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Recent Trends In The Treatment of Acute Kidney Injury

Essay.

Submitted For Fulfillment Of
Master Degree in Intensive Care
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2011

جامعة عين شمس
كلية الطب
قسم التخدير والرعاية المركزة

الاتجاه الحديث للعلاج من الفشل الكلوي الحاد

رسالة مقدمة من

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توطئة للحصول على درجة الماجستير في الرعاية المركزة

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Introduction

Acute renal failure is characterized by a rapid fall in glomerular filtration rate, clinically manifest as an abrupt and sustained rise in urea and creatinine ***(Hilton et al., 2006).*** Definitions of acute renal failure range from severe (i.e. requiring dialysis) to slight increases in serum creatinine concentration. In the absence of a universal definition, acute renal failure is often defined as a significant deterioration in renal function occurring over hours or days ***(Schrier et al., 2004).*** There is now a new definition (RIFLE classification) of acute renal failure. This definition classifies patients with renal dysfunction according to the degree of impairment into patient at risk (R), with injury (I), with failure (F), with sustained loss (L) and with end stage (E) status in relation to their renal function ***(Bellomo et al., 2004).***

The RIFLE classification isa simple,readily available clinical tool to classifyAKI in different populations.It seems to be a good outcome predictor,with a progressive increase in mortality with worsening RIFLE class ***(Ricciz et al., 2008).***

Once renal failure occurs, the physician should attempts to reverse the underlying cause. The intravascular volume and mean arterial pressure should be returned to baseline, and serum electrolyte abnormalities should be corrected. Further damage should be prevented by avoiding nephrotoxic agents. Resuscitation to normal blood pressure and restoring normal cardiac output is a corner stone in management.

The main interventions are monitoring fluid input and output as closely as possible, insertion of a urinary catheter is useful for monitoring urine output as well as relieving possible bladder outlet obstruction, such as with enlarged prostate ***(Harris et al., 2003).*** In the absence of fluid overload, administering intravenous fluid is typically the first step to improve renal function. Fluid administration may be monitored with the use of a central venous catheter to avoid over or under replacement of fluid ***(Finfer et al., 2004).***

Hyperkalemia can be treated medically by B_2 agonists, insulin/glucose and sodium bicarbonate (to neutralize acids) that shift potassium intracellular but not to lower total body potassium ***(Ahee et al., 2000).*** Sodium polystyrene sulfonate (SPS), a potassium binding resin, can be used to decrease total body potassium through gastrointestinal transporters. As most of these transporters lie in the recto sigmoid colon, rectal administration of SPS can result in immediate potassium reduction.

Hypotension is prove as a persistent problem in the fluid repleted patients, inotropes may be given to improve cardiac output and hence renal perfusion. A Swan-Ganz Catheter may be used to measure pulmonary artery occlusion pressure to provide a guide to left atrial pressure (and thus left heart function) as a target for inotropic support.

If renal function and serum creatinine raises renal replacement therapy (RRT) should be initiated ***(Mehta et al., 2002).***Other methods for restoring renal function to normal include:Haemodialysis,haemofiltration,and peritoneal dialysis. More specific experimental tratments include:Anti endothelin antibodies, free radical scavengers,and inhibitors of inducible nitric oxide synthetase, all designed to reduce renal damage,Infusion of atrialnatriuretic peptide(ANP), or synthetic analogue anaritide ,may improve renal perfusion.Recently recombinant erythropoietin can reduce ischemic renal injury in an animal model ***(Scharples et al., 2004).*** Theraputic strategies in the more distant future may include bioartificial kidneys as a renal replacement modality, and stem sell therapy to improve kidney recovery ***(Humes et al., 2004).***

Aim of the Work

Our study aims to discuss the recent trends of treatment of acute renal failure by reversing the underlying pathophysiology, restoration of adequate renal perfusion, avoiding nephrotoxic agents and providing treatment of hyperkalemia, overload. Efficacy of different methods of renal replacement therapy will be evaluated.

