REVIEW ARTICLE

Update of acute kidney injury: intensive care nephrology

Tsagalis G

Renal Unit, Lefkos Stavros Hospital, Athens, Greece

Abstract

Albeit the considerable progress that has been made both in our understanding of the pathophysiology of acute renal failure (ARF) and in its treatment (continuous renal replacement therapies), the morbidity of this complex syndrome remains unacceptably high. The current review focuses on recent developments concerning the definition of ARF, new strategies for the prevention and pharmacological treatment of specific causes of ARF, dialysis treatment in the intensive care setting and provides an update on critical care issues relevant to the clinical nephrologist. Hippokratia 2011; 15 (Suppl 1): 53-68

Key words: N-galactosamine, renal replacement therapy (RRT), sequential organ failure assessment, intensive care nephrology

Corresponding author: Tsagalis G, 9 Areos str, 15122 Maroussi Attikis, Athens, Greece, Tel: 0030-6942632132, 0030-2108083275, e-mail: tsagalis@otenet.gr

Morbidity in acute kidney injury (AKI or acute renal failure [ARF]) remains high (almost 60%) albeit the considerable progress in our understanding (especially in the molecular level) of the mechanisms that induce and maintain the AKI and the innovations in its therapeutic management. Several reasons can explain this discrepancy: (1) the absence of a unanimously accepted clinical definition of AKI, (2) the failure to predict the severity, to evaluate the development and to assess the response to therapy in AKI that have rendered the development of large multicenter prospective studies problematic, (3) the lack of sensitive markers of kidney injury that could diagnose early the AKI (before serum creatinine rises) and assess its severity both in the initiation, maintenance and recovery phase of kidney injury and (4) the heterogeneity of patients with AKI that makes classification and randomization quite difficult.

To address these problems, a new definition and classification system for AKI has been introduced in medical literature, while research has intensified aiming at new indices for detection of early kidney injury. These new indices must fulfil several criteria: ease of use, early detection of AKI, high sensitivity and specificity, ability to assess the severity and to follow the results of any therapeutic intervention.

The present review provides a detailed analysis on the recent literature for AKI, specifically focusing on:

1. New developments in the definition and the pathophysiology of AKI.
2. Strategies for prevention and pharmaceutical treatment of AKI.
3. Evidence based indications for the treatment of AKI using renal replacement therapies and
4. Intensive care issues relevant to patients with acute and chronic kidney disease.

Definition

ARF is a complex syndrome defined by the loss of renal function during a period that varies between a few hours and several weeks. The decrease in the glomerular filtration rate (GFR) and the increase in serum creatinine and urea levels are the common denominator of this syndrome. Urine output and clinical manifestations vary significantly: hence, urine output may either be normal, reduced or even absent and clinical signs may be subtle or prominent (pulmonary oedema, arrhythmias, pericarditis). This variety in clinical manifestations in AKI has halted the development of a mutually accepted clinical definition of AKI. The introduction of a new definition in medical literature should take under consideration the statistically significant correlation between small changes in kidney function with mortality and cardiovascular morbidity in the AKI setting. Characteristically, following cardiac surgery, a 90% increase in patient mortality in the first 30 days was observed when serum creatinine increased by 0.1 to 0.3 mg/dl compared to patients with a stable creatinine concentration or a reduction of $\geq$ 0.3 mg/dl[1].

The Acute Dialysis Quality Initiative (ADQI) suggested a new definition for AKI based on the severity of kidney injury[2]. According to this definition, kidney injury is classified in 3 levels based on the degree of GFR reduction or the duration and severity of oliguria. At level 1(Risk) GFR is reduced >25% (from baseline GFR) or the urine output (UO) is <0.5ml/kg/hour for >6 but <12 hours. At level 2 (Injury) the GFR reduction is >50% and/or UO is <0.5ml/kg/hour for >12 but <24 hours. At level 3 (Failure) GFR is reduced 75% from baseline and/or UO is <0.3ml/kg/hour for >24 hours or the patients is anuric for >12 hours. As the severity of AKI increases (at each level) the specificity of this classification system increases while the sensitivity is reduced. The next 2 lev-

Table 1: RIFLE criteria for AKI diagnosis.

	Increase in serum creatinine	Urine output
Risk of renal injury	1.5 x baseline creatinine	<0.5 ml/kg/h for >6h but <12h
Injury to the kidney	2 x baseline creatinine	<0.5 ml/kg/h for >12h but <24h
Failure of kidney function	3 x baseline creatinine or serum creatinine ≥ 4 mg/dl	<0.3 ml/kg/h for >24 h or anuria >12 h
Loss of kidney function	Persisting renal failure >4 weeks	
End-stage renal disease	Persisting renal failure >3 months	

els (Loss and End-Stage Disease) reflect the severity of prognosis based on the need for renal replacement therapy (Table 1). More recently, a small change was made to the abovementioned criteria for AKI definition based on the suggestions of the American Society of Nephrology, the International Society of Nephrology, National Kidney Foundation (USA) and the European and American Society of Critical Care. At level 1 (Risk) an absolute increase of serum creatinine ≥0.3mg/dl was added to the definition in order to facilitate early diagnosis of AKI. Moreover levels 4 and 5 have been omitted. Disadvantages of the new definition include variability when correlating serum creatinine and baseline GFR, differences in functional renal reserve and creatinine production rate (the same renal parenchymal injury leading to different serum creatinine levels between patients)[3,4]. Furthermore, the change in serum creatinine lags in time relatively to the onset of kidney injury.

To overcome the problems associated with definitions based on changes in serum creatinine levels, research has focused on the identification of new markers that could assess earlier and more accurately kidney injury. These markers belong in 2 groups: (1) glomerular and (2) tubular. In the 1st group cystatin C (an inhibitor of endogenous cysteine proteinase has several advantages:

• Stable production rate from all nucleated cells.

• Free filtration in renal glomeruli, no reabsorbtion, no secretion, no catabolism in renal tubules.

• Early detection of AKI (2 days earlier than the change in serum creatinine-RIFLE) in cases of contrast nephropathy[5,6].

The 2nd group includes markers of tubular function such as KIM-1, NGAL, and IL-18. KIM-1 (Kidney injury molecule) is a transmembrane protein with immunoglobulin and mucus epitopes that is not expressed in normal renal cells. Its production is upregulated in proximal tubular cells following ischemic or nephrotoxic insults[7,8]. Urine excretion of KIM-1 is an early marker of kidney injury.

