Acute renal failure: the new perspectives

Nowicki M, Zwiech R, Szklarek M

Department of Nephrology, Hypertension and Renal Transplantology, Medical University of Łódź, Poland

Abstract

This review updates the progress which has been made in the recent years in the field of diagnosis, prevention and treatment of acute renal failure (ARF). Despite the better recognition of the etiology and risk factors of ARF this disease is still characterized by high mortality especially when developing in patients with multi-organ failure. The origin of ARF is clearly multifactorial but its pathomechanism shows many similarities regardless of a cause. Due to the latest achievements in the understanding of the pathogenesis of ARF better preventive and therapeutic strategies are being developed. Some of them have been successfully tested in experimental settings. Surprisingly most of the human studies showed that preventive methods other than simple hydration could not change the course of the disease or even could be harmful. Also the critical issue remains early ARF detection. In turn in cases of fully developed acute tubular necrosis the major concern is to prevent secondary complications and organ failure and to introduce appropriate dialysis therapy. Although not yet supported by a significant reduction in mortality in most severe cases of ARF some progress has been made due to the development of new convective intermittent or continuous renal replacement therapies, notably hemodiafiltration.

Key words: acute renal failure, renal replacement therapy, hemodialysis.

ADDRESS FOR CORRESPONDENCE:
Prof. Michał Nowicki, M.D.
Department of Nephrology,
Hypertension and Renal Transplantology,
Medical University of Łódź
University Hospital No 1
Kopcińskiego 22, 90-153 Łódź
Tel: 42 6776709, Fax: 42 6783632,
e-mail: nefro@wp.pl

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Introduction

Acute renal failure (ARF) is a common clinical condition that affects as much as 5-7% of all hospitalized patients. Although prevalence rate of ARF substantially decreased in some clinical situations, e.g. after surgical intervention or delivery, surprisingly no significant general improvement in mortality has been recorded [1,2]. Overall this clinical entity still carries a significant mortality rate of 20-70%. The problem of ARF is of major concern especially in cases complicated by non-renal organ failure. The presence of sepsis and associated multi-organ failure results in the highest mortality. Although in mild cases of ARF an average mortality rate is 20% those requiring dialysis have mortality rates of about 40-50% and in the intensive care units patients with ARF carry the highest mortality rate reaching 70% [2]. It is interesting that during the past 50 years these rates remained unchanged mainly because more and more patients developing ARF are older and have multiple co-morbidities [2]. Most of the preventive strategies which appeared promising only several years ago, e.g. loop or osmotic diuretic agents, atrial natriuretic peptide, dopamine, endothelin receptor antagonists, have been found unsuccessful and therefore further studies in this field are mandatory. In contrast some progress has been achieved due to an introduction of new renal replacement modalities which appear to be especially suitable for the treatment of severe cases of ARF. Unfortunately, human studies which have been carried out to date are scarce and the results are conflicting.

Pathophysiology of ARF

Presently it is evident that either the sudden or persistent changes in glomerular filtration, tubular dysfunction or renal perfusion may result in ARF. The knowledge of the pathomechanism is crucial with respect to the development of preventive measures and therapeutic interventions. According to newly proposed classification not three (initiation, maintenance and

recovery) but four phases (initiation, extension, maintenance and recovery) of ARF have been recognized [1]. The initiation phase with nonspecific hemodynamic changes may evolve into the extension phase which is characterized by alterations in renal perfusion leading to hypoxia. In the next phase an inflammatory response predominates resulting in epithelial and endothelial injury which occurs mainly in the cortico-medullary part of a kidney.

ARF is the complex, dynamic process involving renal vasculature and tubules leading to renal injury. The first stage is the reduction of regional renal blood flow which initiates the kind of a chain reaction leading to ARF. Vasoconstriction begins as a result of altered vascular reactivity associated with the endothelial damage and inhibition of the nitric oxide synthase activity. Reduced arteriolar renal blood flow causes cortical proximal tubules cells damage mainly because of cyclic GMP depletion [3]. Additionally endothelial activation and injury result in cell swelling and loss of potency of endothelial barrier leading to mechanical obstruction and interacting with leukocytes and platelets. Those factors may trigger an expression of adhesion molecules (ICAM-1, MIP-2, KC, and CXC) and activate coagulation pathways. That in turn leads to accumulation and activation of leukocytes and the interplay between leukocytes and endothelium which end with cellular infiltration and inflammatory response with whole spectrum of proinflammatory cytokines release (e.g. IL-1, TNF-α). Resulting neutrophil accumulation leads to complement-mediated injury. Tubular cells are also involved in the initiation of the inflammatory response which is accompanied by a massive production of IL-6, TGF-β, RANTES, MCP-1, ENA-76, Gro-α IL-8, TRAF6 and Fas. The prolonged ischemia may also affect parenchymal cells. Finally all of these events may result in cell death which could occur either by necrosis (typically in the proximal tubules) leading directly to elimination of damaged cells during post-ischemic kidney reperfusion events, or apoptosis or programmed cell death (mediated by the expression of bcl2 family genes, i.e. bax, bak, bad and caspases -3, -6, -7) [3,4].