Acute Kidney Injury

Acute kidney injury (AKI) remains one of the major therapeutic challenges facing modern physician. The term describes a syndrome characterized by a rapid decrease in the kidney's ability to eliminate waste products, regulate extracellular volume, and maintain electrolyte and acid base homeostasis. This loss of excretory function is manifested clinically by the accumulation of end products of nitrogen metabolism (e.g., urea and creatinine) a percentage more than 50% or 1.5 fold from baseline. Other typical clinical manifestations include decreased urine output (oliguria less than 0.5ml/kg/hr for more than 6 hours), the accumulation of non volatile acids, and an increased serum potassium concentration ***(Michael et al., 2009).***

Acute kidney injury (AKI) is a frequent complication of hospitalization that is associated with substantial morbidity and mortality**.**There is significant variability in the reported prevalence (1-25%) and mortality (20-60%) associated with AKI in hospitalized patients. This is to some extent related to the lack of a uniform definition for AKI. Two classification systems have emerged that may serve to unify communication concerning AKI (Table 1) ***(Mehta et al., 2007)***. The RIFLE classification system was formulated by the Acute Dialysis Quality Initiative and defines three strata of increasing severity of AKI: Risk, Injury and Failure, based on relative changes in serum creatinine and urine output, and two outcome strata (Loss and End stage renal failure) ***(Ostermann et al., 2007).*** The three stage Acute Kidney Injury Network classification system largely overlaps with the three first stages of RIFLE, with the addition of an absolute serum creatinine increase of 0.3 mg/dL to qualify for stage 1, a limit on the time interval for the creatinine rise to 48hr, and categorization of patients started on renal replacement therapy (RRT) as stage 3 regardless of creatinine or urine output.

In both classification systems, escalating severity of AKI is associated with incrementally worse outcomes ***(Bagshaw et al., 2008).***

Table (1): The Acute Dialysis Quality Initiative and Acute Kidney Injury Network classification systems for AKI.

Stage	Serum creatinine change	Urine output criteria
Acute Dialysis Quality Initiative RIFLE criteria		
Risk	Increase in serum creatinine of 1.5-2 times baseline	Less than 0.5 ml/kg/hour for more than 6 hours
Injury	Increase in serum creatinine of 2-3 times	Less than 0.5 ml/kg/hour for more than 12 hours
Failure	increase in serum creatinine of >3 times baseline or if baseline creatinine >4mg/dL.	less than 0.5ml/kg/h for more than 24h or anuria for >12 hours
Loss	Persistent need for RRT for >4 weeks	
End-stage	Persistent need for RRT for > 3 months	
Acute Kidney Injury Network criteria		
1	Increase in serum creatinine of 1.5-2 times baseline or 0.3mg/dL increase from baseline	less than 0.5 ml/kg/hour for more than 6 hours
2	Increase in serum creatinine of 2-3 times baseline.	Less than 0.5 ml/kg/hour for more than 12 hours
3	increase in serum creatinine of >3 times baseline or if Baseline creatinine >4mg/dL.	less than 0.5ml/kg/h for more than 24h or anuria for >12 hours

(***Bagshaw et al., 2005)***

Despite improvements in therapeutics, the morbidity and mortality associated with acute kidney injury (AKI) remain high. In the ICU more than 30% of patients suffer from AKI (***Moonem et al., 2010).***Depending on the population being studied and the criteria used to define its presence,epidemiologic studies have demonstrated that the incidence of AKI is increasing, and mortality has only marginally improved. There is emerging recognition of the fact that even minor, short term changes in serum creatinine are associated with increased mortality ***(Lassnigg et al., 2004).***

A major limitation in improving outcomes of AKI has been the lack of common standards for diagnosis and classification. Previous studies have used an assortment of definitions for AKI, including those based on changes in serum creatinine, absolute levels of serum creatinine, changes in urine output or blood urea nitrogen concentrations. The lack of a universal definition has resulted in substantial differences in reported incidence, and outcomes of this clinical condition. Because the best way to improve outcomes of AKI is prevention, the definition should have a high diagnostic accuracy and allow early detection of acute kidney injury. Quantifying the extent of injury will also prove valuable to guide therapeutic recommendations and allow reasonable comparisons of outcomes between various treatment strategies (***Robert et al., 2004).***

RIFLE and AKIN criteria:

In 2002, the Acute Dialysis Quality Initiative (ADQI) group proposed a standard definition and classification system for the syndrome of acute renal failure . The classification system named the acronym RIFLE and has three levels: Risk, Injury, and Failure; and two outcomes: persistent acute renal failure (termed Loss) and End stage kidney disease.

