

# Acute Dialysis Quality Initiative

## 4<sup>th</sup> International Consensus Conference

### Workgroup 1

#### Primary Prevention of Acute Renal Failure

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### Introduction

Primary prevention of acute renal failure (ARF) refers to clinical strategies which reduce the occurrence of ARF in patients with or without underlying chronic renal disease who do not yet exhibit evidence of acute renal dysfunction or injury. The lack of sensitive measures of renal injury (biomarkers) as well as the difficulty in assessing renal function in a “non-steady state” condition has led to vagaries in definitions of ARF and identification of at-risk populations. Nonetheless, numerous strategies have been employed for primary prevention of ARF under a variety of clinical scenarios.

### What are the established risk factors for the development of in-hospital ARF?

Numerous epidemiologic studies have identified a number of baseline risk factors, acute clinical conditions and diagnostic/therapeutic agents associated with the development of ARF in hospitalized patients (Table 1). The relative importance of each risk factor has not been established nor have all factors been consistently identified in all studies. In terms of baseline risk, there is sufficient evidence from large epidemiological studies to support the role of older age, diabetes, underlying renal insufficiency, and heart failure as predisposing factors for the development of ARF. These risk factors are frequently combined in individuals and may be additive.<sup>1-6</sup> Other variables are less well established as independent risk factors for ARF. For example, there is conflicting evidence as to a role of gender as a risk for ARF development.<sup>7-10</sup> Similarly, there is insufficient evidence to establish an association between race and/or genetic variation and risk of ARF.<sup>11-15</sup>

A number of clinical conditions have been identified as risk factors for ARF (Table 1). There is strong evidence of an association between sepsis and ARF.<sup>16,17</sup> Absolute or relative hypovolemia appears to be a

significant risk factor for ARF development. Fluid therapy has been shown to be effective in prevention of ARF in certain clinical scenarios.<sup>18-23</sup> Liver failure may result in so-called “hepato-renal syndrome”. However, there is some evidence to support an association between liver failure and acute tubular necrosis (ATN) as well.<sup>24,25</sup> Although a casual relationship has not been established, mechanically ventilated patients appear more at risk of developing ARF.<sup>26-29</sup> While there is widespread agreement that hypotension and shock are related to the development of ARF, these conditions appear to be rare causes of ARF in absence of other predisposing factors.<sup>30,31</sup>

There is good evidence that rhabdomyolysis may lead to ARF; however, there is no consensus as to the level of creatine kinase or myoglobin that are predictive of the risk. In addition, the exact mechanism of rhabdomyolysis-induced ARF has still to be elucidated. Several factors play a role, such as renal vasoconstriction, direct tubular toxicity, indirect oxidative tissue damage and tubular obstruction, increased sympathetic nerve activity, endothelin I, angiotensin II, vasopressin and thromboxane as well as the suppression of prostaglandin synthesis. Furthermore, an important role has been attributed to the release of myoglobin. However, it has been shown that myoglobin per se is not nephrotoxic, but toxicity occurs if and when hypovolemia or renal ischemia are present as well. In rhabdomyolysis there is an enhanced generation of toxic free radicals and free iron. Furthermore, recent studies suggest that cytochrome p450, not myoglobin, may be the source of renal toxicity.<sup>32-35</sup> Since intravascular volume depletion is present to some degree in all patients with rhabdomyolysis,<sup>36</sup> correction of hypovolemia is an essential part of treatment and the prevention of ARF. Sodium chloride should be aggressively administered to restore and maintain intravascular volume and to maintain a urine flow rate of 1 to 1.5L/hr.<sup>33</sup>

While the administration of sodium bicarbonate and mannitol together with saline is widely recommended for the treatment of rhabdomyolysis,<sup>33</sup> the extent to which these interventions provide additional benefit to volume expansion with saline alone remains uncertain. Results of retrospective studies examining the benefits of urinary alkalinization in humans with rhabdomyolysis are contradictory<sup>37-39</sup> and no controlled studies have been done to establish the extent to which urinary alkalinization provides additional benefits to volume expansion with sodium chloride.

There are also a number of theoretical reasons for the use of mannitol. Mannitol increases intravascular volume and urine flow rate and may facilitate the removal of myoglobin from the kidney thereby ameliorating oxidant injury to and obstruction of tubules.<sup>40,41</sup> However, as with urinary alkalinization, no controlled studies have been done in humans that demonstrated that mannitol is beneficial in preventing heme-induced ARF.

