Implementing the KDIGO/AKI guidelines in ICU patients

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Abstract

Purpose of review:

Acute kidney injury (AKI) is a frequent finding in critically ill patients and is associated with adverse outcomes. With the purpose of improving outcome of AKI, the Kidney Disease: Improving Global Outcomes (KDIGO) group, a group of expert in the critical care nephrology, has presented a set of guidelines in 2012, based on evidence gathered until mid 2011. This review will update these guidelines with recent evidence.

Recent findings:

Early application of a set of therapeutic measures - a bundle – is advised for prevention and therapy of AKI.

Hemodynamic optimization remains the cornerstone of prevention and treatment of AKI. Fluid resuscitation should be with isotonic crystalloids. Recent evidence demonstrated a higher risk for RRT and mortality in HES exposed patients. Further, blood pressure should be maintained by use of vasopressors in vasomotor shock.

Nephrotoxic drugs should be avoided or stopped when possible.

Contrast-associated AKI should be prevented by prehydration with either NaCl 0.9% or a bicarbonate solution. Other therapies, including intravenous N-acetylcysteine, and hemofiltration are not recommended.

Optima timing of RRT remains controversial. Fluid overload remains an important determinant for initiation of RRT. Continuous therapies are preferred in hemodynamic unstable patients; otherwise, choice of modality does not impact on outcomes.

Summary:

The KDIGO guidelines as presented in 2012 provide guidelines on the domain of definition of AKI, prevention and treatment, contrast-induced AKI and dialysis interventions for AKI.

Especially early application of a set of measures, the AKI bundle, may prevent AKI and improve outcome.

Introduction:

Acute kidney injury (AKI) is a frequent complication in ICU patients, and is associated with worse outcomes. When defined by the sensitive RIFLE definition for AKI or its modifications the AKIN or KDIGO definitions for AKI, it occurs in one-third to two-thirds of ICU patients [1-8], and approximately 5 to 10 % of ICU patients are treated with renal replacement therapy (RRT) for AKI [9-11]. AKI is associated with worse outcomes such as, longer length of ICU and hospital stay, short-term survival (e.g. 28 d, ICU or hospital survival), also long-term survival (up to 10 years follow up), development of chronic kidney disease, and end stage renal disease, and therefore with increased use of resources and costs.

Despite decades of research, and dozens of compounds evaluated, there are at present still very little therapeutic options for treatment or prevention of AKI. Explanations for this may be the heterogeneous and multifactorial etiology. Despite, the absence of specific therapies for AKI, outcome has improved over years [12, 13]. This may be explained by increased awareness of specific nephrology issues. Several studies showed that simple "kidney-friendly" interventions (e.g. stopping of nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), and early correction of volume status), resulted in less (severe) AKI, and better outcomes [14-19].

Therefore, the guidelines that were issued by the Kidney Disease: Improving Global Outcomes (KDIGO) group are of great importance for advances in treatment of AKI. This process was conducted by a group of experts, using an evidence-base methodology and the GRADING system. As the amount of guidelines is too large to cover them all in this manuscript, we will highlight those that are most pertinent for every day practice.

Definition of AKI

An important accomplishment of the last decade was the introduction by the Acute Dialysis Quality Initiative (ADQI) of the RIFLE consensus definition for AKI [1]. It allows comparisons between studies, interventions in AKI patient cohorts with similar severity stage, and as it is also defines very early AKI with low severity, it allows early intervention. This definition was later modified, first by the Acute Kidney Injury Network (AKIN) [2], and recently by KDIGO [3].

AKI is defined by either an increase of serum creatinine (Scr) or an episode of decreased urine output (UO) (table 1). Important, a patient needs to fulfill only one of the criteria for the definition of AKI. Subsequently, the severity of AKI can be graded into one of 3 severity grades.

There are some issues in this definition that need extra discussion.

