

## An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient

### An International Consensus Conference in Intensive Care Medicine

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**Objectives:** To address the issues of Prevention and Management of Acute Renal Failure in the ICU Patient, using the format of an International Consensus Conference.

**Methods and Questions:** Five main questions formulated by scientific advisors were addressed by experts during a 2-day symposium and a jury summarized the available evidence: (1) Identification and definition of acute kidney insufficiency (AKI), this terminology being selected by the Jury; (2) Prevention of AKI during routine ICU Care; (3) Prevention in specific diseases, including liver failure, lung injury, cardiac surgery, tumor lysis syndrome, rhabdomyolysis and elevated intraabdominal pressure; (4) Management of AKI, including nutrition, anticoagulation, and dialysate composition; (5) Impact of renal replacement therapy on mortality and recovery.

**Results and Conclusions:** The Jury recommended the use of newly described definitions. AKI significantly contributes to the morbidity and mortality of critically ill patients, and adequate volume repletion is of major importance for its prevention, though correction of fluid deficit will not always prevent renal failure. Fluid resuscitation with crystalloids is effective and safe, and hyperoncotic solutions are not recommended because of their renal risk. Renal replacement therapy is a life-sustaining intervention that can provide a bridge to renal

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The International Consensus Conference in Intensive Care Medicine considering the "Prevention and Management of Acute Renal Failure in the ICU Patient" was held in Montreal, Canada, on 3–4 May 2007. It was sponsored by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the Société de Réanimation de Langue Française.

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**recovery; no method has proven to be superior, but careful management is essential for improving outcome.**

## EXECUTIVE SUMMARY

The International Consensus Conference in Intensive Care Medicine considering the "Prevention and Management of Acute Renal Failure in the ICU Patient" was held in Montreal, Canada, on 3–4 May 2007. Five questions formulated by scientific advisors were addressed by experts during a 2-day symposium, and a jury summarized the available evidence in response to the following questions: (1) How can we identify acute renal failure? This question included issues of definitions, outcomes, biomarkers, and risk factors. (2) What can we do to protect against the development of acute renal failure during routine ICU care? This question addressed the role of fluids and their type, use of vasopressors, and prevention against the nephrotoxicity of different agents including contrast dyes and antibiotics. (3) Can we prevent acute renal failure from developing in specific disease states? The different diseases included liver failure, lung injury, cardiac surgery, tumor lysis syndrome, rhabdomyolysis, and elevated intraabdominal pressure. (4) How should we manage a patient who is critically ill who develops acute renal failure? This topic included general management, nutrition, anticoagulation, and dialysate composition. (5) What is the impact of renal replacement therapy on mortality and recovery? This last question addressed issues regarding filter membranes, timing, dose, and mode of renal replacement therapy. The panel recommended the use of newly described definitions and found the designation "acute kidney insufficiency" (AKI) to be the most appropriate. The jury indicated that AKI significantly contributes to the morbidity and mortality of patients who are critically ill, stressed the importance of adequate volume repletion for prevention of AKI, although correction of fluid deficit will not always prevent renal failure. Indeed, when hemodynamics are considered satisfactory, persistent fluid challenges should be avoided if they do not lead to an improvement in renal function or if oxygenation deteriorates. Risk factors for AKI include age, sepsis, cardiac surgery, infusion of contrast medium, diabetes, rhabdomyolysis, and preexisting renal disease, as well as hypovolemia and shock. Fluid resuscitation with crystalloids is as effective and safe as resuscitation with hypooncotic colloids, but hyperoncotic solutions are not recommended for this purpose because of their renal risk. The panel recommended abandoning the use of low-dose dopamine to improve renal function. In case of kidney failure, renal replacement therapy is a life-sustaining intervention that can provide a bridge to renal recovery. The panel indicated that traditional triggers for this treatment derived from studies in chronic renal failure may not be appropriate for critically ill patients with AKI, and when renal support is indicated because of metabolic derangements, treatment should not be delayed. Characteristics of dialysate composition and temperature can greatly improve the hemodynamic tolerance of intermittent hemodialysis. There is no evidence that the use of intermittent hemodialysis or continuous hemofiltration clearly produce superior renal recovery or survival rates in general ICU patient populations. Our understanding of how to optimally prevent, diagnose, and manage AKI in critical illness requires a great deal of additional research.

## METHODS

Despite the decision to use a systematic approach to developing clinical practice guidelines by the ATS in 2006 (1), the

consensus panel method was used. The application for this statement predates the ATS decision. The methods of the consensus were previously established by the National Institutes of Health (2) and adapted subsequently for use in critical care medicine (3). Briefly, the process comprised four phases. First, five key questions were formulated by the Scientific Advisors designed to address issues integral to the prevention and management of acute renal failure in its current and future roles. Second, a comprehensive literature search was performed, and key articles were precirculated to a jury of eleven clinician scientists, referred to as the panel, who were not experts in the field under discussion. Third, authorities in acute renal failure selected by the Organizing Committee and Scientific Advisors delivered focused presentations during a two-day symposium attended by the panel and approximately 200 delegates. Each presentation was followed by debate and discussion. Finally, the panel summarized the available evidence in response to the questions generated over the 2 days immediately after the conference. The panel members did not only rely on experts and scientific advisors, but tried to make their own critical appraisal of the literature with the help of scientific advisors. Debated issues were discussed openly during the 2-day meeting and later by electronic mail after the conference. The panel tried to be careful before making recommendations and considered experimental data, physiological reasoning, and pathophysiological observations, as well as evidence from clinical observations and clinical trials. When insufficient clinical experience existed, the panel tried to carefully weigh the possible risks or side effects of any intervention or drug versus their potential benefits. It was also recommended to the panel to use a standardized format for the recommendations (see examples of implications of strong and weak recommendations for different groups of guideline users [1]). Recommendations are therefore written as close as possible to these standards, although the recommended phrasing could not be adopted in every case. The text below reviews the relevant literature for each question and its interpretation by the panel. Each question is concluded by the recommendations approved by all panel members. In some cases, proposals for future investigations in this specific field are listed.

## I. HOW CAN WE IDENTIFY ACUTE RENAL FAILURE?

### I.1. Definition

**Problems with definitions.** Proper study design and comparison of different studies can only occur when there is a consensus on definitions of the condition of interest. Agreement on the definition of acute renal failure is essential in a symposium on the prevention and management of acute renal failure in an ICU patient. The designation "acute renal failure" seems too broad and there is currently a preference for the term "acute kidney injury" (AKI) (4, 5). The acute dialysis quality initiative came up with criteria for different stages of renal injury summarized by the acronym RIFLE, which stands for risk, injury, failure, loss and end-stage kidney. This was subsequently modified by the Acute Kidney Injury Network (AKIN) criteria, with few comparisons between the two systems (Table 1) (4, 6). Another graded score is the Sequential Organ Failure Assessment (SOFA) renal subscore (7, 8). The advantage of these terms is that renal (or kidney) failure appears to be an end-stage process, and the stages before failure are of high clinical interest. The "injury" component is also problematic because in the early stages the rise in blood urea nitrogen (BUN) and creatinine may be more representative of a change in function rather than of frank injury. Injury ought to refer to histopathologic changes rather than to clinical criteria. In one postmortem

TABLE 1. COMPARISON OF THE RIFLE AND AKIN DEFINITION AND CLASSIFICATION SCHEMES FOR AKI

RIFLE Category	Serum Creatinine Criteria	Urine Output Criteria
A. The acute dialysis quality initiative (ADQI) criteria for the definition and classification of AKI (i.e., RIFLE criteria)		
Risk	Increase in serum creatinine $\geq 1.5 \times$ baseline or decrease in GFR $\geq 25\%$	$<0.5$ ml/kg/h for $\geq 6$ h
Injury	Increase in serum creatinine $\geq 2.0 \times$ baseline or decrease in GFR $\geq 50\%$	$<0.5$ ml/kg/h for $\geq 12$ h
Failure	Increase in serum creatinine $\geq 3.0 \times$ baseline or decrease in GFR $\geq 75\%$ or an absolute serum creatinine $\geq 354$ $\mu\text{mol/L}$ with an acute rise of at least $44$ $\mu\text{mol/L}$	$<0.3$ ml/kg/h $\geq 24$ h or anuria $\geq 12$ h
B. The proposed acute kidney injury network (AKIN) criteria for the definition and classification of AKI		
Stage 1	Increase in serum creatinine $\geq 26.2$ $\mu\text{mol/L}$ or increase to $\geq 150$ – $199\%$ (1.5 to 1.9-fold) from baseline	$<0.5$ ml/kg/h for $\geq 6$ h
Stage 2	Increase in serum creatinine to 200–299% ( $>2$ – $2.9$ fold) from baseline	$<0.5$ ml/kg/h for $\geq 12$ h
Stage 3	Increase in serum creatinine to $\geq 300\%$ ( $\geq 3$ -fold) from baseline or serum creatinine $\geq 354$ $\mu\text{mol/L}$ with an acute rise of at least $44$ $\mu\text{mol/L}$ or initiation of RRT	$<0.3$ ml/kg/h $\geq 24$ h or anuria $\geq 12$ h

Definition of abbreviations: GFR = glomerular filtration rate; RRT = renal replacement therapy.

Adapted from Reference 6;

study, most of the patients labeled as acute tubular necrosis did not have necrosis or excessive apoptosis (9). Other terms used are “dysfunction,” which is a broad term that refers to any deviation of renal function from normal, or “insufficiency” referring to inadequate function relative to the need, which may or may not indicate dysfunction. It may be better to interpret the “I” in AKI as renal “insufficiency” rather than “injury” because it indicates inadequate renal function for the metabolic need.

The RIFLE kidney criteria (4) were an important step forward in defining patients with renal insufficiency as well as prognosticating and assessing prevalence (10–15). The classification system includes separate criteria for creatinine and urine output (Table 1). However, the criteria are not specific and will likely not be useful for predictions in individual ICU patients. The RIFLE criteria do not have a time component for creatinine and thus do not allow for analysis of an otherwise dynamic process and cannot be used to assess the time course. For example, a rise in creatinine of 1 mg/dl in 24 hours is clearly more significant than the same rise in 4 days. There is also a problem with using ratios when the magnitude of the denominators spans a wide range. Because even small rises in creatinine have been shown to have a substantial impact on mortality (16, 17), the RIFLE criteria were modified to create the Acute Kidney Injury Network (AKIN) criteria, which define AKI as an abrupt (within 48 h) reduction in kidney function (Table 1). The urine output criteria will likely be more important for critical care physicians than measurements of creatinine for urine is usually measured on an hourly basis and can rapidly identify risk. The SOFA renal subscore includes different degrees of creatinine or urine output and thus allows for evaluation over time and an assessment of prognosis. “Operational” definitions, in addition to these scoring systems, will be required for case-specific questions. High  $K^+$ , excess volume, high phosphate, or acidemia, can trigger the need for renal replacement therapy (RRT) even without high values of creatinine (18).

The criteria for recovery has been defined as complete or incomplete where complete means return to the baseline condition within the RIFLE criteria, and incomplete means a persistent abnormality by RIFLE criteria but discontinuation of RRT (4). These criteria will undergo further refinement. The lack of a previous definition for AKI makes a detailed assessment of the literature difficult regarding the natural evolution of this dysfunction and its influence on outcome.

**Causes of AKI.** The causes of AKI can be classified as prerenal, postrenal or renal. Prerenal AKI is mainly caused by a reduction in renal perfusion, which can be due to loss of intravascular volume or an obstruction of renal flow. Renal causes of AKI may be due to vascular disorders, nephritis, or acute tubular necrosis; postrenal AKI is mainly caused by extrarenal direct obstruction of the urinary tract or intrarenal obstruction due to crystals.

Management should begin with consideration of prerenal, renal or postrenal causes (19). A postrenal etiology is relatively easy to rule out using renal ultrasound. Urine analysis remains very important for the separation of prerenal and renal failure. The excreted fraction of  $\text{Na}^+$ , urine  $\text{Na}^+$ , urine osmolality and urine creatinine plasma ratio, and urinalysis are used to separate prerenal from renal causes, but the clinical context and fluid balance should also be included in the analysis. However, Bagshaw and colleagues (20) found that in sepsis, these urinary biochemical changes were not reliable markers of renal hypoperfusion (at least with a single determination). Their systematic review reported that the scientific basis for the use of urinary biochemistry indices in patients with septic AKI is weak (20).

#### Panel conclusions.

- We propose using the phrase “acute kidney insufficiency” (AKI), which is preferable to “acute renal failure” and that the “I” in AKI refers to insufficiency instead of injury.
- We propose AKI definitions be based on the criteria of AKIN or RIFLE. The AKIN definition allows earlier recognition of AKI rather than RIFLE and thus might constitute the preferred criteria in the ICU, but it needs further validation in the clinical setting. SOFA renal subscores may be useful to evaluate AKI time course.

#### 1.2. What Is the Incidence and Outcome of Renal Failure in ICU Patients?

The overall incidence of AKI is difficult to assess and varies among different study populations in developing countries, with an overall range from 1 to 25% in critically ill patients (18). The BEST (Beginning and Ending Supportive Therapy for the Kidney) study investigated the incidence of acute renal failure on an international scale among 29,629 patients from 54 centers in 23 countries (21). The prevalence of AKI requiring renal replacement therapy (RRT) was approximately 4% and hospital mortality in these patients was approximately 60%, which is similar to numerous other studies. Data collection was limited to 28 days, and information was not obtained on later events. Other data suggest that occurrence of AKI reaches a plateau only after 30 to 60 days. In a large European study on 3,147 adult patients who were critically ill, the need for hemofiltration and hemodialysis was reported to be 7 and 5% respectively, and reached 13 and 7% when patients suffered from sepsis (22).