NGAL (N-galactosamine) is also expressed in proximal tubular cells following ischemic or nephrotoxic insults and measured in urine[9]. In a clinical study of 61 children that had cardiac surgery, NGAL in urine had a sensitivity of 100%, specificity of 98%, a positive predictive value of 95% and a negative predictive value of 100%[10].

Interleucin-18 (IL-18) is a mediator of ischemic AKI. In preliminary studies its excretion in urine is increased in patients with acute tubular necrosis (ATN)[11]. In patients with acute respiratory distress syndrome (ARDS) the IL-18 excretion rate is increased predicting the development of AKI but the sensitivity and specificity were reduced (50 και 75% respectively)[12].

Epidemiology

New epidemiological data are available through PICARD (Program to Improve Care in Acute Renal Disease) that includes patients with AKI hospitalized in intensive care units in 5 academic centres across the United States[13]. Over a period of 31 months, 1243 pateints were evaluated and finally 618 were included in the study. AKI was defined as an increase in serum creatinine of ≥0.5mg/dl, when baseline creatinine was <1.5mg/dl or an increase of ≥1.0mg/dl, when baseline creatinine was ≥1.5mg/dl but <5mg/dl. Mortality reached 37% and 64% of patients required renal replacement therapy. When chronic kidney disease (CKD) was present, mortality was less (31% versus 41%, P=0.03, in patients without CKD), a result that possibly reflects the implementation of prophylactic strategies (e.g increased hydration, avoidance of nephrotoxic medications) aiming at minimizing the risk for aggravation of kidney function in patients with known CKD compared to those without[13,14].

A multinational, multicenter, epidemiological study of 54 centres in 23 nations in North and South America, Europe, Asia and Australia assessed 29.000 patients hospitalized in intensive care[15]. The incidence of AKI over 16 months was 5.7% (1.4%-25.9%) with 58.9% of patients hospitalized for medical and 41.1% for surgical problems.

AKI is very common after cardiac surgery, representing 25.2% of all cases. Overall, hospital mortality was 60.3%, 52% in those patients that required intensive care support and 13.8% from the survivor group required renal replacement therapy after discharge.

Two recent studies provide epidemiologic data for the occurrence of AKI in children and elderly pa-

tients[16,17]. In children ischemia is the commonest cause of AKI (21%), nephrotoxic medications account for 16%, sepsis for 11% while primary kidney disease for 7% of all cases. Survival is relatively better than in adults (70% versus 40%), especially when age is >1 year. The same holds true for children hospitalized in the intensive care unit (survival 60% and 56% if renal replacement therapy was required). In 2/3 (66%) of survivors kidney function returned back to normal, 14% developed CKD and 5% started chronic renal replacement therapy.

In elderly patients, a 3-year observational study that included 325 ασθενείς ≥ 60 years reached the following conclusions:

• Pre-renal AKI in hospitalized patients is responsible for 58% of all AKI cases

• In the community, post-renal causes of AKI are commoner

• Overall mortality in this age group is 54%

• Mortality is higher (59%) when patients develop AKI during hospitalization compared to AKI in the community (41%)

• Increased mortality was observed when concomitant heart disease was present, in patients with cancer, sepsis, neurological or haematological disease and in case with oliguria.

Outcome and prognosis

The outcome of patients with AKI in the intensive care setting remains high, with percentages that vary between 40-90% depending on the patient group studied. Despite the considerable progress in our understanding of pathophysiological mechanisms that are responsible for the initiation and maintenance of AKI, and the new methods of replacement therapy, results remain poor: the increase in the mean age of patients that are hospitalized in intensive care, the use of multiple interventional procedures irrespectively of co-morbidities, differences in AKI definition between centres and quite often late diagnosis of AKI explain at least in part the dim prognosis of patients with AKI[18].

Mortality in patients hospitalized in intensive care units ranges from 10-20%[19] but when AKI is present increases considerably (X4), even after adjustments for severity of underlying disease, demographic factors, proving that AKI is an independent risk factor for increase mortality and morbidity and that patients in ICU die also because of AKI and not just with AKI.

Ferreira et al showed that the number of failing organs (including the kidneys) correlates with mortality in ICU[20]. In a group of patients with sepsis 11% developed AKI; serum creatinine, prior CKD, central venous pressure (CVP) and liver dysfunction were prognostic factors for the occurrence of AKI. Chertow et al studied the risk for the occurrence of AKI and the associated mortality and found that baseline kidney function is inversely related to mortality:

• When serum creatinine was <1mg/dl the risk for the occurrence of AKI was 0.5%

• When serum creatinine was 2-2.9mg/dl the risk increased to 4.9%

• In patients <40 years the risk for AKI (following coronary artery bypass) was 0% while in patients over 80 years reached 1.8%[21].

The role of renal replacement therapy (dose, method) relatively to mortality in the ICU was not assessed for several years. Recently, two large prospective randomized studies assessed the role of different renal replacement treatments and "dialysis doses" in the outcome (mortality) of critically ill patients. The VA/NIH Acute Renal Failure Trial Network (ATN) study is the largest published randomized controlled trial assessing intensity of renal replacement therapy in AKI[22] (Table 2).

The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study, a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and the George Institute for International Health conducted a multicenter, randomized trial to compare the effect of continuous renal replacement therapy delivered at two different levels of intensity, on 90-day mortality among critically ill patients with acute kidney injury[23]. Critically ill adults with acute kidney injury were randomly assigned to continuous renal replacement therapy in the form of postdilution continuous venovenous hemodiafiltration with an effluent flow of either 40 ml per kilogram of body weight per hour (higher intensity) or 25 ml per kilogram per hour (lower intensity). The primary outcome measure

Table 2: Results of the VA/NIH Acute Renal Failure Trial Network (ATN) study.

INTENSIVE DIALYSIS GROUP				NON INTENSIVE DIALYSIS GROUP			
IHD/SLED (STABLE)	CVVHDF (UNSTABLE)	60-d mortality	Renal recovery	IHD/SLED (STABLE)	CVVHDF (UNSTABLE)	60-d mortality	Renal recovery
6/WEEK	CONTINUOUS	53.6%	SAME	3/WEEK	CONTINUOUS	51.5%	SAME
Kt/V >1.2 per treatment,	21 hours treatment replacement fluid 35 ml/kg/hour			Kt/V >1.2 per treatment	21 hours treatment, replacement fluid 20 ml/kg/hour		

was death within 90 days after randomization. Of the 1508 enrolled patients, 747 were randomly assigned to higher-intensity therapy, and 761 to lower-intensity therapy with continuous venovenous hemodiafiltration.

