorly and extraperitoneally in the abdomen on both sides of the vertebral column. Beneath its fibrous capsule is a 1-2 cm cortex that contains 85% of the glomeruli. The kidneys receive 25% of the cardiac output to be cleared from its waste products (uremic toxins) and to maintain body homeostasis i.e. adjustment of its metabolic changes in body water, electrolytes, osmolality and acid-base. Each kidney is made up of 1-1.5 million functional units called nephrons (Fig. 1). The nephron receives blood via afferent arteriole to form a plexus of capillaries that has lost their muscular wall for filtration. The latter is the glomerulus via which fluids sieve to a collecting capsule called Bowman's capsule. Most of the filtered fluid and its electrolytes are being reabsorbed in the proximal convoluted tubules, ascending limb of Henle, distal convoluted tubule and collecting duct. Sixty% of filtered sodium is being reabsorbed in the PCT, 20% in limb of Henle and 10% in distal tubule. In the latter segment  $\frac{1}{2}$  is in exchange with potassium under the effect of aldosterone. At the same site, calcium and magnesium are reabsorbed under effect of parathyroid hormone. In the terminal part of

the nephron water is being reabsorbed by antidiuretic hormone to maintain body osmolality. Acid base balance of the kidney is mainly done in the DCT by exchange of sodium and potassium with hydrogen ions to regenerate body bicarbonate to maintain blood pH <sup>1</sup>. The interstitium synthesize erythropoietin in response to low oxygenation of the peritubular cells. Moreover, the cholecalciferol formed by ultraviolet effect on subcutaneous cholesterol substrates gets activated in the liver in 25 position to form 25 hydroxycholecalciferol which ultimately needs the kidney to add another hydroxyl group in the alpha position to form the 100 times more active form of vitamin D (1, 25 dihydroxycholecalciferol) <sup>2</sup>. The macula densa are modified cells in the DCT which is in contact with the afferent arteriole forming juxtaglomerular apparatus. The low pressure in the afferent arteriole in hypotensive states and the low salt content delivered in case of dehydration lead to release of Renin which forms ultimately angiotensin II to cause vasoconstriction and raise blood pressure and aldosterone to prevent stimulate more sodium reabsorption in the subsequent segments of DCT to maintain intravascular volume <sup>3</sup>. Angiotensin II generate local prostaglandins in the kidney leading to dilation of the afferent arteriole and

constriction of the efferent one leading to more hydrostatic pressure in the glomerulus to maintain glomerular filtration rate and clearance of wastes of metabolism. Such changes

are referred to as autoregulation and are intended to adjust blood pressure, sodium water content under physiological states i.e. few hours fast <sup>4</sup>.

