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KDIGO Clinical Practice Guideline for Acute Kidney Injury

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Additional information in the form of supplementary materials can be found online at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Notice

Kidney International Supplements (2012) **2,** 1; doi:10.1038/kisup.2012.1

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon the best information available as of February 2011. It is designed to provide information and assist decision-making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Biographical and Disclosure Information section, and is kept on file at the National Kidney Foundation (NKF), Managing Agent for KDIGO.

Work Group Membership

Kidney International Supplements (2012) **2,** 2; doi:10.1038/kisup.2012.2

WORK GROUP CO-CHAIRS

John A Kellum, MD, FCCM, FACP
University of Pittsburgh School of Medicine
Pittsburgh, PA

Norbert Lameire, MD, PhD
Ghent University Hospital
Ghent, Belgium

WORK GROUP

Peter Aspelin, MD, PhD
Karolinska University Hospital
Stockholm, Sweden

Rashad S Barsoum, MD, FRCP, FRCPE
Cairo University
Cairo, Egypt

Emmanuel A Burdmann, MD, PhD
University of São Paulo Medical School
São Paulo, Brazil

Stuart L Goldstein, MD
Cincinnati Children's Hospital & Medical Center
Cincinnati, OH

Charles A Herzog, MD
Hennepin County Medical Center
Minneapolis, MN

Michael Joannidis, MD
Medical University of Innsbruck
Innsbruck, Austria

Andreas Kribben, MD
University Duisburg-Essen
Essen, Germany

Andrew S Levey, MD
Tufts Medical Center
Boston, MA

Alison M MacLeod, MBChB, MD, FRCP
University of Aberdeen
Aberdeen, United Kingdom

Ravindra L Mehta, MD, FACP, FASN, FRCP
UCSD Medical Center
San Diego, CA

Patrick T Murray, MD, FASN, FRCPI, FJFICMI
UCD School of Medicine and Medical Science
Dublin, Ireland

Saraladevi Naicker, MBChB, MRCP, FRCP, FCP(SA), PhD
University of the Witwatersrand
Johannesburg, South Africa

Steven M Opal, MD
Alpert Medical School of Brown University
Pawtucket, RI

Franz Schaefer, MD
Heidelberg University Hospital
Heidelberg, Germany

Miet Schetz, MD, PhD
University of Leuven
Leuven, Belgium

Shigehiko Uchino, MD, PhD
Jikei University School of Medicine
Tokyo, Japan

EVIDENCE REVIEW TEAM

Tufts Center for Kidney Disease Guideline Development and Implementation, Tufts Medical Center, Boston, MA, USA:

Katrin Uhlig, MD, MS, Project Director; Director, Guideline Development
Jose Calvo-Broce, MD, MS, Nephrology Fellow
Aneet Deo, MD, MS, Nephrology Fellow
Amy Earley, BS, Project Coordinator

In addition, support and supervision were provided by:

Ethan M Balk, MD, MPH, Program Director, Evidence Based Medicine

KDIGO Board Members

Kidney International Supplements (2012) **2,** 3; doi:10.1038/kisup.2012.3

Reference Keys

Kidney International Supplements (2012) **2,** 4; doi:10.1038/kisup.2012.4

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

CONVERSION FACTORS OF METRIC UNITS TO SI UNITS

Parameter	Metric units	Conversion factor	SI units
Amikacin (serum, plasma)	μg/ml	1.708	μmol/l
Blood urea nitrogen	mg/dl	0.357	mmol/l
Calcium, ionized (serum)	mg/dl	0.25	mmol/l
Creatinine (serum)	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Gentamicin (serum)	μg/ml	2.09	μmol/l
Glucose	mg/dl	0.0555	mmol/l
Lactate (plasma)	mg/dl	0.111	mmol/l
Tobramycin (serum, plasma)	μg/ml	2.139	μmol/l
Urea (plasma)	mg/ml	0.167	mmol/l

Note: Metric unit × conversion factor = SI unit.

Abbreviations and Acronyms

Kidney International Supplements (2012) **2,** 5; doi:10.1038/kisup.2012.5

AAMI	American Association of Medical Instrumentation
ACCP	American College of Chest Physicians
ACD-A	Anticoagulant dextrose solution A
ACE-I	Angiotensin-converting enzyme inhibitor(s)
ADQI	Acute Dialysis Quality Initiative
AHCPR	Agency for Health Care Policy and Research
AKD	Acute kidney diseases and disorders
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ANP	Atrial natriuretic peptide
aPTT	Activated partial thromboplastin time
ARB	Angiotensin-receptor blocker(s)
ARF	Acute renal failure
ARFTN	Acute Renal Failure Trial Network
ATN	Acute tubular necrosis
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CDC	Centers for Disease Control
CHF	Congestive heart failure
CI	Confidence interval
CI-AKI	Contrast-induced acute kidney injury
CIT	Conventional insulin therapy
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CRF	Chronic renal failure
CRRT	Continuous renal replacement therapy
CT	Computed tomography
CVC	Central venous catheters
CVVH	Continuous venovenous hemofiltration
CVVHDF	Continuous venovenous hemodiafiltration
eCrCl	Estimated creatinine clearance
EGDT	Early goal-directed therapy
eGFR	Estimated glomerular filtration rate
ERT	Evidence Review Team
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HDF	Hemodiafiltration
HES	Hydroxyethylstarch
HF	Hemofiltration
HIT	Heparin-induced thrombocytopenia
HR	Hazard ratio
i.a.	Intraarterial
ICU	Intensive-care unit
IGF-1	Insulin-like growth factor-1
IHD	Intermittent hemodialysis
IIT	Intensive insulin therapy
i.v.	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LOS	Length of stay
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging
MW	Molecular weight
NAC	*N*-acetylcysteine
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation
NKD	No known kidney disease
NKF	National Kidney Foundation
NSF	Nephrogenic Systemic Fibrosis
OR	Odds ratio
PD	Peritoneal dialysis
PICARD	Program to Improve Care in Acute Renal Disease
RCT	Randomized controlled trial
RIFLE	Risk, Injury, Failure; Loss, End-Stage Renal Disease
RR	Relative risk
RRT	Renal replacement therapy
SAFE	Saline vs. Albumin Fluid Evaluation
SCr	Serum creatinine
$ScvO_2$	Central venous oxygen saturation
SLED	Sustained low-efficiency dialysis
TCC	Tunneled cuffed catheter
VISEP	Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis

Abstract

Kidney International Supplements (2012) **2,** 6; doi:10.1038/kisup.2012.6

The 2011 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI) aims to assist practitioners caring for adults and children at risk for or with AKI, including contrast-induced acute kidney injury (CI-AKI). Guideline development followed an explicit process of evidence review and appraisal. The guideline contains chapters on definition, risk assessment, evaluation, prevention, and treatment. Definition and staging of AKI are based on the Risk, Injury, Failure; Loss, End-Stage Renal Disease (RIFLE) and Acute Kidney Injury Network (AKIN) criteria and studies on risk relationships. The treatment chapters cover pharmacological approaches to prevent or treat AKI, and management of renal replacement for kidney failure from AKI. Guideline recommendations are based on systematic reviews of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. Limitations of the evidence are discussed and specific suggestions are provided for future research.

Keywords: Clinical Practice Guideline; KDIGO; acute kidney injury; contrast-induced nephropathy; renal replacement therapy; evidence-based recommendation

CITATION
In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney inter., Suppl.* 2012; **2**: 1–138.

Foreword

Kidney International Supplements (2012) **2,** 7; doi:10.1038/kisup.2012.8

It is our hope that this document will serve several useful purposes. Our primary goal is to improve patient care. We hope to accomplish this, in the short term, by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice. By providing comprehensive evidence-based recommendations, this guideline will also help define areas where evidence is lacking and research is needed. Helping to define a research agenda is an often neglected, but very important, function of clinical practice guideline development.

We used the GRADE system to rate the strength of evidence and the strength of recommendations. In all, there were only 11 (18%) recommendations in this guideline for which the overall quality of evidence was graded 'A,' whereas 20 (32.8%) were graded 'B,' 23 (37.7%) were graded 'C,' and 7 (11.5%) were graded 'D.' Although there are reasons other than quality of evidence to make a grade 1 or 2 recommendation, in general, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there were 22 (36.1%) recommendations graded '1' and 39 (63.9%) graded '2.' There were 9 (14.8%) recommendations graded '1A,' 10 (16.4%) were '1B,' 3 (4.9%) were '1C,' and 0 (0%) were '1D.' There were 2 (3.3%) graded '2A,' 10 (16.4%) were '2B,' 20 (32.8%) were '2C,' and 7 (11.5%) were '2D.' There were 26 (29.9%) statements that were not graded.

Some argue that recommendations should not be made when evidence is weak. However, clinicians still need to make clinical decisions in their daily practice, and they often ask, "What do the experts do in this setting?" We opted to give guidance, rather than remain silent. These recommendations are often rated with a low strength of recommendation and a low strength of evidence, or were not graded. It is important for the users of this guideline to be cognizant of this (see Notice). In every case these recommendations are meant to be a place for clinicians to start, not stop, their inquiries into specific management questions pertinent to the patients they see in daily practice.

We wish to thank the Work Group Co-Chairs, Drs John Kellum and Norbert Lameire, along with all of the Work Group members who volunteered countless hours of their time developing this guideline. We also thank the Evidence Review Team members and staff of the National Kidney Foundation who made this project possible. Finally, we owe a special debt of gratitude to the many KDIGO Board members and individuals who volunteered time reviewing the guideline, and making very helpful suggestions.

Kai-Uwe Eckardt, MD
KDIGO Co-Chair

Bertram L. Kasiske, MD
KDIGO Co-Chair

Summary of Recommendation Statements

Kidney International Supplements (2012) **2,** 8–12; doi:10.1038/kisup.2012.7

Section 2: AKI Definition

2.1.1: AKI is defined as any of the following (*Not Graded*):

- **Increase in SCr by $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) within 48 hours; or**
- **Increase in SCr to $\geqslant$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or**
- **Urine volume $<$0.5 ml/kg/h for 6 hours.**

2.1.2: AKI is staged for severity according to the following criteria (Table 2). (*Not Graded*)

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) increase	$<$0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	$<$0.5 ml/kg/h for $\geqslant$12 hours
3	3.0 times baseline OR Increase in serum creatinine to $\geqslant$4.0 mg/dl ($\geqslant$353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients $<$18 years, decrease in eGFR to $<$35 ml/min per 1.73 m^2	$<$0.3 ml/kg/h for $\geqslant$24 hours OR Anuria for $\geqslant$12 hours

2.1.3: The cause of AKI should be determined whenever possible. (*Not Graded*)

2.2.1: We recommend that patients be stratified for risk of AKI according to their susceptibilities and exposures. (*1B*)

2.2.2: Manage patients according to their susceptibilities and exposures to reduce the risk of AKI (see relevant guideline sections). (*Not Graded*)

2.2.3: Test patients at increased risk for AKI with measurements of SCr and urine output to detect AKI. (*Not Graded*)
Individualize frequency and duration of monitoring based on patient risk and clinical course. (*Not Graded*)

2.3.1: Evaluate patients with AKI promptly to determine the cause, with special attention to reversible causes. (*Not Graded*)

2.3.2: Monitor patients with AKI with measurements of SCr and urine output to stage the severity, according to Recommendation 2.1.2. (*Not Graded*)

2.3.3: Manage patients with AKI according to the stage (see Figure 4) and cause. (*Not Graded*)

2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. (*Not Graded*)

- **If patients have CKD, manage these patients as detailed in the KDOQI CKD Guideline (Guidelines 7–15). (*Not Graded*)**
- **If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD. (*Not Graded*)**

Section 3: Prevention and Treatment of AKI

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

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

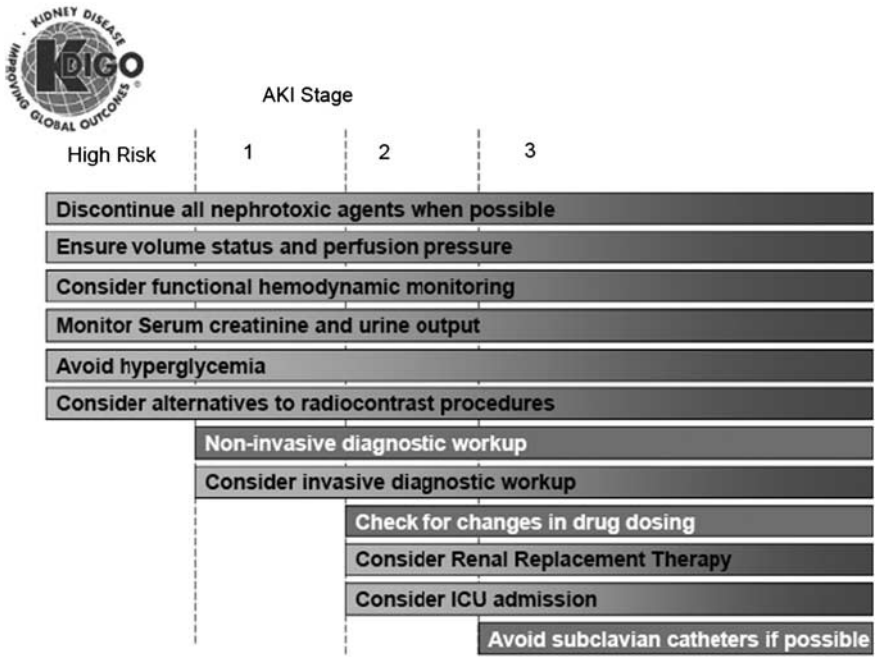

Figure 4 | Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive-care unit.