Timing

As the emphasis is on acute deterioration of kidney function, the patients should fulfill the criteria within a limited time frame. Therefore, one should compare a new Scr measurement to all Scr measurements in the preceding 7-day period for the 50% increase of Scr, or 48-h for the 0.3 mg/dL Scr increase. If the increase of Scr takes place over a longer period the patient may be classified as having Acute Kidney Disease (AKD). Of note, this time frame is only for the *definition* of AKI, and is not applicable for *staging* of the AKI severity grade.

Baseline and reference serum creatinine

When a patient has no Scr measurements available during the preceding 7-day period, one may use the baseline Scr concentration as a reference Scr for the 50% or greater increase of

Scr, if this is presumed to have occurred within the prior 7 days. For the 0.3 mg/dL or greater increase of Scr, one needs a documented increase; therefore, the presumed baseline Scr may not be used for this.

In patients who are in stable condition, ADQI recommended baseline Scr concentration may be obtained within a 3-month period preceding the current event [20].

Clinical judgment is essential for the correct estimation of this baseline Scr. For instance, if Scr is obtained at the end of a preceding ICU admission, it is very unlikely that this value represents the true baseline kidney function. Also, assessment on whether the acute condition of AKI occurred within a 7-day period may be challenging.

When there is no baseline Scr measurement available, the ADQI group advocated the use of the MDRD equation when there is an assumed baseline glomerular filtration rate (GFR) of 75 mL/min or greater [1]. The MDRD equation estimates GFR on gender, age, race, and Scr. This method has obviously limitations. The equation was validated in a cohort of US patients, and is therefore not applicable in patients with different body composition such as in Asia, or as in patients with lower muscle mass, e.g. as in critical illness, cirrhosis or paraplegia. Also, it is less precise in patients who have GFR>60 mL/min. Despite its shortcomings, this MDRD-based estimation of baseline Scr proved reasonably well in a cohort of ICU patients recruited in 3 centers in the USA [21]. Alternatively, baseline Scr may be estimated by use of multiple imputation method [22]. These single center data need to be confirmed in other settings, and the complexity of this method may limits its use in daily practice.

Urine output criteria

The definition requires that urine output is less than 0.5 ml/kg every hour for a 6 period. This limits its use to ICU patients with a urinary catheter. Studies have used variants of the urine

output criteria, e.g. urine output less than 3 ml/kg in a period of 6 hours, use of fixed blocks of 6 or 8 hours similar to the nurses' shift, back calculation of 24-h urine output etc. [23]. There is no indication what patient weight one should use for the oliguria criterion. It seems reasonable to use the "baseline" patients' weight, as actual patient weight in critically ill patients is seldom measured, and varies according to fluid overload, muscle wasting and weight loss secondary to critically illness. In morbidly obese, adjusted body weight may be reasonable although there are no data to support this.

Prevention and treatment of AKI

This section describes a set of measures that are often described as the "AKI bundle" (figure 1, and table 2). Bundles as these are attractive and successful as they guarantee that all patients receive care according to the best evidence available. They allow health care workers, physicians and nurses to simple tick the measures that need to be done in patients at risk. Implementation of care bundles has proven to improve outcomes in for instance sepsis [24, 25]. Also, several studies in AKI patients have demonstrated that early implementation of simple measures by content experts improved outcomes [14-19].

Hemodynamic support

Guideline 3.1.1 "In the absence of hemorrhagic shock, we suggest using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI (2B)."

As colloids remain in the intravascular compartment for a longer period of time compared to crystalloids, they may seem attractive. However, older hydroxyethyl starch (HES) solutions

showed nephrotoxicity, and observational data on gelatin containing solutions, suggest that these solutions have similar risk for nephrotoxicity [26, 27].

Two well-designed studies on modern HES solutions with presumably less nephrotoxic, further addressed this topic. The 6S trial included 798 critically ill patients with severe sepsis or septic shock and compared a potato based 6% HES formulation with 130 kD molecular weight (6% HES 130) to Ringer's acetate [28]. At 90 days patients treated with HES had an increased mortality and a higher prevalence of RRT. The CHEST trial included 7,000 general ICU patients and compared a corn based 6% HES 130 formulation with 0.9% saline [29]. At 90 days the investigators found a lower incidence of AKI in HES treated patients compared to saline, however, there was a greater use of RRT in the HES group. There was no difference in mortality between both groups. Several meta-analyses have been published since. In a meta-analysis, including all types of HES solutions, HES treatment was associated with increased mortality and AKI [30]. Two other meta-analyses on the new HES 130 solutions only, in all type of critically ill patients and in severe sepsis, found higher risk for RRT and mortality in HES exposed patients [31, 32].