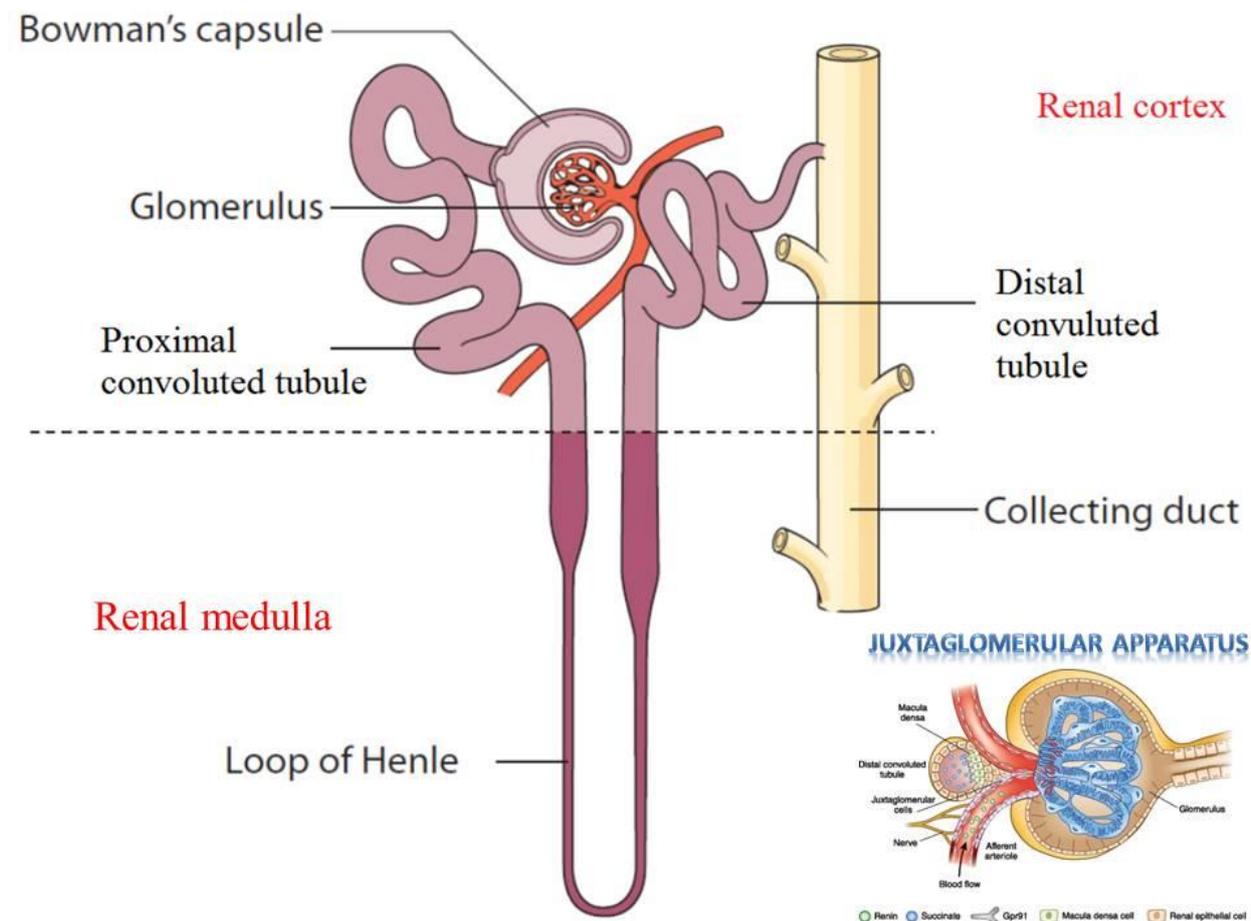


Figure 1: Diagram of the nephron segments and its juxtaglomerular apparatus

## RENAL FAILURE

Renal failure (RF) implies failure of function of; (a) glomeruli, (b) tubules, and interstitium. However, (a) interstitial failure can be corrected by erythropoietin and calcium/active forms of vitamin D, (b) tubular defects are rarely life threatening except for severe Bartter's syndrome and distal RTA. On the other hand, the only life threatening failure is the glomerular one with: (a) uremic intoxication, (b) water and salt retention with fluid overload, and (c) potassium accumulation with cardiac arrest. Hence, extent of glomerular failure which is measured by decrement in glomerular filtration rate (GFR) was used to express kidney failure. GFR is the amount of fluid filtered in 1 minute. Normally it is 80-120 ml/min. Since the average is 100 ml/min; changes in function can be expressed as changes in 100%.

## ASSESSMENT OF KIDNEY FUNCTION

True estimate of GFR is done by a substance that is neither secreted nor excreted. The latter apply to inulin and isothalamate. The Inulin and PAH clearance requires injection of those substances then 24 hour urine collection which is not practical for humans <sup>5</sup>. GFR can be assessed using chromium-51 and technetium-99 nuclear scans yet it is available only in specialized centers <sup>6</sup>. In normal

conditions; serum creatinine is produced from the muscle at a steady state. It can be easily measured and it is the most practical way to test kidney function. However, since secreted by the kidney tubules, its relationship with kidney function is not linear <sup>7</sup>. In early failure, serum creatinine does not rise above higher limit of normal unless 50% of kidney function is lost. Such rise, in urea and creatinine (nitrogenous products) in blood, is referred to as azotemia.