3.1.3: **We suggest using protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (*2C*) or in patients with septic shock (*2C*).**

3.3.1: **In critically ill patients, we suggest insulin therapy targeting plasma glucose 110–149 mg/dl (6.1–8.3 mmol/l). (*2C*)**

3.3.2: **We suggest achieving a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI. (*2C*)**

3.3.3: **We suggest to avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT. (*2D*)**

3.3.4: **We suggest administering 0.8–1.0 g/kg/d of protein in noncatabolic AKI patients without need for dialysis (*2D*), 1.0–1.5 g/kg/d in patients with AKI on RRT (*2D*), and up to a maximum of 1.7 g/kg/d in patients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients. (*2D*)**

3.3.5: **We suggest providing nutrition preferentially via the enteral route in patients with AKI. (*2C*)**

3.4.1: **We recommend not using diuretics to prevent AKI. (*1B*)**

3.4.2: **We suggest not using diuretics to treat AKI, except in the management of volume overload. (*2C*)**

3.5.1: **We recommend not using low-dose dopamine to prevent or treat AKI. (*1A*)**

3.5.2: **We suggest not using fenoldopam to prevent or treat AKI. (*2C*)**

3.5.3: **We suggest not using atrial natriuretic peptide (ANP) to prevent (*2C*) or treat (*2B*) AKI.**

3.6.1: **We recommend not using recombinant human (rh)IGF-1 to prevent or treat AKI. (*1B*)**

3.7.1: **We suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI. (*2B*)**

3.8.1: **We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (*2A*)**

3.8.2: **We suggest that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single dose daily rather than multiple-dose daily treatment regimens. (*2B*)**

3.8.3: **We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 hours. (*1A*)**

3.8.4: **We suggest monitoring aminoglycoside drug levels when treatment with single-daily dosing is used for more than 48 hours. (*2C*)**

3.8.5: **We suggest using topical or local applications of aminoglycosides (e.g., respiratory aerosols, instilled antibiotic beads), rather than i.v. application, when feasible and suitable. (*2B*)**

3.8.6: **We suggest using lipid formulations of amphotericin B rather than conventional formulations of amphotericin B. (*2A*)**

3.8.7: **In the treatment of systemic mycoses or parasitic infections, we recommend using azole antifungal agents and/or the echinocandins rather than conventional amphotericin B, if equal therapeutic efficacy can be assumed. (*1A*)**

3.9.1: We suggest that off-pump coronary artery bypass graft surgery not be selected solely for the purpose of reducing perioperative AKI or need for RRT. (*2C*)
3.9.2: We suggest not using NAC to prevent AKI in critically ill patients with hypotension. (*2D*)
3.9.3: We recommend not using oral or i.v. NAC for prevention of postsurgical AKI. (*1A*)

Section 4: Contrast-induced AKI

4.1: Define and stage AKI after administration of intravascular contrast media as per Recommendations 2.1.1–2.1.2. (*Not Graded*)
4.1.1: In individuals who develop changes in kidney function after administration of intravascular contrast media, evaluate for CI-AKI as well as for other possible causes of AKI. (*Not Graded*)

4.2.1: Assess the risk for CI-AKI and, in particular, screen for pre-existing impairment of kidney function in all patients who are considered for a procedure that requires intravascular (i.v. or i.a.) administration of iodinated contrast medium. (*Not Graded*)
4.2.2: Consider alternative imaging methods in patients at increased risk for CI-AKI. (*Not Graded*)
4.3.1: Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. (*Not Graded*)
4.3.2: We recommend using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media in patients at increased risk of CI-AKI. (*1B*)
4.4.1: We recommend i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no i.v. volume expansion, in patients at increased risk for CI-AKI. (*1A*)
4.4.2: We recommend not using oral fluids alone in patients at increased risk of CI-AKI. (*1C*)
4.4.3: We suggest using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (*2D*)
4.4.4: We suggest not using theophylline to prevent CI-AKI. (*2C*)
4.4.5: We recommend not using fenoldopam to prevent CI-AKI. (*1B*)
4.5.1: We suggest not using prophylactic intermittent hemodialysis (IHD) or hemofiltration (HF) for contrast-media removal in patients at increased risk for CI-AKI. (*2C*)

Section 5: Dialysis Interventions for Treatment of AKI

5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (*Not Graded*)
5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (*Not Graded*)
5.2.1: Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (*Not Graded*)
5.2.2: We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT. (*2B*)
5.3.1: In a patient with AKI requiring RRT, base the decision to use anticoagulation for RRT on assessment of the patient's potential risks and benefits from anticoagulation (see Figure 17). (*Not Graded*)
5.3.1.1: We recommend using anticoagulation during RRT in AKI if a patient does not have an increased bleeding risk or impaired coagulation and is not already receiving systemic anticoagulation. (*1B*)

5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:
5.3.2.1: For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. *(1C)*
5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. *(2B)*
5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. *(2C)*

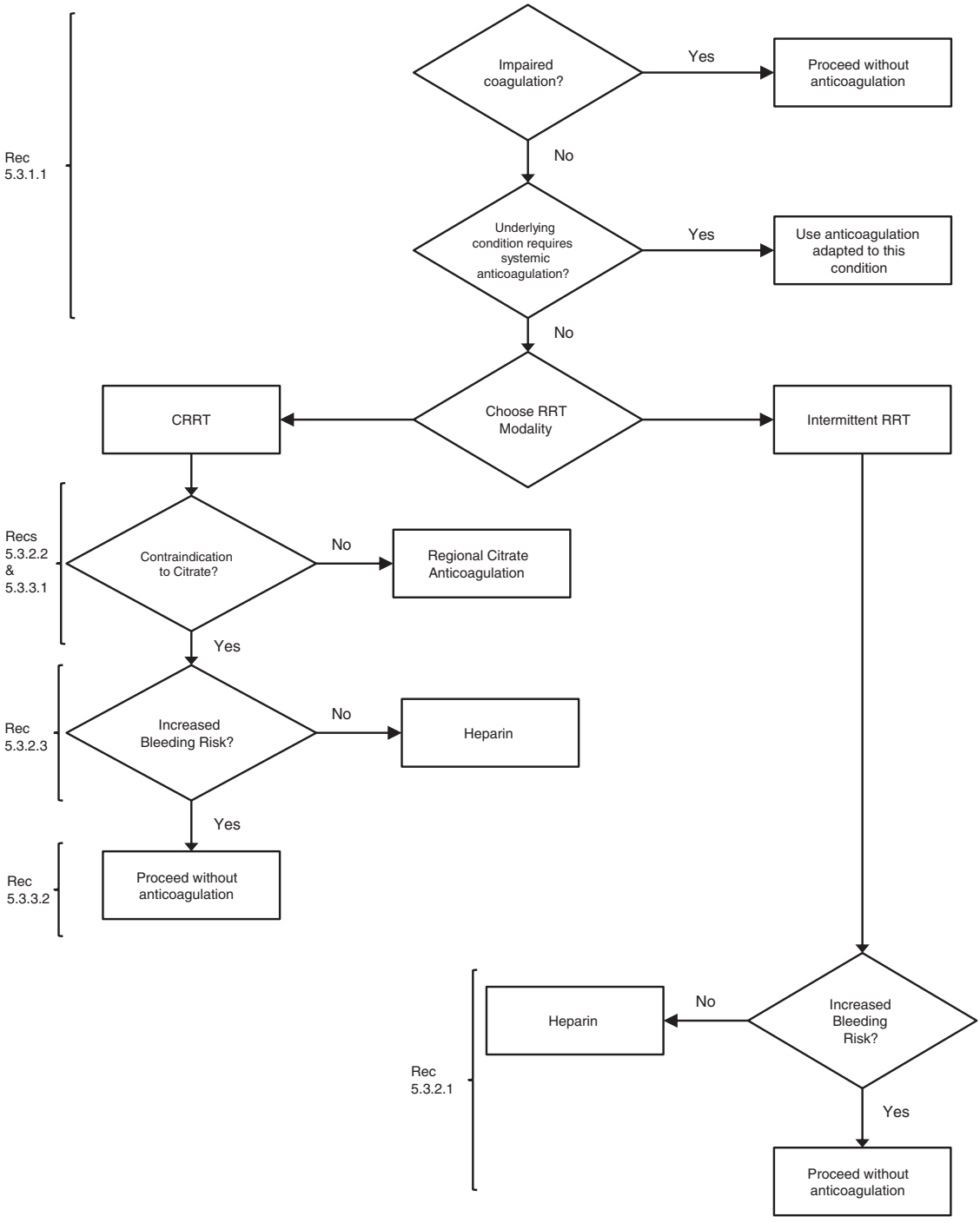

Figure 17 | Flow-chart summary of recommendations. Heparin includes low-molecular-weight or unfractionated heparin. CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:

5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. ***(2C)***

5.3.3.2: We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. ***(2C)***

5.3.4: In a patient with heparin-induced thrombocytopenia (HIT), all heparin must be stopped and we recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. (*1A*)

5.3.4.1: In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (*2C*)

5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. (*2D*)

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (*Not Graded*):

- **First choice: right jugular vein;**
- **Second choice: femoral vein;**
- **Third choice: left jugular vein;**
- **Last choice: subclavian vein with preference for the dominant side.**

5.4.3: We recommend using ultrasound guidance for dialysis catheter insertion. (*1A*)

5.4.4: We recommend obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter. (*1B*)

5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. (*2C*)

5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. (*2C*)

5.5.1: We suggest to use dialyzers with a biocompatible membrane for IHD and CRRT in patients with AKI. (*2C*)

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (*Not Graded*)

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (*2B*)

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)

5.7.1: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI. (*2C*)

5.7.2: We recommend using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and circulatory shock. (*1B*)

5.7.3: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and liver failure and/or lactic acidemia. (*2B*)

5.7.4: We recommend that dialysis fluids and replacement fluids in patients with AKI, at a minimum, comply with American Association of Medical Instrumentation (AAMI) standards regarding contamination with bacteria and endotoxins. (*1B*)

5.8.1: The dose of RRT to be delivered should be prescribed before starting each session of RRT. (*Not Graded*) We recommend frequent assessment of the actual delivered dose in order to adjust the prescription. (*1B*)

5.8.2: Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs. (*Not Graded*)

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. (*Not Graded*)

Section 1: Introduction and Methodology

Kidney International Supplements (2012) **2,** 13–18; doi:10.1038/kisup.2011.31

Chapter 1.1: Introduction

The concept of acute renal failure (ARF) has undergone significant re-examination in recent years. Mounting evidence suggests that acute, relatively mild injury to the kidney or impairment of kidney function, manifest by changes in urine output and blood chemistries, portend serious clinical consequences.[1–5] Traditionally, most reviews and textbook chapters emphasize the most severe reduction in kidney function, with severe azotemia and often with oliguria or anuria. It has only been in the past few years that moderate decreases of kidney function have been recognized as potentially important, in the critically ill,[2] and in studies on contrast-induced nephropathy.[4]

Glomerular filtration rate and serum creatinine

The glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function in health and disease. However, GFR is difficult to measure and is commonly estimated from the serum level of endogenous filtration markers, such as creatinine. Recently, Chertow *et al.*[1] found that an increase of serum creatinine (SCr) of >0.3 mg/dl (>26.5 μmol/l) was independently associated with mortality. Similarly, Lassnigg *et al.*[3] saw, in a cohort of patients who underwent cardiac surgery, that either an increase of SCr $\geqslant 0.5$ mg/dl ($\geqslant 44.2$ μmol/l) or a decrease >0.3 mg/dl (>26.5 μmol/l) was associated with worse survival. The reasons why small alterations in SCr lead to increases in hospital mortality are not entirely clear. Possible explanations include the untoward effects of decreased kidney function such as volume overload, retention of uremic compounds, acidosis, electrolyte disorders, increased risk for infection, and anemia.[6] Although, these changes in SCr could simply be colinear with unmeasured variables that lead to increased mortality, multiple attempts to control for known clinical variables has led to the consistent conclusion that decreased kidney function is independently associated with outcome. Furthermore, more severe reductions in kidney function tend to be associated with even worse outcome as compared to milder reductions.

Oliguria and anuria

Although urine output is both a reasonably sensitive functional index for the kidney as well as a biomarker of tubular injury, the relationship between urine output and GFR, and tubular injury is complex. For example, oliguria may be more profound when tubular function is intact. Volume depletion and hypotension are profound stimuli for vasopressin secretion. As a consequence the distal tubules and collecting ducts become fully permeable to water. Concentrating mechanisms in the inner medulla are also aided by low flow through the loops of Henle and thus, urine volume is minimized and urine concentration maximized (>500 m Osmol/kg). Conversely, when the tubules are injured, maximal concentrating ability is impaired and urine volume may even be normal (i.e., nonoliguric renal failure). Analysis of the urine to determine tubular function has a long history in clinical medicine. Indeed, a high urine osmolality coupled with a low urine sodium in the face of oliguria and azotemia is strong evidence of intact tubular function. However, this should not be interpreted as "benign" or even prerenal azotemia. Intact tubular function, particularly early on, may be seen with various forms of renal disease (e.g., glomerulonephritis). Sepsis, the most common condition associated with ARF in the intensive-care unit (ICU)[7] may alter renal function without any characteristic changes in urine indices.[8,9] Automatically classifying these abnormalities as "prerenal" will undoubtedly lead to incorrect management decisions. Classification as "benign azotemia" or "acute renal success" is not consistent with available evidence. Finally, although severe oliguria and even anuria may result from renal tubular damage, it can also be caused by urinary tract obstruction and by total arterial or venous occlusion. These conditions will result in rapid and irreversible damage to the kidney and require prompt recognition and management.