On the basis of currently available evidence the US Food and Drug Administration (FDA), issued a boxed warning on the drug's label that HES solutions should not be used in critically ill patients. Also, the European Medicine Agency (EMA) suspended the marketing authorization for HES formulations, and started a new review on its use (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starch-containing_medicines/human_referral_prac_000029.jsp&mid=WC0b01ac05805c516f, accessed July 22nd, 2013).

The guideline also advises against the use of albumin, this because the greater cost of this fluid is not associated with benefit. Albumin was evaluated in the SAFE study and was found to be equally effective as saline for fluid resuscitation in ICU patients [33]. Importantly, this was not associated with greater need for RRT. Unfortunately, this study did not report on AKI defined by more sensitive criteria. Albumin treated patients had a less positive fluid balance compared to saline treated patients. As, a positive fluid balance may impact occurrence of AKI and outcome, this may be an argument in favor of the use of albumin [34-38].

It is important to notice that the guideline specifically mentions that isotonic crystalloid solutions should be used for volume resuscitation. Two large studies found that non-isotonic crystalloid solutions containing high concentrations of chloride, such as in NaCl 0.9%, are associated with worse outcomes, including AKI, when compared to crystalloid solutions with lower chloride content such as Plasma-Lyte®[39, 40]. These data illustrate that fluids should be seen as drugs with benefit, but also potential toxicity (figure 2)[41].

Guideline 3.1.2 "We recommend the use of vasopressors in conjunction with fluids in patients with vasomotor shock with, or at risk for, AKI (1C)."

In critically ill patients, systemic hypotension may instigate a decreased renal perfusion eventually leading to AKI. To counter for this vasopressor therapy is often used in these patients. In a state of vasomotor paralysis, the use of norepinephrine, an alpha-adrenergic agonist, has beneficial effects on renal blood flow and GFR [42-45].

Guideline 3.1.3 Protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (2C) or in patients with septic shock.

Goal directed therapy has been studied extensively in the perioperative setting, and in meta-analysis, it was shown that this resulted in less postoperative AKI [46]. Although the beneficial effect of early goal-directed therapy (EGDT) in ICU patients on prevention of AKI is plausible, the evidence is still limited. The landmark study by Rivers et al. on EGDT for severe sepsis unfortunately reported no data on AKI [47]. In another study on EGDT in septic ICU patients by Lin et al., EGDT patients had a lower incidence of AKI compared to controls (38.9% vs. 55.2%, p = 0.015) [48]. At present several large multicenter studies on EGDT are under way that will provide additional evidence for its use.

Glycemic control and nutritional support

AKI patients are severely catabolic and nutritional support is therefore an important aspect in the therapeutic plan for these patients. KDIGO summarized the available evidence on this topic and could only formulate recommendations with 2C or 2D grade of evidence, i.e. suggestions, with low or very low quality of evidence, mostly based upon expert opinion.

The landmark study of Van de Berghe and colleagues introduced the concept of intensive insulin therapy (IIT) in the ICU. In surgical -, and a subgroup of medical ICU patients IIT protocol improved outcome and lowered the incidence of AKI [49, 50][51]. These beneficial results could not be reproduced in subsequent studies on IIT [26, 52]. One of the great concerns about IIT is the occurrence of hypoglycemia and its impact on outcome [53]. The

KDIGO group suggests the use of a less stringent insulin therapy protocol targeting plasma glucose 110-149 mg/dL in critically ill patients.

Based on guidelines by expert panels, a total energy intake of 20-30 kcal/kg/d is suggested, preferably via enteral route. Proteins should not be restricted with the aim for preventing or delaying RRT. It is suggested to administer 0.8-1.0 g/kg/d in AKI patients not treated with RRT, and 1.0-1.5 g/kg/d in patients treated with RRT, up to 1.7 g/kg/d in patients treated with CRRT.