Based on the RIFLE criteria assessments of heterogeneous ICU patients, investigators found that hospital mortality with AKI is in the range of 5 to 10% with no renal dysfunction, 9 to 27% in patients classified as at risk, 11 to 30% with injury, and 26 to 40% with failure (11, 13, 23).

Studies to date fail to give an indication of the causes of mortality in the patients with AKI. In addition, patients who develop acute in addition to chronic acute kidney insufficiency may need to be individualized. Thus, although AKI is a significant risk factor for death in multivariable regression analysis (24), it is not possible to know whether there is a cause and effect relationship or whether AKI is just a marker of disease severity.

#### Research recommendations.

- We conclude that attention needs to be paid to study population characteristics when assessing the incidence of AKI in future studies. In addition, the “time” component needs to be better characterized in criteria for AKI and the specific causes of mortality in patients with AKI need to be investigated further.

### I.3. Do Creatinine-clearance Markers and Other Biomarkers Help Identify Early Acute Kidney Injury?

**Serum value and creatinine clearance.** There are important limits to the usefulness of creatinine and creatinine clearance in identifying early AKI. However, serum creatinine is readily available and should continue to be the primary guide for the assessment of renal dysfunction. Factors affecting creatinine, including body size, catabolic state, presence of rhabdomyolysis, dilutional effects and drugs, or other substances that affect its secretion, need to be considered when interpreting results (18). BUN is affected by even more factors than creatinine but correlates better with uremic complications. Observing changes in serum creatinine over shorter periods of time and the use of 6-hour creatinine clearance can be useful (25). Prediction equations can be used to estimate the glomerular filtration rate (GFR) from serum creatinine. In adults, the most commonly used formulae for estimating GFR are those derived from the Modification of Diet in Renal Disease (MDRD) study population (26) and that by Cockcroft and Gault (27). When creatinine is changing quickly, however, standard steady-state formulae for calculating creatinine-clearance cannot be used to predict the glomerular filtration rate. Caution should be applied in using these formulae to estimate glomerular filtration rate for therapeutic decisions (28). Furthermore, clearance calculations cannot be performed in oligo-anuric patients.<sup>1</sup>

**New markers of AKI.** Many new markers of AKI are being investigated (28). These markers can be considered physiological, such as with creatinine, or as markers of injury.

Cystatin-C is a 13 kD endogenous cysteine-proteinase inhibitor that is produced by all cells and is undergoing evaluation as a physiological biomarker (28, 29). It is freely filtered across the glomerulus and, in contrast to creatinine, it is not secreted by renal epithelial cells. Importantly, serum cystatin-C has been shown to rise earlier than creatinine in ICU patients with AKI (29–31).

Urinary neutrophil gelatinase (NGAL) (32), kidney injury molecule-1 (33) and interleukin-18 (34) are urinary markers that are being evaluated for their potential to separate prerenal from postrenal causes of AKI, but their discriminating power has not been high. Notably, these markers will not be useful when marked oliguria is present. The usefulness of new markers should be compared with composite endpoints based on currently available markers including creatinine, BUN and the

<sup>1</sup>MDRD equation for GFR:  $170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times \text{SUN}^{-0.170} \times \text{SAlb}^{+0.318}$  (0.762 female)  $\times$  (1.180 black); Cockcroft and Gault equation for GFR:  $\{[(140 - \text{age}) \times \text{weight}]/[72 \times \text{SCr} (\text{mg/dl})]\} \times (0.85 \text{ if female})$ . SCr = serum creatinine (mg/dl); SUN = serum urea nitrogen (mg/dl); SAlb = serum albumin (g/dl)

ratio of urine to blood, fractional excretion of sodium, urine output, and analysis of urine sediment (18, 20, 28).

#### Panel recommendations.

- We recommend that serum creatinine remain as the primary biomarker (in association with urine output when available) for evaluating the clinical evolution of patients with AKI.
- In patients who are not in steady state, we recommend that creatinine measurements should not be used in standard formulae for estimating clearance. *Remark:* In particular, these formulae do not apply to patients with oliguria or anuria.
- In patients who have not received diuretics, we suggest that clinicians use the excreted fraction of  $\text{Na}^+$  and urinalysis for distinguishing AKI due to inadequate renal perfusion from intrinsic renal causes. *Remark:* These tests have many limitations especially in patients with sepsis. Biomarkers for kidney injury are currently being tested but are not yet ready for regular use.

#### Panel conclusions.

- To assess glomerular filtration rate, creatinine clearance can be measured reliably over 6 hours. Techniques over shorter time periods would be highly desirable but are not currently available.

Cystatin-C is a promising marker in situations where changes in creatinine secretion are an issue and where detecting rapid changes in glomerular filtration rate is important, but further clinical evaluation is needed.

### I.4. How Should We Assess Renal Perfusion in an ICU Patient?

Several methods to measure and/or estimate renal perfusion have been suggested, however, all have limited clinical usefulness in the ICU setting. The possible techniques include clearance of dyes (para-aminohippurate) (35), isotopic markers, Doppler (36), thermal dilution (37, 38), magnetic resonance imaging (39) and CT angiography (40). Some authors (41) suggest that Doppler-based determination of resistive index on Day 1 in patients with septic shock may help identify those who will develop AKI. However, the significance of flows cannot be determined without simultaneously obtaining information on renal function (glomerular filtration rate, clearance, excreted fraction of  $\text{Na}^+$ ) and oxygen consumption. For example, flow is low when metabolic activity is low, but this does not mean that it cannot increase if metabolic need increases. Doppler measurements can be useful in anuric patients or patients with kidney transplant (42) but primarily through the use of a yes/no type of answer (is flow present or not). Doppler studies are technically difficult and require an experienced operator as well as baseline data before the insult, especially in patients who are obese (36). Their use is promising in specific categories of patients but cannot be recommended at this time as a routine examination in patients who are critically ill. Clinical evaluation is always important for the correct interpretation of these data. The difficulties in doing these techniques also somewhat limit their usefulness to research settings.

#### Research questions.

- Develop accurate methods to measure renal blood flow and metabolic renal activity.

### Panel recommendations.

- We suggest Doppler measurements for assessing renal viability, by determining whether there is flow, in patients with kidney transplant or with anuria who possibly have cortical necrosis. *Remarks:* Quantitative measures of flow are currently reserved for research purposes at this time and, optimally, should be combined with measures of renal function and oxygen consumption.

## I.5. Can We Predict Which Patient in the ICU Will Develop Acute Renal Failure?

Risk factors for AKI have been well established (21) but are so broad and nonspecific that they do not provide much guidance for the establishment of preventative trials. Risk factors include age (19), sepsis (43), cardiac surgery (44, 45), infusion of contrast (46), diabetes, rhabdomyolysis, preexisting renal disease (47–50), hypovolemia, and shock. Many other factors are associated with an increased incidence of AKI but their impact will be highly dependent on the specific nature of the population.

### Panel recommendations.

- We recommend that specific prevention programs in the ICU target patients with established risks of AKI such as advanced age, sepsis, cardiovascular surgery, contrast nephropathy, rhabdomyolysis, and diabetes.
- In patients at particularly high risk of AKI, such as patients with preexisting renal disease, we recommend meticulous management of these patients to prevent AKI.

## II. WHAT CAN WE DO TO PROTECT AGAINST DEVELOPING ACUTE RENAL FAILURE DURING ROUTINE ICU CARE?

### II.1. Is Fluid Resuscitation Helpful in Preventing Acute Kidney Insufficiency?

**Renal hypoperfusion.** For fluid resuscitation to uniformly prevent AKI, the dominant mechanism responsible for its development needs to be renal hypoperfusion (prerenal azotemia). This pathophysiologic framework, however, does not recognize that, in patients who are critically ill, AKI commonly involves multiple mechanisms, including hypovolemia and various types of shock. For example, sepsis and trauma can cause AKI through a combination of renal hypoperfusion and the release of endogenous nephrotoxins (51, 52). Therefore, it is not surprising that, in a recent prospective investigation conducted in 129 septic patients, 19% required RRT despite aggressive fluid resuscitation (53). Similarly, aggressive fluid resuscitation in battlefield casualties decreases, but does not eliminate, the risk of developing AKI (54). This means that, when hemodynamics are considered satisfactory and have promoted resuscitation of extra-renal organs, persistent fluid challenges should be avoided if they do not lead to an improvement in renal function, or if oxygenation deteriorates (55). In other words, correction of fluid deficit, while essential, will not always prevent renal failure.

Besides patients with prerenal azotemia, specific groups of patients may benefit from fluid administration to prevent AKI—even if renal hypoperfusion is not its prevailing mechanism. These specific conditions include myoglobinuria, surgery, the use of nephrotoxic drugs such as of amphotericin B, platinum, and contrast media, and the use of drugs associated

with tubular precipitation of crystals such as acyclovir, sulphonamides, and methotrexate (51).

**Volume status and resuscitation strategies.** In addition to the multifactorial nature of AKI, a second difficulty in assessing the role of fluid resuscitation in preventing AKI is the limited accuracy of current diagnostic techniques to determine volume status (56) and the absence of practical tests to quantify renal blood flow. Then, diagnosis of prerenal azotemia can be made with certainty only retrospectively in accordance to the response to fluids. Also, it is often difficult for clinicians to gauge the amount of fluids to administer to a given patient. Insufficient fluid exposes the patient to the risk of underperfusion of vital organs including the kidneys. Excess volume administration can lead to pulmonary edema (52), and precipitate the need for mechanical ventilation (54, 57).

Studies that are specifically designed to determine the impact of resuscitation strategies on renal function have not been conducted. Indirect data can be used, however, to shed some light on this topic (see the online supplement for more details). A study performed to analyze the effect of pulmonary artery catheters on morbidity and mortality in a mixed group of 201 patients who were critically ill (58) found a higher incidence of AKI on Day 3 postrandomization in the pulmonary artery catheter group than in the control group (35 vs. 20%,  $P < 0.05$ ). The greater incidence of AKI occurred even though patients managed with pulmonary artery catheters received more fluids in the first 24 hours. Similarly, the results of the Fluids and Catheters Treatment Trial (FACTT) (57) suggest that, in selected patients with acute lung injury, conservative fluid management may not be detrimental to kidney function. Mean fluid balance over 7 days was  $-136$  ml in the conservative group versus  $+6,992$  ml in the liberal fluid strategy group. In addition, compared with the liberal strategy, the conservative strategy increased the number of ventilator-free days, reduced the number of ICU days, and had similar 60-day mortality. These benefits were not associated with an increase in the frequency of RRT, which occurred in 10% of the conservative-strategy group and 14% of the liberal-strategy group, despite slightly higher creatinine values in the conservative-strategy group. Several points limit the application of this study in the development of recommendations for patients who are critically ill. The study was not designed to assess different fluid management strategies to prevent AKI in critically ill patients, and no patient with overt renal failure was enrolled. Hemodynamics and filling pressures of most patients were already optimal at enrollment. Also, Serum creatinine was the marker of kidney function, which has limitations in identifying early AKI or distinguishing prerenal azotemia and AKI (54). Last, no data on the recovery of kidney function was provided, whereas many critically ill patients with AKI have preexisting chronic kidney disease (59).

It is unknown whether the current recommendation to maintain a mean arterial pressure (MAP) at or above 65 mm Hg in patients who are critically ill (60) is adequate for preventing AKI. It is likely that some patients—especially those with history of hypertension and the elderly—may require higher MAP to maintain adequate renal perfusion.

**Research questions.** Investigations are required to:

- Identify specific targets of MAP and cardiac output to achieve appropriate renal blood flow for each individual patient.
- Identify biomarkers that allow early detection of prerenal azotemia, track response to therapy, and differentiate

between prerenal azotemia and AKI in patients with or without preexisting kidney disease.

- Determine whether resuscitation strategies titrated according to measures of renal blood flow (or other biomarker of renal perfusion) can improve renal outcome and patient outcome.

#### **Panel recommendations.**

- We recommend hemodynamic optimization to reduce the development (and progression) of AKI of any cause. In particular, we recommend adequate volume loading and use of vasopressors as needed to reach a sufficient mean arterial pressure. *Remark:* The optimal fluid resuscitation to prevent AKI is unknown. A MAP target of at least 65 mm Hg appears appropriate for most patients except for those with a history of long-standing hypertension or for the elderly where autoregulation of renal blood flow might be impaired, and thus MAP above 65 mm Hg may be required.
- For risks other than renal hypoperfusion or hypertension and risks of renal injury from myoglobinuria, tumor lysis syndrome, or following the administration of certain medications and contrast media, we suggest volume loading to establish high urine flow.