Data on primary outcomes were available for 1464 patients (97.1%): 721 in the higher-intensity group and 743 in the lower-intensity group. The two study groups had similar baseline characteristics and received the study treatment for an average of 6.3 and 5.9 days, respectively (p= 0.35). At 90 days after randomization, 322 deaths had occurred in the higher-intensity group and 332 deaths in the lower-intensity group, for a mortality of 44.7% in each group (odds ratio, 1.00; 95% confidence interval [CI], 0.81 to 1.23; p= 0.99). At 90 days, 6.8% of survivors in the higher-intensity group (27 of 399), as compared with 4.4% of survivors in the lower-intensity group (18 of 411), were still receiving renal-replacement therapy (odds ratio, 1.59; 95% CI, 0.86 to 2.92; p= 0.14). The results of the RENAL study confirm the results of the VA/NIH Acute Renal Failure Trial Network (ATN) study according to which, in critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal replacement therapy does not reduce mortality at 90 days.

The majority of patients that survive after hospitalization in the ICU have the same mortality thereafter irrespectively of the presence of AKI. Preservation of kidney function depends (following discharge from the ICU) on the cause of kidney injury and renal reserve (Table 3).

Table 3: Renal function concerning the cause of AKI.

Renal function (5 years after AKI)	Cause of AKI
Good	Henoch-Schonlein purpura
⇓	Tubulointerstitial nephritis
⇓	Post infectious nephritis
⇓	Acute tubular necrosis
⇓	Diffuse proliferative lupus nephritis
⇓	Membranoproliferative glomerulonephritis
⇓	TTP/HUS
⇓	Extracapillary glomerulonephritis
Bad	Acute cortical necrosis

Prognostic systems for AKI in the ICU

The APACHE II is the most well known system that provides prognostic information for ICU patients. It includes 3 different elements: a physiology scoring system that assesses acute changes in physiology, an adjustment for age scoring system and a chronic health adjustment score. The APACHE II doesn't include specific criteria for kidney function and moreover uses the Glasgow coma index in patients on mechanical ventilatory support. For these reasons it has been replaced by the APACHE III[24,25]. The Sequential Organ Failure Assessment (SOFA system) has been developed as an alternative for understanding the evolution of injury and the interrelations of failing organs (Table 4).

In a recent study, according to the SOFA system, oliguric patients, those with>3 failing organs and the coexistence of heart failure and renal dysfunctions predicted a high morbidity[26]. The sensitivity and specificity of the PICARD study model was greater than the SOFA model but the complexity of the former renders its use problematic. A mathematical equation, based on the SOFA system gives the log odds death (Table 5).

The accuracy of existing predicting models is shown in table 6.

The ROC is the graphic design of the likelihood ratio (LR=sensitivity/false positive). The closer (the area under the ROC) to 1.0 the higher the sensitivity and specificity of the method; on the contrary, when the area under the ROC is around 0.5, the method doesn't have any prognostic value.

Pathophysiology of AKI

Acute tubular necrosis (ATN) is the commonest diagnosis in AKI in hospitalized and especially in critically ill patients. In the present review, we will focus only in new data concerning only the pathophysiology of ATN.

The principal contributing factors for the development of ATN are:

- Ischemia
- Nephrotoxic medications/substances
- Sepsis
- Mechanical ventilation

Experiments in rats[27] have showed that usually the presence of one risk factor is not sufficient for the occurrence of ATN. In humans, the same holds true especially in hospitalized and critically ill patients; in these cases a variety of potentially "nephrotoxic" factors is usually present.

The pathophysiology of ischemic ATN comprises 5 distinct phases:

(1) Prerenal, (2) initiation, (3) augmentation, (4) maintenance and (5) repair of injury.

During the prerenal phase, the compromised renal blood flow causes vasoconstriction, activation of the renin-angiotensin-aldosterone system (RAAS), increases endothelin production while at the same time prostacyclin PGI_2 and nitric oxide (NO) are reduced resulting in a reduction in oxygen delivery to renal cells. The initiation phase is characterized by the loss of the brush border of proximal tubular epithelial cells, the destruction of the cytoskeleton, the tight intracellular junctions and the redistribution of transport proteins (Na-K-ATPase pumps) that are translocated from the basolateral to the apical surface resulting in the loss

Table 4: The Sequential Organ Failure Assessment (SOFA) system.

Parameters	Points 0	Points 1	Points 2	Points 3	Points 4
Respiratory PaO_2/FiO_2 (mmHg)	>400	≤400	≤300	≤200	≤100
Coagulation Platelets($x10^3/\mu L$)	>150	≤150	≤100	≤50	≤20
Liver (bilirubin mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular (Hypotension)	Nil	MAP<70 mmHg, no inotropes	Dopamine <5 or dobutamine	Dopamine >5, epinephrine ≤0.1, norepinephrine ≤0.1	Dopamine >15, epinephrine>0.1, norepinephrine>0.11
Central nervous system (Glasgow coma scale)	15	13-14	10-12	6-9	<6
Kidney function (Serum Creatinine [mg/dl] or urine output [ml/day]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 <500	≥5.0 <200

FiO_2: fraction of inspired oxygen, PaO_2: pressure of arterial O_2, MAP: mean arterial pressure. Drug doses are in mg/kg/min

Table 5: Mathematical equation (based on SOFA system) for log odds of death.

Log odds death= 0.170(age) + 0.8605 (male) +0.0144 (serum BUN) – 0.3309 (serum creatinine)+1.2242 (haematological abnormality) +1.183 (liver failure) +0.9637 (respiratory failure) +0.0119 (heart rate)-0.4432 x log (urine output)-0.7207

of cellular polarity[27,28]. The adhesion molecules that anchor epithelial cells to the basement membrane are also redistributed leading to the detachment of tubular cells and to the formation of casts that obstruct the tubular lumen[29]. Tubular cell loss leads to a reduction in glomerular filtration due to the increased pressure in renal tubules and the backflow of the glomerular filtrate caused by the denudation of basement membranes. The augmentation and maintenance phases are characterized by the development of microvascular changes especially in the renal medulla. The renal medulla is particularly sensitive to changes in blood flow due to reduced oxygenation and increased energy demands (urine concentration and NaCl reabsorption in the thick ascend-

Table 6: Accuracy of existing predicting models. in AKI.