Guideline 3.4 We recommend not using diuretics to prevent or treat AKI, except in the management of fluid overload.

The available evidence from small studies cannot demonstrate that AKI is prevented with use of diuretics, or that AKI patients have faster recovery [54, 55]. So far, diuretics only have a role in the management of volume overload.

Guideline 3.5 and 3.7: It is not recommend to use low-dose dopamine to prevent or treat AKI, similar it is suggested not to use fenoldopam or atrial natriuretic peptide to prevent or treat AKI.

Although vasodilation and increasing renal blood flow may seem a logic therapy for prevention and therapy of AKI, this has not been proven in studies. The evidence for being not beneficial is strongest for low-dose dopamine [56-58].

Guideline 3.6: Growth factor intervention.
Three observational studies in cardiac surgery found that EPO treated patients prevented

AKI [59-61]. However, these results could not be confirmed in an early intervention study in

ICU patients and in cardiac surgery patients [62, 63].

KDIGO recommends therefore evaluating the usefulness of EPO in RCTs.

Guideline 3.8 Prevention of aminoglycoside- and amphotericin-related AKI
Given the nephrotoxicity of aminoglycosides and amphotericin, it is suggested to limit their

use to infections where no alternative antimicrobial drug is available. Aminoglycosides

should be administered preferably once daily, and drug levels should be monitored daily.

Amphotericin should be given as a lipid formulation in order to reduce the nephrotoxicity.

Contrast-induced AKI

Contrast media cause nephrotoxicity, but other risk factors for the development of AKI are

often present in the critically ill patient. For that reason, the term contrast associated AKI

(CA-AKI) may seem more appropriate [64]. CA-AKI occurs in 10% to 22.5% of ICU patients,

seldom requires RRT, and is associated with mortality, even on long-term follow up [64-

67][64, 68].

ICU patients should be assessed for risk for CA-AKI (pre-existing renal impairment, diabetes,

nephrotoxic agents, advanced age, hemodynamic instability or hypertension). One should

always consider not administering iodinated contrast. The lowest possible dose of modern

low or iso-osmolar contrast agents should be used. Ideally NSAIDs, metformin, and diuretics

are stopped one day on beforehand. In patients who are at risk for CA-AKI, intravenous volume expansion is recommended, either by administering saline (NaCl 0.9%) or a bicarbonate solution (846 mL Glucose 5% + 154 mL of 1000 mEg/L NaHCO3) at a rate of 3 m/kg, for 1 h before and 1 mL/kg per hour for 6 h after contrast administration [69-72]. Although meta-analyses suggest benefit for the bicarbonate solution over saline, bias and heterogeneity limit this recommendation. In case the bicarbonate solution needs to be prepared, this may be associated with errors.

Since the data on prevention of CA-AKI by N-acetycysteine (NAC) are conflicting, intravenous NAC is not recommended. But, given its beneficial potential and low toxicity, <u>oral</u> NAC should be administered in patients at risk for developing AKI. For most ICU patients, this seems less applicable, as most studies on oral NAC were performed in patients undergoing elective coronary angiography, with administration the night before contrast.

Evidence for the administration of fenoldopam or theophylline in patients at risk for AKI is lacking. Similarly, data supporting the prophylactic use of RRT in patients at increased risk for CA-AKI are insufficient.

Dialysis Interventions for treatment of AKI

Although renal replacement therapy (RRT) has been in use for more than half a century, many aspects of this therapy remain controversial.

Timing and initiation of renal replacement therapy

It seems plausible that early initiation of RRT may positively impact on outcomes in ICU patients with AKI. But because of the possible side effects of this invasive therapy (hypotension, arrhythmia, hemorrhage, and complications of vascular access), there is a tendency to avoid RRT as long as possible. Also, RRT induced hypoperfusion of the kidneys may impair kidney recovery and increase the progression of chronic kidney disease (CKD) [73].