Acute tubular necrosis (ATN)

When mammalian kidneys are subjected to prolonged warm ischemia followed by reperfusion, there is extensive necrosis destroying the proximal tubules of the outer stripe of the medulla, and the proximal convoluted tubules become necrotic as well.[10] Distal nephron involvement in these animal experiments is minimal, unless medullary oxygenation is specifically targeted.[11] Although these animals develop severe ARF, as noted by Rosen and Heyman, not much else resembles the clinical syndrome in humans.[12] Indeed these authors correctly point out that the term "acute tubular necrosis does not accurately reflect the morphological changes in this condition".[12] Instead, the term ATN is used to describe a clinical situation in which there is adequate renal perfusion to largely maintain tubular integrity, but not

to sustain glomerular filtration. Data from renal biopsies in patients with ATN dating back to the 1950s[13] confirm the limited parenchymal compromise in spite of severe organ dysfunction.[12] Thus, the syndrome of ATN has very little to do with the animal models traditionally used to study it. More recently, investigators have emphasized the role of endothelial dysfunction, coagulation abnormalities, systemic inflammation, endothelial dysfunction, and oxidative stress in causing renal injury, particularly in the setting of sepsis.[14,15] True ATN does, in fact, occur. For example, patients with arterial catastrophes (ruptured aneurysms, acute dissection) can suffer prolonged periods of warm ischemia just like animal models. However, these cases comprise only a small fraction of patients with AKI, and ironically, these patients are often excluded from studies seeking to enroll patients with the more common clinical syndrome known as ATN.

ARF

In a recent review, Eknoyan notes that the first description of ARF, then termed *ischuria renalis*, was by William Heberden in 1802.[16] At the beginning of the twentieth century, ARF, then named *Acute Bright's disease*, was well described in William Osler's *Textbook for Medicine* (1909), as a consequence of toxic agents, pregnancy, burns, trauma, or operations on the kidneys. During the First World War the syndrome was named "war nephritis",[17] and was reported in several publications. The syndrome was forgotten until the Second World War, when Bywaters and Beall published their classical paper on crush syndrome.[18] However, it is Homer W. Smith who is credited for the introduction of the term "acute renal failure", in a chapter on "Acute renal failure related to traumatic injuries" in his textbook *The kidney-structure and function in health and disease* (1951). Unfortunately, a precise biochemical definition of ARF was never proposed and, until recently, there was no consensus on the diagnostic criteria or clinical definition of ARF, resulting in multiple different definitions. A recent survey revealed the use of at least 35 definitions in the literature.[19] This state of confusion has given rise to wide variation in reported incidence and clinical significance of ARF. Depending on the definition used, ARF has been reported to affect from 1% to 25% of ICU patients and has lead to mortality rates from 15–60%.[7,20,21]

RIFLE criteria

The Acute Dialysis Quality Initiative (ADQI) group developed a system for diagnosis and classification of a broad range of acute impairment of kidney function through a broad consensus of experts.[22] The characteristics of this system are summarized in Figure 1. The acronym RIFLE stands for the increasing severity classes Risk, Injury, and Failure; and the two outcome classes, Loss and End-Stage Renal Disease (ESRD). The three severity grades are defined on the basis of the changes in SCr or urine output where the worst of each criterion is used. The two outcome criteria, Loss and ESRD, are defined by the duration of loss of kidney function.

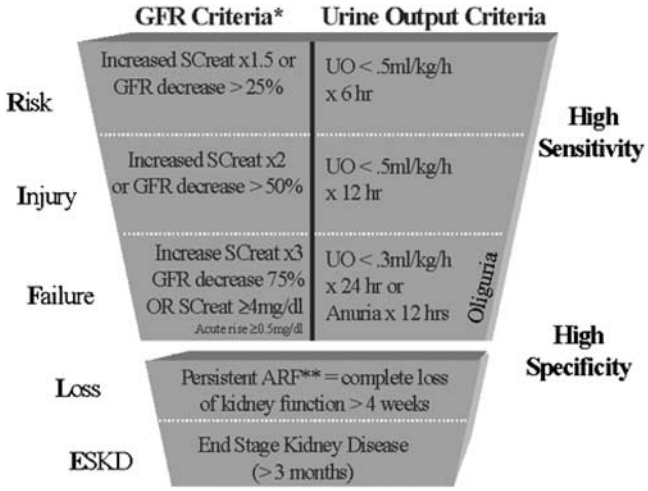

Figure 1 | The RIFLE criteria for AKI. ARF, acute renal failure; GFR, glomerular filtration rate; Screat, serum creatinine concentration; UO, urine output. Reprinted from Bellomo R, Ronco C, Kellum JA, *et al*. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-212 with permission from Bellomo R *et al*.;[22] accessed http://ccforum.com/content/8/4/R204

AKI: acute kidney injury/impairment

Importantly, by defining the syndrome of acute changes in renal function more broadly, RIFLE criteria move beyond ARF. The term "acute kidney injury/impairment" has been proposed to encompass the entire spectrum of the syndrome from minor changes in markers of renal function to requirement for renal replacement therapy (RRT).[23] Thus, the concept of AKI, as defined by RIFLE creates a new paradigm. AKI is not ATN, nor is it renal failure. Instead, it encompasses both and also includes other, less severe conditions. Indeed, as a syndrome, it includes patients without actual damage to the kidney but with functional *impairment* relative to physiologic demand. Including such patients in the classification of AKI is conceptually attractive because these are precisely the patients that may benefit from early intervention. However, it means that AKI includes both *injury* and/or *impairment*. Rather than focusing exclusively on patients with renal failure or on those who receive dialysis or on those that have a clinical syndrome defined by pathology, which is usually absent (ATN), the strong association of AKI with hospital mortality demands that we change the way we think about this disorder. In a study by Hoste *et al*.,[2] only 14% of patients reaching RIFLE "F" received RRT, yet these patients experienced a hospital mortality rate more than five times that of the same ICU population without AKI. Is renal support underutilized or delayed? Are there other supportive measures that should be employed for these patients? Sustained AKI leads to profound alterations in fluid, electrolyte, acid-base and hormonal regulation. AKI results in abnormalities in the central nervous, immune, and coagulation systems. Many patients

with AKI already have multisystem organ failure. What is the incremental influence of AKI on remote organ function and how does it affect outcome? A recent study by Levy *et al.* examined outcomes for over 1000 patients enrolled in the control arms of two large sepsis trials.[24] Early improvement (within 24 hours) in cardiovascular ($P = 0.0010$), renal ($P < 0.0001$), or respiratory ($P = 0.0469$) function was significantly related to survival. This study suggests that outcomes for patients with severe sepsis in the ICU are closely related to early resolution of AKI. While rapid resolution of AKI may simply be a marker of a good prognosis, it may also indicate a window of therapeutic opportunity to improve outcome in such patients.

Validation studies using RIFLE

As of early 2010, over half a million patients have been studied to evaluate the RIFLE criteria as a means of classifying patients with AKI.[25–28] Large series from the USA,[28] Europe,[29,30] and Australia,[25] each including several thousand patients, have provided a consistent picture. AKI defined by RIFLE is associated with significantly decreased survival and furthermore, increasing severity of AKI defined by RIFLE stage leads to increased risk of death.

An early study from Uchino *et al.* focused on the predictive ability of the RIFLE classification in a cohort of 20 126 patients admitted to a teaching hospital for >24 hours over a 3-year period.[5] The authors used an electronic laboratory database to classify patients into RIFLE-R, I, and F and followed them to hospital discharge or death. Nearly 10% of patients achieved a maximum RIFLE-R, 5% I, and 3.5% F. There was a nearly linear increase in hospital mortality with increasing RIFLE class, with patients at R having more than three times the mortality rate of patients without AKI. Patients with I had close to twice the mortality of R and patients with F had 10 times the mortality rate of hospitalized patients without AKI. The investigators performed multivariate logistic regression analysis to test whether RIFLE classification was an independent predictor of hospital mortality. They found that class R carried an odds ratio of hospital mortality of 2.5, I of 5.4, and F of 10.1.

Ali *et al.* studied the incidence of AKI in Northern Scotland, a geographical population base of 523 390. The incidence of AKI was 2147 per million population.[31] Sepsis was a precipitating factor in 47% of patients. RIFLE classification was useful for predicting recovery of renal function ($P < 0.001$), requirement for RRT ($P < 0.001$), length of hospital stay for survivors ($P < 0.001$), and in-hospital mortality ($P = 0.035$). Although no longer statistically significant, subjects with AKI had a high mortality at 3 and 6 months as well.

More recently, the Acute Kidney Injury Network (AKIN), an international network of AKI researchers, organized a summit of nephrology and critical care societies from around the world. The group endorsed the RIFLE criteria with a small modification to include small changes in SCr ($\geqslant 0.3$ mg/dl or $\geqslant 26.5$ μmol/l) when they occur within a 48-hour period.[23] Two recent studies examining large databases in the USA[28] and Europe[29] validated these modified criteria. Thakar *et al.* found that increased severity of AKI was associated with an increased risk of death independent of comorbidity.[28] Patients with Stage 1 ($\geqslant 0.3$ mg/dl or $\geqslant 26.5$ μmol/l) increase in SCr but less than a two-fold increase had an odds ratio of 2.2; with Stage 2 (corresponding to RIFLE-I), there was an odds ratio of 6.1; and in Stage 3 (RIFLE-F), an odds ratio of 8.6 for hospital mortality was calculated. An additional modification to the RIFLE criteria has been proposed for pediatric patients in order to better classify small children with acute-on-chronic disease.[32]

Limitations to current definitions for AKI

Unfortunately, the existing criteria—while extremely useful and widely validated—are still limited. First, despite efforts to standardize the definition and classification of AKI, there is still inconsistency in application.[26,27] A minority of studies have included urinary output criteria despite its apparent ability to identify additional cases[6,29] and many studies have excluded patients whose initial SCr is already elevated. Preliminary data from a 20 000-patient database from the University of Pittsburgh suggests that roughly a third of AKI cases are community-acquired[33] and many cases may be missed by limiting analysis to documented increases in SCr. Indeed, the majority of cases of AKI in the developing world are likely to be community-acquired. Thus, few studies can provide accurate incidence data. An additional problem relates to the limitations of SCr and urine output for detecting AKI. In the future, biomarkers of renal cell injury may identify additional patients with AKI and may identify the majority of patients at an earlier stage.

Rationale for a guideline on AKI

AKI is a global problem and occurs in the community, in the hospital where it is common on medical, surgical, pediatric, and oncology wards, and in ICUs. Irrespective of its nature, AKI is a predictor of immediate and long-term adverse outcomes. AKI is more prevalent in (and a significant risk factor for) patients with chronic kidney disease (CKD). Individuals with CKD are especially susceptible to AKI which, in turn, may act as a promoter of progression of the underlying CKD. The burden of AKI may be most significant in developing countries[34,35] with limited resources for the care of these patients once the disease progresses to kidney failure necessitating RRT. Addressing the unique circumstances and needs of developing countries, especially in the detection of AKI in its early and potentially reversible stages to prevent its progression to kidney failure requiring dialysis, is of paramount importance.

Research over the past decade has identified numerous preventable risk factors for AKI and the potential of improving their management and outcomes. Unfortunately, these are not widely known and are variably practiced

worldwide, resulting in lost opportunities to improve the care and outcomes of patients with AKI. Importantly, there is no unifying approach to the diagnosis and care of these patients. There is a worldwide need to recognize, detect, and intervene to circumvent the need for dialysis and to improve outcomes of AKI. The difficulties and disadvantages associated with an increasing variation in management and treatment of diseases that were amplified in the years after the Second World War, led in 1989 to the creation in the USA of the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality). This agency was created to provide objective, science-based information to improve decision making in health-care delivery. A major contribution of this agency was the establishment of a systematic process for developing evidence-based guidelines. It is now well accepted that rigorously developed, evidence-based guidelines, when implemented, have improved quality, cost, variability, and outcomes.[36,37]

Realizing that there is an increasing prevalence of acute (and chronic) kidney disease worldwide and that the complications and problems of patients with kidney disease are universal, Kidney Disease: Improving Global Outcomes (KDIGO), a nonprofit foundation, was established in 2003 "to improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines".[38]

Besides developing guidelines on a number of other important areas of nephrology, the Board of Directors of KDIGO quickly realized that there is room for improving international cooperation in the development, dissemination, and implementation of clinical practice guidelines in the field of AKI. At its meeting in December of 2006, the KDIGO Board of Directors determined that the topic of AKI meets the criteria for developing clinical practice guidelines.

These criteria were formulated as follows:

- AKI is common.
- AKI imposes a heavy burden of illness (morbidity and mortality).
- The cost per person of managing AKI is high.
- AKI is amenable to early detection and potential prevention.
- There is considerable variability in practice to prevent, diagnose, treat, and achieve outcomes of AKI.
- Clinical practice guidelines in the field have the potential to reduce variations, improve outcomes, and reduce costs.
- Formal guidelines do not exist on this topic.

Summary

Small changes in kidney function in hospitalized patients are important and associated with significant changes in short- and long-term outcomes. The shift of terminology from ATN and ARF to AKI has been well received by the research and clinical communities. RIFLE/AKIN criteria provide a uniform definition of AKI, and have become the standard for diagnostic criteria. AKI severity grades represent patient groups with increasing severity of illness as illustrated by an increasing proportion of patients treated with RRT, and increasing mortality. Thus, AKI as defined by the RIFLE criteria is now recognized as an important syndrome, alongside other syndromes such as acute coronary syndrome, acute lung injury, and severe sepsis and septic shock. The RIFLE/AKIN classification for AKI is quite analogous to the Kidney Disease Outcomes Quality Initiative (KDOQI) for CKD staging, which is well known to correlate disease severity with cardiovascular complications and other morbidities.[39] As CKD stages have been linked to specific treatment recommendations, which have proved extremely useful in managing this disease,[39] we have developed recommendations for evaluation and management of patients with AKI using this stage-based approach.