Prediction models		**Area under the ROC**
General prediction models	APACHE II APACHE III SAPS II SOFA	0.634 0.756 0.766 0.756
Prediction models (specific for the kidney)	Paganini (CCF) Liano Schaefer PICARD	0.718 0.630 0.650 0.832

APACHE: Acute Physiology and Chronic Health Evaluation, CCF:Cleveland Clinic Foundation, PICARD:Project to Improve Care in Acute Renal Disease, ROC: Receiver operation curve, SAPS: Simplified acute physiology Score, SOFA: Sequential Organ Failure Assessment.

ing limb of Henle's loop take place in the renal medulla and require significant amounts of energy[30,31]. Moreover, the disruption of the balance between vasodilatory (NO, prostacyclin) and vasoconstrictive substances (endothelin, thromboxane) in favour of the latter activates the coagulation cascade and the adhesion of leucocytes mainly in the corticomedullary junction and the renal cortex. Inflammatory cells that infiltrate the renal interstitium further compromise blood flow and degrade the extracellular matrix by releasing enzymes and reactive oxygen species[32,33].

The repair phase includes the death and desquamation of tubular epithelial cells and the colonization of the injured area by dedifferentiated epithelial cells that finall differentiate in tubular cells. The dedifferentiated cells are endogenous renal cells that can potentially repair the injury under the influence of growth factors[34] and bone marrow cells that migrate to the injured kidney to facilitate the repair process through modifications in the production of inflammatory cytokines[35-37].

Specific causes of AKI

Contrast nephropathy (CN) is one of the commonest causes of AKI in hospitalized patients (10% of total cases). 24 to 48 hours after the administration of intravenous iodinated contrast, serum creatinine begins to rise reaching a plateau in 3-5 days while in 7-10 days returns back to baseline levels. Predisposing factors for the occurrence of CN are a history of diabetes, congestive heart failure, plasma cell disorders and the contrast itself. First and second generation contrasts had increased osmolality (1400-1800 mosm/kg and 500-850 mosm/kg respectively) relatively to plasma while the third generation contrasts are iso-osmolal (approximately 290 mosm/kg). Recent studies in patients that had coronary angiography and balloon angioplasty showed that:

- Age >75 years
- Baseline creatinine cleareance <60ml/min/1.73m^2
- Intraaortic pump use
- Coronary catheterization in an emergency setting
- Diabetes mellitus
- Congestive heart failure
- Peripheral vascular disease and
- Volume of adminestered contrast >260 ή 300 ml

are risk factors for the occurrence of CN[38,39].

Marenzi et al concluded that CN prolongs hospitalization from 8±3 days to 13±7 days and increases in-hospital mortality from 0.6 to 31%[40].

Prevention of Contrast Nephropathy

Contrast nephropathy is one of the few cases in which AKI can be prevented if all the necessary measures are undertaken. An analysis of the studies published in the last decade provides useful strategies for the prevention of CN:

1. The use of isotonic sodium bicarbonate solution reduced more the risk for the occurrence of CN than isotonic sodium chloride (0.9% NaCl) when administered 1 hour prior to contrast administration with an infusion rate of 3ml/kg and 6 hours after the procedure with an infusion rate of 1ml/kg. This study had a small statistical power, was not multicenter and the fluid infusion was not the same as the usual protocol (1ml/kg/h for 12 hours before and after contrast administration)[41].

2. N-acetylcysteine (NAC) was once regarded as a promising agent for the prevention of CN due to its ability to deactivate the reactive oxygen species. From the 5 recent studies (in the last 5 years) only one showed a positive result[42] for NAC while according to the other 4 NAC does not offer an advantage in CN prevention.

3. Four meta-analyses for theophylline or aminophyllin that compete with the vasoconstrictive substance adenosine didn't offer significant protection for the occurrence of CN[43-45].

Therefore, the prevention of CN continues to be based on the following principles:

- Identification of high risk patients
- Hydration with either isotonic saline or isotonic sodium bicarbonate
- Discontinuation of all potentially nephrotoxic medications (especially non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors)
- Use of 3rd generation contrasts (low osmolality), never exceeding 260 ml
- Given the low cost and the absence of toxicity NAC can be used as an additional measure in high risk patients.

AKI after cardiac surgery

Cardiac surgery (CS) is a common cause of in- hospital AKI. The incidence of AKI varies from 7.7% to 42 % in patients with normal baseline renal function. Mortality after cardiac surgery increases substantially when AKI is severe enough to require initiation of renal replacement therapy. Mangano et al estimated that mortality after cardiac surgery was 0.9% in patients without CKD reaching 19% and 63% when CKD was present and renal replacement therapy was required respectively[46].

The presence of CKD, diabetes mellitus, congestive heart failure, age >70 years and cardiopulmonary bypass (with artificial perfusion) >3 hours are risk factors for the occurrence of AKI. The risk increases respectively to the duration and severity of surgery: aortic valve and coronary artery by-pass grafting (CABG) > valve repair or reoperation-CABG alone> 1st CABG[47]. Concerning the off-pump coronary artery bypass surgery (OPCAB) and the occurrence of AKI, a recent review and meta-analysis showed conflicting results. So far, 22 studies (6 randomized controlled trials-RCTs and 16 observational studies) comprising 27,806 patients have addressed this issue. The pooled effect from both study cohorts showed a significant reduction in overall AKI (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.43 to 0.76; p for effect < 0.001; I(2) = 67%; p for heterogeneity < 0.001) and AKI requiring renal replacement therapy (RRT) (OR, 0.55; 95% CI, 0.43 to 0.71; p for effect < 0.001; I(2) =

0%; p for heterogeneity = 0.5) in the OPCAB group compared with the CAB group. In RCTs, overall AKI was significantly reduced in the OPCAB group (OR, 0.27; 95% CI, 0.13 to 0.54); however, no statistically significant difference was noted in AKI requiring RRT (OR, 0.31; 95% CI, 0.06 to 1.59). In the observational cohort, both overall AKI (OR, 0.61; 95% CI, 0.45 to 0.81) and AKI requiring RRT (OR, 0.54; 95% CI, 0.40 to 0.73) were significantly less in the OPCAB group. RCTs were noted to be underpowered and biased toward recruiting low-risk patients. The lack of uniform AKI definition in the included studies, the heterogeneity for overall AKI outcome and the absence of adequately powered RCTs to detect a difference in AKI requiring RRT do not permit definitive conclusions and emphasize the need for future studies that should apply a standard definition of AKI and target a high-risk population[48,49].