Due to the lack of evidence, the KDIGO recommendations concerning timing of RRT in AKI are not graded. Initiation of RRT is advised in life-threatening changes in fluid, electrolyte and acid-base balance.

Extracorporeal therapy can either function as renal replacement (when no kidney function is present) or renal support RRT (as an adjunct to kidney function) (table 3).

Historically, timing of initiation of RRT was based on **serum urea**. However, serum urea is determined by many other variables that have no relation to kidney function [74]. In addition, recent studies could not demonstrate that urea differentiates between outcomes [75-77].

Metabolic acidosis is a complication that frequently occurs in ICU patients with AKI, but initiation of RRT in ICU patients with AKI and metabolic acidosis is still a matter of debate. As RRT does not treat the underlying cause of the acidosis, it can only provide restoration of homeostatic equilibrium and fluid balance, enabling specific therapeutic measures [78]. Numerous observational studies indicate **fluid overload** as an important determinant of worse outcomes [34-38]. Further, a subanalysis from the RENAL study showed that a negative fluid balance during CRRT was associated with better survival [79]. Therefore fluid

overload may be an important determinant for initiation of RRT. But also on this topic, prospective studies that randomized initiation of RRT based upon fluid status are absent.

Criteria for stopping renal replacement therapy

In literature, data considering the decision to stop RRT is even scarcer. Therefore KDIGO issues a pragmatic and non-graded recommendation that RRT should be discontinued when kidney function has recovered.

Anticoagulation

Patients without increased bleeding risk on intermittent RRT are recommended anticoagulation with unfractionated or low-molecular-weight heparin.

When CRRT is used, citrate anticoagulation is recommended, unless there are contra-indications for citrate such as reduced liver function or shock with reduced muscle perfusion. Data from 5 randomized studies showed that citrate based protocols were associated with longer filter life, less bleeding, and in 1 study also better survival [80-84].

Regional heparin anticoagulation, where unfractionated heparin is neutralized after the filter with protamine is not advised. This, because the longer half-life of heparin makes it extremely difficult to titrate.

In patients with heparin induced thrombocytopenia (HIT), heparin must be stopped, and thrombin inhibitors such as argatroban, or Factor Xa inhibitors (danaparoid or fondaparinux) are recommended.

Vascular access for renal replacement therapy in AKI

As in ESRD patients, central vein stenosis is more frequently seen in subclavian dialysis catheters [85, 86], KDIGO recommends the right jugular vein, followed by the femoral vein as the optimal insertion place.

Modality of RRT in AKI patients

Generally, the choice of modality of RRT is based on the availability of a specific modality or local experiences. A Cochrane Collaboration meta-analysis including RCTs that compared CRRT to IHD in AKI patients, could not demonstrate differences in hospital and ICU mortality, length of hospital stay or renal recovery [87, 88]. CRRT and IHD should therefore be seen as complementary therapies except for patients with AKI who are hemodynamically unstable or present with increased intracranial pressure. In these cases, CRRT is considered the optimal modality of RRT.

Dose of renal replacement therapy in patients with AKI

The concept of dialysis dose is frequently addressed in literature. However, the available evidence is limited and conflicting due to differences in study design and poor quality of reporting data [89]. Two recently published trials have assessed dialysis dose in critically ill patients with AKI. Both the RENAL and ATN trial compared high dose versus normal dose RRT and could not demonstrate differences in mortality or renal recovery [90, 91]. Based on these data, KDIGO recommends in IHD and extended dialysis to deliver a weekly Kt/V of 3.9.

For CRRT an effluent volume of 20-25 mL/kg/min is recommended. Because of down time, this will require a higher prescription.

Conclusions

The guidelines proposed by KDIGO propose an extensive overview of the current state of the art for AKI. The RIFLE and AKIN definitions for AKI have been modified into an updated version: the KDIGO definition and grading system. Similar to e.g. sepsis, early application of a bundle of measures is proposed for prevention of AKI: the "KDIGO AKI bundle". These include avoidance of nephrotoxic agents, optimizing hemodynamic status, guidelines for prevention of contrast associated AKI, and guidelines for processes of care for RRT.