There is evidence to support an association between open-heart surgery for myocardial revascularization and risk of ARF. Substantial evidence indicates that valve replacement adds an additional risk for ARF. The risk of ARF appears to correlate with the duration of cardio-pulmonary bypass and aorta cross-clamping. The risk of ARF may not be significantly reduced by utilizing off-pump techniques.<sup>1;10;42-44</sup> The risk of ARF is increased in non-renal solid organ transplantation; possible contributing factors included

prolonged anesthesia, surgery, blood loss, and administered medications.<sup>25;45;46</sup> There is increasing evidence that intra-abdominal hypertension may contribute to the development of ARF—potential mechanisms include a decreased venous return, relative outflow obstruction, and decreased renal perfusion pressure.<sup>47-49</sup>

Intravascular radio-contrast agents have long been associated with the development of ARF in high-risk patients. Mechanisms of contrast-media induced nephrotoxicity include alterations in intra-renal blood flow, direct tubular toxicity, and generation of reactive oxygen species. ARF induced by contrast media usually occurs in people with diabetes and baseline renal dysfunction. Low osmolality contrast media has been associated with reduced nephrotoxicity compared with high osmolality contrast media.<sup>50-54</sup> One recent RCT (n=129) in patients with diabetes mellitus and serum creatinine concentrations between 1.5–3.5 mg/dL) compared non-ionic iso-osmolar contrast media (iodixanol) versus low osmolar (iohexol) contrast media.<sup>51</sup> It found that iso-osmolar contrast medium significantly reduced contrast-nephropathy compared with low osmolar contrast medium (nephropathy, defined as an increase in serum creatinine >0.5 mg/dL: 2/64 [3%] with iso-osmolar v 17/56 [26%] with low osmolar contrast medium; OR 0.09, 95% CI 0.02 to 0.4). In patients with no known risk factors for contrast nephropathy, there is little information to support an association between total dose of contrast and risk for ARF. In patients with risk factors, the dose of contrast media is positively correlated with contrast nephropathy. Intra-arterial administration of contrast media appears more nephrotoxic than the intra-venous route.<sup>55;56</sup>

Consensus Statement: Numerous baseline factors have been identified that appear to increase the risk of ARF. The strongest associations appear to exist for diabetes and pre-existing renal disease. A variety of clinical conditions including sepsis, non-renal organ failure, hypovolemia and shock are important risk factors for ARF, often occurring in combination. Myoglobinuria, in the presence of hypovolemia or renal ischemia may induce ARF. The mechanisms are complex and yet to be fully elucidated. Radio-contrast and anti-microbial agents appear to be the most common causes of nephrotoxic ARF.

Recommendations for Clinical Practice: When possible, nephrotoxins should be avoided. Avoidance of nephrotoxins is increasingly important with increasing number of risk factors although precise quantification of risk is difficult (Grade E). Aggressive early fluid resuscitation reduces the nephrotoxicity associated with myoglobinuria and may prevent ARF (Grade D). Neither mannitol nor alkalinization of the urine has been shown to be beneficial in controlled trials. Non-ionic, iso-osmolar IV contrast should be used in all high-risk patients—grade C recommendation based on level 2 evidence. What constitutes “high-risk” is unclear but diabetics with baseline renal insufficiency seem to represent the highest risk.

Recommendations for Future Research: Additional, large, population-based, epidemiologic studies are needed to establish relative risks for the development of ARF. Specific studies of prevention of ARF in certain high-risk population are also needed.

## Are biomarkers available to early detection of ARF?

Urine output and serum creatinine lack sensitivity and specificity in ARF. However, these clinical variables can be used to classify risk. Oliguria (<400 ml/d) and anuria (<50 ml/d) portend a worse prognosis than non-oliguria and may be indicative of a greater renal insult. Greater changes from baseline serum creatinine correspond with more severe renal failure. More precise measures of GFR are of limited clinical value in absence of steady-state conditions. While urine sediment is widely used and useful to establish the etiology of ARF, there are no prospective studies determining its predictive value in ATN. Urine electrolytes are also of limited value in most clinical situations and are significantly influenced by treatment (e.g. diuretics). Questionable lack of clinical utility of these measures underscores the need for early more specific markers of renal injury. Several blood and urinary markers have been investigated as indicators of tubular injury or function; however their specificity and clinical utility remain to be established.<sup>57-59</sup> Serum cystatin C appears to predict the development of ARF defined by RIFLE criteria by at least 24 hrs.<sup>59</sup>

Consensus Statement: Currently, serum creatinine and urine output are the only reliable measures of acute renal function. Cystatin C and other biomarkers are under evaluation, and early results indicate better (earlier) sensitivity for detecting renal dysfunction or injury.