Prevention of AKI after Cardiac surgery

Until now, there are no major clinical trials proving that a specific preventive strategy reduces the risk for AKI after CS

Experimental data in animals[50] suggest that the renal blood flow during cardiopulmonary bypass (CAB) depends on renal perfusion pressure. Under these circumstances the autoregulation of renal blood flow is lost and the increase in mean arterial pressure (MAP) with inotropes doesn't increase renal perfusion when the pump flow is low[51]. On the contrary, when the pump flow is low, an increase in MAP can increase renal perfusion[52,53].

Drug therapy for the prevention of AK after Cardiac surgery

Two RCTs showed that the α_2 adrenergic agonist clonidine improved creatinine clearance and was associated with greater hemodynamic stability after CAB surgery in patients with normal renal function[54, 55].

Diuretic use as a preventive measure is associated with deterioration in kidney function and therefore should be avoided[56].

The use of atrial natriuretic peptide (ANP) reduces the need for dialysis or the risk of death compared to placebo[57].

Another study[58] compared the use of low doses of ANP to the use of furosemide (aiming at prevention of AKI after CAB surgery) . The results are shown in Table 7.

Although furosemide increases urine output and reduces O_2 consumption more than ANP, it decreases GFR and the filtration fraction and therefore is considered inferior to ANP.

Dopamine doesn't prevent AKI –even when renal doses are used- and moreover increases the risk for atrial fibrillation/atrial flutter when used after CAB surgery[59].

Fenoldopam is a selective agonist of dopamine receptors (type I) without a systemic action in α- and β- receptors. Until now, results remain conflicting[60,61].

AKI in patients with HIV/AIDS

The commonest causes of AKI in patients with HIV/AIDS are prerenal azotemia and ATN secondary to opportunistic infections or medication use, while thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS), rhabdomyolysis and acute interstitial nephritis are also encountered quite often in these patients[62]. The use of highly active antiretroviral therapy (HAART) that includes 2 reverse transcriptase inhibitors and a protease inhibitor or alternatively 3 reverse transcriptase inhibitors has changed the survival of patients with HIV infection; in medical literature there are even reports that correlate HAART with improvement of HIV nephropathy. Nevertheless, during the last years the use of HAART has increased nephrotoxicity from antiretroviral medication:

• Indinavir is a protease inhibitor that causes nephrolithiasis, crystal nephropathy, ATN and interstitial nephritis[62].

• Ritinavir, a protease inhibitor has been associated with the occurrence of ATN

• Tenofovir and adefovir are reverse transcriptase inhibitors while cidofovir is a nucleotide analogue used for the treatment of cytomegalovirus infection. These medications are eliminated via tubular secretion in the proximal tubule and can result in tubular dysfunction and Fanconi syndrome[62].

• The nucleoside inhibitors of reverse transcriptase (didanoside, lamivudine and stavudine) can also result in kidney injury for unknown reasons. In rare cases they can cause mitochondrial injury with concomitant lactic acidosis and ATN.

Rhabdomyolysis

Although ATN secondary to rhabdomyolysis was initially described following severe and extensive traumatic injury, currently, the majority of case are attributed to non-traumatic causes:

Table 7: Low dose ANP versus furosemide for prevention of AKI after CAB surgery.

	Urine output	Tubular reabsorption of Na	O_2 consumption	GFR	Filtration fraction	Fractional excretion of Na
ANP (20-50 ng/kg/min)	Increase	Decrease 9%	Increase 26%	Increase	Increase	Increase
Furosemide (0.5mg/kg/)/h	Increase x10	Decrease 28%	Decrease 23%	Decraese 12%	Decrease 7%	Increase x 15

• Passive muscle compression due to immobilization (crush syndrome)

• Rhabdomyolysis caused by medication (statins, zidovudine, ephedrine)

• Alcohol abuse

• Seizures

• Insect bite

The prevalence of drug induced rhabdomyolysis increases. Vigorous exercise combined to statin use can result in rhabdomyolysis[63].

Fernandez et al and Sharp et al examined in 2 separate studies predictive factors for AKI secondary to rhabdomyolysis[64,65]. They concluded that baseline serum creatinine (≥1.7mg/dl and ≥1.5mg/dl respectively) and maximum value of CPK during hospitalization were associated with the occurrence of AKI and sustained kidney failure.

Prevention

The Bingol earthquake in south-eastern Turkey on 1/5/2003 offered a unique opportunity for examining the role of early and aggressive hydration to prevent the development of AKI caused by rhabdomyolysis. The therapeutic protocol that was used (even before removal of the victim from the ruins) included the following:

1. Infusion of 1L/hour of isotonic saline

2. Upon arrival to the hospital the fluid regimen was changed: 50 mmol of bicarbonate were added to every litre of hypotonic sodium chloride solution

3. When diuresis was >20 ml/hour, 50 ml of mannitol solution 20% were added.

The results were impressive: 14 of 16 victims did not require renal replacement therapy although CPK>20.000 U/L in 60% of victims. In all 4 patients that required dialysis, the lag time between rescue and initiation of therapy was significantly longer (9.3±1.7 hours versus 3.7±3.3 hours in those that did not require dialysis)[66].

The role of mannitol and bicarbonate has not been completely clarified yet. In a recent study of >1750 patients admitted in the ICU for trauma, the need for dialysis, the occurrence of AKI and overall mortality didn't differ between the group that received bicarbonate and mannitol and the group treated only with hydration[67]. Based on these results, the early and aggressive infusion of isotonic saline reduces the risk and severity of AKI and the need for initiation of renal replacement therapy.

AKI in oncology

As in other case of AKI, the cause can be divided in pre-renal, renal and post-renal.

Vomiting and reduced fluid intake are the commonest cause of pre-renal AKI in oncology patients while prostate, bladder cancer and gynaecological cancers are responsible for obstructive nephropathy. Renal causes can further be classified in 4 groups:

• ATN due to medication use (cisplatin, ifosfamide, interleukin-2) or sepsis

• TTP/HUS after stem cell transplantation

• Infiltration of the renal parenchyma from cancer cells (leukemia, lymphoma, myeloma)

• Intratubular obstruction (cast nephropathy-multiple myeloma, tumor lysis syndrome, methotrexate)

Cisplatin and ifosfamide are potentially nephrotoxic and IL-2 increases capillary permeability and vasodilation resulting in a clinical syndrome reminiscent of sepsis.