Chapter 1.2: Methodology

INTRODUCTION

This chapter provides a very brief summary of the methods used to develop this guideline. Detailed methods are provided in Appendix F. The overall aim of the project was to create a clinical practice guideline with recommendations for AKI using an evidence-based approach. After topics and relevant clinical questions were identified, the pertinent scientific literature on those topics was systematically searched and summarized.

Group member selection and meeting process

The KDIGO Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled the Work Group to be responsible for the development of the guideline. The Work Group consisted of domain experts, including individuals with expertise in nephrology, critical care medicine, internal medicine, pediatrics, cardiology, radiology, infectious diseases and epidemiology. For support in evidence review, expertise in methods, and guideline development, the NKF contracted with the Evidence Review Team (ERT) based primarily at the Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA. The ERT consisted of physician-methodologists with expertise in nephrology and internal medicine, and research associates and assistants. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project. The Work Group, KDIGO Co-Chairs, ERT, liaisons, and NKF support staff met for four 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

Evidence selection, appraisal, and presentation

We first defined the topics and goals for the guideline and identified key clinical questions for review. The ERT performed literature searches, organized abstract and article screening, coordinated methodological and analytic processes of the report, defined and standardized the search methodology, performed data extraction, and summarized the evidence. The Work Group members reviewed all included articles, data extraction forms, summary tables, and evidence profiles for accuracy and completeness. The four major topic areas of interest for AKI included: i) definition and classification; ii) prevention; iii) pharmacologic treatment; and iv) RRT. Populations of interest were those at risk for AKI (including those after intravascular contrast-media exposure, aminoglycosides, and amphotericin) and those with or at risk for AKI with a focus on patients with sepsis or trauma, receiving critical care, or undergoing cardiothoracic surgery. We excluded studies on AKI from rhabdomyolysis, specific infections, and poisoning or drug overdose. Overall, we screened 18 385 citations.

Outcome selection judgments, values, and preferences

We limited outcomes to those important for decision making, including development of AKI, need for or dependence on RRT, and all-cause mortality. When weighting the evidence across different outcomes, we selected as the "crucial" outcome that which weighed most heavily in the assessment of the overall quality of evidence. Values and preferences articulated by the Work Group included: i) a desire to be inclusive in terms of meeting criteria for AKI; ii) a progressive approach to risk and cost such that, as severity increased, the group put greater value on possible effectiveness of strategies, but maintained high value for avoidance of harm; iii) intent to guide practice but not limit future research.

Grading the quality of evidence and the strength of recommendations

The grading approach followed in this guideline is adopted from the GRADE system.[40,41] The strength of each recommendation is rated as level 1 which means "strong" or level 2 which means "weak" or discretionary. The wording corresponding to a level 1 recommendation is "We recommend … should" and implies that most patients should receive the course of action. The wording for a level 2 recommendation is "We suggest … might" which implies that different choices will be appropriate for different patients, with the suggested course of action being a reasonable choice in many patients. In addition, each statement is assigned a grade for the quality of the supporting evidence, A (high), B (moderate), C (low), or D (very low). Table 1 shows the implications of the guideline grades and describes how the strength of the recommendations should be interpreted by guideline users.

Furthermore, on topics that cannot be subjected to systematic evidence review, the Work Group could issue statements that are not graded. Typically, these provide guidance that is based on common sense, e.g., reminders of the obvious and/or recommendations that are not sufficiently specific enough to allow the application of evidence. The GRADE system is best suited to evaluate evidence on comparative effectiveness. Some of our most important guideline topics involve diagnosis and staging or AKI, and here the Work Group chose to provide ungraded statements. These statements are indirectly supported by evidence on risk relationships and resulted from unanimous consensus of the Work Group. Thus, the Work Group feels they should not be viewed as weaker than graded recommendations.

Table 1 | Implications of the strength of a recommendation

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

SPONSORSHIP

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SUPPLEMENTARY MATERIAL

Appendix F: Detailed Methods for Guideline Development.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Section 2: AKI Definition

Kidney International Supplements (2012) **2,** 19–36; doi:10.1038/kisup.2011.32

Chapter 2.1: Definition and classification of AKI

INTRODUCTION

AKI is one of a number of conditions that affect kidney structure and function. AKI is defined by an abrupt decrease in kidney function that includes, but is not limited to, ARF. It is a broad clinical syndrome encompassing various etiologies, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g, ischemia, toxic injury); as well as extrarenal pathology (e.g., prerenal azotemia, and acute postrenal obstructive nephropathy)—see Chapters 2.2 and 2.3 for further discussion. More than one of these conditions may coexist in the same patient and, more importantly, epidemiological evidence supports the notion that even mild, reversible AKI has important clinical consequences, including increased risk of death.[2,5] Thus, AKI can be thought of more like acute lung injury or acute coronary syndrome. Furthermore, because the manifestations and clinical consequences of AKI can be quite similar (even indistinguishable) regardless of whether the etiology is predominantly within the kidney or predominantly from outside stresses on the kidney, the syndrome of AKI encompasses both direct *injury* to the kidney as well as acute *impairment* of function. Since treatments of AKI are dependent to a large degree on the underlying etiology, this guideline will focus on specific diagnostic approaches. However, since general therapeutic and monitoring recommendations can be made regarding all forms of AKI, our approach will be to begin with general measures.

Definition and staging of AKI

AKI is common, harmful, and potentially treatable. Even a minor acute reduction in kidney function has an adverse prognosis. Early detection and treatment of AKI may improve outcomes. Two similar definitions based on SCr and urine output (RIFLE and AKIN) have been proposed and validated. There is a need for a single definition for practice, research, and public health.

2.1.1: AKI is defined as any of the following (*Not Graded*):

- **Increase in SCr by $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) within 48 hours; or**
- **Increase in SCr to $\geqslant$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or**
- **Urine volume $<$0.5 ml/kg/h for 6 hours.**

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) increase	$<$0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	$<$0.5 ml/kg/h for $\geqslant$12 hours
3	3.0 times baseline OR Increase in serum creatinine to $\geqslant$4.0 mg/dl ($\geqslant$353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients $<$18 years, decrease in eGFR to $<$35 ml/min per 1.73 m^2	$<$0.3 ml/kg/h for $\geqslant$24 hours OR Anuria for $\geqslant$12 hours

2.1.2: AKI is staged for severity according to the following criteria (Table 2). (*Not Graded*)

2.1.3: The cause of AKI should be determined whenever possible. (*Not Graded*)

RATIONALE

Conditions affecting kidney structure and function can be considered acute or chronic, depending on their duration. AKI is one of a number of acute kidney diseases and disorders (AKD), and can occur with or without other acute or chronic kidney diseases and disorders (Figure 2). Whereas CKD has a well-established conceptual model and definition that has been useful in clinical medicine, research, and public health,[42–44] the definition for AKI is evolving, and the concept of AKD is relatively new. An operational definition of AKD for use in the diagnostic approach to alterations in kidney function and structure is included in Chapter 2.5, with further description in Appendix B.

The conceptual model of AKI (Figure 3) is analogous to the conceptual model of CKD, and is also applicable to AKD.[42,45] Circles on the horizontal axis depict stages in the development (left to right) and recovery (right to left) of AKI. AKI (in red) is defined as reduction in kidney function, including decreased GFR and kidney failure. The criteria for the diagnosis of AKI and the stage of severity of AKI are based on changes in SCr and urine output as depicted in the triangle above the circles. Kidney failure is a stage of AKI highlighted here because of its clinical importance. Kidney failure is defined as a GFR $<$15 ml/min per 1.73 m^2 body

surface area, or requirement for RRT, although it is recognized that RRT may be required earlier in the evolution of AKI. Further description is included in Chapter 2.5 and Appendix A.

It is widely accepted that GFR is the most useful overall index of kidney function in health and disease, and changes in SCr and urine output are surrogates for changes in GFR. In clinical practice, an abrupt decline in GFR is assessed from an increase in SCr or oliguria. Recognizing the limitations of the use of a decrease in kidney function for the early detection and accurate estimation of renal injury (see below), there is a broad consensus that, while more sensitive and specific biomarkers are needed, changes in SCr and/or urine output form the basis of all diagnostic criteria for AKI. The first international interdisciplinary consensus criteria for diagnosis of AKI were the RIFLE criteria[32] proposed by the ADQI. Modifications to these criteria have been proposed in order to better account for pediatric populations (pRIFLE)[32] and for small changes in SCr not captured by RIFLE (AKIN criteria).[23] Recommendations 2.1.1 and 2.1.2 represent the combination of RIFLE and AKIN criteria (Table 3).

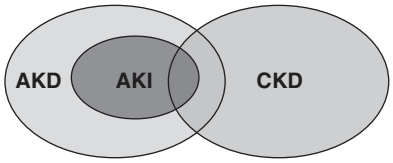

Figure 2 | Overview of AKI, CKD, and AKD. Overlapping ovals show the relationships among AKI, AKD, and CKD. AKI is a subset of AKD. Both AKI and AKD without AKI can be superimposed upon CKD. Individuals without AKI, AKD, or CKD have no known kidney disease (NKD), not shown here. AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease.

Existing evidence supports the validity of both RIFLE and AKIN criteria to identify groups of hospitalized patients with increased risk of death and/or need for RRT.[2,5,25,28–30] Epidemiological studies, many multicentered, collectively enrolling more than 500 000 subjects have been used to establish RIFLE and/or AKIN criteria as valid methods to diagnose and stage AKI. Recently, Joannidis *et al.*[29] directly compared RIFLE criteria with and without the AKIN modification. While AKI classified by either criteria were associated with a similarly increased hospital mortality, the two criteria identified somewhat different patients. The original RIFLE criteria failed to detect 9% of cases that were detected by AKIN criteria. However, the AKIN criteria missed 26.9% of cases detected by RIFLE. Examination of the cases missed by either criteria (Table 4) shows that cases identified by AKIN but missed by RIFLE were almost exclusively Stage 1 (90.7%), while cases missed by AKIN but identified by RIFLE included 30% with RIFLE-I and 18% RIFLE-F; furthermore, these cases had hospital mortality similar to cases identified by both criteria (37% for I and 41% for F). However, cases missed by RIFLE but identified as Stage 1 by AKIN also had hospital mortality rates nearly twice that of patients who had no evidence of AKI by either criteria (25% vs. 13%). These data provide strong rationale for use of both RIFLE and AKIN criteria to identify patients with AKI.

Staging of AKI (Recommendation 2.1.2) is appropriate because, with increased stage of AKI, the risk for death and need for RRT increases.[2,5,25,28–31] Furthermore, there is now accumulating evidence of long-term risk of subsequent development of cardiovascular disease or CKD and mortality, even after apparent resolution of AKI.[47–49]

For staging purposes, patients should be staged according to the criteria that give them the highest stage. Thus when creatinine and urine output map to different stages,

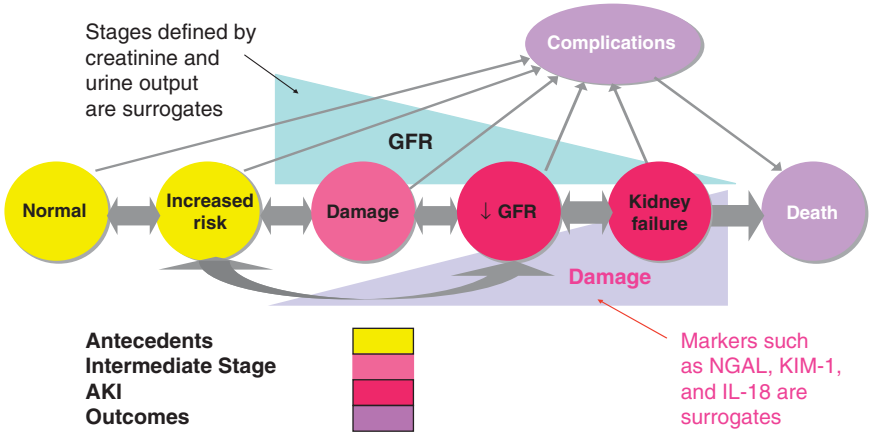

Figure 3 | Conceptual model for AKI. Red circles represent stages of AKI. Yellow circles represent potential antecedents of AKI, and the pink circle represents an intermediate stage (not yet defined). Thick arrows between circles represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions. Purple circles represent outcomes of AKI. "Complications" refers to all complications of AKI, including efforts at prevention and treatment, and complications in other organ systems. AKI, acute kidney injury; GFR, glomerular filtration rate. Adapted from Murray PT, Devarajan P, Levey AS, *et al.* A framework and key research questions in AKI diagnosis and staging in different environments. Clin J Am Soc Nephrol 2008; 3: 864–868 with permission from American Society of Nephrology[45] conveyed through Copyright Clearance Center, Inc.; accessed http://cjasn.asnjournals.org/content/3/3/864.full

Table 3 | Comparison of RIFLE and AKIN criteria for diagnosis and classification of AKI

AKI staging	Urine output	RIFLE	
Serum creatinine	(common to both)	Class	Serum creatinine or GFR
Stage 1 Increase of more than or equal to 0.3 mg/dl (≥26.5 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg/h for more than 6 hours	Risk	Increase in serum creatinine × 1.5 or GFR decrease >25%
Stage 2 Increased to more than 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours	Injury	Serum creatinine × 2 or GFR decreased >50%
Stage 3 Increased to more than 300% (>3-fold) from baseline, or more than or equal to 4.0 mg/dl (≥354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l) or on RRT	Less than 0.3 ml/kg/h for 24 hours or anuria for 12 hours	Failure	Serum creatinine × 3, or serum creatinine >4 mg/dl (>354 μmol/l) with an acute rise >0.5 mg/dl (>44 μmol/l) or GFR decreased >75%
		Loss	Persistent acute renal failure=complete loss of kidney function >4 weeks
		End-stage kidney disease	ESRD >3 months

Note: For conversion of creatinine expressed in SI units to mg/dl, divide by 88.4. For both AKIN stage and RIFLE criteria, only one criterion (creatinine rise or urine output decline) needs to be fulfilled. Class is based on the worst of either GFR or urine output criteria. GFR decrease is calculated from the increase in serum creatinine above baseline. For AKIN, the increase in creatinine must occur in <48 hours. For RIFLE, AKI should be both abrupt (within 1–7 days) and sustained (more than 24 hours). When baseline creatinine is elevated, an abrupt rise of at least 0.5 mg/dl (44 μmol/l) to >4 mg/dl (>354 μmol/l) is sufficient for RIFLE class Failure (modified from Mehta *et al.*[23] and the report of the Acute Dialysis Quality Initiative consortium[22]).