Recommendations for Future Research: Biomarkers for the early detection and severity stratification of ARF are urgently needed.

## What are the physiologic targets for preventive interventions and strategies?

While there are no controlled trials, there is wide consensus that supporting the following parameters is appropriate to reduce the risk for ARF: cardiac output, mean arterial pressure, and renal perfusion pressure. Although cardiac dysfunction is an acknowledged risk factor for ARF, there are no controlled studies suggesting a cardiac output threshold to achieve. Nonetheless, increasing cardiac output should increase renal perfusion. In the appropriate clinical conditions, cardiac output may be increased by fluids, inotropes, intra-aortic balloon pumps, and/or ventricular-assist devices. It has been shown that loss of auto-regulation of blood flow and GFR in the mammalian kidney occurs at a mean arterial pressure of 75-85 mmHg. Inadequate renal perfusion in humans may occur above or below such a threshold, and there is no defined level. In states of long-standing hypertension or intense vasoconstriction, loss of autoregulation may occur with higher mean arterial pressures. Once ARF has developed, intra-renal auto-regulation may be lost.<sup>60,61</sup> Importantly, surrogate markers such as renal blood flow and physiologic markers of renal function such as urine output, glomerular filtration rate have not been established as clinically useful endpoints of preventive strategies.

Consensus Statement: No validated physiologic targets/endpoints have been established for the prevention of ARF.

Recommendations for Clinical Practice: While potentially useful for research, physiologic endpoints should not be used as clinical evidence of effectiveness for strategies to prevent ARF.

Recommendations for Future Research: Better studies correlating physiologic targets and clinical endpoints are needed. Evolving physiologic evidence suggest the following additional areas should be the focus of future research in the prevention of ARF: alterations in regional blood flow, oxidative stress, and growth factors.

### What are useful non-pharmacologic strategies to prevent acute renal injury?

In addition to reducing the exposure to nephrotoxins (reviewed above), fluids have been widely used to reduce the risk of ARF from a variety of etiologies. There is level 1 evidence that the use of isotonic IV hydration is effective in reducing the incidence of contrast-induced nephropathy. One RCT (n =1620) compared hydration using 0.9% saline infusion with 0.45% saline in dextrose for prevention of contrast-induced nephropathy, in patients undergoing coronary angiography.<sup>62</sup> This study found that hydration with 0.9% saline infusion significantly reduced contrast-induced nephropathy (0.7% with 0.9% saline v 2% with 0.45% saline; P = 0.04). One study (n=53) in non-emergency cardiac catheterization compared IV saline (0.9% saline 1 mL/kg/hour begun 12 hours before x 24h) vs unrestricted oral fluids.<sup>19</sup> There was an increase in sCr 0.5 mg/dl at 48hrs 1/27 [3.7%] with IV saline v 9/26[34.6%] with oral fluids; RR 0.11, 95% CI 0.015 to 0.79. A single small prospective study suggests an added benefit of a bicarbonate infusion when compared to normal saline.<sup>52</sup> The role of colloids compared to crystalloids remains unclear. Though not the primary end-point, a recent multi-centered study of 6997 critically ill patients found no difference between albumin and saline for fluid resuscitation in terms of risk of ARF.<sup>63</sup> A much smaller study compared fluid resuscitation with 6% hydroxyethylstarch (200 kDa, 0.60-0.66 substitution) to 3% fluid-modified gelatin in 129 patients.<sup>64</sup> Gelatin appeared to be associated with significantly less renal dysfunction (OR for ARF with hydroxyethylstarch 2.57 [1.13-5.83], p=0.026) compared to this preparation of hydroxyethylstarch in saline.

Consensus Statement: Isotonic IV fluids are indicated for the prevention contrast-induced nephropathy and possibly for prevention of other forms of nephrotoxic ARF. The optimal composition of this fluid, beyond being isotonic, is controversial but colloids do not appear to offer any advantage and some starch preparations may offer less protection compared to gelatin. Similarly, saline-based solutions may not be as effective as bicarbonate-based solution.

Recommendations for Clinical Practice: A grade B recommendation based on level 1 evidence for the use of iso-tonic IV hydration to prevent contrast-induced nephropathy. Sodium Bicarbonate-based isotonic fluids may be superior to sodium chlorine (Grade C) based on a single level II study. Colloids do not appear to offer any advantage over crystalloids for the prevention of ARF in critically ill patients (Grade A). Although rates of fluid administration have not been directly compared, most studies have used a rate of 1 ml/kg/h for 6-12 hours before and after the procedure. Ad lib oral hydration is less effective compared to IV (Grade C).