Definitions of ARF

Till now several different definitions of ARF have been proposed. Most of them used arbitrary defined rise of the serum creatinine concentrations as a major criterion for ARF diagnosis. According to them in order to fulfill the criteria of ARF serum creatinine should rise of more than 50% from the baseline value or to over 3.0 mg% (270 μmol/l). Thus, the current definition of ARF is based on serum creatinine or a volume of urine produced which frequently cannot support adequate decisions for therapeutic intervention. However no widely accepted ARF definition has been proposed. Such definition should ideally show the association between the development of ARF and the risk of mortality or the likelihood of recovery of renal function. Extremely complex definitions [5] are likely impractical for clinical evaluation. Precise quantification of the glomerular filtration rate (GFR) with inulin clearance technique might be useful for research purposes but is impractical, cumbersome and expensive. Serum creatinine concentration changes may not reflect GFR precisely enough to be used for monitoring of kidney function [3]. The heterogeneity of ARF and the lack of widely available markers of renal injury, the need for effective diagnostic and classification scheme are points to reconsider ARF definition.

Classification of ARF

The proper assessment of kidney function should take into account several elements such as a function of glomeruli, endothelium, renal tubules and urinary tract. Not only the severity, type and site of injury but also an individual patient's susceptibility can modify the course of ARF. The vital factors that should be taken into consideration are therefore age, sex, co-morbidities, etiology and nature of ARF (e.g. coexisting oliguria), timing of ARF, the nature of an underlying disease, presence of sepsis and nutritional status. The ARF definition relies neither on the presence of specific markers nor on the severity of signs or symptoms. ARF, with its complexity and subsequent multi-organ effects, should be seen in similar manner to other critical clinical entities like sepsis or acute pancreatitis. When all these factors are taken into account the term "ARF syndrome" should be used [3]. It is easy to compose this with RIFLE (Risk, Injury, Function, Loss, End-stage) criteria suggested by ADQI (Acute Dialysis Quality Initiative) [6]. Mehta et al. has recently proposed a new classification of acute renal failure which could help clinicians to categorize patients with ARF (*Tab. 1*) [3]. This allows individual assessment of a patient according to his clinical stage including preexisting diseases (each element is pointed 1 to 4 in each of the following categories – susceptibility, the response to an insult, and end-organ damage). Although appearing promising this classification needs to be tested in clinical settings. For clinical decision making also some sensitive and specific markers of the severity of renal injury and renal response to injury would be helpful.

New insights into a diagnosis of ARF

A rise of serum creatinine concentration often follows an initiating event of ARF with highly variable delay and therefore cannot be recognized as an early marker of its development. Recently KIM-1 (kidney injury molecule 1) – type 1 transmembrane glycoprotein that is upregulated in post-ischemic regenerating rat kidney has been proposed as an early marker of ARF. The physiologic role of this molecule includes the dedifferentiation of epithelial cells, promotion of proliferation and epithelial-mesenchymal transition. Studies of Ichimura et al. and Han et al. provided a strong evidence that this marker for renal injury is highly specific for tubular destruction [7,8]. KIM-1 appeared to be a very sensitive indicator of toxemic ARF and its expression was enhanced in proximal tubule epithelial cells in biopsy specimens taken from patients suffering from ARF [7]. KIM-1 urinary excretion increases after mild tubular injury even before urinary casts appear, and then returns to baseline when the tubular epithelium regenerates. In addition, increased expression of KIM-1 in the proximal tubule shows a tight correlation