A unique feature of the RIFLE classification is that it provides retrospectively for three grades of severity of renal dysfunction on the basis of a maximum change in serum creatinine, reflecting changes in GFR or duration and severity of decline in urine output from the baseline. The RIFLE criteria have the potential advantage of providing definitions for the stage at which kidney injury still can be prevented (risk), when the kidney has already been damaged (injury), and when renal failure is established (failure). The RIFLE criteria have been evaluated in clinical practice and seem to be at least coherent with regard to outcomes in patients with AKI ***(Uchino et al., 2006).*** However, the RIFLE classification is not a diagnostic one, but a staging system based, retrospectively, upon the maximum serum creatinine. This has created confusion as the stage (risk, injury or failure) can and does evolve in the same patient from risk to failure depending upon when the diagnosis is completed. For instance, a patient with severe AKI will satisfy the criteria for risk, then injury and finally failure as the serum creatinine rises daily. In epidemiologic studies, this patient would be counted as failure. Therefore, RIFLE does not offer real time quantitative diagnosis regarding severity of injury that can be used to stratify patients for clinical therapeutic studies ***(Ostermann et al.,2010).***

At Risk:

According to RIFLE classification, Risk (R) is defined as an increase of baseline serum creatinine 1.5-2.0 folds or decrease of urine output 0.5 ml/kg per h for 6 h. Urine output was included as a diagnostic criteria because in intensive care unit patients mostly had renal dysfunction before the onset of changes in serum creatinine. Recent studies showed that even small changes in serum creatinine were associated with increased morbidity and mortality. Lassnigg demonstrated a two fold

increase in the risk for death for patients who experienced increase in serum creatinine (SCr) 48 hr. after cardiothoracic surgery>0.5 mg/dL compared with patients who experienced a small increase in serum creatinine (SCr) (<0.5 mg/dl) ***(Lassnigg et al., 2004).*** Loef et al., found an association between a 25% increase in SCr during the first postoperative week and short and long term mortality ***(Loef et al., 2005).*** Based on the findings that small alterations of serum creatinine result in adverse outcomes, the Acute Kidney Injury International collaborative Network (AKIN) recently changed the definition of Risk group to include patients with an increase in serum creatinine of 0.3 mg/dL (Table 1) ***(Loef et al., 2005).*** Serum creatinine is the most widely used parameter for everyday assessment of glomerular filtration rate (GFR), but it has poor sensitivity and specificity in AKI because serum creatinine lags behind both renal injury and renal recovery. Furthermore, creatinine is produced non enzymatically in skeletal muscle, and the amount of creatinine is directly related to muscle mass (***Michael et al., 2009).***

Decreased urine output is another important criteria of AKI staging. AKIN proposed documented oliguria of less than 0.5 ml/kg/ hour for more than six hours to define stage 1 of AKI (Risk stage by RIFLE classification). The urine output criteria was included based on the predictive importance of this measure but with the awareness that urine output may not be measured routinely in non intensive care unit settings ***(Robert et al., 2004).***

The differential diagnosis between prerenal AKI and acute tubular necrosis (ATN) is particularly important because restoration of circulating volume may improve renal function and/or prevent further progression of AKI. The differential diagnosis should be based on history of illness, physical findings, and lab results. Urine microscopy should be performed

on every patient with AKI. Evaluation of urine sediment and urine chemistries helps to differentiate between renal vasoconstriction with intact tubular function and established AKI . The fraction of filtered sodium that is reabsorbed by intact tubules of the vasoconstricted kidney is greater than 99% resulting in low fractional excretion of sodium (FeNa) (<1%). FeNa may not be diagnostic in patients with preexisting chronic kidney disease (CKD) or patients taking diuretics because both conditions result in FeNa >1% even in patients with pre renal azotemia.