## **II.2. Should We Use Crystalloids or Colloids for Fluid Resuscitation?**

Fluid resuscitation is the therapeutic cornerstone for patients with renal hypoperfusion due to absolute or relative hypovolemia (when hypoperfusion results from reduced renal perfusion pressure, e.g., sepsis or liver failure, or reduced cardiac output, e.g., severe congestive heart failure, fluid administration does not necessarily correct renal function). Crystalloids (electrolytes and small molecules with no oncotic properties) and colloids (containing molecules of molecular weight usually >30 kDA) are the two broad categories of fluids used (61). Crystalloids have no oncotic power and their volume-expansion effect is based on their sodium concentration. They pass freely across the capillary membrane. Crystalloids distribute to the whole extracellular space, and only a portion remains in the bloodstream (62). This increases the risk for tissue edema (63). Hyperchloremic acidosis has been reported in surgical patients resuscitated using large volume of saline, whereas in patients with shock, a large volume of saline can reverse acidosis (64, 65).

Colloids can be synthetic (gelatins, dextrans, hydroxyethylstarches) and natural (albumin). Due to larger molecular weight, colloids remain in the bloodstream longer than crystalloids (62). This favorable characteristic is reduced when capillary permeability is increased (62). The oncotic pressures and, thus, the capacity of commercially available colloids to increase plasma volume are not uniform. Hyperoncotic solutions (dextrans, hydroxyethylstarches, and 20–25% albumin) have the highest volume expansion effect. Hypooncotic solutions (gelatins and 4% albumin) have a volume expansion effect that is lower than the volume infused (50).

Although experimental studies have found advantages of colloids over crystalloids in restoring systemic and regional circulations (66), no large Randomized Controlled Trial (RCT) (67) or meta-analysis (68, 69) has shown better survival using colloids (natural or synthetic, hypooncotic or hyperoncotic) than using crystalloids. Hypooncotic colloids are not superior to crystalloids in protecting the kidneys (53, 67), except for

a subset of patients with liver disease (70). Moreover, hyperoncotic colloids can be associated with development of renal dysfunction (50, 53, 71, 72).

In the Saline versus Albumin Fluid Evaluation (SAFE) Study (67), nearly 7,000 patients who were critically ill were fluid resuscitated with either 4% albumin or 0.9% saline. At completion, there were no differences between the groups in the percentage of patients who required RRT (1.3 and 1.2%), in the mean ( $\pm$  SD) number of days of RRT ( $0.5 \pm 2.3$  and  $0.4 \pm 2.0$ , respectively;  $P = 0.41$ ) and in the number of days of mechanical ventilation ( $4.5 \pm 6.1$  and  $4.3 \pm 5.7$ , respectively;  $P = 0.74$ ).

More recently, multicenter international investigation of more than 1,000 patients in shock (50) concluded that fluid resuscitation with crystalloids or gelatin was associated with a lower incidence of AKI than resuscitation with artificial hyperoncotic colloids (dextran in 3% of patients and starches in 98% of patients) (adjusted odds ratio, 2.48) or hyperoncotic albumin (adjusted odds ratio, 5.99); the incidence of renal adverse events was similar in patients resuscitated using modern starches (i.e., 130 kD/0.4) or older starches. Similarly, in the recent VISEP study (72) of more than 500 patients with severe sepsis, fluid resuscitation with hyperoncotic colloids (hydroxyethylstarch 200 kD/0.5) was associated with higher incidence of renal dysfunction and need for RRT than in patients resuscitated with crystalloids. Decreased glomerular filtration pressure due to increased intracapillary oncotic pressure and (direct) colloid nephrotoxicity (osmotic nephrosis) are the two purported mechanisms responsible for the higher incidence of renal dysfunction with hyperoncotic colloids than with crystalloids or hypooncotic colloids (73). In addition, many adverse effects have been described using synthetic colloids (73). These include anaphylactic and anaphylactoid reactions, blood coagulation disorders, and, in the case of starches, also liver failure and pruritus.

#### **Research questions.**

- Investigations are required to identify subpopulations of patients in whom colloids might be preferred over crystalloids to preserve glomerular filtration pressure.
- Investigations are required to further compare the efficacy of albumin versus crystalloid resuscitation in preserving the glomerular filtration pressure of patients who are hypoalbuminemic.
- Investigations are required to further assess the potential renal adverse effects of hyperoncotic colloids other than hydroxyethylstarches.

#### **Panel recommendations.**

- We consider fluid resuscitation with crystalloids to be as effective and safe as fluid resuscitation with hypooncotic colloids (gelatins and 4% albumin).
- Based on current knowledge, we recommend that hyperoncotic solutions (dextrans, hydroxyethylstarches, or 20–25% albumin) not be used for routine fluid resuscitation because they carry a risk for renal dysfunction.

## **II.3. What Is the Role of Vasoactive Drugs to Protect against the Development of Acute Renal Failure?**

**Treatment of hypotension.** Persistent hypotension (MAP <65 mm Hg), despite ongoing aggressive fluid resuscitation or after optimization of intravascular volume in patients with shock, places patients at risk for development of AKI. In patients with persistent hypotension, vasopressors are used to increase MAP

and/or cardiac output with the goal of ensuring optimal organ perfusion, including renal perfusion. Ideally, to protect against the development of AKI, vasopressors should be titrated based on their effects on renal blood flow and glomerular filtration. Such information is not clinically available, and vasopressors are titrated according to extrarenal hemodynamic variables such as MAP (a surrogate of renal perfusion pressure), cardiac output, and/or global oxygen supply/demand parameters. The impact of such titration on kidney perfusion is inferred from the observed change in urine output, serum creatinine, and/or creatinine clearance.

Titration of vasopressors to a MAP of 85 mm Hg versus 65 mm Hg has been tested in two small clinical trials using norepinephrine (74, 75). In both studies, higher MAP was associated with increased cardiac output but no difference in urine output or creatinine clearance. In an earlier investigation, the rate of AKI was not decreased by the normalization of mixed venous oxygen saturation or by increasing oxygen delivery to supranormal levels (76, 77).

**Type of vasopressor.** In patients with sepsis, small open-label studies have shown improvement in creatinine clearance following a 6- to 8-hour infusion of norepinephrine (78) or terlipressin (79). In patients with sepsis, vasopressin reduced the need for norepinephrine and increased urine output and creatinine clearance (80). Results of the Vasopressin and Septic Shock Trial (VASST) (81) conducted in nearly 800 patients with sepsis suggests that, compared with norepinephrine, vasopressin may reduce the progression to severe AKI only in a prespecified subgroup of patients with less severe septic shock (norepinephrine dose  $<15 \mu\text{g}/\text{minute}$ ) (81). No difference was observed in the need for RRT in any subgroup. In patients who have undergone surgery, relatively small studies suggest that perioperative hemodynamic optimization using epinephrine, dopexamine, or dobutamine may improve overall outcome (82, 83). It remains unclear whether perioperative hemodynamic optimization decreases the incidence of AKI in these surgical patients. Until the results of ongoing trials regarding the merit of different vasopressors become available, norepinephrine alone or in combination with other vasoactive drugs such as dobutamine and/or vasopressin constitutes a reasonable initial choice to attempt to maintain kidney perfusion and function in septic patients (84).

Current clinical data are insufficient to conclude that one vasoactive agent is superior to another in preventing development of AKI (85).

**Dopamine and dobutamine.** Stimulation of renal dopamine receptor-1 can increase renal blood flow (86). In patients with or at risk for—AKI, low-dose dopamine may increase diuresis on the first day of use but it does not protect against the development of AKI (86). The latest meta-analysis and RCT both confirmed the lack of protective effect of dopamine against kidney dysfunction, and in patients with AKI, low-dose dopamine has the potential to worsen renal perfusion and function (86, 87). In human studies, dobutamine has been reported to increase renal blood flow in some studies (88) but not consistently so (89, 90). Fenoldopam, a short-acting dopamine receptor-1 agonist, has been tested in a prospective study of 160 ICU patients to determine whether it can decrease the need for RRT and improve a 21-day survival (91) in patients with evidence of early AKI (serum creatinine increased 50% or more). Fenoldopam did not affect the need for RRT and survival at 21 days. In secondary analysis, however, fenoldopam reduced the need for RRT and the incidence of death in patients without diabetes and in postoperative patients who have undergone cardiothoracic surgery. A recent meta-analysis suggests that fenoldopam may decrease the need for RRT and

mortality (92). Further investigations are needed assess these results. Atrial natriuretic peptide is another renal vasodilator that has been used with mixed results (93, 94).

**Research questions.** Investigations are required to:

- Compare the impact of different vasoactive drugs including vasopressin on renal function and patients' outcome.
- Assess the role of renal vasodilators, including fenoldopam, atrial natriuretic peptide, and adenosine receptor antagonist to protect against the development of AKI.

**Panel recommendations.**

- In patients with signs of hypoperfusion such as oliguria and persisting hypotension (MAP  $<65$  mm Hg) despite ongoing adequate fluid resuscitation, we recommend the use of vasopressors. *Remark:* No data support the use of one vasoactive agent over another to protect the kidneys from AKI. Therefore, the choice of vasoactive agent to optimize the MAP should be driven by the hemodynamic characteristics specific to each patient.
- In patients who are not undergoing surgery, we recommend against the use of vasoactive drugs to increase cardiac output to supraphysiologic levels to improve renal function.
- We recommend against the use of low-dose dopamine to improve renal function.

#### II.4. How Can We Prevent Contrast-induced Nephropathy?

**Contrast-induced nephropathy.** Acute deterioration of renal function after intravenous administration of radiocontrast media is referred to as contrast-induced nephropathy (CIN) and is generally defined as an increase in serum creatinine concentration of more than 0.5 mg/dl (44 micromole/L) or 25% above baseline within 48 hours after contrast administration (95, 96). The risk of developing CIN is largely determined by preprocedural renal function and by the volume of radiocontrast agent given (95). In patients who are not critically ill and do not have preexisting renal disease, CIN is relatively uncommon in the general population (0.6–2.3%) (97) but has been reported as high as 8% in one large trial (98). Similarly, CIN requiring RRT is rare ( $<1\%$  of patients undergoing percutaneous coronary intervention) (99) unless preinfusion creatinine clearance is less than 47 ml per minute per 1.73 m<sup>2</sup> of body surface area (100) and the volume of contrast required is large (101), e.g., approximately equal or larger than twice the baseline GFR in milliliters (102). The incidence of CIN in critically ill patients is probably higher than patients who are not critically ill: patients who are critically ill frequently have risk factors for CIN (age  $>75$  yr, elevated serum creatinine concentration, anemia, proteinuria, dehydration, hypotension, intra-aortic balloon pump, concomitant administration of nephrotoxic drugs, sepsis, diabetes mellitus, multiple myeloma, nephrotic syndrome, cirrhosis, congestive heart failure, or pulmonary edema) (97, 103, 104). A risk score for CIN has been proposed (104), but in the absence of validation in the ICU its use remains uncertain. Second, renal oxidative stress and intrarenal hypoxia due to reduced renal blood flow and enhanced oxygen demand (96)—all triggered by contrast media—can be amplified by critical illnesses and hemodynamic alterations. For instance, left ventricular dysfunction was found to be associated with increased risk of CIN (105). CIN can prolong hospital stay and can require dialysis (105–107).

**Drugs to prevent contrast-induced nephropathy (discussed with more detail in the online supplement).** Recent recommendations to prevent CIN in patients who are not critically ill have been published (95, 108). Despite a lack of solid data regarding the optimal fluid regimen, these recommendations stress the importance of adequate fluid administration (95, 108). Randomized studies, most of which enrolled a limited number of patients, have not provided conclusive evidence that vasodilators (dopamine, fenoldopam, atrial natriuretic peptides, calcium blockers, prostaglandin E1, and endothelin receptor antagonist) protect against CIN, and some appear to be harmful. In a recent prospective randomized study of more than 300 patients at risk for CIN, fenoldopam failed to prevent CIN after contrast administration (107). Theophylline and aminophylline have been reported to modestly limit contrast induced rise in serum creatinine level, the clinical significance of these findings is unclear (109). In a recent meta-analysis, however, theophylline protective effect did not reach statistical significance (110).

Administration of oral N-acetylcysteine (NAC) has been proposed as a means to prevent CIN (110). Its role remains controversial given the inconsistent results observed across multiple studies (96, 105, 111–113). In addition, using different markers of renal function, it has been suggested that NAC could have a specific effect on serum creatinine levels, dissociated from an effect on renal function (114). High doses of NAC may be needed to achieve a renal protection in patients at risk for CIN. One large study in patients undergoing primary angioplasty found that creatinine increased 25% or more after angioplasty in 33% of the control patients, 15% of the patients receiving standard-dose of intravenous NAC, and 8% of patients receiving high-dose of intravenous NAC (105). Such results contrast with those of other randomized controlled trials with intravenous NAC, especially in aortic or cardiac surgery (111, 113). The variable efficacy of intravenous NAC against AKI could be explained by differences in associated risk factor for AKI in the above clinical settings. These contrasting results call for specific studies in patients who are critically ill. Intravenous NAC may lead to side effects in up to 10% of patients (110, 116). Serious complications, such as hypotension, angioedema, bronchospasm, hyponatremia, seizure, and volume overload, appear to be dose dependent (116–119).