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RIFLE, risk, injury, failure, loss, and end stage; RRT, renal replacement therapy. Reprinted from Endre ZH. Acute kidney injury: definitions and new paradigms. Adv Chronic Kidney Dis 2008; 15: 213–221 with permission from National Kidney Foundation[46]; accessed http://www.ackdjournal.org/article/S1548-5595(08)00049-9/fulltext

Table 4 | Cross-tabulation of patients classified by RIFLE vs. AKIN

		RIFLE				
AKIN		Non-AKI	Risk	Injury	Failure	Total (AKIN)
Non-AKI	n*	8759 (12.9%)	781 (27.7%)	452 (37.4%)	271 (41.3%)	10 263 (15.9%)
Stage1	n*	457 (25.2%)	282 (33.0%)	243 (44.0%)	95 (60.0%)	1077 (34.5%)
Stage 2	n*	36 (30.6%)	21 (47.6%)	885 (25.9%)	91 (54.9)	1033 (29.0%)
Stage 3	n*	11 (18.2%)	8 (12.5%)	16 (62.5%)	1948 (41.3)	1983 (41.2%)
Total (RIFLE)	n*	9263 (13.6%)	1092 (29.2%)	1596 (32.3%)	2405 (42.6%)	14 356 (21.7%)

*Number of patients classified into the respective stages of AKI by AKIN or RIFLE are cross-tabulated against each other. Hospital mortality of each group is given in parentheses. Shaded fields denote patients assigned to the same degree of AKI by both classification systems.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; RIFLE, risk, injury, failure, loss, and end stage. With kind permission from Springer Science+Business Media: Intensive Care Med. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. 35 (2009): 1692–1702. Joannidis M, Metnitz B, Bauer P *et al.*[29]; accessed http://www.springerlink.com/content/r177337030550120/

the patient is staged according to the highest (worst) stage. The changes in GFR that were published with the original RIFLE criteria do not correspond precisely to changes in SCr. As SCr is measured and GFR can only be estimated, creatinine criteria should be used along with urine output for the diagnosis (and staging) of AKI. One additional change in the criteria was made for the sake of clarity and simplicity. For patients reaching Stage 3 by SCr >4.0 mg/dl (>354 μmol/l), rather than require an acute increase of ≥0.5 mg/dl (≥44 μmol/l) over an unspecified time period, we instead require that the patient first achieve the creatinine-based change specified in the definition (either ≥0.3 mg/dl [≥26.5 μmol/l] within a 48-hour time window or an increase of ≥1.5 times baseline). This change brings the definition and staging criteria to greater parity and simplifies the criteria.

Recommendation 2.1.2 is based on the RIFLE and AKIN criteria that were developed for average-sized adults. The creatinine change–based definitions include an automatic Stage 3 classification for patients who develop SCr >4.0 mg/dl (>354 μmol/l) (provided that they first satisfy the definition of AKI in Recommendation 2.1.1). This is problematic for smaller pediatric patients, including infants and children with low muscle mass who may not be able to achieve a SCr of 4.0 mg/dl (354 μmol/l). Thus, the pediatric-modified RIFLE AKI criteria[32] were developed using a change in estimated creatinine clearance (eCrCl) based on the Schwartz formula. In pRIFLE, patients automatically reach Stage 3 if they develop an eCrCl <35 ml/min per 1.73 m^2. However, with this automatic pRIFLE threshold, the SCr change based AKI definition (recommendation 2.1.1) is applicable to pediatric patients, including an increase of 0.3 mg/dl (26.5 μmol/l) SCr.[32]

There are important limitations to these recommendations, including imprecise determination of risk (see Chapter 2.2) and incomplete epidemiology of AKI, especially outside the ICU. Clinical judgment is required in order to determine if patients seeming to meet criteria do, in fact, have disease, as well as to determine if patients are likely to have AKI even if incomplete clinical data are available to apply the diagnostic criteria. The application of the diagnostic and staging criteria

Table 5 | Causes of AKI and diagnostic tests

Selected causes of AKI requiring immediate diagnosis and specific therapies	Recommended diagnostic tests
Decreased kidney perfusion	Volume status and urinary diagnostic indices
Acute glomerulonephritis, vasculitis, interstitial nephritis, thrombotic microangiopathy	Urine sediment examination, serologic testing and hematologic testing
Urinary tract obstruction	Kidney ultrasound

AKI, acute kidney injury.

is discussed in greater detail, along with specific examples in Chapter 2.4.

The use of urine output criteria for diagnosis and staging has been less well validated and in individual patients the need for clinical judgment regarding the effects of drugs (e.g., angiotensin-converting enzyme inhibitors [ACE-I]), fluid balance, and other factors must be included. For very obese patients, urine output criteria for AKI may include some patients with normal urine output. However, these recommendations serve as the starting point for further evaluation, possibly involving subspecialists, for a group of patients recognized to be at increased risk.

Finally, it is axiomatic that patients always be managed according to the cause of their disease, and thus it is important to determine the cause of AKI whenever possible. In particular, patients with decreased kidney perfusion, acute glomerulonephritis, vasculitis, interstitial nephritis, thrombotic microangiopathy, and urinary tract obstruction require immediate diagnosis and specific therapeutic intervention, in addition to the general recommendations for AKI in the remainder of this guideline (Table 5).

It is recognized that it is frequently not possible to determine the cause, and often the exact cause does not dictate a specific therapy. However, the syndrome of AKI includes some patients with specific kidney diseases (e.g., glomerulonephritis) for which a specific treatment is available. As such, it is always necessary to search for the underlying cause of AKI (see Chapter 2.3).

Research Recommendations

- The role of biomarkers other than SCr in the early diagnosis, differential diagnosis, and prognosis of AKI patients should be explored. Some important areas in which to focus include:
  - Early detection where the gold standard is AKI by clinical diagnosis after the fact and the biomarker is compared to existing markers (SCr and urine output) at the time of presentation.
  - Prognosis where a biomarker is used to predict risk for AKI or risk for progression of AKI.
  - Prognosis where a biomarker is used to predict recovery after AKI vs. death or need for long-term RRT.
- The influence of urinary output criteria on AKI staging needs to be further investigated. Influence of fluid balance, percent volume overload, diuretic use, and differing weights (actual, ideal body weight, lean body mass) should be considered. Also, it is currently not known how urine volume criteria should be applied (e.g., average vs. persistent reduction for the period specified).
- The influence of SCr or eGFR criteria on AKI staging needs to be further investigated. The use of different relative and absolute SCr increments or eGFR decrements at different time points and with differently ascertained baseline values requires further exploration and validation in various populations.

SUPPLEMENTARY MATERIAL

Appendix A: Background.

Appendix B: Diagnostic Approach to Alterations in Kidney Function and Structure.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 2.2: Risk assessment

The kidney is a fairly robust organ that can tolerate exposure to several insults without suffering significant structural or functional change. For this reason, any acute change in kidney function often indicates severe systemic derangement and predicts a poor prognosis. Risk for AKI is increased by exposure to factors that cause AKI or the presence of factors that increase susceptibility to AKI. Factors that determine susceptibility of the kidneys to injury include dehydration, certain demographic characteristics and genetic predispositions, acute and chronic comorbidities, and treatments. It is the interaction between susceptibility and the type and extent of exposure to insults that determines the risk of occurrence of AKI.

Understanding individual "risk factors" may help in preventing AKI. This is particularly gratifying in the hospital setting, where the patient's susceptibility can be assessed before certain exposures as surgery or administration of potentially nephrotoxic agents. Accordingly, some susceptibility factors may be modified, and contemplated exposures avoided or tailored to reduce the risk of AKI.

Risk assessment in community-acquired AKI is different from hospital-acquired AKI, for two main reasons: i) Available evidence on risk factors is largely derived from hospital data and extrapolation to the community setting is questionable. ii) The opportunity to intervene, prior to exposure, is quite limited. Most patients are seen only after having suffered an exposure (trauma, infection, poisonous plant, or animal). However, there is still room to assess such patients, albeit after exposure, in order to identify those who are more likely to develop AKI, thereby requiring closer monitoring and general supportive measures. It may also be helpful to identify such patients in order to avoid additional injury. A more complete discussion of the approach to identification and management of risk for AKI is provided in Appendices C and D.

2.2.1: We recommend that patients be stratified for risk of AKI according to their susceptibilities and exposures. (*1B*)

2.2.2: Manage patients according to their susceptibilities and exposures to reduce the risk of AKI (see relevant guideline sections). (*Not Graded*)

2.2.3: Test patients at increased risk for AKI with measurements of SCr and urine output to detect AKI. (*Not Graded*) Individualize frequency and duration of monitoring based on patient risk and clinical course. (*Not Graded*)

RATIONALE

There are many types of exposures that may cause AKI (Table 6) and these are discussed in detail in Appendix C.

Table 6 | Causes of AKI: exposures and susceptibilities for non-specific AKI

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

CKD, chronic kidney disease; CPB, cardiopulmonary bypass.

However, the chances of developing AKI after exposure to the same insult differ among different individuals. This is attributed to a number of susceptibility factors which vary widely from individual to individual. Our understanding of susceptibility factors (Table 6) is based on many observational studies that address different settings with regards to the type, severity, duration, and multiplicity of insults. While this heterogeneity provides insight into some susceptibility factors that are common across various populations, the generalizability of results from one particular setting to the next is uncertain.

The course and outcome of AKI are modified by other factors, but since these are manifested within the context of actual disease, they must be categorized as "prognostic" rather than "risk" factors, hence being discussed separately in Appendix D. Lastly, the fact that some 30% of patients who recover from AKI remain at increased risk of CKD, cardiovascular disease, and death calls for the identification of the risk factors that can identify such patients in the hopes of providing them with timely preventive measures.[50–52]

Finally, it is important to screen patients who have undergone an exposure (e.g., sepsis, trauma) and to continue monitor high-risk patients until the risk has subsided. Exact intervals for checking SCr and in which individuals to monitor urine output remain matters of clinical judgment; however, as a general rule, high risk in-patients should have SCr measured at least daily and more frequently after an exposure, and critically ill patients should have urine output monitoring. This will necessitate urinary bladder catheterization in many cases, and the risks of infection should also be considered in the monitoring plan.

A recent clinical practice assessment in the UK concluded that only 50% of patients with AKI were considered to have received a "good" overall standard of care. This figure fell to

just over 30% if AKI developed during a hospital admission rather than being diagnosed before admission.[53] The authors also felt that there was an unacceptable delay in recognizing AKI in 43% of those that developed the condition after admission, and that in a fifth of such patients its development was predictable and avoidable. Their recommendations were simple: risk assessment for AKI as part of the initial evaluation of emergency admissions, along with appropriate serum biochemistry on admission and at frequent intervals thereafter.[53]

RESEARCH RECOMMENDATIONS

- Better delineation of risk for hospital- and community-acquired AKI is needed.
- Better delineation of the effects of age on the risk for AKI is needed.
- Studies are needed to develop and validate scoring systems for AKI risk prediction in various settings, in addition to cardiac surgery and exposure to radiocontrast material.
- Genome-wide association studies are needed to determine risk of AKI in different hospital settings and with respect to long-term outcomes.
- Studies are needed on risk factors for the development of, recovery from, and long-term outcomes of community-acquired AKI, including sepsis, trauma, tropical infections, snake bites, and ingestion of toxic plants, etc.

SUPPLEMENTARY MATERIAL

Appendix C: Risk Determination.
Appendix D: Evaluation and General Management Guidelines for Patients with AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 2.3: Evaluation and general management of patients with and at risk for AKI

Given that AKI is associated with significant morbidity and mortality, and because no specific treatment is available to reverse AKI, early recognition and management is paramount. Indeed, recognition of patients at risk for AKI, or with possible AKI but prior to clinical manifestations, is likely to result in better outcomes than treating only established AKI. Chapter 2.2 introduced the approach to risk assessment with further detail provided in Appendix C. This chapter will concern itself with the evaluation and general management of patients with, or even at risk for, AKI. Further detail is provided in Appendix D. We highlight the importance of beginning management at the earliest point in the development of AKI—in patients with suspected AKI or even in those at increased risk who have been exposed to the various factors discussed in Chapters 2.2 and Appendix C.

Although much of the remaining chapters in this guideline pertain to management of specific aspects of AKI, there are general management principles that are common to all patients and these will be discussed here and further expounded upon in Appendix D. Treatment goals in patients with AKI include both reducing kidney injury and complications related to decreased kidney function.