On the other hand, contrast induced nephropathy and some cases of myoglobinuria may actually be associated with FeNa less than 1% during the early period post injury ***(Esson et al., 2002).***

Renal Injury:

Injury stage is defined as a doubling of serum creatinine or urine output below 0.5 ml/kg/h for more than 12 hours. In one retrospective cohort study 5,383 ICU patients were evaluated. Patients with Injury stage of AKI (26.7% of total) had in hospital mortality rate 11.4% compared with 5.5% for patients without acute kidney injury. More than 50% of the patients with RIFLE class R progressed to RIFLE class I within the next day ***(Uchino et al., 2006)***.

As the severity of AKI progresses, the urine concentrating capacity is abolished. At this stage of AKI, kidney concentrating capacity, assessed by urinary osmolality may complement the use of fractional excretion of sodium in the differential diagnosis of renal vasoconstriction from established ATN. Urine osmolality is usually higher in patients with pre-renal azotemia (> 500 mOsm/kg) and lower in those with ATN (<400 mOsm/ kg) this diagnostic parameter may be less sensitive than fractional excretion of sodium in patients with advanced age or with low protein intake (***Joseph et al., 2003***).

Failure:

Failure stage of AKI in RIFLE classification is defined as a 3 or higher fold increased serum creatinine or higher than 4 mg/dL. Failure stage also is confirmed by urine output criteria: urine output below 0.3 ml/kg/h for 24 hours or anuria for 12 hours.

AKIN proposed to use the same criteria for defining stage 3 of AKI. Additionally, the AKIN classification considers patients receiving renal replacement therapy to have met criteria for stage 3.

Causes of AKI:

Classically, the causes of AKI have been subdivided into three groups: prerenal, intrinsic, and post renal. While there is considerable overlap between these, especially the first two, it remains a useful clinical guide.

Prerenal causes:

Reduced renal perfusion, attributable to hypovolaemia, hypotension, or drugs, which is usually reversible on correction of the underlying cause (***Waiker et al., 2008).***

Intrinsic causes:

Commonly results from tubular cell injury or death attributable to prolonged, or inadequately corrected prerenal failure(ischaemic acute tubular necrosis) (ATN). Drugs may also cause direct tubular damage (nephrotoxic ATN). Acute interstitial nephritis (AIN) may result from allergic drug reactions, infections, or occasionally systemic disease (for example, sarcoidosis). (***Joseph et al., 2003).***

Postrenal causes:

Obstruction of urine outflow of both kidneys, and a single functioning kidney, may arise anywhere from renal pelvis to urethra. Relief of obstruction usually leads to recovery of function (***Michael et al., 2009).***

Prerenal failure is the most frequent cause, at least in hospitalised patients, although obstruction secondary to prostatic disease is as common in some community studies . Intrinsic disease is most probably attributable to ischemic ATN (50% of cases of intrinsic ARF), with nephrotoxic ATN, interstitial nephritis, and glomerulonephritis ***(Michael et al., 2009).*** The condition is often multifactorial, for example, the septic, hypotensive patients given aminoglycosides and intravenous contrast. Elderly patients, diabetic patients, and those with pre-existing renal disease are all at higher risk.***(Waikar et al.,2008)***.

Pathogenesis:

Renal blood flow is 25% of cardiac output but some areas are particularly sensitive to ischaemic damage. Most of the blood flow supplies the cortex, which contains the glomeruli and convoluted tubules,which are areas that require good perfusion to achieve filtration and reabsorption, the latter with high energy demands ***(Brezis et al., 1995).*** The outer medulla is comparatively starved of oxygen, its blood supply first traversing the glomerular capillary bed, and losing hydrostatic pressure, and then on entering the medulla, losing oxygen by countercurrent exchange with the venous vasa recta. These features are essential to maintain the osmotic gradients within the medulla and thus generate concentrated urine, but render the outer medulla very susceptible to variations in blood flow . This area contains the thick ascending limb of the loop of Henle and S3 segment of the proximal tubule, both with high oxygen requirements. Impaired tubular sodium reabsorption attributable to reduced perfusion causes constriction of the afferent arteriole and a further reduction in glomerular filtration rate (GFR).