**Protocolized intravenous fluid administration (alone and in combination with NAC) and hemofiltration to prevent CIN (discussed with more details in the online supplement).** Protocolized administration of intravenous fluids alone (154 meq/L sodium chloride (120) or isotonic sodium bicarbonate (121), or protocolized fluid administration plus intravenous NAC (sodium chloride (105, 115) or sodium bicarbonate (122, 123) solution) have the potential to reduce the incidence of CIN and the need for dialysis. In 119 patients with slightly elevated creatinine, i.e., at least 1.1 mg/dl (97.2 micromole/L or more), hydration with intravenous sodium bicarbonate before contrast administration was reported to be more effective than hydration with intravenous sodium chloride (121). In several studies, including patients with slightly elevated baseline creatinine level who underwent at risk procedures, intravenous sodium bicarbonate reduced the incidence of CIN more than intravenous sodium chloride with or without concomitant oral NAC administration (121–124). Sodium bicarbonate may therefore confer more protection against CIN than saline alone and oral NAC may not add to the renal protective effects of intravenous sodium chloride.

The safety of these protocols has not been established in patients who are critically ill, particularly those at risk of developing pulmonary edema or in those with hypotension or acid base disorders. To what extent the protective effects of intravenous sodium chloride and sodium bicarbonate and the

possible benefits of NAC observed in non-ICU patients can be extrapolated to patients who are critically ill remains to be determined. It has been reported that hemofiltration prevents CIN in high risk patients (patient with baseline serum creatinine >2 mg/dl [176  $\mu$ mol/L] who received  $\sim$ 250 ml of i.v. contrast) (106). The applicability of this investigation is, however, limited. Renal function was assessed using plasma creatinine levels, a marker that is directly altered by the proposed intervention (i.e., hemofiltration). Second, patients were randomized to be treated in different settings (ultrafiltration was performed in the ICU, whereas routine care was performed in a step down unit). Overall, the published literature suggests that periprocedural extracorporeal blood purification has no protective effect against CIN (125).

The choice of the contrast medium may also be important but will only be discussed briefly as the intensivist is typically not involved in the choice. A meta-analysis reported in 1993 that high osmolar contrast media is more nephrotoxic than low osmolar contrast media (reduced odd ratio [OR] 0.67; confidence interval [CI] 0.48–0.77) (126). A recent meta-analysis suggested that the isosmolar compound might be slightly less nephrotoxic than low contrast medium in patients at risk of CIN (127). In the absence of a demonstrated clinically relevant advantage of isosmolar contrast agent over low contrast medium in patients with critical illness, both contrast media constitute a reasonable choice in this population.

**Research questions.** Investigations are required:

- To develop methods allowing stratification of patients who are critically ill with regard to risk of CIN.
- To assess the safety and efficacy of NAC, bicarbonate, and hemofiltration in patients who are critically ill.

**Panel recommendations.**

- We recommend evaluating the risk of CIN in all patients before the administration of contrast medium.
- In patients at risk of AKI for whom risks outweigh potential benefits, we recommend against the use of contrast medium.
- We recommend the use of low-osmolar or iso-osmolar contrast medium and recommend that the volume of contrast medium be as low as possible. We recommend that clinicians determine whether nephrotoxic drugs can be withheld or substituted with a lesser nephrotoxic drug before and immediately after contrast medium administration.
- We recommend that volume status be optimized before administration of contrast medium.
- In patients admitted to the ICU who are at risk for CIN, using infusions of isotonic sodium bicarbonate (154 mEq/L) may be considered, but the evidence is not sufficient for a strong recommendation.
- In patients that are high risk, pharmacologic prevention with intravenous NAC in combination with fluids (isotonic sodium chloride or preferably sodium bicarbonate) may be considered but safety and efficacy of intravenous NAC in this specific population has not been established. The panel considers that the evidence is not sufficient for recommending its use.
- The panel makes no specific recommendations on how to adjust the protocols for sodium chloride or sodium bicarbonate (6) administration to the acid-base status and hemodynamic conditions of ICU patients.

## II.5. What Can We Do to Protect against Renal Failure in the Presence of Antibacterial, Antifungal and Antiviral Agents?

**Risk factors for nephrotoxicity of anti-infective agents.** It has been reported that approximately 20% of the most commonly prescribed medications in the ICU have nephrotoxic potential (128). Nearly half of these medications are anti-infective agents (antibacterial, antifungal or antiviral medications) (128). Anti-infective agents can be directly or indirectly nephrotoxic. Direct nephrotoxicity is caused by inherent nephrotoxic potential and by idiosyncratic reactions. Direct nephrotoxicity can present as prerenal AKI, intrinsic AKI (renal arterial vasoconstriction, acute tubular necrosis, allergic interstitial nephritis, nephrotic syndrome, acute glomerulonephritis), and tubular obstruction. In addition to AKI, direct nephrotoxicity can also cause distinct renal syndromes, such as renal tubular acidosis, Fanconi-like syndrome, and nephrogenic diabetes insipidus (129). Indirect nephrotoxicity occurs when anti-infective agents damage non-renal tissues whose breakdown products cause renal failure (e.g., drug-induced hemolytic anemia or drug-induced rhabdomyolysis) (130) or when they interfere with the metabolism of other nephrotoxic medications. For instance, tacrolimus and cyclosporine are metabolized primarily by the cytochrome P450, family 3, subfamily A (CYP3A). Anti-infective agents that inhibit CYP3A such as the protease inhibitors used as a component of highly active antiretroviral therapy to treat HIV/AIDS (e.g., amprenavir, atazanavir, darunavir, fosamprenavir, indinavir), macrolide antibiotics, chloramphenicol, tirazole antifungals (e.g., fluconazole, itraconazole, voriconazole) and metronidazole, can increase tacrolimus and cyclosporine concentrations and thus the potential nephrotoxicity of these compounds. Risk factors for the development of AKI induced by anti-infective agents include duration of therapy, excessive anti-infective serum levels, preexisting impaired kidney function, renal hypoperfusion, sepsis, and concurrent use of other nephrotoxic medications, including diuretics (131) and the concurrent administration of two or more potentially nephrotoxic anti-infective agents (132). Controversy still exists whether the combination of vancomycin with an aminoglycoside increases the risk of nephrotoxicity due to either antibiotic (132–135).

**Strategies to prevent AKI.** The most successful strategy to prevent anti-infective-induced kidney insufficiency is to decrease a patient's exposure to these agents, that is, by using these agents only when the indication that they are needed is very clear. When possible, clinicians should choose the least nephrotoxic anti-infective agent either at the start of treatment or as soon as the identification and susceptibility of the infective agent are available (128). Duration of therapy should not exceed the time considered sufficient to treat specific infections. In some instances, such as with aminoglycosides, once-a-day administration may be used (128). When available, close monitoring of antibiotic concentration in the blood may also prevent dose-related renal toxicity.

For agents with renal clearance, dosing is adjusted according to creatinine clearance. Creatinine clearance is frequently estimated with the use of predicting formulae but, as mentioned above, these formulae are only useful when creatinine metabolism is in a steady state, such as in stable patients with advanced renal disease. In patients who are critically ill identification of the correct dosing (including loading dose) of anti-infective—and other medications—is further compounded by occasional increased renal clearance due to hyperdynamic state (136) and by the frequent expansion of the volume of distribution (the apparent volume required to contain the entire amount of drug in the body at the same concentration as in the blood or plasma), which may result in

subtherapeutic serum concentrations and in a need for increased dosing of anti-infectives (136, 137). When AKI is present, nonrenal clearance of anti-infective agents can be greater than the nonrenal clearance of anti-infective agents in patients with chronic renal failure but is still less than in healthy subjects (138, 139).

Occasionally, antibiotics are given as a one-time dose while awaiting results from cultures (137). Although not proven, some clinicians reason that this strategy is probably safe even in patients who are critically ill and at risk for AKI: when Buijk and colleagues administered one dose of aminoglycosides in patients with shock, 11% experienced a reversible increase in creatinine (137). Prompt treatment of life-threatening infections must take precedence over considerations of potential nephrotoxicity.

In the case of kidney toxicity due to renal vasoconstriction (amphotericin B), glomerular obstruction (foscarnet) (129) and tubular obstruction (sulphonamides, acyclovir, gancyclovir, indanavir), volume loading may decrease nephrotoxicity and thus prevent anti-infective-induced AKI (51, 128). Probenecid is recommended to prevent renal toxicity due to cidofovir (129). Whether it is useful to pretreat patients who are given foscarnet or indinavir with calcium channel blockers remains unknown (140).

The initiation of quality improvement programs for drug dosing and monitoring can be clinically useful (141, 142). Therapeutic drug monitoring of aminoglycosides and vancomycin in patients in the ICU leads to reduced nephrotoxicity (142–144). The optimal therapeutic drug monitoring service should incorporate sound recommendations based on pharmacokinetic behavior, patient characteristics, patient response, drug analysis, interpretation, and dose adjustment (142, 144). Therapeutic drug monitoring services that provide test results (i.e., drug levels) without appropriate interpretation and recommendations may predominantly generate costs without substantial clinical benefit (142).

### Research questions.

- To develop accurate biomarkers for early detection of AKI induced by anti-infective agents.
- To assess the role of urinary pH modulation to prevent tubular precipitation of anti-infective agents.

### Panel recommendations.

- We recommend avoiding nephrotoxic anti-infective drugs whenever possible. When using potentially nephrotoxic anti-infective agents, we recommend that clinicians monitor levels, when possible, and use appropriate dosing, dose interval, and duration of treatment.
- We recommend the implementation of institution-wide quality-assurance programs for therapeutic drug monitoring.
- We suggest that clinicians identify drug-related risk factors (e.g., inherent nephrotoxic potential) and, when possible, treat specific patient-related risk factors (e.g., volume depletion, preexisting renal impairment).

## III. CAN WE PREVENT ACUTE RENAL FAILURE FROM DEVELOPING IN SPECIFIC DISEASE STATES?

### III.1. Liver Failure

**AKI in patients with liver failure.** Patients with liver failure and cirrhosis have increased susceptibility to AKI (145). There may be differences in susceptibility, types of kidney injury, and responses in patients with acute, noncirrhotic hepatic failure

compared with those with chronic underlying liver disease. The incidence of AKI is high in patients with cirrhosis because of physiologic predispositions, complications of cirrhosis such as portal hypertensive bleeding and sepsis, and medications (70, 146–152). A recent multicenter retrospective study documented that hepatorenal syndrome (HRS) and acute tubular necrosis accounted for more than 98% of AKI in patients with cirrhosis (58% HRS vs. 41% for acute tubular necrosis) (153). Patients with cirrhosis have abnormal hemodynamics including splanchnic vasodilation with decreased effective arterial circulating volume, increased sympathetic nervous system activity with increased renin/angiotensin levels, and predisposition to cardiac dysfunction, resulting in renal arterial vasoconstriction (151). Patients with cirrhosis have a susceptibility to exogenous drug toxicity (including aminoglycosides), endogenous nephrotoxins such as bile acids and endotoxin, immunologic impairment with increased risks of infection, and elevated cytokine levels that lead to potential HRS and acute tubular necrosis (145, 146). AKI in patients with cirrhosis is associated with poor acute and poor long-term prognosis (152, 154) suggesting that aggressive measures for preventing and treating AKI are important. The International Ascites Club has defined major criteria for the diagnosis of HRS (155). Two types of HRS are recognized. Type 1 is a rapidly progressive renal failure with a doubling of serum creatinine to a level greater than 2.5 mg/dl or by 50% reduction in creatinine clearance to a level less than 20 ml/min in less than 2 weeks. Type 2 is a moderate, steady deterioration in renal function with a serum creatinine of greater than 1.5 mg/dl (151).

**Treatment of AKI.** Treatment and prevention recommendations of type 1 HRS include: early detection avoidance of known precipitating causes, consideration of volume status assessment, discontinuation of diuretics, consideration of large volume paracentesis (which should be accompanied by plasma expansion with albumin), and evaluation for other precipitating factors for HRS or acute tubular necrosis (151). Recent studies suggest that pharmacologic interventions can improve or reverse HRS in a substantial proportion of patients, thus prolonging and improving survival in patients who can undergo definitive treatment with liver transplantation (151, 156) or until palliation with transjugular intrahepatic portosystemic shunt (TIPS) (157). Pharmacologic therapies that have been reported to be effective with varying degrees of supporting evidence include  $\alpha$  agonists, norepinephrine, vasopressin analogs, and combination therapies (153, 158–161); concurrent administration of albumin for plasma expansion may improve response rates (151, 161). Midodrine and octreotide have also been reported to improve renal function in type 2 HRS (151, 162). RRT has been used as a bridge to transplantation in patients with AKI and liver failure (163, 164). RRT has not been shown to significantly alter outcomes in patients with liver failure and AKI in the absence of liver transplantation (151). The use of molecular adsorbent recirculating system (MARS) treatment, an extracorporeal liver support, has also been proposed as a bridging option in patients awaiting living donor liver transplantation (165). Other systems exist (166).

Liver transplantation is currently the optimal treatment for HRS (167), but survival rates for patients with pretransplant creatinine levels greater than 2.0 mg/dl are reduced following liver transplantation compared with those with creatinine levels less than 2.0 mg/dl (163, 168). Aggressive treatment of HRS and pretransplant correction of creatinine levels appears to be associated with improvement in post-transplant survival.