Recommendations for Future Research: Additional studies are needed to clarify the effective of supra-physiologic concentrations of chloride in various preparations of IV fluids on renal function.

## What are useful pharmacologic strategies to prevent acute renal injury?

A variety of drugs have been tried in primary prevention of ARF (Table 2). Currently, no agents have been conclusively demonstrated to protect against ARF in any clinical scenario. However, for a variety of agents, sufficient evidence is available to make recommendations.

### *Loop diuretics*

One RCT, n=121 randomized patients to receive 1 mg/hour of furosemide or placebo immediately after major thoracoabdominal or vascular surgery, and maintained during stay in the ICU.<sup>65</sup> It found no significant difference between furosemide and placebo in creatinine clearance. Both groups had significant reductions in creatinine clearance compared with baseline, but no differences were found between groups. The study did not address the use of loop diuretics given during the procedure.<sup>65</sup> Diuretics seem to worsen outcomes in acute tubular necrosis induced by contrast media<sup>18</sup> and after cardiac surgery.<sup>66</sup> In patients with chronic renal insufficiency who underwent cardiac angiography, Solomon et al. found that ARF was significantly more likely to occur when patients were treated with furosemide.<sup>18</sup> Similarly, Lassnigg et al. found that furosemide compared with 0.9% sodium chloride was associated with an increased risk of development of ARF post-cardiac surgery.<sup>66</sup> Finally, a systematic review (7 RCTs), which compared fluids alone with diuretics in patients at risk of ARF from various causes found no evidence of improved survival, decreased incidence of acute renal failure, or need for dialysis associated with diuretics.<sup>67</sup>

### *Mannitol*

Several small RCTs have found no reduction in the incidence of ARF with mannitol over hydration alone in a variety of conditions, including coronary artery bypass surgery,<sup>68</sup> traumatic rhabdomyolysis,<sup>32</sup> and vascular,<sup>69</sup> and biliary tract surgery.<sup>70</sup> In contrast media-induced ATN, mannitol was not associated with any reduction in risk compared with saline and there was a trend toward harm.<sup>18</sup>

### *Natriuretic peptides (ANP, BNP, urodilatin)*

Four large RCTs failed to demonstrate any improvement in survival or need for dialysis in patients treated with ANP or urodilatin.<sup>71-74</sup> Studies with ANP suggest harm in non-oliguric patients.<sup>72</sup> There is increasing use of b-type natriuretic peptide (BNP) for treatment of refractory congestive heart failure. BNP induces natriuresis, often when other therapies are ineffective. However, there is no evidence that BNP improves renal function or prevents renal injury. Indeed, given the discouraging results with other natriuretic peptides, BNP should probably be avoided in patients with non-oliguric ARF. Although BNP appears to inhibit the renin-angiotensin system, and may therefore have effects in CHF beyond diuresis, its effects are unproven.

### *Dopamine agonists*

A Grade A recommendation based on Level Ib evidence can be made against the use of dopamine for prevention of ARF (two meta-analyses that agree with each other but include heterogeneous studies)<sup>75;76</sup>. In addition, a large randomized trial of dopamine in early ARF (see workgroup 2) failed to show any benefit regarding, progression, need for RRT or death.<sup>77</sup> To date, small prospective studies suggest a potential benefit in terms of renal perfusion and reduction in serum creatinine with Fenoldopam.<sup>78</sup> However, this agent does not prevent further renal function deterioration after contrast administration in patients with chronic renal insufficiency.<sup>79</sup>

#### *Adenosine agonists*

Current evidence does not support a role for theophylline in the prevention of ARF. In two RCTs<sup>80;81</sup> theophylline appeared to reduce the change in Scr or GFR associated with radio-contrast administration in high-risk patients. However, hydration status of patients receiving the radiocontrast agent was unclear. In a subsequent RCT (n=80) GFR was preserved with hydration alone and did not change significantly with additional theophylline compared with placebo. Two patients in the theophylline group and one in the placebo group (5.7% v 3.4%) developed ARF (defined as an increase in serum creatinine of at least 0.5 mg/dL).<sup>82</sup> Similarly, negative results have been found with theophylline to prevent ARF after coronary artery bypass grafting.<sup>83</sup>