## AUTOREGULATION IN HEALTH AND DISEASE

Due to autoregulation; any decrease in kidney function is compensated by an increment of 10%. Hence, when stages of kidney failure were described; stage 3 (azotemia) starts if GFR is  $\leq 60\%$  rather than the actual 50% of kidney failure. On the other hand; stage 4 if GFR  $< 30\%$  defines a stage where the use of ACEI/ARB is contraindicated. Those drugs abolish the 10% hyperfiltration (due to efferent arteriolar constriction) and bring patients to stage 5 which  $< 15\%$ . The latter stage is uremic i.e. symptomatic renal failure and hence indicates dialysis. Similar effect if NSAID abolish the dilatation of afferent arteriole by blocking prostacyclins induced by angiotensin II activation.

## DEFINITIONS OF RF

To avoid using follow up measurements of creatinine clearance and the increment of serum creatinine above normal range; changes in the patient's own serum creatinine can be used to detect an acute change in function. Hence, an increment  $> 26 \mu\text{mol/L}$  over 48 hours or  $> 50\%$  decrease CrCl was labeled as an Acute RF or acute kidney injury (AKI) [8].

## ETIOLOGY OF AKI

The causes of AKI can be divided into three categories (Fig. 2). They include; prerenal (decreased perfusion), intrinsic renal (caused by a damage to the kidney itself), and postrenal (caused by obstruction to urine excretion).

### "Causes of acute kidney injury"

#### Pre-renal

##### 1- External fluid loss:

bleeding, excessive diuresis & losses from gut or skin

##### 2- Translocation of intravascular volume:

Pancreatitis, Peritonitis, ileus, nephrotic crisis

##### 3- Poor cardiac output:

LV dysfunction, valvular and pericardial disease

##### 4- Decreased peripheral vascular resistance:

sepsis & drugs

##### 5- Excessive local vasoconstriction:

Hypercalcemia & hepatorenal syndrome

##### 6- Blocking of dilating prostaglandins:

NSAID in CRF or ACEI/ARB in renovascular or stage 4,5 RF

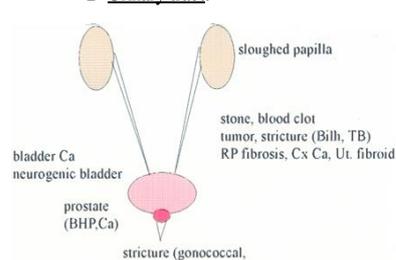
Both in: decrease effective intravascular volume (pre-renal states)

#### Intrinsic

#### Post-renal (obstruction)

1- Tubular: crystals & myeloma casts

2- Urinary tract:



#### Tubulointerstitial

##### A- Acute tubular necrosis:

A- Ischemic ATN: (severe & prolonged pre-renal state)

B- Nephrotoxic ATN:

Drugs: aminoglycosides, amphotericin B, Cis-platinum

Chlorinated organic solvents:

Ethylene glycol, carbon tetra, herbicides

Heavy metals:

Organic lead & mercury

Radioccontrast media:

Cell-lysis proteins:

Rhabdomyolysis & hemolysis

##### B- Acute interstitial nephritis:

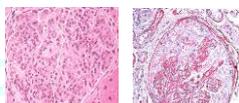
Drugs, infections & autoimmune

#### Glomerular

1- Proliferative & Crescentic GN

2- If systemic manifestations:

SLE & vasculitis



#### Vascular

##### A- Large vessel:

I- Bilateral renal artery

(stenosis, thrombosis, emboli)

II- Bilateral renal vein thrombosis

##### B- Small vessel:

1- Vasculitis (PAN)

2- Malignant hypertension

3- Scleroderma

4- Cholesterol atheroembolism

Figure 2: Algorithm for diagnosis of the etiology of acute kidney injury

## EPIDEMIOLOGICAL PROFILE OF AKI

AKI is a major world-wide health problem with its high incidence rate among hospitalized patients, mortality rate and cost of treatment. In our area, a prospective study conducted over 18 months disclosed features of its epidemiological profile [9]. The calculated annual incidence of AKI was 14.7 per 100,000 populations. Cases of community acquired AKI were double the hospital-acquired one. Sepsis, urinary tract obstruction, volume depletion and glomerular diseases were the most frequent causes of community acquired AKI while drug-induced, volume depletion and sepsis dominated the hospital one. The prognosis of AKI depended on 2 major factors; (a) type of etiological insult and the presence of predisposing co-morbid conditions. Multiple insults, though common, did not affect mortality rate. The overall mortality rate was only 14% yet sepsis-induced AKI had 36% cause-specific mortality.