Key points

- AKI is defined and staged by the KDIGO consensus definition and classification system, and prevention and treatment of AKI is best performed by early application of a "KDIGO AKI bundle" of measures.

- Hemodynamic optimization with isotonic crystalloids and vasopressors is the cornerstone for prevention of AKI

- Consider not using iodinated contrast in risk patients; stop NSAIDs, metformin, diuretics and other nephrotoxic drugs when possible, and prehydrate with NaCl0.9% or a bicarbonate solution.

- The optimal timing of RRT is uncertain, but RRT is advised in life-threatening changes in fluid, electrolyte and acid-base balance.

- High dose of RRT offers no benefit over a normal dose, but as the actual dose of RRT is lower than the delivered dose of RRT, the prescription should aim for a bit higher dose, and the dose delivered should be measured.

Acknowledgements

Tables

Table 1: definition and classification of AKI

a) AKI is defined by either an increase of Scr or an episode of oliguria:

- Increase of Scr ≥0.3 mg/dL within 48-hours, or

- Increase of Scr by ≥1.5-fold above baseline, know or assumed to have occurred within 7 days, or

- Urine volume < 0.5 mL/kg/h for 6 hours.

b) AKI severity is staged by the worst of either Scr changes or oliguria

Stage	Scr	Urine output
1	≥ 1.5 to 1.9 times baseline OR > 0.3 mg/dL increase	<0.5 mL/kg/h for 6-12 h
2	≥ 2.0 to 2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	≥ 3.0 times baseline OR Increase of Scr to ≥ 4.0 mg/dL OR RRT OR In patients <18y, decrease of eGFR to <35 mL/min per 1.73m2	<0.3 mL/kg/h for ≥ 24 h OR Anuria for ≥12 h

Table 2: Summary of the KDIGO recommendations for prevention and treatment of AKI

Hemodynamic management:

- Isotonic crystalloids rather than colloids

- Vasopressors in conjunction with fluids

- Protocol-based management of HD and oxygenation in perioperative setting or septic shock

Metabolism

- Target blood glucose at 110-149 mg/dL

- Energy intake of 20-30 kcal/kg/d

- Preferable enteral route

- Avoid protein restriction

    o 0.8-1.0 g/kg/d of protein in non-catabolic AKI without RRT

    o 1.0-1.5 g/kg/d of protein in AKI on RRT, up to 1.7 g/kg/d in patients on CRRT and hypercatabolic patients

Pharmacologic management

- No diuretics for prevention or treatment of AKI

- No dopamine for prevention or treatment of AKI

- No fenoldopam for prevention or treatment of AKI

- No NAC for prevention of AKI in hypotension and postsurgery.

- No atrial natriuretic peptide for prevention or treatment of AKI

- No recombinant human Insuline Growth Factor-1 ((rh)IGF-1) for prevention or treatment of AKI

- No aminoglycosides unless no suitable, less nephrotoxic alternatives are available

    o Aminoglycosides: once daily

- Monitor drug level in multiple dosing after 24-h, and in once daily dosing when more than 48-h

- Use topical or local instead of iv

- Amphotericine B:

  - Lipid formulations

  - Prefer azoles/echinocandins

Non-pharmacologic management

- OPCAB not for AKI reasons

Contrast-induced AKI

- Define CI-AKI according to the KDIGO definition

- Assess risk for CI-AKI

- Consider not using contrast

- Use low- or iso-osmolar contrast

- Pre-, and post-hydrate with saline or bicarbonate solution

- Oral NAC, no IV NAC

- Insufficient data on fenoldopam and theophyllin

- No RRT

Table 3: potential applications for RRT

1. Renal replacement: when there is no residual kidney function

a. Life threatening indications
Hyperkalemia
Acidemia
Pulmonary edema
Uremic complications (pericarditis, bleeding, etc)

b. Nonemergent indications
Solute control
Fluid removal
Correction of acid-base abnormalities