The tumor lysis syndrome (TLS) is characterized by severe electrolyte changes (hyperkalemia, hyperphosphatemia, hyperurichemia and metabolic acidosis) as a result of massive cell destruction of the tumour following chemotherapy, irradiation or initiation of steroid treatment in lymphoproliferative disease. The increased uric acid in an acid environment (urine) leads to the precipitation of uric acid crystals in renal tubules and the development of AKI. A urine uric acid/ urine creatinine ratio >1 is useful for the diagnosis of uric acid nephropathy while a value of <0.6 suggests that uric acid is not the cause of AKI. For the prevention of uric acid nephropathy, both general and specific measures should be undertaken:

• General measures include hydration and urine alkalinisation. The latter reduces the risk for uric acid nephropathy but increases the risk for calcium phosphate deposition especially if hyperphosphatemia is present.

• Specific measures include the administration of allopurinol that inhibits xanthine oxidase and reduces uric acid production. The disadvantage of allopurinol is that xanthine is less soluble than uric acid and can be theoretically deposited in renal tubules causing AKI. Rasburicase is the recombinant form of uric acid oxidase (uricase) whose use was abandoned due to the increased frequency of anaphylactic reactions. Rasburicase converts uric acid in allantoin and reduces its levels considerably 4 hours after administration without requiring urine alkalinization.

AKI secondary to medication use

The use of multiple medications in an aging population has increased the prevalence of AKI especially in elderly patients for the following reasons:

• A reduced GFR results in accumulation of the drug and/or its metabolites in the body

• Alterations in liver metabolism can lead to prolongation of the drug half-life

• The total body water is reduced in elderly patients; this changes the distribution volume of several medications

Non-steroidal anti-inflammatory drugs (NSAIDs)

All NSAIDs [both selective inhibitors of cycloxygenase 2 (COX-2) and non-selective inhibitors of COX-1 and COX-2 that inhibit the production of vasodialtory prostaglandins that antagonize the constriction of the efferent arteriole by angiotensin-II, can result in AKI specially when dehydration or CKD is present. In a recent study in the United Kingdom, both short and long term

use of NSAIDs is associated with an increased risk (3-4 times higher) for AKI in patients with a history of: heart failure, diabetes mellitus, hospitalization during the last year, diuretic use, calcium channel blocker use while the use of angiotensin converting enzyme inhibitors (ACEIs) was not associated with an increased risk for AKI[68].

A recent case series of 5 patients that were receiving NSAIDs showed that selective COX-2 inhibitors cause pre-renal azotemia[69].

In conclusion both selective and non-selective NSAIDs are associated with the occurrence of AKI especially in elderly patients with a reduced effective circulating blood volume (heart failure, true hypovolemia secondary to diuretic use or gastrointestinal losses).

Anti-viral medications

Acyclovir and indinavir can cause crystal nephropathy. Increased dosing, dehydration and the presence of CKD are risk factors for AKI. Especially for acyclovir, the rate of intravenous administration is important for the development of AKI. Although indinavir cause crystalluria in 20%, only 0.5% of patients require drug cessation[70]. Good hydration (2-3 L/day) reduces the risk of crystalluria from indinavir.

Propofol

Propofol is used for induction and maintenance of sedation; when used continuously for (>48 hours) in doses that overcome 5 mg/kg/hour in combination with catecholamines and/or steroids in patients with an acute neurological syndrome or inflammatory disease complicated with severe infection or sepsis can lead to the development of a syndrome characterized by myocardial damage, metabolic acidosis and rhabdomyolysis with AKI[71].

Colistin

The antibiotic colistin belongs to the polymyxin group of antibiotics and is used in multiresistant Gram negative infections especially in the ICU. Due to the relatively narrow therapeutic window, dosing should not exceed 2-5 mg/kg/day and its use should be restricted only in case with multiresistant strains[72].

AKI in rare cases

Severe acute respiratory distress syndrome (SARS)

The SARS is a respiratory disease in humans which is caused by the SARS coronavirus (bats are the natural reservoir of this virus)[73,74]. This syndrome became well known in the medical community and in the general public due to a one near pandemic that started in the Guandong province of China in November 2002 to rapidly infect individuals in 37 countries. Finally it was contained 8 months later (July 2003) after causing 900 deaths.

The SARS is diagnosed on the basis of the following criteria according to the World Health Organization (WHO):

- Fever >38^{0}C
- Cough or shortness of breath
- History of close contact with an individual diagnosed with SARS or a recent journey in an area where SARS had occurred in the last 10 days before the onset of the disease

The characteristics of AKI in patients with SARS have been described in a series of 544 patients that were hospitalized in Hong Kong in 2003[75]. AKI occurred in 6.7% of these patients, 20 days (mean time) after the onset of the disease and 28% of them were treated with dialysis (11% with continuous hemofiltration and 17% with peritoneal dialysis). The rest (72%) developed AKI in the setting of multiple organ dysfunction syndrome (MODS). Mortality was 91.7% in patients with AKI versus 8.8% in patients with normal renal function. Renal biopsy revealed ATN that was attributed to multiorgan failure and not the virus itself since viral particles were not identified in the renal parenchyma when examined with electron microscopy.

AKI following snake bite

The WHO has estimated that annually 2.500.000 poisonous snake bites are reported causing 125.000 deaths. In recent medical literature, 3 case studies deal with AKI following snake bites:

- In the 1st study a 12-year old boy developed haemolytic anaemia, thrombocytopenia and AKI 4 days after a snake bite (possibly Echis carinatus) in India. The patient was treated with multivalent antisnake serum, antibiotics, plasma transfusion, platelets and dialysis and survived with an impaired renal function[76]. The venom acts by activation of the coagulation factor X resulting in induction of disseminated intravascular coagulation.
- The 2nd study involved the Sahara horned vipers (Cerastes cerastes). Although this type of venom usually causes only local inflammation without systemic manifestations, the authors reported the occurrence of microangiopathic haemolytic anaemia, thrombocytopenia and AKI in 2 patients[77].
- In the 3rd study, data from 100 Brazilian patients with bites from snakes of the family Crotalus durissus were analyzed. Prognostic factors for the development of AKI (due to rhabdomyolysis) were: lag time>2 hours for the administration of antiserum, age<12 years and CPK>2000U/L[78].

AKI following ingestion of DTT

DTT inhibits the γ-aminobutiric acid receptors in the brain and causes generalized seizures and hyperthermia due to prolonged muscle contraction and rhabdomyolysis[79].

AKI induced by phosphate

Multiple reviews emphasize the need for seriously considering the risks when administering phosphate enemas for bowel cleansing before colonoscopy[80, 81]. The nephropathology laboratoty of Columbia University reported 21 patients between 2000-2004 that developed AKI following bowel cleansing with phosphate enemas.