## MANAGEMENT OF AKI

### Management indicates knowledge on:

(a) Renal derangement, (b) AKI and its etiology, (c) chronic RF and its previous stage, (d) co-morbid condition, (d) interaction between diagnostic tests, drug therapy, RF and co-morbid conditions. Integration of clinical data as well as laboratory, radiological and serological tests are essential for diagnosis and management.

### Diagnosis of renal derangement:

Practically; 3 elements should be tested to assess for RF; (a) serum creatinine, (b) urine routine and microscopy, and (c) kidneys ultrasound. A single abnormality indicates disease. Urine tests for osmolality and sodium are not useful. Urinary sodium is high if associated with chronic RF. Urine proteinuria  $> 2 \text{ g/day}$  indicates glomerular etiology and absence rule it out.

### Diagnosis of setting of AKI:

If abnormal RF; diagnosis of AKI, chronic RF or AKI on top of chronic disease should be defined as shown in the algorithm in (Figure 1). Aids in diagnosis include:

- 1- History & physical examination.
- 2- Ultrasound for kidney size & shape since any abnormal size or shape indicates chronicity except for hydronephrosis.
- 3- Renal osteodystrophy (not hypocalcemia/hyperphosphatemia or high PTH since may develop within 2 weeks.
- 4- Kidney biopsy if needed especially in interstitial nephritis, glomerular disease and vasculitis.

### Management of patient with renal failure:

As shown in Figure 1; return to normal can be established with treatment of acute RF. Despite the presence of chronic disease viz. diabetic glomerulosclerosis; treatment of acute insult such as dehydration from uncontrolled hyperglycemia, sepsis, obstruction by a papillary necrosis or an incidental drug side-effect, is rewarding and improves stage of RF. Moreover, early intervention, in the initiation phase, is essential to clear the insult, decrease the need for supportive dialysis and prevent the complications. The latter complications can be associated with RF, worsening of comorbid conditions, dialysis technique and kidney loss. The latter phenomenon is associated with delay in diagnosis of autoimmune diseases (glomerulonephritis and vasculitis) and/or inadequate therapy<sup>10</sup>. Three months is the limited time factor in correction of acute RF and establishment of a chronic damage<sup>11</sup>. Uremic patients with acute RF are supported with dialysis till correction of the acute component. If did not improve; will need renal replacement therapy (RRT) in the form of maintenance dialysis or future kidney transplantation if fit. If by the end of 3 months; stage 4 RF; patients should have dialysis access (preferably fistula) and transplant work up.

### Dialytic support:

Initially, hemodialysis was provided for those with traumatic rhabdomyolysis during World War II by William Kolff<sup>12</sup>. Subsequently, the technique has improved with smaller filters, better machines that resulted in less dialysis duration and better patient's safety. Initially, peritoneal dialysis was preferred for uremic patients with unstable cardiovascular status due to sepsis with/without hypotension and those with cardiac disease including myocardial infarctions<sup>13</sup>. The technique of blood purification has improved dramatically in the past 20 years with the introduction of high-flux filters and continuous veno-venous hemodiafiltration<sup>14</sup>. The latter is a slow yet effective technique, even for unstable patients, and had replaced acute peritoneal therapy. However, it is expensive and needs continuous monitoring which limited it to specialized hospital-based ICU, CCU and renal units<sup>15</sup>.

### Prognosis of acute RF:

Prompt and proper correction of acute pre- and post-renal insults as well as tubulointerstitial disease is rewarding. Unfortunately, and as has been stated previously, kidney survival is limited with maltreated autoimmune and vascular diseases.

**In conclusion;** acute RF is a common condition, frequently encountered in both community practice and hospital inpatients. While it remains a heterologous condition, early diagnosis and prompt establishment of therapy is corner stones in kidney and patients' survival.

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