2. Renal support: RRT is used as an adjunct
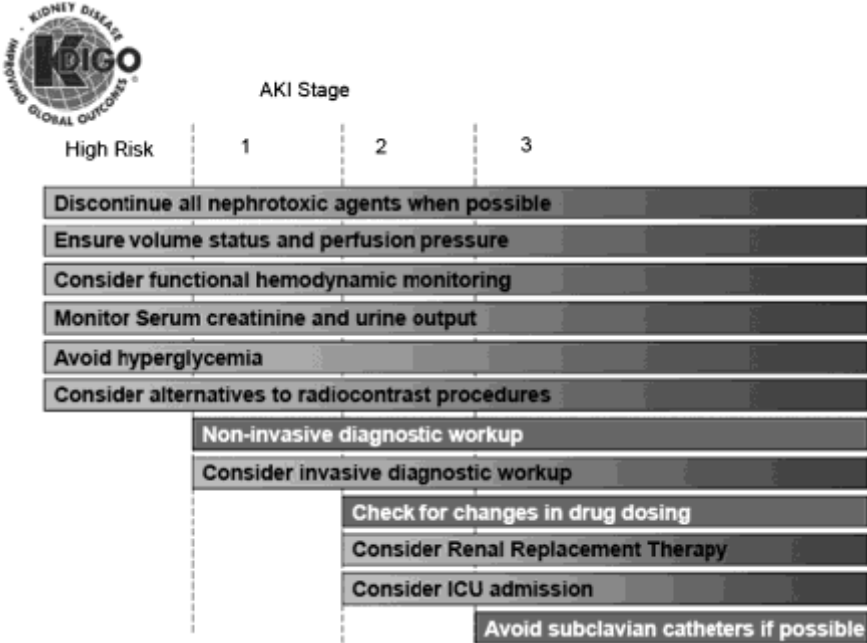Volume control
Nutrition
Drug delivery
Regulation of acid-base and electrolyte status
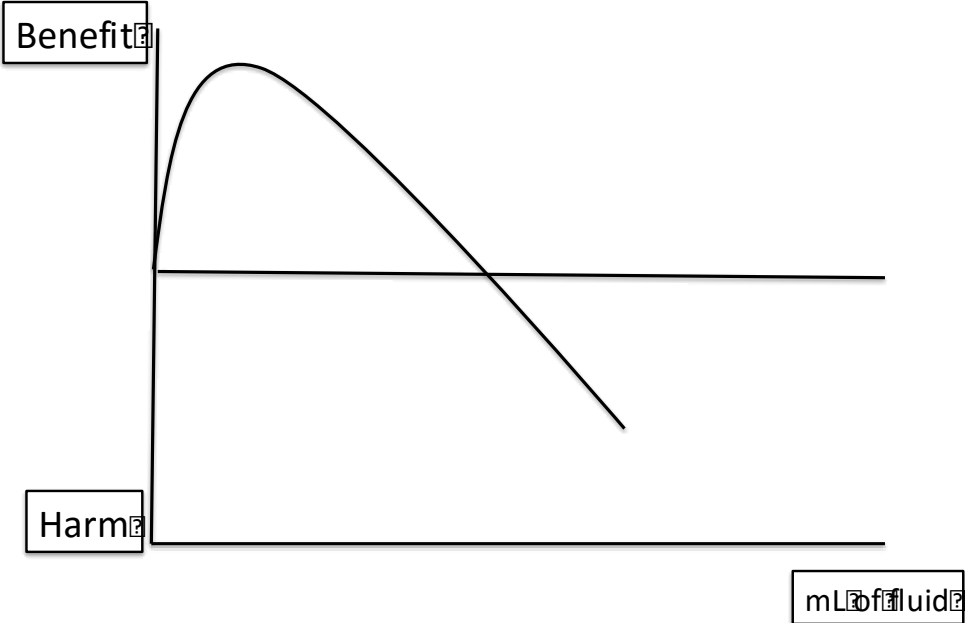Solute modulation

Figures:

Figure 1: The KDIGO AKI bundle: AKI-stage based management

Legend: reproduced with permission from [3].

Figure 2: Relationship between fluid volume administered and beneficial and adverse effects.

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