Renal biopsy revealed nephrasbestosis and the majority of these patients had CKD 16.7 months after the initial insult.

Drug therapy for AKI

Although several attempts have been made -both in clinical and experimental level- aiming at modifying the course of AKI, none of them has succeeded in doing so. Nevertheless, certain medications merit special interest since they are used very often in clinical practice.

Dopamine, – even when "renal doses" (1-3μg/kg/min) are used- failed to prevent the occurrence of AKI and accelerate renal recovery. Several studies that have assessed the efficacy of dopamine either for prevention or for treatment of AKI include cases of contrast nephropathy, aortic aneurysm surgery, orthotopic liver transpalnatation, nephrectomy, renal transplantation and interferon therapy[82]. In a recent, placebo controlled, randomized trial of 328 patients hospitalized in the ICU, a reduced dopamine dose didn't affect renal function, the need for dialysis, the duration of hospitalization in the ICU or in the hospital and overall mortality[83]. Moreover, after cardiac surgery, dopamine can cause tachyarrhythmia, myocardial ischemia, a reduction in intestinal blood flow, hypothyroidism and suppression of T-cells.

Furosemide, the most widely used loop diuretic, has several advantages for prevention and treatment of AKI:

• Causes vasodilation

• Reduces O_2 consumption by inhibiting the NKCC pump in the thick ascending limb of the loop of Henle increases urine flow and reduces tubular obstruction the backflow of glomerular filtrate

Despite these theoretical advantages, in clinical practice furosemide doesn't increase renal recovery, doesn't reduce the need for renal replacement therapy and finally doesn't increase survival[84].

Mannitol is an osmotic diuretic that reduces cell oedema, binds reactive oxygen species, increases the production of renal prostaglandins and causes vasodilation in renal vessels[85]. Apart from its use in solutions used for preservation of allografts, mannitol should not be used in cases of AKI due to important side effects:

• Acute pulmonary oedema

• Increase in plasma osmolality

• AKI (osmotic nephrosis)

The ANP acts by inducing vasodilation of the afferent and constriction of the efferent arteriole; the ensuing increase in glomerular pressure augments GFR. Moreover, the ANP inhibits sodium reabsorption and increase natriuresis. Sackner-Benstein et al analyzed data from 12 randomized studies in which nesiritide (an ANP analogue) was used. In 3 studies, mortality increased in patients treated with nesiritide during the 1st month of treatment[86]. In 5 randomized studies, nesiritide use was associated with a deterioration of renal function[87]. Based on these data, an expert committee suggested that for the time being, nesiritide should only be used in cases of acute decompensated heart failure (ADHR).

Renal replacement therapy in AKI

Renal replacement therapy in AKI differs from that of CKD stage 5, for a variety of reasons:

• Many patients with AKI have hemodynamic instability

• Usually patients are hyper catabolic

• Need nutritional support

• Receive I.V fluids

Until now, there is no unanimity in the answers of 4 core questions concerning renal replacement therapy (RRT) in patients with AKI.

Question 1: When is the right timing for initiation of renal replacement therapy in patients with AKI?

Beyond the general indications for initiation if RRT (volume overload that can't be managed with diuretics, severe hyperkalemia resistant to drug therapy, severe metabolic acidosis and the presence of uremic symptoms), specific recommendations for initiation of RRT in AKI don't exist. Several studies tried to answer the role of "early" versus "late" initiation of RRT in terms of mortality and recovery of renal function:

• In a retrospective study of 100 patients with post-traumatic AKI a survival advantage was found when RRT was started earlier (BUN<60 mg/dl)[88].

• In a small prospective study that compared early versus late initiation of continuous venovenous hemofiltration, no differences in survival were found[89,90].

• Another single centre retrospective study compared early (urine output <100 ml in 8 hours despite the use of furosemide) initiation of continuous hemofiltration versus late initiation (BUN≥84mg/dl, serum creatinine >2.8mg/dl or serum potassium>6 meq/L) in 64 adult patients aftercardiac surgery during 1 year[91]. The early initiation group had reduced mortality (22% versus 43% for late initiation). The limitations of this study were that it was retrospective and non-randomized and therefore "early" initiation can't be recommended on the basis of these data.

Question 2: Which is the best method for RRT in the AKI setting?

The best method for RRT in AKI has not been determined yet. Table 8 summarizes the advantages and disadvantages of each method.

Question 3: What is the optimal dialysis dose in AKI?

As previously mentioned, both the RENAL study and the Acute Renal Failure Trial Study concluded that increased dialysis (either continuous or intermittent) doesn't offer a survival advantage to patients with AKI.

Question 4: What is the optimal method of anticoagulation in patients dialysed for AKI?

Anticoagulation for hemodialysis includes the administration of heparin, either systemically or regionally or the use of citrate (4% or a replacement solution for citrate). The characteristics, disadvantages and advantages of each method are shown in table 9.

Intensive care update for the nephrologist

Mechanical ventilation in Acute Lung Injury (ALI) and in Adult Respiratory Distress Syndrome (ARDS)

The network studying ARDS has proved that low volume ventilation (6ml/kg) increases survival in ARDS, reduces inflammation and IL-6, IL-8 levels[92]. The pathophysiological mechanism that explains the beneficial effect of low volume ventilation is the auto-PEEP (automatic Positive End-Expiratory Pressure) phenomenon. Ventilation with a low tidal volume imposes an increase in respiratory rate resulting in air trapping and the development of auto-PEEP. The latter leads to alveolar recruitement, reduces shunting and improves oxygenation. Therefore, according to the study network for ARDS, in patients with ALI that are on mechanical ventilation or ARDS, low tidal volumes should be used to achieve a level of 30 cm of end-inspiratory pressure while PEEP should be adjusted to attain adequate oxygenation in arterial blood with a non toxic fraction of inspired oxygen.

The effects of mechanical ventilation on renal function

Positive pressure ventilation increases intrathoracic pressure, reduces venous return and especially in volume depleted patients can lead to hypovolemic shock. Furthermore, it activates the sympathetic nervous system, the renin-angiotensin system, causes vasopressin release and inhibits ANP production resulting in vasoconstriction both in the systemic and renal circulation, and a reduction in renal blood flow and GFR. The increased pressure in the inferior vena cava and the renal veins contributes to fluid retention[93] while a diversion of renal blood flow from the cortex to the renal medulla during mechanical ventilation has been reported in some studies[94]. Ranieri et al showed that the use of low volume ventilation combined with an increased end-expiratory pressure causes less lung inflammation and reduces the number of patients with organ failure including the kidney[95].