#### **Panel recommendations.**

- In patients with liver disease we recommend that clinicians make an aggressive effort to prevent the develop-

ment AKI and to treat AKI aggressively when it occurs. *Remark:* Early recognition and treatment of sepsis, hypotension, bleeding, elevated abdominal compartment pressures, and avoidance of nephrotoxins such as aminoglycosides, when possible, are of primary importance. Albumin volume expansion reduces renal risks in patients with peritonitis and during therapeutic paracentesis for tense ascites. When AKI occurs, determination of the causes defines management approaches. Prompt intervention for HRS including vasopressors and albumin may reverse renal dysfunction.

- In patients with liver failure and AKI who are not candidates for liver transplant, we recommend that RRT not be used. *Remarks:* Liver transplantation is the optimal therapy for patients with HRS, although survival is higher in patients with creatinine levels less than 2.0 mg/dl. RRT is potentially a useful bridge for transplantation but does not appear to alter outcomes in patients with liver failure and AKI who are not candidates for liver transplant.

### **III.2. Lung Injury**

Although lung injury that requires mechanical ventilation is commonly associated with AKI, little is known about the relationships between respiratory failure and AKI. In patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS), excessive alveolar distention associated with mechanical ventilation can cause additional lung damage, manifested by increased vascular permeability and increased production of inflammatory mediators (169). A large multicenter trial demonstrated that mechanical ventilation with lower tidal volume (VT) significantly decreased mortality in patients with ARDS when compared to those with ventilation at higher VT (170). In this study, patients ventilated with lower VT had more days without nonpulmonary organ or system failure in general and of renal failure in particular.

Animal and human studies suggest that lung overdistension during mechanical ventilation exerts deleterious effects on renal function. A study in rabbits showed that injurious mechanical ventilation with high VT and low levels of positive end-expiratory pressure (PEEP) caused systemic release of inflammatory mediators: the serum of these animals caused apoptosis of kidney cells in culture (171). In a short-term physiological study, maintaining spontaneous breathing during ventilatory support in patients with acute lung injury resulted in a decreased level of airway pressure, increased cardiac index, and improved renal function, assessed by an increase of the effective renal blood flow and glomerular filtration rate (172). This strategy may help in preventing deterioration of renal function in mechanically ventilated patients.

#### **Panel recommendations.**

- In patients with ALI/ARDS we recommend ventilation using lung protective ventilatory strategies avoiding high VT and airway plateau pressure higher than 30 cm H<sub>2</sub>O. *Remark:* This may help avoid AKI and/or promote renal recovery in patients with ARDS who develop AKI.

### **III.3. Cardiac Surgery**

Following cardiac surgery, the incidence of AKI in patients depends on the definition, ranging from 1% (when RRT is required) to 30% (173) and is highly associated with poor prognosis (44).

The kidney injury associated with cardiac surgery seems multifactorial and is related to intraoperative hypotension, inflammation, microemboli secondary to cardiopulmonary bypass, medications, oxidative stress and hemolysis, among others (173). The risk factors most commonly associated with acute kidney failure (AKF) requiring RRT include left ventricular dysfunction, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, emergent surgery, use of intraaortic counter pulsation, female sex, cardiopulmonary bypass time, and, with chronic kidney disease, elevated preoperative serum creatinine is the most relevant. The only modifiable risk factors are related to bypass time and administration of nephrotoxins (i.e., radiocontrast medium as part of the cardiac angiogram) in the presurgery period (173).

Cardiac surgery performed without cardiopulmonary bypass, known as off-pump coronary bypass grafting, was shown to decrease the risk of AKI requiring RRT in a retrospective case-control study (174). However, coronary artery surgery with bypass has superior graft patency rates when compared with off-pump coronary bypass grafting (175). Moreover, cardiac surgery procedures that involve valves or aortic surgery often cannot be done without placing patients on cardiopulmonary bypass. A large randomized controlled trial currently in progress (clinicaltrials.gov identifier NCT00032630) should help determine whether the off-pump procedure can reduce AKI in patients following cardiac surgery.

Among pharmacological interventions, perioperative treatment with nesiritide has recently been associated with a lower incidence of AKI in patients with left ventricular dysfunction after cardiac surgery (176). The beneficial effects were restricted to those patients with previously impaired renal function. Controversies exist, however, regarding a possible negative impact of nesiritide on the survival rate of patients with congestive heart failure, especially in the presence of AKI (48, 177, 178). Therefore, the use of nesiritide cannot be recommended. In one large randomized controlled trial, intensive insulin therapy administered to patients who were post-surgical and in the ICU, approximately 60% of whom were postcardiac surgery, was associated with a lower incidence of AKI (179). This result has not been confirmed in other populations, and the safety of this approach has been questioned.

**Panel conclusions.** The panel found it challenging to make recommendations but acknowledged that the following factors have been associated with a lower incidence of AKI in patients of post-cardiac surgery:

- The use of off-pump coronary bypass grafting instead of cardiopulmonary bypass in patients undergoing less complex surgical procedures. The potential benefit in reducing the incidence of AKI should be balanced with the risk of inferior graft patency rates.
- The reduction of the duration of cardiopulmonary bypass in patients undergoing more complex surgical procedures who require this approach.

### III.4. Tumor Lysis Syndrome

Tumor lysis syndrome refers to the metabolic derangements that result from the rapid destruction of malignant cells and the abrupt release of intracellular ions, nucleic acids, proteins and their metabolites into the extracellular space after the initiation of cytotoxic therapy. Risk factors for tumor lysis syndrome include lymphoproliferative malignancies highly sensitive to chemotherapy, bulky disease, preexistent renal dysfunction, and treatment with nephrotoxic agents. Metabolic disorders that occur in tumor lysis syndrome include hypocalcemia,

hyperuricemia, hyperkalemia, metabolic acidosis, and AKI (most often oligo-anuric) and hyperphosphatemia (180, 181).

Deposition of uric acid and calcium phosphate crystals in the renal tubules may lead to AKI, which is often exacerbated by concomitant intravascular volume depletion. Preventive measures include aggressive fluid loading and diuretics to maintain a high urine output and allopurinol administered at least 2 days before chemotherapy or radiotherapy in patients at risk (181). Prophylaxis with recombinant urate oxidase (rasburicase, which catalyzes the oxidation of uric acid to the more water-soluble allantoin) may be preferable to allopurinol in selected patients at high risk of tumor lysis to prevent uric acid nephropathy (182, 183). Urine alkalization is not required in patients receiving rasburicase and is not routinely recommended in the others. Although urine alkalization with bicarbonate may reduce uric acid precipitation in renal tubules it also promotes calcium phosphate deposition in renal parenchyma and other tissues.

In established tumor lysis syndrome, management of electrolyte abnormalities, aggressive hydration and RRT to remove uric acid, phosphate and potassium, and correction of azotemia, are the main supportive measures. Continuous RRT (CRRT) is preferred over intermittent hemodialysis (IHD) because of its greater cumulative solute removal and avoidance of solute rebound (184). Return of diuresis and AKF recovery usually occur within a few days after normalization of metabolic complications of the syndrome.

#### **Panel recommendations.**

- The panel recommends that intensive hydration be started for patients with malignancies at risk of developing tumor lysis syndrome in the days before cytotoxic therapy. We do not recommend administration of sodium bicarbonate.
- We suggest using allopurinol or rasburicase during this period. *Remark:* Although experience is limited, rasburicase appears to be more effective than allopurinol in reducing the incidence of uric acid nephropathy in patients at risk for tumor lysis syndrome.
- In patients with established tumor lysis syndrome, we suggest CRRT over IHD.

### III.5. Rhabdomyolysis

Rhabdomyolysis is characterized by muscle necrosis and release of muscle cell constituents into the circulation. Causes of rhabdomyolysis include direct muscle injury (crush, burns, pressure), excessive exercise, seizures, ischemic necrosis (vascular, compression), metabolic disorders, polymyositis, tetanus, drugs (cocaine, neuroleptics, statins), and toxins (snake and insect bites) (185, 186). In crush injuries, morbidity is attributed to the leakiness of potentially cardiotoxic and nephrotoxic metabolites (potassium, phosphate, myoglobin, urates) and massive uptake by muscle cells of extracellular fluid causing hypovolemic shock. In such conditions, extreme hyperkalemia may be lethal within a few hours, and the entire extracellular fluid compartment can be sequestered in the crushed muscles leading to circulatory collapse and death, thus justifying early and aggressive medical intervention (187, 188).

Serum creatine kinase may be markedly increased in rhabdomyolysis. Myoglobin is released in parallel with creatine kinase. Myoglobinuria occurs when serum myoglobin exceeds 1,500 to 3,000 ng/ml. Initial serum creatinine above 150  $\mu\text{mol/L}$  and creatine kinase levels above 5,000 U/L are associated with the development of AKI or need for RRT (189).

Measures to prevent AKI in rhabdomyolysis include volume resuscitation to restore and/or increase urine flow in an attempt

to avoid myoglobinuric tubular injury. After volume repletion, a forced diuresis with mannitol is controversial (189). Alkalinization of urine to a pH greater than 6.5 or 7 can be attempted with bicarbonate, but does not appear advantageous over saline diuresis because large amounts of crystalloids are sufficient *per se* to increase urine pH (189).

The prognosis of rhabdomyolysis-induced AKI is usually good, with renal recovery within 3 months. RRT may be indicated for correcting hyperkalemia, hyperphosphatemia, metabolic acidosis, and azotemia. In some instances, depending on filter type, continuous veno-venous hemofiltration (CVVH) has been used for myoglobin removal, as well as for correcting rhabdomyolysis-induced metabolic alterations (190–192). However, its clinical use remains hypothetical, and prophylactic CVVH, based on the presence of elevated creatine kinase or myoglobin levels, cannot be recommended.

#### Panel recommendations.

- In patients with initial serum levels of creatinine greater than 150  $\mu\text{mol/L}$  as well as creatine kinase greater than 5,000 U/L, we recommend close monitoring of renal function. *Remark:* Initial elevation of serum levels of creatinine ( $>150 \mu\text{mol/L}$ ), as well as creatine kinase greater than 5,000 U/L, is associated with increased risk of AKI or need for RRT.
- We suggest intensive hydration with isotonic crystalloids after volume restoration to maintain a large urine output. *Remark:* The amount of volume administration is not established. Maintaining a urine pH greater than 6.5 or 7 is desirable.
- We suggest that using sodium bicarbonate is not necessary. Diuretics should be used with caution, avoiding hypovolemia. *Remark:* Bicarbonate has not been shown to be superior to saline diuresis in increasing urine pH.
- CVVH may help remove some myoglobin, but the clinical efficacy of this measure has not been established. The evidence is not sufficient for recommending its use.

### III.6. Increased Intra-Abdominal Pressure

**Definitions and measurements.** Increased intra-abdominal pressure (IAP) or intra-abdominal hypertension (IAH) is a cause of renal dysfunction and is independently associated with mortality (193–196). The role of IAH in renal dysfunction is complex, and understanding is limited by disparate reported definitions, patient populations, underlying disease states, measurement methods, comorbidities, treatments, and difficulties differentiating the degree to which IAH is a primary contributor to organ dysfunction as opposed to an indicator of severity of underlying disease.

A recent international conference on intra-abdominal hypertension and abdominal compartment syndrome defined IAH as a sustained or repeated pathological elevation in IAP greater than or equal to 12 mm Hg (194, 195). The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25 ml of sterile saline. The following definitions are proposed for IAH: grade I: IAP 12–15 mm Hg; grade II: IAP 16–20 mm Hg; grade III: IAP 21–25 mm Hg; grade IV: IAP greater than 25 mm Hg (194).

Abdominal compartment syndrome (ACS) is defined as a sustained IAP greater than 20 mm Hg that is associated with new organ dysfunction or failure (194, 195). Some studies suggest that abdominal perfusion pressure (APP), defined as mean arterial pressure minus intra-abdominal pressure (MAP–IAP), may be a better indicator of critical abdominal organ

perfusion (197–201). Theoretical and some clinical evidence suggest that renal function may be more sensitive to intra-abdominal pressure increases than to decreases in mean arterial pressure because the renal filtration gradient (FG) is proportional to the mean arterial pressure minus twice the IAP; ( $\text{FG} = \text{MAP} - 2 \cdot \text{IAP}$ ) (194).

**Management of elevated IAP.** There are few controlled prospective trials to determine the correct relationship between elevated IAP and organ dysfunction in patients who are critically ill, and it is well accepted that the association between elevated IAP and ACS does not clearly imply causation. Questions persist regarding the effectiveness of reduction in IAP on reversal of ACS (202–204). For those with a sustained IAH and organ dysfunction, a number of medical interventions have been used including: (1) increase abdominal wall compliance with sedation/analgesia, neuromuscular blockade, and/or changes in body positioning; (2) evacuate intraluminal abdominal contents with nasogastric decompression, rectal decompression/enemas, and use of prokinetic agents; (3) in patients with abnormal fluid collections, perform percutaneous decompression; and (4) correct positive fluid balance through fluid restriction, diuretics, and hemodialysis/ultrafiltration (193). In those who are not candidates for or are unresponsive to medical treatment options, decompressive laparotomy should be considered (193, 198, 204). Decompressive laparotomy has been shown to improve urine output, but long-term and short-term effects on renal function have not been definitively determined. Established renal dysfunction from IAH may not be responsive to laparotomy, suggesting that early intervention may potentially be necessary to prevent development of IAP-induced renal failure. The risks of laparotomy must be weighed against benefits in considering surgical intervention (193, 198, 204, 205).