Table 1. **The new classification of acute renal dysfunction (S-I-R-E) [3]**

	Stage			
Domain	**1**	**2**	**3**	**4**
Susceptibility **(S)**	None GRF>90	Known preexisting kidney disease (CKD 2) 60<GFR<89	Known chronic preexisting kidney disease (CKD 3) GFR<60	Known preexisting kidney disease (CKD 2) 60<GFR<89 Presence of one risk factor
Insult **(I)** nature time	Known<24 hours	24<Known<48 hours	Unknown >48 h	Both unknown
Response **(R)** Cr increase mg% GFR decrease %	0.5<increase<1 25<decrease<49	1<increase<2 50<decrease>74	increase>2 decrease>75	increase>3 decrease<10
Nonrenal organ failing (E)	None	Single organ	Two organs	>2 organs

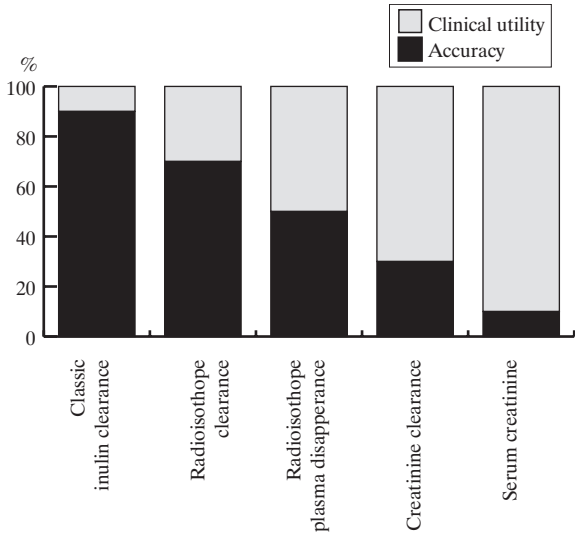
creatinine serum concentration (Cr) – mg%, GFR – ml/min according RIFLE criteria risk factors: diabetes mellitus with microalbuminuria, dehydration, multiple myeloma, congestive heart failure, decompensated cirrhosis organs failing includes: respiratory, CV, neurological, liver, hematological failure

with the development of ARF. Most importantly, no expression of KIM-1 has so far been detected in the normal human kidney [8]. Several other studies tested other suspected early markers of renal injury. Recently another new protein has been discovered. It was named after its chemical structure a cystein-rich protein (CYR 61). CYR 61 could be detected in large quantities in the urine shortly after ischemia reperfusion injury develops [9,10]. Recently, Pilar et al. proposed a new marker asmac/diablo protein (a mitochondrial protein which may block an apoptosis inhibitor IAPs) which may play and important role in regulating amplification of lethal stimuli potential in renal cells during AFR [11]. Although this protein measurement in vivo may be of potential relevance in the detection of early changes in ARF its clinical usefulness has not yet been proven. Still the whole spectrum of biomarkers is being extensively studied in the kidney proteom [12,13]. Another extensively studied protein – cystatin C appears to be a promising marker of changes in GFR, but its serial measurements during the ARF will still require validation in both experimental and clinical conditions [12].

GFR measurements are still of major importance in monitoring the course of ARF. Quantification of GRF could help to modify doses of drugs and more precisely assess the timing of dialysis initiation. An accurate GFR estimation may be also of importance with respect to prognosis. Additionally, GFR assessment could help us to assess the effect of specific therapeutic interventions and provide information on the severity of renal dysfunction (*Fig. 1*). Rapid changes of serum creatinine during ARF are a major limitations to use methods of indirect assessments of GFR which are based on serum creatinine. The most useful is the GFR estimation based sorely on serum concentrations of such markers as inulin or iothalamate. With this method even the rapid changes in GFR could be detected. The new HPLC technique for the measurement of iothalamate concentration has recently been introduced and validated [14]. The use of plasma clearance of radioactive markers (e.g. 51CR-EDTA, 99mTc-DTPA) allows avoiding invasive procedures and also shows an excellent correlation with the GFR measured with standard iothalamate method. In addition those techniques combine estimation of GFR with renal imaging. Modern techniques of GFR estimation should provide more accurate measurements in the case of rapid changes of GFR in the course of ARF [14].