2.3.1: Evaluate patients with AKI promptly to determine the cause, with special attention to reversible causes. (*Not Graded*)

2.3.2: Monitor patients with AKI with measurements of SCr and urine output to stage the severity, according to Recommendation 2.1.2. (*Not Graded*)

2.3.3: Manage patients with AKI according to the stage (see Figure 4) and cause. (*Not Graded*)

2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. (*Not Graded*)

- **If patients have CKD, manage these patients as detailed in the KDOQI CKD Guideline (Guidelines 7–15). (*Not Graded*)**
- **If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD. (*Not Graded*)**

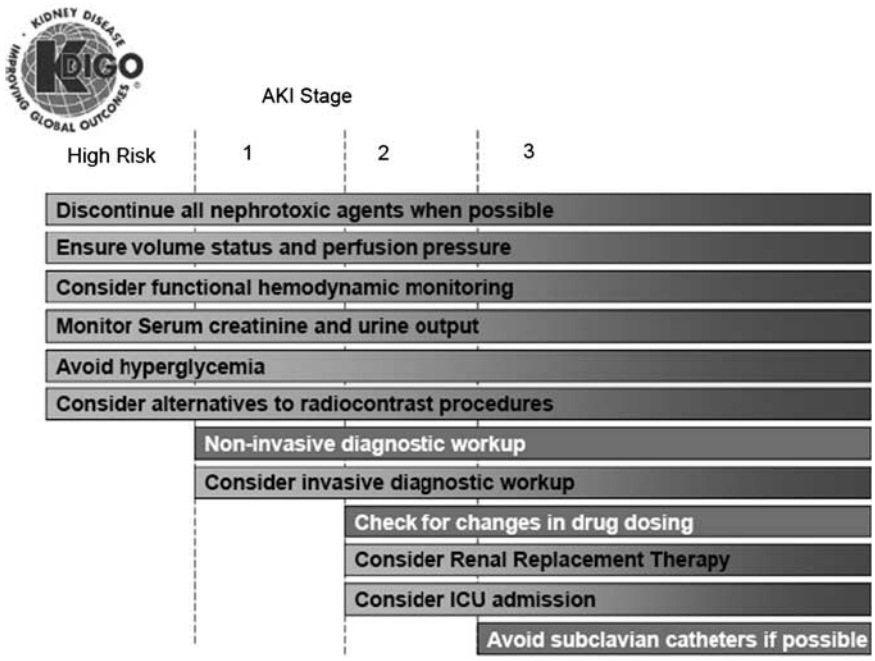

Figure 4 | Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive-care unit.

RATIONALE

As emphasized in Chapter 2.2, AKI is not a disease but rather a clinical syndrome with multiple etiologies. While much of the literature examining epidemiology and clinical consequences of AKI appear to treat this syndrome as a homogeneous disorder, the reality is that AKI is heterogeneous and often is the result of multiple insults. Figure 5 illustrates an approach to evaluation of AKI. Further discussion of evaluation in clinical practice is provided in Appendix D.

The clinical evaluation of AKI includes a careful history and physical examination. Drug history should include over-the-counter formulations and herbal remedies or recreational drugs. The social history should include exposure to tropical diseases (e.g., malaria), waterways or sewage systems, and exposure to rodents (e.g., leptospirosis, hantavirus). Physical examination should include evaluation of fluid status, signs for acute and chronic heart failure, infection, and sepsis.

Measurement of cardiac output, preload, preload responsiveness, and intra-abdominal pressure should be considered

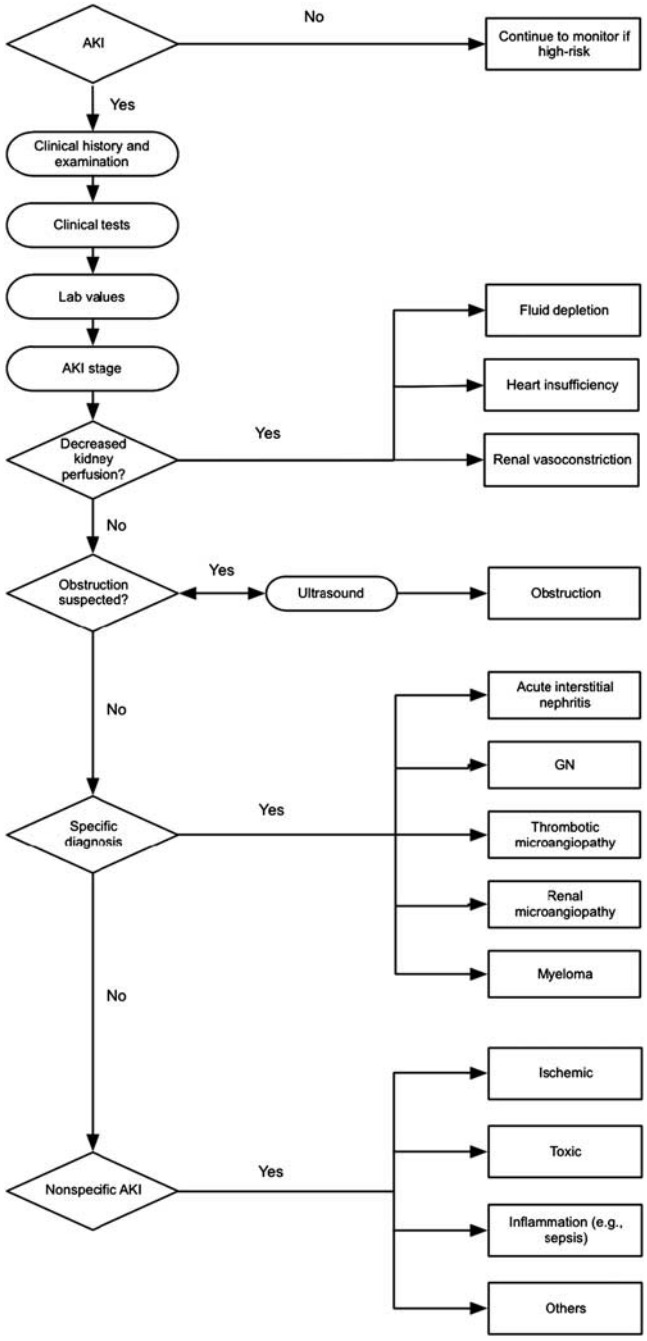

Figure 5 | Evaluation of AKI according to the stage and cause.

in the appropriate clinical context. Laboratory parameters—including SCr, blood urea nitrogen (BUN), and electrolytes, complete blood count and differential—should be obtained. Urine analysis and microscopic examination as well as urinary chemistries may be helpful in determining the underlying cause of AKI. Imaging tests, especially ultrasound, are important components of the evaluation for patients with AKI. Finally, a number of biomarkers of functional change and cellular damage are under evaluation for early diagnosis, risk assessment for, and prognosis of AKI (see Appendix D for detailed discussion).

Individualize frequency and duration of monitoring based on patient risk, exposure and clinical course. Stage is a predictor of the risk for mortality and decreased kidney function (see Chapter 2.4). Dependent on the stage, the intensity of future preventive measures and therapy should be performed.

Because the stage of AKI has clearly been shown to correlate with short-term[2,5,27,29] and even longer-term outcomes,[31] it is advisable to tailor management to AKI stage. Figure 4 lists a set of actions that should be considered for patients with AKI. Note that for patients at increased risk (see Chapters 2.2 and 2.4), these actions actually begin even before AKI is diagnosed.

Note that management and diagnostic steps are both included in Figure 4. This is because response to therapy is an important part of the diagnostic approach. There are few specific tests to establish the etiology of AKI. However, a patient's response to treatment (e.g., discontinuation of a possible nephrotoxic agent) provides important information as to the diagnosis.

Nephrotoxic drugs account for some part of AKI in 20–30% of patients. Often, agents like antimicrobials (e.g., aminoglycosides, amphotericin) and radiocontrast are used in patients that are already at high risk for AKI (e.g., critically ill patients with sepsis). Thus, it is often difficult to discern exactly what contribution these agents have on the overall course of AKI. Nevertheless, it seems prudent to limit exposure to these agents whenever possible and to weigh the risk of developing or worsening AKI against the risk associated with not using the agent. For example, when alternative therapies or diagnostic approaches are available they should be considered.

In order to ensure adequate circulating blood volume, it is sometimes necessary to obtain hemodynamic variables. Static variables like central venous pressure are not nearly as useful as dynamic variables, such as pulse-pressure variation, inferior vena cava filling by ultrasound and echocardiographic appearance of the heart (see also Appendix D).

Note that while the actions listed in Figure 4 provide an overall starting point for stage-based evaluation and management, they are neither complete not mandatory for an individual patient. For example, the measurement of urine output does not imply that the urinary bladder catheterization is mandatory for all patients, and clinicians should balance the risks of any procedures with the benefits. Furthermore, clinicians must individualize care decisions based on the totality of the clinical situation. However, it is advisable to include AKI stage in these decisions.

The evaluation and management of patients with AKI requires attention to cause and stage of AKI, as well as factors that relate to further injury to the kidney, or complications from decreased kidney function. Since AKI is a risk factor for CKD, it is important to evaluate patients with AKI for new onset or worsening of pre-existing CKD. If patients have CKD, manage patients as detailed in the KDOQI CKD Guideline (Guidelines 7–15). If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD.

RESEARCH RECOMMENDATIONS

- Clinical research aimed at testing early management strategies is urgently needed. Such trials should also address the risks and benefits of commonly used fluid-management strategies, including intravenous (i.v.) fluids and diuretics.
- Methods to better assess fluid status in critically ill and other hospitalized patients at risk for AKI are needed.
- Research is needed, with follow-up beyond hospital stay, to better understand the clinical consequences of AKI in patients with and without underlying CKD.

SUPPLEMENTARY MATERIAL

Appendix C: Risk Determination.
Appendix D: Evaluation and General Management Guidelines for Patients with AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 2.4: Clinical applications

This chapter provides a detailed application of the AKI definition and staging for clinical diagnosis and management. The definitions and classification system discussed in Chapter 2.1 can be used easily in many patients and requires little clinical interpretation. However, in real time, clinicians do not always have a complete dataset to work with and individual patients present with unique histories. As discussed in the previous chapter, it is difficult to distinguish AKI from CKD in many cases. In addition, as many as two-thirds of all cases of AKI begin prior to hospitalization (community-acquired AKI). Therefore, clinicians may be faced with patients in whom kidney function is already decreased and, during the hospitalization, improves rather than worsens. Finally, many patients do not have a prior measurement of kidney function available for comparison. This chapter provides detailed examples of the application of these definitions to the clinical setting.

Examples of application of AKI definitions

Table 7 illustrates a number of examples whereby patients presenting with possible AKI can be diagnosed. Cases A-F have a measurement of baseline SCr. To simplify decision-making, baseline estimated glomerular filtration rate (eGFR) exceeds 60 ml/min per 1.73 m^2 in these patients, so none has pre-existing CKD. Cases A-F can all be diagnosed with AKI by applying the first two criteria in Recommendation 2.1.1. (a documented increase of at least 0.3 mg/dl (>26.5 μmol/l) [within 48 hours or a 50% increase from presumed baseline). Note that a patient can be diagnosed with AKI by fulfilling either criterion 1 or 2 (or 3, urine output) and thus cases B,C,D, and F all fulfill the definition of AKI. Note also that patients may be diagnosed earlier using criterion 1 or 2. Early diagnosis may improve outcome so it is advantageous to diagnose patients as rapidly as possible. For example, case A can be diagnosed with AKI on day 2 by the first criterion, whereas the second criterion is not satisfied until day 3 (increase from 1.3 to 1.9). However, this is only true because the episode of AKI began prior to medical attention, and thus the day 1 SCr level was already increased. If creatinine measurements had available with 48 hours prior to day 1 and if this level had been at baseline (1.0 mg/dl [88.4 μmol/l]), it would have been possible to diagnose AKI on day 1 using the second criterion.

Cases F-H do not have a baseline measurement of SCr available. Elevated SCr (reduced eGFR) on day 1 of the hospitalization is consistent with either CKD or AKD without AKI. In Case F, baseline SCr can be inferred to be below the day 1 value because of the subsequent clinical course; thus, we can infer the patient has had an episode of AKI. In case G, AKI can be diagnosed by application of criterion 2, but the patient may have underlying CKD. Case H does not fulfill the definition for AKI based on either criteria, and has either CKD or AKD without AKI.