Sedation in mechanically ventilated patients

The intermittent cessation of sedation in patients that are mechanically ventilated in a daily basis prevents several complications (infections, gastrointestinal complications, venous thrombosis and barotrauma)[96] and reduces post-traumatic stress[97].

Fluid administration in critically ill patients

For the time being it has not been clarified whether the type of fluids adminesterd in ICU patients improve prognosis. The SAFE (Saline versus Albumin Fluid Evaluation) study didn't show any difference in mortality, renal function or the need for renal replacement therapy[98]. Nevertheless, in special cases, the type of fluids seems to be important (e.g in CN isotonic saline is better than hypotonic saline).

Anaemia treatment in the ICU

Blood transfusion in the ICU has been considered standard practice for the majority of intensivists for several years. During the last few years, a series of studies has demonstrated that the implementation of a policy that restricted transfusions reduced mortality in several cases.

Although the restriction of transfusions is beneficial in trauma and septic shock, it is not the case in acute coronary syndromes. According to Bracey et al, the reduction if the transfusion threshold from 9 g/dl to 8 g/dl, neither increases nor reduces the complications after coronary artery by-pass surgery[99]. According to current early goal

Table 8: Advantages and disadvantages of different dialysis methods for severe AKI.

	Hemodialysis	CRRT	PD
Advantages	Effective (K/h) Commonly used Ease of use Short duration	Very effective (K/w) Hemodynamic stability Permits continuous administration of IV fluids Restores acid-base balance continuously Doesn't increase IP	Hemodynamic stability Low cost No need for anticoagulation No need for vascular access Doesn't increase IP
Disadvantages	Less effective Need for anticoagulation Common hypotensive episodes Increases IP Limited ability for fluid removal Doesn't favour nutritional support	Need for continuous anticoagulation Losses from the dialyzer Increased cost	Reduced dialysis Risk for infection Affects respiration Risk for hyperglycemia Peritoneal leak

K/h: clearance per hour, K/w: clearance per week, IP: intracranial pressure, CRRT: Continuous Renal Replacement Therapy, PD: Peritoneal Dialysis.

Table 9: Characteristics, disadvantages and advantages of different anticoagulation methods.

	Heparin	Regional Heparin	4% Citrate	Citrate replacement solution
Administration system	Heparin pre-pump infusion	Heparin pre-pump infusion Protamine sulphate in the venous line of the catheter	Pre- pump (150-200 ml/min) Calcium systemically (8g/L, 40- 45ml/h)	Solution pre-dialyzer: • 145 meq/l Na • 1,106.5 meq/l Cl • 140 meq/l Mg • 1,200 mg/dl glucose Replacement rate: 1.5 L/h Calcium systemically (20g/L, 50-70ml/h)
Monitoring	PTTor ACT (system)	PTT or ACT (system or patient)	ACT (system) Ionized and total Ca (patient) Acid-base balance	ACT (system) Ionized and total calcium (patient)
Method of RRT			CVVHF or CVVHDF	CVVHF
Aims	PTT 70-90 sec ACT 180-220 sec	System: PTT >100 sec (ACT>250 sec) Patient: PTT 45 s		
Advantages	Ease of use and monitoring No electrolyte or acid-base derangements	Regional anticoagulation Efeective No electrolyte or acid-base derangements	No systemic anticoagulation	No systemic anticoagulation Isotonic administration of citrate
Disadvantages	Increased bleeding risk Risk for HIT	Risk for HIT Requires protamine Difficult to monitor	Low ionized calcium Increased anion gap Alkalosis Hypotonic Solution Requires experience	Low ionized calcium Increased anion gap Alkalosis Hypotonic Solution Requires experience

PTT: partial thromboplastin time, ACT: activated clotting time, CVVHDF: Continuous Veno-Venous HemoDiafiltration, CVVHF: Continuous Veno-Venous Hemofiltration. HIT: Heparin Induced Thrombocytopenia, RRT: Renal Replacement Therapy.

therapy in septic shock (Rivers et al), blood transfusions have beneficial effects. In the abovementioned study, the group of patients that was transfused to achieve an Hct>30% (± dobutamine) when the oxygen saturation of mixed venous blood was <70% irrespectively of achieving the other resuscitation goals (MAP=65-90 mmHg, CVP=8-12 mmHg, urine output >0.5 ml/kg/hour) had a reduced hospital mortality (30.5% versus 46.5% in controls).

Concerning the role of erythropoietin in patients hospitalized in the ICU, studies have shown that although it reduced the transfusion needs, it doesn't affect morbidity or mortality[100,101].

Vasopressin in septic shock

Physiology: Vasopressin is synthesized in the hypothalamus, stored in the posterior pituitary and secreted following several triggers such as the increase in plasma osmolality and the reduction of the effective arterial blood volume. Vasopressin acts in the renal collecting tubules via V_2 receptors increasing water reabsorption and in V_1 vascular receptors causing vasoconstriction in the systemic circulation.

In septic shock, vasopressin increases GFR by increasing the MAP and the perfusion pressure of the kidney and by causing vasoconstriction of the efferent arteriole thereby augmenting the filtration fraction[102,103].

Vasopressin increases GFR and urine output more than epinephrine[104,105].

The concerns for causing coronary and cerebral ischemia have not been confirmed so far. As for the risk for mesenteric ischemia, Tsuneyoshi et al found a reduction of lactic acidosis in patients treated with vasopressin[106].

Therefore, taking under consideration the side effects of catecholamines (arrythmias, ischemia), vasopressin has a role in the treatment of patients with septic shock.

Steroids in septic shock

Annane et al, suggested that small glucocorticoid and alatocorticoid doses in patients with septic shock and adrenal failure had beneficial effects[107-109]. In patients with adrenal failure, plasma cortisol remained ≤9μg/dl after ACTH administration. The administration of a low dose hydrocortisone (≤300mg) for ≥ 5 days resulted in a significant decrease in mortality (reduction of the relative risk of death by 18%).

Conclusions

The development of AKI in the ICU increases substantially mortality albeit the considerable progress that has been made during the last years both in terms of understanding its pathophysiology and its management. Most patients die not as a result of uremia but from the complications of concomitant diseases. The new definitions for AKI aiming at an earlier diagnosis of kidney injury before the development of kidney failure combined with improvements in prevention and management are expected to reduce mortality of this complex syndrome.

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