#### *N-acetylcysteine*

The use of N-acetylcysteine (NAC) has been shown in several trials to decrease the incidence of contrast nephropathy (defined by a 25% increase in serum creatinine). Several meta-analyses have concluded that NAC results in a ~50% reduction in the incidence of contrast nephropathy in high-risk patients.<sup>84-87</sup> However, NAC has not been shown to improve survival or need for dialysis. Importantly, NAC may affect Scr independently of GFR through at least two mechanisms. First, NAC appears to affect creatinine metabolism through activation of creatinine kinase.<sup>88</sup> Second, healthy volunteers given NAC exhibited a decrease in Scr but no change in cystatin-C levels.<sup>89</sup>

Consensus Statement: No pharmacologic strategies have been conclusively demonstrated to be effective in preventing acute renal failure secondary to any insult and many therapies have shown a potential for harm. With the possible exception of NAC for contrast nephropathy, drugs should not be used to prevent ARF.

Recommendations for Clinical Practice: A Grade A recommendation based on Level I evidence can be made against the use of diuretics for prevention of ARF. There is a Grade C recommendation based on Level II-III evidence against the use of mannitol to prevent ARF. There is a Grade A recommendation based on Level I evidence against the use of ANP for the prevention of ARF. A Grade A recommendation based on Level Ib evidence can be made against the use of dopamine for prevention of ARF (two meta-analyses that agree with each other but include heterogeneous studies). NAC has been shown to prevent the increase in serum creatinine in high risk patients given IV radiocontrast agents (level Ib evidence from heterogenous meta-analyses). Although there is some evidence that NAC may reduce serum creatinine

without increasing GFR, in absence of further evidence, NAC should be considered in high-risk groups, in addition to fluid administration (Grade D based on surrogate endpoint data only). NAC (oral or IV) may be administered to high-risk patients at least 12 hrs before and continuing for 12 hrs after contrast administration. The risks of NAC, apart from potentially obscuring a diminution in renal function, are minimal. Use of this agent should not replace the use of hydration or the use of iso-osmolar radiocontrast agents in patients at risk.

Recommendations for Future Research: All future studies of agents to prevent ARF should use “hard” clinical endpoints such as death or development of renal failure persisting at least 48 hours after the intervention. Furthermore, given the potential effects of drugs on creatinine without influencing GFR, an independent marker of renal function (e.g. cystatin C) is required to establish effectiveness if a biochemical endpoint is used. An intriguing study of secondary prevention (see work group 2) using a longer duration of therapy with human recombinant ANP showed some benefit. Despite discouraging results in previous studies, further investigation using this agent for primary prevention may be warranted. However, given the disappointing results of interventions targeting diuresis and renal hemodynamics so far, the study of other targets (e.g. inflammation, oxidative stress, growth factors) is recommended.

## How does general ICU management affect the incidence of ARF?

Given the number of risk factors identified for the development of ARF in critically ill patients (table 1), improvements in ICU care that result in reductions in the frequency or severity of these risk factors should reduce the incidence of ARF. For example, better management of shock could result in less ARF. Use of an intensive care unit based medical emergency team to provide earlier, more definitive resuscitation of unstable patients resulted in an 88.5% relative reduction in ARF in one observational, before and after, trial.<sup>90</sup>

In addition to fluid resuscitation, vasopressor agents are used to manage shock. The choice of vasopressors is dependent on the underlying pathophysiologic process and patient-specific responses. However, some generalities are supported by the literature. First, norepinephrine and dopamine are excellent first line  $\alpha$ -adrenergic agents (vasopressors) of similar efficacy and an associated lesser degree of  $\beta$ -adrenergic activity (inotropes). Few direct comparison studies exist. However, studies have found that patients with septic shock often respond better to norepinephrine<sup>91</sup>, and one recent retrospective study documented that norepinephrine treatment was associated with a survival advantage as compared to all other forms of vasopressor therapy when patients were compared across similar severity of illnesses.<sup>92</sup> Many clinicians are concerned about the potential for norepinephrine to impair renal and mesenteric perfusion based on studies in normotensive animals. However, there is no evidence that reversing hypotension with norepinephrine compromises mesenteric or renal blood flow. Indeed, animal data show an increase in renal blood flow when norepinephrine is used to reverse septic shock<sup>93</sup> and human studies have shown an improvement in gastric mucosal PCO<sub>2</sub> when hypotension was reversed with norepinephrine.<sup>94</sup> Both norepinephrine and dopamine have the ability to increase peripheral vasomotor tone while providing additional increased

inotropy to minimize the afterload-increasing effects on reducing cardiac output. Dopamine has additional side effects, such as tachycardia and immunosuppression.<sup>95</sup>