The example of Case A raises several important issues. First, frequent monitoring of SCr in patients at increased risk of AKI will significantly improve diagnostic time and accuracy. If Case A had not presented to medical attention (or if SCr had not been checked) until day 7, the case of AKI would likely have been missed. Frequent measurement of SCr in high-risk patients, or in patients in which AKI is suspected, is therefore encouraged—see Chapter 2.3. The second issue highlighted by Case A is the importance of baseline SCr measurements. Had no baseline been available it would still have been possible to diagnose AKI on day 3 (by either using criterion 2 or by using criterion 1 and accepting the baseline SCr as 1.3); however, not only would this have resulted in a

Table 7 | AKI diagnosis

	Serum creatinine mg/dl (μmol/l)					Diagnosis AKI?	
Case	Baseline	Day 1	Day 2	Day 3	Day 7	Criterion 1 50% from baseline	Criterion 2 $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) rise in $\leqslant$48 hours
A	1.0 (88)	1.3 (115)	1.5 (133)	2.0 (177)	1.0 (88)	Yes	Yes
B	1.0 (88)	1.1 (97)	1.2 (106)	1.4 (124)	1.0 (88)	No	Yes
C	0.4 (35)	0.5 (44)	0.6 (53)	0.7 (62)	0.4 (35)	Yes	No
D	1.0 (88)	1.1 (97)	1.2 (106)	1.3 (115)	1.5 (133)	Yes	No
E	1.0 (88)	1.3 (115)	1.5 (133)	1.8 (159)	2.2 (195)	Yes	Yes
F	?	3.0 (265)	2.6 (230)	2.2 (195)	1.0 (88)	Yes	No
G	?	1.8 (159)	2.0 (177)	2.2 (195)	1.6 (141)	?	Yes
H	?	3.0 (265)	3.1 (274)	3.0 (265)	2.9 (256)	?	No

Table 8 | Overview of the approaches to determine baseline SCr in the application of RIFLE classification in previous studies

Study	No. of pts analyzed	Multi-/ single-center	Criteria used	Method to determine baseline SCr	% recorded	% estimated
Bagshaw[25]	120123	multi	cr+uo	estimated by MDRD formula	0	100
Ostermann[30]	41972	multi	cr	estimated by MDRD formula	0	100
Uchino[5]	20126	single	cr	retrieved from hospital database, or estimated by MDRD formula	N/A	N/A
Bell[54]	8152	single	cr+uo	retrieved from hospital database, or estimated by MDRD formula	N/A	N/A
Hoste[2]	5383	single	cr+uo	estimated by MDRD formula, or admission creatinine value, whatever was lower	N/A	N/A
Ali[31]	5321	multi	cr	retrieved from hospital database, or admission creatinine value	100	0
Cruz[55]	2164	multi	cr+uo	retrieved from hospital database, or estimated by MDRD formula	78	22
Perez-Valdivieso[56]	1008	single	cr	estimated by MDRD formula	0	100
Kuitunen[57]	813	single	cr+uo	preoperative value	100	0
Coca[58]	304	single	cr	the lowest s-creatinine value in the first 5 hospital days	100	0
Arnaoutakis[59]	267	single	N/A	N/A	N/A	N/A
Abosaif[60]	247	single	cr+uo	retrieved from hospital database, or admission creatinine value	100	0
Maccariello[61]	214	multi	cr+uo	retrieved from hospital database, or estimated by MDRD formula	N/A	N/A
Jenq[62]	134	single	cr+uo	admission creatinine value, or estimated by MDRD formula	90	10

cr, creatinine criteria; MDRD, Modification of Diet in Renal Disease; N/A, not available; pts, patients; SCr, serum creatinine; uo, urine output criteria.
Reprinted from Zavada J, Hoste E, Cartin-Ceba R *et al*. A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transplant 2010; 25(12): 3911–3918 (Ref. 64) by permission from The European Renal Association-European Dialysis and Transplant Association; accessed http://ndt.oxfordjournals.org/content/25/12/3911.long

Table 9 | Estimated baseline SCr

Age (years)	Black males mg/dl (μmol/l)	Other males mg/dl (μmol/l)	Black females mg/dl (μmol/l)	Other females mg/dl (μmol/l)
20–24	1.5 (133)	1.3 (115)	1.2 (106)	1.0 (88)
25–29	1.5 (133)	1.2 (106)	1.1 (97)	1.0 (88)
30–39	1.4 (124)	1.2 (106)	1.1 (97)	0.9 (80)
40–54	1.3 (115)	1.1 (97)	1.0 (88)	0.9 (80)
55–65	1.3 (115)	1.1 (97)	1.0 (88)	0.8 (71)
>65	1.2 (106)	1.0 (88)	0.9 (80)	0.8 (71)

Estimated glomerular filtration rate=75 (ml/min per 1.73 m^2)=186 × (serum creatinine [S_{Cr}]) − 1.154 × (age) − 0.203 × (0.742 if female) × (1.210 if black)=exp(5.228 − 1.154 × ln [S_{Cr}]) − 0.203 × ln(age) − (0.299 if female) + (0.192 if black).
Reprinted from Bellomo R, Ronco C, Kellum JA *et al*. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-212 with permission from Bellomo R *et al*.[22]; accessed http://ccforum.com/content/8/4/R204

delay in diagnosis, it would have resulted in a delay in staging (see Table 7). On day 7, it can be inferred that the patient's baseline was no higher than 1.0 mg/dl (88 μmol/l) and thus correct staging of Case A as Stage 2 (two-fold increase from the reference SCr, see below and Table 7) on day 3 could have been determined in retrospect. However, if a baseline SCr was available to use as the reference, the correct stage could be determined on day 3.

Case B illustrates why criterion 2 can detect cases of AKI missed by criterion 1. It also clarifies why these cases are unusual. Had the SCr increased to 1.5 mg/dl (132.6 μmol/l) as opposed to peaking at 1.4 mg/dl (123.8 μmol/l), it would have been picked up by criterion 1 as well. By contrast Cases C, D, and even F illustrate how criterion 2 may miss cases identified by criterion 1. Note that Case F can only be diagnosed by inference. By day 7, it can be inferred that the baseline was no higher than 1.0 mg/dl (88 μmol/l) and thus it can be determined that the patient presented with AKI. However, if the baseline SCr could be estimated it would be possible to make this inference as early as day 1.

Estimating baseline SCr

Many patients will present with AKI without a reliable baseline SCr on record. Baseline SCr can be estimated using the Modification of Diet in Renal Disease (MDRD) Study equation assuming that baseline eGFR is 75 ml/min per 1.73 m^2 (Table 9).[22] This approach has been used in many, but not all, studies of AKI epidemiology using RIFLE[2,5,25,30–32,54–63] (see Table 8) and has recently been validated.[64] Hence, most current data concerning AKI defined by RIFLE criteria are based on estimated baseline SCr for a large proportion of patients.

Table 9 shows the range of estimated SCr obtained by back-calculation for various age, sex, and race categories. When the baseline SCr is unknown, an estimated SCr can be used provided there is no evidence of CKD (see Appendix B). Fortunately, when there is a history of CKD, a baseline SCr is usually available. Unfortunately, many cases of CKD are not identified, and thus estimating the baseline SCr may risk labeling a patient with AKI when in reality the diagnosis was unidentified CKD. As discussed further in Appendix B, it is essential to evaluate a patient with presumed AKI for

Table 10 | AKI staging

	Serum creatinine mg/dl (μmol/l)						
Case	Baseline	Day 1	Day 2	Day 3	Day 7	Reference creatinine	Max AKI stage
A	1.0 (88)	1.3 (115)	1.5 (133)	2.0 (177)	1.0 (88)	1.0 (88)	2
B	1.0 (88)	1.1 (97)	1.2 (106)	1.4 (124)	1.0 (88)	1.0 (88)	1
C	0.4 (35)	0.5 (44)	0.6 (53)	0.7 (62)	0.4 (35)	0.4 (35)	1
D	1.0 (88)	1.1 (97)	1.2 (106)	1.3 (115)	1.5 (133)	1.0 (88)	1
E	1.0 (88)	1.3 (115)	1.5 (133)	1.8 (159)	2.2 (195)	1.0 (88)	2
F	?	3.0 (265)	2.6 (230)	2.2 (195)	1.0 (88)	1.0 (88)	3
G	?	1.8 (159)	2.0 (177)	2.2 (195)	1.6 (141)	?	$\geqslant$1
H	?	3.0 (265)	3.1 (274)	3.0 (265)	2.9 (256)	?	?

AKI, acute kidney injury.

presence of CKD. Furthermore, CKD and AKI may coexist. By using all available clinical data (laboratory, imaging, history, and physical exam) it should be possible to arrive at both an accurate diagnosis as well as an accurate estimate of baseline SCr. Importantly, excluding some cases of hemodilution secondary to massive fluid resuscitation (discussed below), the lowest SCr obtained during a hospitalization is usually equal to or greater than the baseline. This SCr should be used to diagnose (and stage) AKI. For example, if no baseline SCr was available in Case A, diagnosis of AKI could be made using the MDRD estimated SCr (Table 9). If Case A were a 70-year-old white female with no evidence or history of CKD, the baseline SCr would be 0.8 mg/dl (71 μmol/l) and a diagnosis of AKI would be possible even on day 1 (criterion 1, $\geqslant$50% increase from baseline). However, if the patient was a 20-year-old black male, his baseline SCr would be estimated at 1.5 mg/dl (133 μmol/l). Since his admission SCr is lower, this is assumed to be the baseline SCr until day 7 when he returns to his true baseline, and this value can be taken as the baseline. These dynamic changes in interpretation are not seen in epidemiologic studies, which are conducted when all the data are present, but are common in clinical medicine. Note that the only way to diagnose AKI (by SCr criteria) in Case H is to use an estimated SCr.

Examples of application of AKI stages

Once a diagnosis of AKI has been made, the next step is to stage it (Recommendation 2.1.2). Like diagnosis, staging requires reference to a baseline SCr when SCr criteria are used. This baseline becomes the reference SCr for staging purposes. Table 10 shows the maximum stage for each Case described in Table 7. Staging for Case A was already mentioned. The maximum stage is 2 because reference SCr is 1.0 mg/dl (88 μmol/l) and the maximum SCr is 2.0 mg/dl (177 μmol/l). Had the reference SCr been 0.6 mg/dl (53 μmol/l), the maximum stage would have been 3. Case F was staged by using the lowest SCr (1.0 mg/dl [88 μmol/l]) as the reference. Of course, the actual baseline for this case might have been lower but this would not affect the stage, since it is already Stage 3. Note that if this patient was a 35-year-old white male, his MDRD estimated baseline SCr would be 1.2 mg/dl (106 μmol/l) (Table 9) and his initial stage on admission (day 1) would be assumed to be 2. However, once his SCr recovered to 1.0 mg/dl (88 μmol/l) on day 7, it would be possible to restage him as having had Stage 3. Once he has recovered, there may be no difference between Stage 2 or 3 in terms of his care plan. On the other hand, accurately staging the severity of AKI may be important for intensity of follow-up and future risk.

Note that Cases G and H can only be staged if the reference SCr can be inferred. Case G may be as mild as stage 1 if the baseline is equal to the nadir SCr on day 7. On the other hand, if this case were a 70-year-old white female with no known evidence or history of CKD, the reference SCr would be 0.8 mg/dl (71 μmol/l) based on an estimated baseline (Table 9). In this case, the severity on day 1 would already be stage 2.

Urine output vs. SCr

Both urine output and SCr are used as measures of an acute change in GFR. The theoretical advantage of urine output over SCr is the speed of the response. For example, if GFR were to suddenly fall to zero, a rise in SCr would not be detectable for several hours. On the other hand, urine output would be affected immediately. Less is known about the use of urine output for diagnosis and staging compared to SCr, since administrative databases usually do not capture urine output (and frequently it is not even measured, especially outside the ICU). However, studies using both SCr and urine output to diagnose AKI show increased incidence, suggesting that the use of SCr alone may miss many patients. The use of urine output criteria (criterion 3) will also reduce the number of cases where criterion 1 and criterion 2 are discordant (cases B,C,D, and F in Table 7), as many of these cases will be picked up by urine output criteria.

Timeframe for diagnosis and staging

The purpose of setting a timeframe for diagnosis of AKI is to clarify the meaning of the word "acute". A disease process that results in a change in SCr over many weeks is not AKI (though it may still be an important clinical entity: see Appendix B). For the purpose of this guideline, AKI is defined in terms of a process that results in a 50% increase in

SCr within 1 week or a 0.3 mg/dl (26.5 μmol/l) increase within 48 hours (Recommendation 2.1.1). Importantly, there is no stipulation as to when the 1-week or 48-hour time periods can occur. It is stated unequivocally that it does not need to be the first week or 48 hours of a hospital or ICU stay. Neither does the time window refer to duration of the inciting event. For example, a patient may have a 2-week course of sepsis but only develop AKI in the second week. Importantly, the 1-week or 48-hour timeframe is for diagnosis of AKI, not staging. A patient can be staged over the entire episode of AKI such that, if a patient develops a 50% increase in SCr in 5 days but ultimately has a three-fold increase over 3 weeks, he or she would be diagnosed with AKI and ultimately staged as Stage 3.

As with any clinical criteria, the timeframe for AKI is somewhat arbitrary. For example, a disease process that results in a 50% increase in SCr over 2 weeks would not fulfill diagnostic criteria for AKI even if it ultimately resulted in complete loss of kidney function. Similarly, a slow process that resulted in a steady rise in SCr over 2 weeks, and then a sudden increase of 0.3 mg/dl (26.5 μmol/l) in a 48-hour period, would be classified as AKI. Such are the inevitable vagaries of any disease classification. However, one scenario deserves specific mention, and that is the case of the patient with an increased SCr at presentation. As already discussed, the diagnosis of AKI requires a second SCr value for comparison. This SCr could be a second measured SCr obtained within 48 hours, and if it is $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) greater than the first SCr, AKI can be diagnosed. Alternatively, the second SCr can be a baseline value that was obtained previously or estimated from the MDRD equation (see Table 9). However, this poses two dilemmas. First, how far back can a baseline value be retrieved and still expected to be "valid"; second, how can we infer acuity when we are seeing the patient for the first time?

Both of these problems will require an integrated approach as well as clinical judgment. In general, it is reasonable in patients without CKD to assume that SCr will be stable over several months or even years, so that a SCr obtained 6 months or even 1 year previously would reasonable reflect the patient's premorbid baseline. However, in a patient with CKD and a slow increasing SCr over several months, it may be necessary to extrapolate the baseline SCr based on prior data. In terms of inferring acuity it is most reasonable to determine the course of the disease process thought to be causing the episode of AKI. For example, for a patient with a 5-day history of fever and cough, and chest radiograph showing an infiltrate, it would be reasonable to infer that the clinical condition is acute. If SCr is found to be $\geqslant$50% increased from baseline, this fits the definition of AKI. Conversely, a patient presenting with an increased SCr in the absence of any acute disease or nephrotoxic exposure will require evidence of an acute process before a diagnosis can be made. Evidence that the SCr is changing is helpful in establishing acuity.