**Panel recommendations.** Because of uncertainties regarding the limited means for preventing ACS-induced AKI through medical and surgical interventions, the panel found it challenging to delineate optimal monitoring and treatment recommendations. Given the high prevalence of IAH/ACS in high-risk subgroups, the benign nature of IAP bladder pressure monitoring, and some potential possibility of improving the bleak prognosis of untreated ACS, the panel made the following recommendations, but emphasizes the necessity for further clinical study:

- In high-risk medical and surgical patients, we suggest monitoring IAP.
- In patients meeting criteria for ACS, we suggest the following timely medical or surgical interventions for improving abdominal wall compliance: evacuation of intraluminal contents, evacuation of abdominal fluid collections, and correction of positive fluid balance
- In patients who fail to respond to medical intervention or who are not candidates for medical management, we suggest urgent abdominal decompression surgery.

## IV. HOW SHOULD WE MANAGE A PATIENT WHO IS CRITICALLY ILL AND DEVELOPS ACUTE RENAL FAILURE?

### IV.1. General Management

**Principles.** In the early stages of renal injury the situation is in many cases still (quickly) reversible. Urgent measures should be taken to reverse factors that have caused or contributed to renal

dysfunction and, if possible, to restore renal blood flow and homeostasis. A number of the principles that have been outlined in the section on preventive measures are also applicable here. It is of key importance to avoid hypovolemia, and if it is clear that a patient is volume-depleted, fluids should be given rapidly. Careful consideration should be given to the type of fluid used to resuscitate patients with AKI.

**Volume.** Saline infusion has been shown to have a beneficial effect in experimental AKI and to attenuate the nephrotoxic potential of certain drugs such as aminoglycosides and amphotericin. In contrast, there is evidence that some types of colloid solutions, in particular hyperoncotic starches and dextran, can cause additional renal injury (72, 206–208). The mechanism is not yet entirely clear, but as long as this has not been sufficiently addressed, it seems prudent to use crystalloids for volume resuscitation in patients with AKI, and in particular, to avoid the use of starches and dextrans. If a patient's volume status is unknown, a fluid challenge should be applied (209).

It should be appreciated that volume expansion normally leads to a drop in serum creatinine levels. If serum creatinine levels remain stable in spite of large fluid volumes, this should be regarded as a sign of kidney dysfunction. If urine production is not restored after adequate fluid resuscitation, administration of fluids should be discontinued to avoid volume overloading.

**Diuretics.** Diuretics can be given to test renal responsiveness after adequate fluid loading, but should be discontinued if there is no or insufficient response to avoid side effects such as ototoxicity. Diuretics do not reduce mortality or morbidity nor improve renal outcome (210–213). However, if urine production is restored this will facilitate fluid management in patients who are critically ill, and this can be a reason for use of diuretics provided that the kidneys are still responsive.

**Nephrotoxic drugs.** Discontinuing all potentially nephrotoxic drugs is another cornerstone of therapy. In particular, the use of nonsteroidal anti-inflammatory agents should be discontinued immediately. It is unclear whether low-dose aspirin has a similar significant influence (214, 215). Use of aminoglycosides may be avoided if an alternative antibiotic regimen is available.

**Mean arterial pressure.** Autoregulation of renal perfusion is blunted in AKI and, as discussed above, hypotension with signs of shock should be corrected in general by fluid infusion and, if required, by administration of vasopressors. As a general rule, MAP should be kept at or above 65 mm Hg.

#### **Research questions.**

- Evaluate the potential nephrotoxicity of starches with lower oncotic values (6%) for potential nephrotoxicity.

#### **Panel recommendations.**

- We recommend that hypovolemia should be corrected quickly and preferably with infusion of crystalloids, as hyperoncotic fluids may induce or aggravate AKI.
- We suggest that diuretics be given to test renal responsiveness after adequate fluid loading but that clinicians discontinue their use if there is no or insufficient response, to avoid side effects such as ototoxicity. *Remark:* The use of diuretics does not reduce mortality or morbidity nor improve renal outcome in patients with AKI.
- We recommend avoiding and discontinuing all potentially nephrotoxic drugs (nonsteroidal anti-inflammatory agents, aminoglycosides [whenever possible], intravenous

radiocontrast, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers). *Remark:* The panel concludes that it is also important to correct hypotension as quickly as possible with a target MAP of 65 mm Hg or greater in most patients with shock or higher if patients have a history of hypertension.

## **IV.2. Renal Support**

Physicians using dialysis as a tool for organ support should realize that performing dialysis does not achieve the same level of homeostasis as a normally functioning kidney. The term “RRT” is therefore not quite accurate, because it is not possible to replace all functions of the kidney. Renal support therapy could be a better description of this treatment.

In patients with AKI who require renal support to correct metabolic derangements and/or fluid overload, treatment should not be delayed because, for example, there is still urine production but insufficient clearance. The “traditional” thresholds used in stable patients with chronic renal failure may be inappropriately high for patients with AKI for a number of reasons: (1) AKI in the ICU often occurs in the setting of multiple organ dysfunction, and the impact of renal failure on other failing organs such as the lungs (ARDS, pulmonary edema) and brain (encephalopathy) should be considered in the timing of RRT; (2) the increased catabolism associated with critical illness and the need to administer adequate nutritional protein will lead to increased urea generation; (3) it is often difficult to limit fluid intake in these patients, in part due to the administration of intravenous medications (antibiotics, vasopressors, etc.); and (4) patients who are critically ill may be more sensitive to metabolic derangements, and swings in their acid-base and electrolyte status may be poorly tolerated. Hence waiting for “conventional” or “absolute” indications for initiation of RRT in patients who are critically ill with AKI may be inappropriate.

There is some clinical evidence supporting early initiation of renal support in patients who are critically ill, which will be discussed later in this document.

**Panel recommendations.** We recommend the following specific objectives for RRT in patients in the ICU with AKI:

- Correct metabolic derangements, reduce fluid overload, and mitigate the harmful effects of these disturbances on other failing organs.
- Allow administration of necessary fluids (IV medications, blood products, etc.) and adequate nutrition; to reduce/prevent edema formation.
- In patients who require renal support because of metabolic derangements, we recommend that treatment should not be delayed if there is still (some) urine production. *Remark:* Traditional triggers for treatment derived from studies in chronic renal failure in patients who are stable may not be appropriate for patients who are critically ill with AKI. Patients who are critically ill with multiple organ dysfunction may have less tolerance of metabolic disorders such as acidosis and electrolyte disorders.

## **IV.3. Nutritional Support**

Patients who are critically ill and with AKI are usually in a catabolic state. In addition, intermittent dialysis leads to a loss of 6 to 8 g of protein and amino acids per day; in CVVH this number increases to 10 to 15 g/day. Moreover, when energy

expenditure is measured to assess feeding requirements of patients with AKI the formulae typically used may substantially underestimate the actual energy needs, because they rely on normal body fluid distribution (216). A limitation of nutritional supplementation is a potential side effect. Excessive protein supplementation results in increased accumulation of end products of protein and amino acid metabolism in patients with AKI who have diminished clearance (217). Accordingly, there are no established recommendations on the optimal amount of protein content of the nutritional supplementations. In addition, the fluid infusion that is required to provide nutrients may predispose these patients to volume overload. Aggressive nutrition with parenteral nutrition may predispose patients to metabolic and electrolyte derangements, such as hyperglycemia, hyperlipidemia, hypernatremia, or hyponatremia.

Regarding the best type of nutritional support, no specific formula exists specifically for patients with AKI, and commonly used standard feeds may not have the optimum composition for these patients. At the moment the formulae with a chemical composition approaching the theoretical ideal for patients with AKI are hepatic formulations. This issue should be addressed in future studies.

#### **Recommended studies.**

- Investigate different feeding formulae specifically designed for patients who are critically ill with AKI.
- Assess a possible role of markers for oxidative stress (carbonyls, others) and scavenger molecules (thiols) to guide therapy.

#### **Panel recommendations.**

- Patients critically ill and with AKI are in a catabolic state, which often requires additional protein. The panel makes the following recommendations regarding protein administration:
- We recommend protein administration of up to 2.0 g/kg/day. *Remark:* RRT can cause additional protein losses of 10 to 15 g/day for CVVH and 6 to 8 g/day for intermittent dialysis. We recommend protein supplementation between 1.1 to 2.5 g/kg/day of protein for patients on CVVH, between 1.1 and 1.2 g/kg/day for patients on intermittent RRT, and between 0.6 and 1.0 g/kg/day for patients with AKI who are not (yet) receiving RRT. We suggest determining protein and caloric requirements on an individual basis using metabolic measurements.

#### **IV.4. Should Anticoagulation Regimen Vary with Renal Replacement Therapy Technique or Comorbid Condition?**

Anticoagulation is often required for CRRT to optimize treatment efficacy and minimize blood loss in the circuit. IHD can almost always be performed without anticoagulation when necessary. The ideal anticoagulant for RRT (which does not exist) should prevent clotting of the extracorporeal circuit and not induce systemic bleeding. In chronic dialysis, systemic anticoagulation with unfractionated heparin (UH) or low molecular weight heparin (LMWH) is the standard approach, with sometimes preference for LMWH because of the ease of administration with similar safety and efficacy (218).

Patients with acute kidney failure (AKF) (i.e., requiring RRT), represent a very heterogeneous group with respect to bleeding risk, disorders of hemostasis, underlying disease, alternative indications for anticoagulation and susceptibility to nonhemorrhagic side-effects of anticoagulants. This will

require an individualized approach to anticoagulation seeking a trade-off between the inherent risks of anticoagulation (bleeding, pharmacological side effects like heparin-induced thrombocytopenia) and that of filter clotting (reduced efficiency, blood loss, increased workload and costs). In addition, timing of RRT (intermittent, continuous), use of convection or diffusion, membrane choice and treatment dose, blood flow, hematocrit, predilution may all affect anticoagulant requirements. Studies on anticoagulation for RRT in AKF are scarce, and there is considerable variability in the criteria to define the bleeding risk.

**IV.4.1. Patients' underlying diseases.** Many patients with AKF have a clinical condition that will require systemic anticoagulation (e.g., valvular surgery, acute coronary syndrome, atrial fibrillation, deep venous thrombosis, pulmonary embolism). In these patients the degree of anticoagulation will be determined by this condition and not by the RRT. Limited data exist on the use of warfarin as the sole anticoagulant for RRT and suggest that standard oral anticoagulation with INR between 2 and 3 is insufficient to prevent clotting during hemodialysis (219).

Various underlying diseases among patients with AKF may require drugs with anticoagulant effect, such as activated protein C in patients with severe sepsis. A small series showed that these patients do not require additional anticoagulation for CRRT (220). Many patients who are critically ill have acquired antithrombin deficiency that will result in heparin resistance and decreased filter life in CRRT (221, 222). A recent case-control study showed that antithrombin III supplementation in patients with CRRT improves filter survival (223). However, this drug is expensive, and more evidence will be required before routine antithrombin supplementation can be justified. The presence of hepatic insufficiency may alter the elimination of anticoagulants that are predominantly cleared by the liver such as argatroban (224) or citrate (225, 226).

**IV.4.2. Patients' bleeding risk.** The major complication of anticoagulant therapy is bleeding. Patients with AKF requiring RRT often present with increased bleeding risk due to recent trauma or surgery and/or the need for invasive procedures or even active bleeding (227). The reported incidence of bleeding complications during RRT with UH in patients with increased bleeding risk varies widely (<10–60%) and clear definitions of bleeding risk are lacking. Bleeding risk should be weighed against the risk of filter clotting with associated reduced treatment efficiency (228–230). Many alternative anticoagulation strategies have been proposed, but few have been compared.

THE FIRST STRATEGY CONSISTS OF NO ANTICOAGULATION. The feasibility of CRRT without anticoagulation has been reported in observational studies, with this methodology being reserved for patients with severely disturbed coagulation profiles. Reported mean filter lives vary between 12 and 41 hours (227, 231). Platelet count seems to be an important predictor of whether CRRT without anticoagulation is feasible (231, 232). Measures usually recommended in chronic hemodialysis are either difficult to obtain in hemodynamically unstable patients (increasing blood flow) or have little effect on filter life (saline flushes) (233). The addition of predilution (prefilter infusion of the replacement fluid) may prolong filter life (234, 235) at the expense of treatment efficacy (235). Not receiving anticoagulation appears to be one of the risk factors for inadequate treatment dosing in IHD for AKF (236). Premature treatment interruption has been reported in 25 to 40% of cases when sustained-low efficiency dialysis (SLED) is performed without anticoagulation (237–239).

REGIONAL ANTICOAGULATION WITH PROTAMINE REVERSAL is an option but does not appear to offer advantages over low-dose UH (213, 227, 228, 240) because it is cumbersome and may

induce rebound bleeding (241). In addition, the side effects of long-term protamine infusion remain unknown. Citrate results in true regional anticoagulation. Randomized trials have shown reduced bleeding complications compared with low-dose UH (242) or LMWH (243) in IHD and compared with full-dose UH in CRRT (221, 244). Nonrandomized studies have suggested lower bleeding complications with citrate than using nadroparin or heparin (245, 246). Potential side-effects of citrate anticoagulation include metabolic alkalosis, hypernatremia, and citrate accumulation in patients with reduced liver function or reduced muscle perfusion, resulting in high-anion gap metabolic acidosis (unlikely to have clinical consequences) and reduced ionized calcium levels with increased calcium gap (225, 226, 247, 248). In case of liver ischemia (e.g., shock) this can result in dangerous consequences. The use of citrate anticoagulation therefore requires intensive metabolic monitoring.