Vasopressin induces vasoconstriction by stimulating vasopressin receptors and by potentiating the actions of catecholamines. Vasopressin can be effective in reversing shock when catecholamines are ineffective, particularly in sepsis<sup>96,97</sup> and post-cardiac surgery.<sup>98</sup> For this indication the dosage of vasopressin is low; 0.05 to 0.1 units/min achieves blood levels ~150pg/ml.<sup>99</sup> However, even in this range, vasopressin reduces mesenteric and renal blood flow. There are no randomized controlled trials comparing catecholamines to vasopressin or catecholamines plus vasopressin in terms of clinical outcomes including the development of ARF.

Strategies that reduce overall ICU mortality might be expected to reduce the development of ARF. For example, tight glucose control achieved with intravenous insulin therapy in critically ill patients has been shown to improve outcome, including a decrease incidence of acute renal failure.<sup>100</sup>

Consensus Statement: There is evidence that strategies that improve survival in critically ill patients also reduce the incidence of organ failure, including ARF. Earlier resuscitation of unstable patients may result in a lower risk of ARF. Although the treatment of hypotension is vital to preventing ARF, there is no evidence that one type of vasopressor agent is superior to another in terms of preventing ARF.

Recommendations for Clinical Practice: When required for the treatment of shock, norepinephrine does not increase the risk of ARF (level II). There is no evidence that vasopressin results in a reduction in ARF compared to catecholamines. Consideration should be given to the development of rapid response or medical emergency teams to enable earlier recognition and management of unstable patients at risk of development of ARF.

Recommendations for Future Research: Given the paucity of data comparing available agents for the treatment of shock, studies comparing these agents in terms of outcomes such as development of ARF are needed. In addition, observational or interventional studies are needed to define the therapeutic targets for management of shock (including blood pressure).

## Is there a role for prophylactic extracorporeal therapies?

There is insufficient evidence to recommend prophylactic hemofiltration to prevent radio-contrast nephropathy. There appears to be no role for prophylactic dialysis (level 2 evidence) despite removal of contrast with therapy.<sup>53</sup> The use of hemofiltration has been evaluated by one (n=114) RCT enrolling very high-risk patients receiving high-dose contrast and uncertain hydration.<sup>101</sup> Although this study was positive, it employed less than “best-evidence” (non-iso-osmotic contrast media, loop diuretics, no NAC) and is therefore difficult to interpret.

Consensus Statement: The pre-procedural use of extracorporeal therapies to prevent ARF is controversial. There is currently insufficient evidence to recommend such approaches. Although these therapies can remove contrast media, no benefit has been established, and some studies suggest harm.

Recommendations for Clinical Practice: Available evidence does not support the use of prophylactic renal replacement therapy for the prevention of ARF.

Recommendations for Future Research: Prophylactic renal replacement therapy has not been evaluated in many forms of nephrotoxic ARF. Pre-clinical studies may be useful in determining the potential for benefit of prophylactic renal replacement therapy.

**Table 1. Baseline risks, acute clinical conditions and diagnostic/therapeutic agents associated with the development of in-hospital acute renal failure.**

<b>Baseline risks</b>	<b>Acute clinical conditions</b>	<b>Nephrotoxic agents</b>
Advanced age	Sepsis	Contrast media
Diabetes Mellitus	Hypotension/shock	Antimicrobial agents
Chronic kidney insufficiency	Volume depletion	Chemotherapeutic agents
Heart failure	Rhabdomyolysis	NSAIDs
Liver failure	Cardiac/vascular surgery	
Male gender	Non-renal solid organ transplantation	
Race and genetic variation	Abdominal compartment syndrome	
Hypoalbuminemia	Mechanical ventilation	
Arterial Vascular Disease		

**Table 2. Pharmacologic agents studied for primary prevention of ARF**

**Diuretic agents**

Loop diuretics

Mannitol

Thiazides

**Natriuretic agents**

Atrial natriuretic peptide

Urodilatin

B-type natriuretic peptide

**Miscellaneous**

Growth factors

Anti-inflammatory agents

Anti-apoptosis agents

**Vasodilators**

Dopamine agonists

Adenosine agonists

Endothelin receptor antagonist

Calcium antagonists

Prostaglandin analogues

**Anti-oxidants**

N-acetylcysteine

Lazaroids

MESNA

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