Magnetic resonance imaging is a method which usefulness cannot be underestimated. Whole-body three dimensional MR angiograms may show occlusion or stenosis of the renal arteries as well as kidney diameters or contrast-enhanced images of perfusion changes within renal cortex and medulla. Two new MRI techniques have been extensively studied. Blood oxygenation level-dependent (BOLD) MRI depends on hemoglobin as an endogenous contrast agent according to its paramagnetic (deoxyhemoglobin) and diamagnetic (oxyhemoglobin) capabilities. It provides the non-invasive estimation of tissue pO_2 which reflects medullary hypoxia. Unfortunately with this method one cannot distinguish between alterations of oxygenation caused by perfusion changes or changes in oxygen consumption. Blood pool contrast agents improve high-resolution MRI imaging (allowing better visualization of small vessels) due to reduced interstitial diffusion and prolonged circulation in the blood. This technique detects medullary perfusion defects precisely and may differentiate a cortical from medullary perfusion. Thereby it could offer us the possibility of studying vascular pathology [14]. Recently the micro-MRI methods have been developed in order to measure tubular function and the extent of renal inflammation (the two factors which role in the pathogenesis of ARF may be relevant). Unfortunately, both techniques are in the early stages of experimental research. The first method is based on the use of dendrimer-based contrast agents (also known as the 4^{th} generation agents) and allows to precisely monitoring proximal tubule function after injury [15]. The latter uses negative imaging agent (e.g. dextran-coated ultra small superparamagnetic iron oxide – USPIO) which is quickly internalized after the administration by monocytes/macrophages

Figure 1. **The comparison of the methods used to assess the glomerular filtration rate**



what makes the severity of infiltration and inflammation easy to monitor. Currently USPIO is being used in preclinical studies [16]. The non-invasive examining of patients with ARF using MRI may increase our understanding of the pathomechanism of this disease and likely change the therapeutic regimens in the future.

Two-photon fluorescence microscopy is a method of imaging which allows quantifying apoptotic changes with the near-infrared light. Due to this unique feature this method could be helpful in monitoring of wide spectrum of pathologic conditions including ischemic kidney injury [14].

Some recent experimental studies suggested that ischemia or transient ureteral obstruction may have the protective effect against subsequent ischemia. This protection is associated with a decreased inflammatory response and KIM-1 expression [12].

The new perspectives for therapy

Erythropoietin is a growth agent that has a strong cytoprotective and anti-apoptic properties. Vesey et al. proved that Epo may have an inhibitory role in the regulation of tubular cells apoptosis in vitro and their functional recovery [17]. This concept, although promising, has not been so far supported by clinical studies.

New exciting possibilities are also provided by the studies on stem-cells applications in ARF. Such therapy could give the opportunity to replace damaged kidney structures and a chance for an easiest and an earliest recovery of patients suffering from ARF. Still the great barrier has to be overcome because unlike the heart muscle the kidney consists of at least 26 major types of cells and each of them is highly specialized and differentiated. Thus to achieve the full renal recovery these cell types should be replaced in order to give them a potential to form kidney structures such as glomeruli. Recently with the application of new engineering methods it was shown that the stem-cells could differentiate and form renal tissues [18]. In the recent studies bone marrow stem-cells were found to differentiate in vitro into such kidney structures as tubular epithelium and whole proximal tubules, glomeruli, mesenchymal cells or small vessels [19]. With this technique it was found that hematopoietic stem-cell introduction led to complete renal tubules regeneration after ischemic injury [20]. Unfortunately, the stem-cell science is still at the early stage of development. It has a great potential but also brings huge controversies about embryonic researches and human cloning procedures.

Recently a number of new genes which regulate cell cycle regeneration after renal injury have been identified. Therapeutic interventions involving this gene expression can become most potent and simplest future method of reparation and regeneration of kidney cells [21].

Management strategies

The complexity of causes of ARF and heterogeneity of patients' populations which are at risk of ARF make clinical studies an extremely difficult task. It would therefore be very challenging to propose a uniform management strategy.

Numerous initially promising therapies of ARF based on such agents as loop diuretics or low ("renal") doses of dopamine which could dilate the renal vasculature have been found of no or only of very limited value in clinical conditions [22]. To date volume correction stays the most efficient and evidence-based intervention in most patients with ARF [23]. In the last two years several studies were published which showed that a mucolytic agent with potent antioxidative properties – acetylcysteine could be effective for the prevention of contrast media-induced acute worsening of renal failure. Most of the patients in those studies had chronic renal disease which is a major risk factor of ARF. Seven of those studies which comprised a total number of 805 patients were included in the recent meta-analysis which showed that the administration of acetylcysteine reduced the risk of contrast nephropathy by 56% compared to hydration alone [24]. There is no doubt, however, that fluid balance should be adequately controlled. It is to note that not only dehydration but also excessive hydration should be avoided since Lowell et al. recently reported a strong positive association between fluid overload and mortality, suggesting that fluid management should be carefully observed and limited [25].