**USE OF DIALYSIS MEMBRANES THAT HAVE BEEN COATED WITH ANTICOAGULANTS:** Heparin-bound Hemophan (85, 249), heparin-binding to surface-treated AN69 membranes (250, 251) and complete covalent coating of the whole extracorporeal system with LMWH (252) have been reported to allow successful IHD entirely without or with reduced systemic anticoagulation. Experience is limited to chronic dialysis so far.

**LOW DOSE UH REGIMENS,** with tight dose adjustment according to aPTT monitoring have been proposed (227, 232, 253, 254). The relationship between heparin dose, antithrombotic effect (prevention of filter clotting), anticoagulant effect (reflected in laboratory monitoring with aPTT) and bleeding complications appears complex. LMWH are used for routine anticoagulation in dialysis patients because of their ease of administration and the possibility of less bleeding complications (255). This has, however, not been confirmed by a randomized trial in CRRT (256). In addition, LMWH do accumulate in AKI and are therefore not approved everywhere for this use. There are debates on the need to monitor LMWH with anti-Xa levels, especially in patients with unpredictable kinetics (obesity, reduced renal function) and high bleeding risk (257–259).

**PROSTAGLANDINS,** short-acting inhibitors of platelet aggregation, have been suggested to be beneficial in patients with bleeding risk, because their low molecular weight allows extracorporeal removal thus limiting the systemic effect. In CRRT, when used in combination with UH, they prolong filter life in a dose-dependent way (260) and reduce heparin requirements and bleeding complications (261). The only randomized trial comparing prostaglandins with heparin reports no bleeding complications in either group, and comparable filter life (262). Observational studies report bleeding in 6–8% and hypotension in 15–25% of the patients with filter life of 15 hours in CRRT and 10% premature treatment interruptions in SLED (238, 263).

**IV.4.3. Coagulopathy.** Heparin-induced thrombocytopenia (HIT) is the most frequent procoagulant condition encountered clinically (264). It may lead to recurrent clotting of the extracorporeal system in patients requiring RRT. In hospitalized patients receiving heparin the incidence of HIT ranges from 0.1 to 5%, but the incidence in AKF patients requiring RRT has not been determined.

The diagnosis of HIT should prompt immediate discontinuation of heparin and adequate anticoagulation with an alternative anticoagulant. Argatroban is often used as the first-line agent for HIT but drug availability, liver function, and monitoring availability should be considered in making this choice. Argatroban has attractive characteristics in patients with renal failure and HIT (265), but limited data are available in patients undergoing dialysis (266–268) and in the AKF setting. Lepirudin is another possible treatment (269, 270).

#### **Panel recommendations.**

- In patients with AKF under systemic anticoagulation for an associated clinical condition, we recommend no additional anticoagulation. *Remark:* In some patients on oral anticoagulants, reduced doses of UH or LMWH may be needed.

For patients with increased bleeding risk:

- The panel considers that CRRT without anticoagulation and with predilution represents a reasonable approach in patients with high risk of bleeding, especially with hypo-coagulable states.
- In patients with increased bleeding risk in whom anticoagulation of the circuit is necessary, regional anticoagulation with citrate is an option in patients without liver failure. It requires a systematic team-based approach and intensive metabolic monitoring.
- In patients with moderate bleeding risk and/or frequent filter clotting, we suggest low-dose UH or LMWH.
- We suggest IHD without anticoagulation.

For patients with HIT:

- We suggest the use of argatroban

#### **IV.5. Can Hemodynamic Tolerance of Intermittent Hemodialysis Be Improved? (Role of Dialysate Composition, Thermal Balance, Fluid Balance)**

The influences of thermal balance, composition of fluids, and fluid balance on hemodynamic tolerance of intermittent hemodialysis have primarily been studied in chronic maintenance hemodialysis. There are fewer studies about their influence on hemodynamic tolerance of RRT in patients in the ICU with AKF, although their importance may be even greater than in the chronic setting. The objective of a better hemodynamic tolerance in SLED is based on similar grounds (i.e., a slower solute removal rate that reduces extracellular to intracellular water shift and a lower rate of ultrafiltration allowed by prolongation of dialysis duration). Modifications introduced in dialysate composition and temperature can greatly improve the hemodynamic tolerance of IHD.

**IV.5.1. Dialysate composition.** IV.5.1.1 Calcium ion (iCa) concentration. Calcium ions have a pivotal role in the contractile process of both vascular smooth muscle and cardiac myocytes. Modest variations in iCa are correlated with clinically significant changes in myocardial contractility and a decrease in iCa during dialysis is associated with hypotension (271).

In IHD, dialysate calcium concentration is probably the main determinant of plasma iCa. Plasma iCa levels are also affected by pH with decreases in iCa when blood pH increases (272). Thus, a rapid correction of metabolic acidosis can be associated with more hypotension, a problem that would respond to raising the calcium concentration in the dialysate (273).

IV.5.1.2 Sodium. During the early phase of IHD, blood urea concentration and urea removal are high, resulting in a decrease in plasma osmolality and a shift of water from the vascular compartments into cells. Higher dialysate sodium concentration during the early period of IHD tends to lessen plasma osmolality changes and dialysis related hypotension (274, 275).

IV.5.1.3 Buffers. Buffers used in the currently available dialysates are acetate, lactate, citrate (metabolized to bicarbonate in the body), or bicarbonate. The negative impact of acetate-buffered dialysates on left ventricular function and arterial pressure are well documented (276, 277). Acetate-buffered fluid is associated with a decrease in cardiac index and lower blood pH (276, 278). Compared with bicarbonate-

buffered fluids, lactate-buffered fluids might be associated with a higher plasma lactate level, depending on the rate of lactate load (279). Some studies suggest that bicarbonate-buffered fluids are associated with a better hemodynamic control (280, 281).

**IV.5.2. Thermal balance.** It is well accepted that an increase in body temperature during RRT is associated with hemodynamic instability. A large multicenter randomized study in hypotension-prone patients has shown that isothermic dialysis (a procedure aimed at keeping core temperature unchanged) decreased the incidence of intradialytic hypotension (282).

In patients who were critically ill and treated by RRT cooling was associated with an increase in systemic vascular resistance and mean arterial pressure and a decrease in cardiac output without a significant effect on regional perfusion and metabolism (275, 283). Excessive cooling, inducing hypothermia, may be associated with an elevated risk of infectious complications. During CRRT, body temperature may fall with a risk of hypothermia, which could also have deleterious consequences in terms of recognition of infection. Experimental data have suggested that a rewarming system may be important (284).

**IV.5.3. Fluid balance.** Excessive ultrafiltration rates induce hypovolemia and hypotension (274). In a randomized study comparing daily versus alternate-day hemodialysis in patients with acute renal failure, the mean ultrafiltration rates were 357 ml per hour in the daily dialysis group and 1,025 ml per hour in the alternate-day dialysis group, with significantly fewer hypotensive episodes in the daily dialysis group (5 vs. 25%) (230). It is usually recommended to start the hemodialysis session with both lines of the circuit filled with saline. Sessions should start with dialysis alone followed by ultrafiltration. Ultrafiltration is poorly tolerated in patients with sepsis.

A before and after study demonstrated that combining all of the above-mentioned recommendations (sodium and calcium concentration, bicarbonate buffer, and a dialysate temperature 37°C or less), showed increased hemodynamic tolerance patients in the ICU undergoing IHD (275).

**Panel recommendations.** The following recommendations apply to management strategies for IHD:

- We recommend the use of dialysate with sodium concentrations of 145 mmol/L or greater.
- We recommend dialysate temperature between 35 and 37°C.
- In patients who are hemodynamically unstable, we recommend starting IHD without ultrafiltration, which should then be adjusted according to hemodynamic response.
- We recommend fluid priming in an isovolemic state.
- We suggest considering decreased ultrafiltration rates and increased session durations in hemodynamically unstable patients.
- We recommend against the use of acetate buffered dialysate for IHD in patients in the ICU.

## V. WHAT IS THE IMPACT OF RENAL REPLACEMENT THERAPY ON MORTALITY AND RECOVERY?

### V.1. Filter Membranes

There is no single, standard method for determining the biocompatibility of filter membranes used for RRT. Generally, biocompatibility is a concept based on the degree to which a filter activates the complement cascade and/or causes leukopenia or thrombocytopenia. The activation of coagulation, stimulation of leukocytes, and release of cytokines are other

potential ways by which biocompatibility might be assessed. Available dialyzer membranes are currently categorized as unsubstituted cellulose (e.g., cuprophan), substituted cellulose (e.g., hemophan, cellulose diacetate, or triacetate) or synthetic (e.g., polysulfone, polyamide, polymethyl methacrylate, or polyacrylonitrile) membranes. Unsubstituted cellulose is the least biocompatible membrane and is associated with reduced survival in chronic renal failure (285, 286).

In the past decade, several prospective studies compared the effects of cellulose-derived or synthetic dialyzer membranes on clinical outcomes of patients with AKF receiving IHD. Three meta-analyses have been published summarizing these studies (287–289). They included nonrandomized controlled trials and observational (prospective or retrospective) studies. None of the meta-analyses demonstrated an overall impact of dialysis membrane on recovery of renal function. A meta-analysis found a significant survival advantage for synthetic membranes, but sensitivity analysis indicated that this benefit was largely limited to comparison with unsubstituted (cuprophan) and not substituted cellulose (cellulose acetate) (289). The two remaining meta-analyses, one of which was an update of the other, failed to demonstrate the superiority of synthetic membranes with respect to survival though a nonsignificant trend was again seen compared with unsubstituted cellulose (287, 288). These latter meta-analyses examined a slightly different set of studies; neither included one early study of synthetic membranes compared with unsubstituted cellulose; the later update also added two new trials.

Some polyacrylonitrile membranes (AN69) are negatively charged and therefore adsorb positively charged proteins. These filters can bind and activate Hageman factor (Factor XII), which can then convert kininogen to bradykinin (290, 291). This can rarely lead to vasodilatation and hypotension, particularly in patients receiving angiotensin-converting enzyme inhibitors, which block the inactivation of bradykinin. AN69 filters should be avoided in patients receiving such drugs. Other than this concern, membrane selection is based on the blood volume, surface area, and maximum ultrafiltration rate of the filter, as determined by the needs of individual patients.

### V.2. RRT Initiation (Timing)

The optimal time to initiate RRT in patients who are critically ill with AKF is not known (292). Aside from life-threatening complications of AKF, such as severe hyperkalemia, intractable acidosis, or diuretic unresponsive pulmonary edema, there is wide variability in clinical practice as to when RRT is initiated in the ICU. In chronic renal failure, most nephrologists tend to delay dialysis as long as possible insofar as this step generally indicates the start of dialysis dependency (292). Conversely, most survivors of AKF in the ICU do not require dialysis at hospital discharge (21). Although unnecessary RRT may worsen renal function and slow renal recovery, the judicious initiation of RRT in AKF to prevent cardiopulmonary dysfunction secondary to fluid overload as well as clinically significant metabolic derangements or bleeding diatheses seems prudent.

Whether very early RRT improves outcome in ICU patients with AKF is not known. Data from the Program to Improve Care in Acute Renal Disease (PICARD) study were used to compare early versus late start of RRT; an odds ratio for adverse outcome of 1.97 (95% confidence interval [CI] 1.21–3.20) was associated with late start of RRT (BUN <76 mg/dl versus BUN >76 mg/dl) (293). In another retrospective study of 100 adult patients with trauma, treated with CRRT between 1989 and 1997, early compared with late starters (BUN 42.6 ± 12.9 vs. 94.5 ± 28.3 mg/dl; mean ± SD) had increased survival

**TABLE 2. COMPARISON OF RANDOMIZED CONTROLLED TRIALS ON THE EFFECT OF RENAL REPLACEMENT DOSE ON MORTALITY AND RECOVERY OF RENAL FUNCTION**

Study (Ref)	Randomization (Number of Patients)	Mean Delivered Dose		Survival (%)	OR [95% CI]
		ml/kg/h	Kt/Vd/wk		
VA/NIH ARF Trial Network (308)	CVVHD 20 ml/kg/h and/or alternate day IHD (561)	22	≥3.9	48 <i>Day 14 after end IHD</i>	0.92 [0.73–1.16]
Schiffli (230)	Alternate day IHD (72)		3.0	46	2.27 [1.17–4.38]
	Daily IHD (74)		5.8	28 <i>Day 15 after end CVVH</i>	
Ronco (229)	CVVH 20 ml/kg/h (143)	19	5.3	41	1.93 [1.28–2.89]
	CVVH 35 ml/kg/h (136)	34	9.5	57	
	CVVH 45 ml/kg/h (137)	42	11.8	58 <i>Day 28 after inclusion</i>	
Bouman (297)	ELV 1.5 L/h (35)	20	5.6	69	1.13 [0.45–2.84]
	LLV 1.5 L/h (35)	19	5.3	75	
	EHV 4 L/h (36)	48	13.4	74 <i>Day 28 after inclusion</i>	
Saudan (307)	CVVH 25 ml/kg/h (101)	22	6.2	39	2.20 [1.26–3.84]
	CVVHD 42 ml/kg/h (103)	34	9.4	59 <i>30 d or ICU discharge</i>	
Tolwani (345)	CVVHD 20 ml/kg/h	NR	NR	66	0.77 [0.44–1.35]
	CVVHD 35 ml/kg/h			49	

*Definition of abbreviations:* ARF = acute renal failure; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodiafiltration; E = early; EHV = early high volume hemofiltration; ELV = early low-volume hemofiltration; HV = high volume; IHD = intermittent hemodialysis; Kt/Vd = clearance times duration of treatment divided by volume of distribution; L = late; LHV = late high-volume hemofiltration; LLV = late low-volume hemofiltration; LV = low volume.