The patients in whom serum creatinine concentration increases or oliguria (<400 ml/day) develops are usually consulted by nephrologists. Surprisingly in one study it was found that the timing of nephrologists referral has no significant influence on mortality rate [26], but according to the other analysis patients who were delayed with nephrology consultation had higher non-renal organ failure rates [27].

The natural history, clinical needs, the course of the disease/ /pattern of illness with the predicted therapy response determine and could identify the exact time point of intervention. Each of initial three phases of the aforementioned new ARF classification, may be a target for therapies aimed at prevention, limiting extension or treatment of established ARF, respectively. That helps to characterize the renal response, to institute supportive

therapy (adequate dialyses type) and to stabilize non-renal organ dysfunction. However, each of a new schemes, even the most adequate, has limitations and therefore should be tested to prove its utility.

In severe cases of ARF when there is no chance of early recovery of renal function and serum creatinine rises renal replacement therapy (RRT) should be initiated. Unfortunately, the dose of RRT is often low and inappropriate. The most probable reasons are the presence of high catabolic rate, recirculation of blood and cardiovascular instability that occur frequently in cases of ARF [27]. Despite intensive research leading to a substantial improvement of dialytic procedures especially in intensive care units (timing, duration frequency, dose and modality of RRT) no uniform therapeutic scheme has been established [3]. Although the timing of intervention, the amount and frequency of dialyses may affect outcome, dialysis treatment should be clearly individualized [27]. Continuous renal replacement therapies (CRRT) may show an advantage over intermittent hemodialysis or hemofiltration. It was found that although those methods allows better fluid and metabolic control than standard hemodialysis, it did not increase patient survival rate and decrease the time to renal recovery. Recent studies showed the association between the severity of illness and outcomes after CRRT. Similarly dialyzer membrane biocompatibility or its permeability (low vs high-flux membranes) had no major influence on survival of patients with ARF [28]. There is also no clear advantage of intensive vs less intensive dialysis in ARF although Ronco et al. [29] showed that large volume of ultrafiltration in continuous veno-venous hemofluction (CVVH) improves survival. The retrospective study analyzing the influence of frequency of a dialytic procedure on survival showed that the highest mortality rate was observed in a group of patients who had one dialysis session during the course of the ARF (74.8%), lower for those dialyzed 2-10 times (66.7%), and 10-20 times (50%). If the patients had more than 20 sessions the mortality was even higher (61.5%) [27,29]. No definite conclusions could be drawn from such analyses, however, since the patients who were dialyzed more intensively and longer periods must have had more severe course of the disease.

In patient with end stage renal disease (ESRD) a proper dose of hemodialysis is usually set based on Kt/V calculation and clinical condition. The dose of dialysis prescribed to patients with ARF is much more difficult to establish. Kanagasundarm et al. [30] showed that the calculation of equilibrated Kt/V is also of potential value in patients with ARF. In general, hemodialysis sessions (when using intermittent therapies) should be more frequent in ARF than in patients with ESRD because of the differences in the distribution of urea and invalidity of a steady state assumption in ARF.

Peritoneal dialysis is an acceptable method of treatment of ARF, however, due to technical and practical limitations it is mainly used in small children. In general it could be used in patients without associated severe infections. Since the efficiency of this type of dialysis is generally lower than of hemodialysis, this method should not be used in cases of ARF with multi-organ failure or in case of prominent hypercatabolism [31].

The coupled plasma filtration adsorption (CPFA) is a new and promising method of blood purification which can be used in patients with sepsis and multi-organ failure. This method may be used to efficiently reduce levels of pro- and anti-inflammatory mediators. It also decreases mononuclear cell proliferation [32].

Conclusions

In summary, the knowledge of ARF pathophysiology, definition, classification, prevention and treatment is a dynamic matter. Each year brings new concepts and insights, reveal novel perspectives or management strategies. Despite heterogeneity of ARF patient's population new promising preventive and management strategies are being tested. The reduction in the incidence rate of ARF is seen in the younger patients mainly due to improved preventive methods and awareness of the problem among medical professionals. Still a lot has to be done in the treatment of ARF in the elderly and in patients with multi-organ failure. The reduction in mortality rate in ARF remains a major challenge for nephrologists in the new millennium.

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