Table adapted from Reference 346.

rates (39 vs. 20%) (294). However, reasons for starting CRRT likely differed between the groups, and some early starters might have otherwise never required RRT. Two smaller retrospective studies in patients who developed AKI after cardiothoracic surgical procedures also suggested a benefit from early CRRT, but these studies are not interpretable for similar reasons (295, 296). Nonetheless, these observational studies all had consistent findings and are clinically plausible. To date, only one RCT has tested the effect of RRT timing on outcome in patients who are critically ill (297). No difference was found in 28-day survival (intention to treat analysis) when CRRT was started early ( $\leq 12$  h after the onset of oliguria) as compared with late (BUN  $>112$  mg/dl and/or pulmonary edema) (297). However, this study (that also evaluated CRRT dose) was underpowered (106 patients divided among 3 arms); only 36 patients received late therapy. Furthermore, early and late CRRT had different eligibility criteria, creating the potential for selection bias.

### V.3. RRT Intensity (Dose)

**Optimal dose of RRT.** Like timing, the optimal dose of RRT for AKF in the ICU has not been determined (298–300). Quantification of urea removal is an important parameter in the evaluation of RRT efficiency and is usually referred to as the dose of dialysis. For IHD, the Kt/Vd measurement (K: dialyzer clearance of urea; t: duration of dialysis session; Vd: urea distribution volume), derived from the urea kinetic modeling, is used based on formulae validated in patients with chronic renal failure. Inadequate dialysis (single pool, Kt/Vd  $< 3.6$ /wk) has been associated with higher mortality rates in chronic renal failure (301–304). Note that a Kt/Vd equal to 1 indicates that total body water has been cleared of urea once. Although Kt/Vd is a useful method for thinking about and discussing RRT dose, its precise measurement in the ICU is challenging (305). Based on its impact in chronic renal failure, RRT dose may be a determinant of outcome in critically ill patients with AKF. A retrospective evaluation of 844 patients in the ICU with AKF requiring IHD or CRRT (306) reported that dialysis dose did not affect outcome in patients with very low or very high

severity of illness scores but was correlated with the outcome of patients with intermediate degrees of illness. However, only three of six randomized controlled trials examining dose of RRT in the ICU (Table 2) have shown increased mortality in low dose groups (229, 230, 297, 307, 308). Importantly, the largest, best designed trial among these found no benefit of higher dose RRT (308).

**Details of trials.** Table 2 shows the main results of these trials. These studies are discussed in detail in the online supplement. The Acute Renal Failure Trial Network study in the United States (Table 2) investigated low and high doses of RRT using a flexible design allowing patients to move between IHD (3 times/wk vs. 6 times/wk; each session Kt/Vd 5 1.2 to 1.4), SLED and CVVHD (20 ml/kg/h vs. 35 ml/kg/h; replacement component for both prefilter) within each dosing arm, as hemodynamic status changes (cardiac SOFA score of 0–2 or 2–4) (308). Another large study is ongoing and likely to provide additional important data regarding the impact of RRT intensity on the outcome of patients with AKF in the ICU. The Randomized Evaluation of Normal versus Augmented Level [RENAL] Replacement Therapy Study. RENAL study recently published conducted in Australia and New Zealand compared two doses of continuous venovenous hemodiafiltration (CVVHD) (25 and 40 ml/kg/h) in 1464 patients (309). At 90 days, mortality was similar in both arms (odds ratio 1.00; 95% confidence interval [CI], 0.81 to 1.23). Collectively, these results indicate that RRT doses of 3.6 Kt/Vd or greater for IHD and 20 ml/kg/h or greater for CRRT are adequate for the vast majority of ICU patients with AKF.

### V.4. RRT Mode

More than 20 retrospective studies and randomized controlled trials and three meta-analyses have compared the impact of RRT mode (IHD vs. CRRT) on outcome (228, 310–326). Neither mode has been shown to clearly produce superior renal recovery or survival rates in general ICU populations. However, these modes, as well as sustained low-efficiency dialysis (SLED) (237) are very different with regard to a number of clinically

**TABLE 3. ADVANTAGES AND DISADVANTAGES OF INTERMITTENT HEMODIALYSIS (IHD) COMPARED TO CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)**

Intermittent Hemodialysis	Continuous Renal Replacement Therapy
<b>I. Advantages</b>	<b>Disadvantages</b>
Rapid clearance of acidosis, uremia, potassium, and certain toxins	Slow
Patient mobility	Immobility
Can perform without anticoagulation	More frequent need for anticoagulation
Reduced exposure to artificial membrane	Continuous exposure to artificial membrane
*Reduced incidence of hypothermia	*Interventions required to prevent hypothermia
Masks fever temporarily	Masks fever continuously
Less blood loss from monitoring and/or filter clotting	Greater potential blood loss from monitoring and/or filter clotting
Lower costs in most centers	Higher costs in most centers
Less risk of dialysate compounding errors	Greater risks of replacement fluid and/or dialysate compounding errors
*Less removal of amino acids, endogenous hormones, and cofactors	*Increased removal of amino acids, endogenous hormones, and cofactors
<b>II. Disadvantages</b>	<b>Advantages</b>
Rapid solute and fluid shifts	Gradual solute and fluid shifts
—hemodynamic instability	—greater hemodynamic stability
—disequilibrium syndrome	—no or little risk of disequilibrium syndrome
—worsens brain edema	—no worsening of brain edema
Frequent need for fluid or nutritional restrictions	Less need for fluid or nutritional restrictions
Only allows for intermittent adjustment of prescription; less control of uremia, acidosis, phosphate, and fluid balance	Allows for continuous titration and integration of renal support with other ICU care and treatment goals
In many centers, requires a dialysis nurse and other resources that may limit ability to provide extended run-times and/or daily therapy in selected patients	Procedure performed by ICU nursing staff overall better clearance of uremia, correction of acidosis, and removal of excess fluid
*Even with high flux membranes, removes less “middle” molecules	*When configured to use convection as its primary mechanism of solute clearance, removes more “middle molecules”

\* Differences of unknown or hypothetical importance.

relevant considerations such as rate of solute flux (speed), patient mobility, and the ability to safely reach large fluid removal goals (Table 3). Therefore, these modalities may not be completely interchangeable in individual patients across a heterogeneous ICU population.

**Details of the prospective randomized trials.** Six prospective randomized studies have been published to date (310, 317, 321, 322, 324, 327, 328) (Table 4). Abundant methodological information concerning these trials are available in a recent meta-analysis (326). These studies are discussed in details in the online supplement.

**RRT mode selection.** Collectively, these trials found that RRT mode had no significant impact on clinically important endpoints in a heterogeneous ICU population. However, the studies were largely designed to examine outcome regardless of

patient differences that often drive the selection of RRT modality in clinical practice (316, 318). For an individual patient, each modality may have distinct advantages and disadvantages (Table 3). Therefore, the misapplication of either modality has the potential to have unfavorable consequences in particular patients. For example, IHD would be the best modality for the majority of stable patients who have entered the recovery phase of their critical illness. IHD would also be indicated for patients who require, but cannot tolerate, anticoagulation for CRRT. Conversely, a patient in severe shock with massive fluid overload is likely to hemodynamically tolerate CRRT better than IHD. Likewise, patients with brain edema may be harmed by the rapid fluid shifts caused by IHD. These clinical considerations indicate that RRT mode selection should be individualized.

**TABLE 4. COMPARISON OF PROSPECTIVE RANDOMIZED TRIAL OF RRT MODE**

Author	IHD Compared With	Patients, N	Patients, N	Severity of Illness	IHD/Comparator Mechanically Ventilated, %	Receiving Vasopressors, %	Dialysis Dose Controlled	IHD/Comparator Mortality, %
Mehta* 2001 (318)	CAVHD or CVVHD	166	82/84	APACHE III 88/96*	—	—	No	41.5/59.5 (ICU) <sup>†</sup>
John 2001 (329)	CVVHF	30	10/20	APACHE II 33/34	100/100	100/100	No	70/70 (ICU)
Gasparovic 2003 (328)	CVVHF	104	52/52	APACHE II 20/22	—	—	No	60/71
Augustine 2004 (311)	CVVHD	80	40/40	—	—	52.5/55	Yes	70/67.5 (Hosp)
Uehlinger 2005 (323)	CVVHD	125	55/70	SAPS II (55/55)	77/76	70/80	No	38/34 (ICU)
Vinsonneau* 2006 (325)	CVVHD	360	184/176	SAPS II (64/65)	95/98	86/89	No	68/67 (D60)

*Definition of abbreviations:* CAVHD = continuous arterio-venous hemodiafiltration; CVVHD = continuous veno-venous hemodiafiltration; CVVHF = continuous veno-venous hemofiltration.

\* Indicates a multicenter trial.

<sup>†</sup>  $P < 0.05$ .

### V.5. High-Volume Hemofiltration for Sepsis in the Absence of AKF

High volume hemofiltration for sepsis in the absence of AKF has been proposed as a therapeutic strategy to improve outcome (329–331). Although some small, underpowered trials and one larger observational study have suggested possible benefits (332–336), this approach lacks a strong scientific rationale. Reproducible, proof-of-principle efficacy has not been demonstrated in well-designed preclinical (99, 337) and clinical studies (332). Mediator removal by this approach is nonselective and therefore its effects are not easy to model or predict. Although some mediator removal does occur, calculations and actual measurements indicate that clearances are trivial compared with production and the large pool of cytokines and other mediators that are bound to tissue (338–340). Given that potent, specific antiinflammatory therapies have failed to significantly improve survival in human septic shock (341), high volume hemofiltration for mediator removal seems somewhat implausible and could even be harmful. Consistent with this notion, a recent multicenter trial in patients with sepsis showed that early hemofiltration (2 L/h for 96 h) delayed organ failure recovery (342). However, this study was underpowered ( $n = 76$ ) and the treatment arm was not truly high-volume. A large ongoing study of patients with sepsis and acute renal injury in the absence of overt failure (IVOIRE) is comparing hemofiltration at 35 ml/kg/h to 70 ml/kg/h and will hopefully provide additional insights into this complex issue (309). Ultimately, improved basic science and convincing preclinical work seem necessary before any new clinical trials of high volume hemofiltration are conducted in patients without renal failure.

#### Panel recommendations. General

- RRT in the ICU environment requires a systematic, team-based approach. The RRT prescription should be chosen to optimally support the overall ICU management plan.

#### Membranes

- We recommend substituted cellulose or synthetic RRT filters over unsubstituted cellulose membranes such as cuprophane *Remark:* Unsubstituted cellulose membranes have been associated with worsened mortality in chronic renal failure and with delayed renal recovery in AKF.

#### Timing

- In patients who are critically ill with AKF we suggest initiating RRT before the development of extreme metabolic derangements or other life-threatening events. *Remarks:* Clinical scoring systems and biomarkers are needed that identify patients who are likely to benefit from early RRT.

#### Intensity

- For IHD and SLED, we recommend clearances at least equal to minimum requirements for chronic renal failure (3.6 Kt/Vd/wk) *Remark:* Optimal target clearances for RRT in the ICU have not been firmly established. Higher clearances may be appropriate for selected patients.
- For CRRT (CVVH or CVVHD), we recommend clearance rates for small solutes of 20 ml/kg/h (actual delivered dose).
- Higher doses of CRRT cannot be generally recommended and should only be considered by teams that can

administer them safely. *Remark:* Higher doses of CRRT ( $\geq 30$  ml/kg/h) in the initial management of patients who are severely ill and catabolic have not consistently demonstrated benefits.

#### Modes

- We suggest that CRRT be considered for patients with brain edema, severe hemodynamic instability, persistent ongoing metabolic acidosis, and large fluid removal requirements. *Remarks:* IHD and CRRT have distinct operating characteristics, and modality selection should therefore be individualized (Table 3). If IHD is used in acutely ill patients with hemodynamic instability, daily, longer-than-standard sessions, and other special approaches described above are strongly recommended to promote physiologic stability. SLED is a promising alternative modality that has been less extensively studied.

#### High-volume hemofiltration in sepsis

- In patients with severe sepsis or septic shock without renal failure, we recommend against high-volume hemofiltration.

## SUMMARY

Acute Kidney Insufficiency substantially contributes to the morbidity and mortality of patients who are critically ill and injured. When AKI progresses to AKF, RRT is a life-sustaining intervention that provides a bridge to renal recovery in the majority of survivors. However, our understanding of how to optimally prevent, diagnose, and manage AKI in critical illness is deficient and requires a great deal of additional research. Although definitive data is lacking in many areas, systematic, team-based approaches to AKI, predicated on existing knowledge, is likely to improve outcomes (343).

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