Clinical judgment

While the definitions and classification system discussed in Chapter 2.1 provide a framework for the clinical diagnosis of AKI, they should not be interpreted to replace or to exclude clinical judgment. While the vast majority of cases will fit both AKI diagnostic criteria as well as clinical judgment, AKI is still a clinical diagnosis—not all cases of AKI will fit within the proposed definition and not all cases fitting the definition should be diagnosed as AKI. However, exceptions should be very rare.

Pseudo-AKI. As with other clinical diagnoses defined by laboratory results (e.g., hyponatremia), the clinician must be cautious to interpret laboratory data in the clinical context. The most obvious example is with laboratory errors or errors in reporting. Erroneous laboratory values should obviously not be used to diagnose disease and suspicious lab results should always be repeated. Another example is when two SCr measurements are obtained by different laboratories. While the coefficient of variation for SCr is very small ($<$5%) by various clinical testing methods, variation (bias) from one laboratory to the next may be considerably higher, although it is unlikely to approach 50%. Given that the SCr definition of AKI always uses at least two values, the variation and bias between each measure is further magnified—the coefficient of variation for comparison of two lab tests is equal to the square root of the sum of each coefficient squared. Although the international standardization of SCr measurements will largely eliminate interlaboratory bias in the future, care is needed in interpreting lab values obtained from different labs. Furthermore, daily variation in SCr due to differences in diet and activity may be as great as 10%. Finally, endogenous chromogens (e.g., bilirubin, ascorbic acid, uric acid) and exogenous chromogens and drugs (e.g., cephalosporins, trimethoprim, cimetidine) may interfere with the creatinine assay. The cumulative effect of these various factors influencing precision, bias, and biological variation may approach the level at which it could impact the diagnosis of AKI. A similar problem exists with urine output. Particularly outside the ICU, urine output is not often reported and urine collections may be inaccurate, especially in noncatheterized patients. Finally, as discussed in Chapter 2.1, a weight-based criterion for urine output will mean that some very obese patients will fulfill the definition of AKI without any kidney abnormality. Clinical judgment should always be exercised in interpreting such data.

Atypical AKI. A complementary problem to pseudo-AKI is the situation where a case of AKI fails to meet the definition. These cases should be distinguished from conditions in which data are simply missing (discussed above) and refer to situations in which existing data are unreliable. For example, a patient might receive very large quantities of intravascular fluids such that SCr is falsely lowered.[65] Similarly, massive blood transfusions will result in the SCr more closely reflecting the kidney function of the blood donors than the patient. It is unusual for these cases not to result in oliguria and, thus, most patients will be diagnosed with AKI even if

SCr is not increased. Nevertheless, the clinician should be cognizant of possibility that SCr may be falsely lowered by large-volume fluid resuscitation or transfusion; thus, a normal value may not rule out AKI. Changes in creatinine production are also well known in conditions such as muscle breakdown where production increases and in muscle wasting (including advanced liver disease) where production is decreased. Creatinine production may also be decreased in sepsis[66] possibly due to decreased muscle perfusion.

SUPPLEMENTARY MATERIAL

Appendix B: Diagnostic Approach to Alterations in Kidney Function and Structure.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 2.5: Diagnostic approach to alterations in kidney function and structure

Definitions of AKI, CKD and AKD

AKI and CKD were defined by separate Work Groups according to different criteria. The definition for each is based on alterations in kidney function or structure. AKI and CKD have many causes which may lead to alterations of kidney function and structure that do not meet the criteria for the definition of either AKI or CKD, yet patients with these diseases and disorders may need medical attention to restore kidney function and reverse damage to kidney structure to avoid adverse outcomes. A uniform and systematic nomenclature could enhance understanding and communication about these diseases and disorders, and lead to improved medical care, research, and public health. For these reasons, the Work Group proposed an operational definition for AKD to provide an integrated clinical approach to patients with abnormalities of kidney function and structure.

Table 11 compares the definitions for AKI, CKD, and AKD. We have also included an operational definition of "no known kidney disease" (NKD) for those who do not meet these criteria, with the understanding that clinical judgment is required to determine the extent of the evaluation that is necessary to assess kidney function and structure. In the following sections, we will elaborate on each component of these definitions.

Table 11 | Definitions of AKI, CKD, and AKD

	Functional criteria	Structural criteria
AKI	Increase in SCr by 50% within 7 days, *OR* Increase in SCr by 0.3 mg/dl (26.5 μmol/l) within 2 days, *OR* Oliguria	No criteria
CKD	GFR <60 ml/min per 1.73 m^2 for >3 months	Kidney damage for >3 months
AKD	AKI, *OR* GFR <60 ml/min per 1.73 m^2 for <3 months, *OR* Decrease in GFR by $\geqslant 35\%$ or increase in SCr by $>50\%$ for <3 months	Kidney damage for <3 months
NKD	GFR $\geqslant 60$ ml/min per 1.73 m^2 Stable SCr	No damage

GFR assessed from measured or estimated GFR. Estimated GFR does not reflect measured GFR in AKI as accurately as in CKD. Kidney damage assessed by pathology, urine or blood markers, imaging, and—for CKD—presence of a kidney transplant. NKD indicates no functional or structural criteria according to the definitions for AKI, AKD, or CKD. Clinical judgment is required for individual patient decision-making regarding the extent of evaluation that is necessary to assess kidney function and structure.
AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

GFR and SCr

CKD, AKD, and AKI are defined by parameters expressing the level of kidney function. Table 12 gives examples of each condition based on GFR and different magnitudes of increase in SCr.

To illustrate the relationship of changes in SCr to changes in eGFR, we simulated changes in eGFR that would result from changes in SCr corresponding to the KDIGO definition of AKI in the Chronic Kidney Disease Epidemiology Collaboration cohort.[67,68] Figure 6 shows the relationship of these changes in eGFR to the definition and stages of AKI. Not all patients with AKI would meet the eGFR criteria for the definition of AKD.

GFR/SCr algorithm

Figure 7 provides a diagnostic algorithm based on a sequential approach through three questions: i) Is GFR decreased or is SCr increased (according to the criteria in Table 12)?; ii) Is SCr increasing or GFR decreasing (according to the criteria in Table 12)?; and iii) Does the decrease in GFR or increase in SCr resolve within 3 months? Based on a "yes" or "no" response to these three sequential questions, all combinations of AKI, AKD, and CKD can be identified. In this section, we review the algorithm and illustrate its use for classification of patients with acute and chronic kidney disease in two previously reported cohorts.

Table 12 | Examples of AKI, CKD, and AKD based on GFR and increases in SCr

Baseline GFR (ml/min per 1.73 m^2)	Increase in SCr during 7 consecutive days	GFR during next 3 months	Diagnosis
>60	$>1.5\times$	NA	AKI
>60	$<1.5\times$	<60	AKD without AKI
>60	$<1.5\times$	>60	NKD
Baseline GFR (ml/min per 1.73 m^2)	**Change in SCr during next 7 days**	**GFR during next 3 months**	**Diagnosis**
<60	$>1.5\times$	NA	AKI + CKD
<60	$<1.5\times$	$>35\%$ decrease	AKD without AKI + CKD
<60	$<1.5\times$	$<35\%$ decrease	CKD

GFR assessed from measured or estimated GFR. Estimated GFR does not reflect measured GFR in AKI as accurately as in CKD.
AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

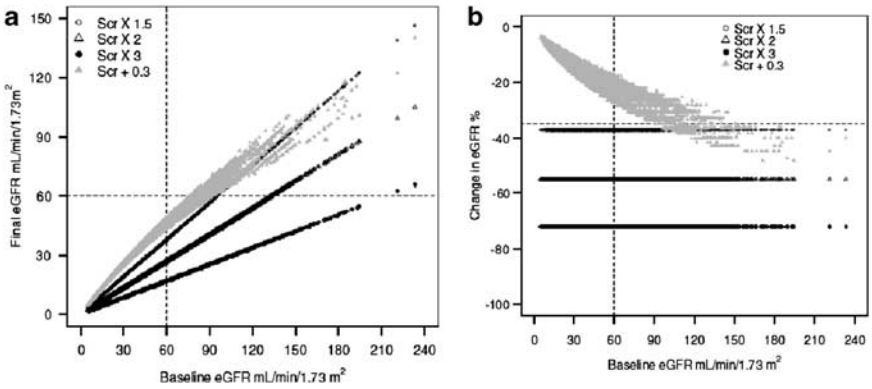

Figure 6 | Chronic Kidney Disease Epidemiology Collaboration cohort changes in eGFR and final eGFR corresponding to KDIGO definition and stages of AKI. Panels (**a**) and (**b**) show the final eGFR and the percent changes in eGFR, respectively, corresponding to the KDIGO definition and stages of AKI. The horizontal line in panel a and b indicates the threshold value for AKD (<60 ml/min per 1.73 m^2 and >35% reduction in initial GFR, respectively). Points above the horizontal line indicate subjects who meet the SCr criteria for the definition of AKI but do not meet eGFR criteria for the definition of AKD. AKD, acute kidney disorder/disease; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine. (Lesley Inker, personal communication.)

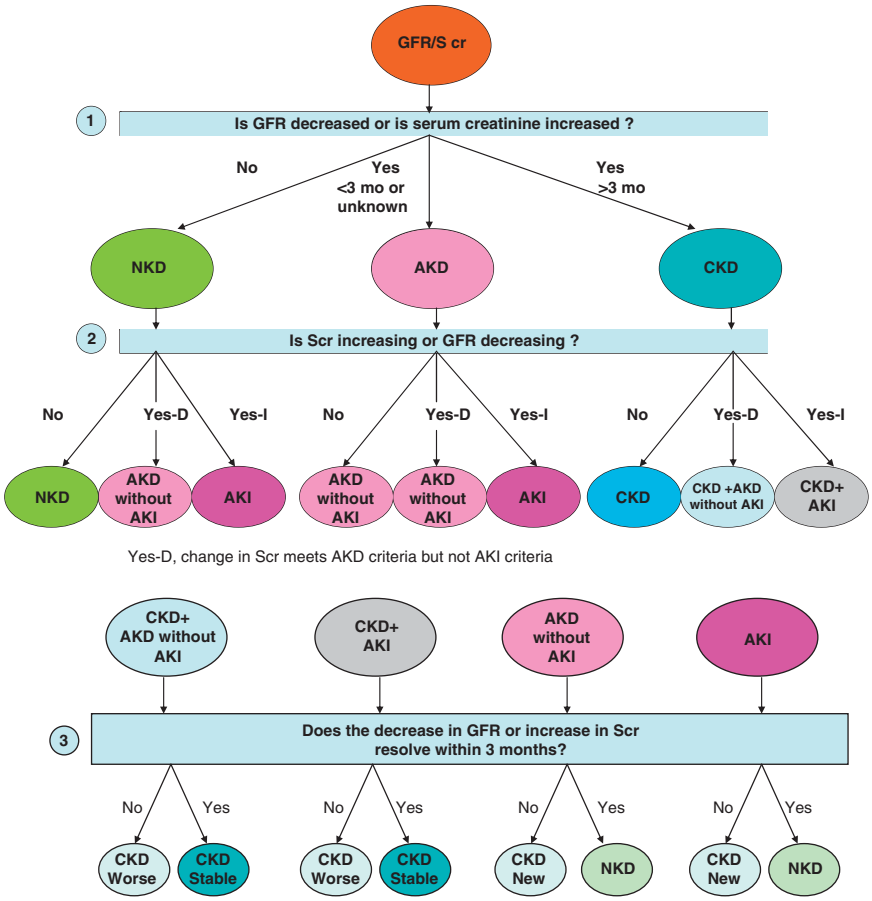

Figure 7 | GFR/SCr algorithm. See text for description. AKD, acute kidney disease/disorder; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

The answer to Question 1 requires ascertainment of an index GFR/SCr as well during the prior 3 months. The index GFR/SCr can be assigned as any of the GFR/SCr measures during the interval of observation. The answer classifies patients into three categories: NKD, AKD, and CKD. Question 2 requires repeat ascertainment of kidney function after the index measure. "No" indicates that the increase in SCr or decrease in GFR after the index measure does not

meet AKI or AKD criteria; "Yes-D" indicates that increase in SCr and decrease in GFR meets the AKD criteria but not AKI criteria; and "Yes-I" indicates that increase in SCr meets AKI criteria. Question 3 requires repeat ascertainment of GFR/SCr 3 months after the index measure. "Yes" indicates GFR >60, indicating NKD. No indicates GFR <60, and based on prior level of GFR, may indicate stable, new, or worse CKD.

Oliguria as a measure of kidney function

Although urine flow rate is a poor measure of kidney function, oliguria generally reflects a decreased GFR. If GFR is normal (approximately 125 ml/min, corresponding to approximately 107 ml/kg/h for a 70-kg adult), then reduction in urine volume to <0.5 ml/kg/h would reflect reabsorption of more than 99.5% of glomerular filtrate. Such profound stimulation of tubular reabsorption usually accompanies circulatory disturbances associated with decreased GFR. Oliguria is unusual in the presence of a normal GFR and is usually associated with the non–steady state of solute balance and rising SCr sufficient to achieve the criteria for AKI. As a corollary, if GFR and SCr are normal and stable over an interval of 24 hours, it is generally not necessary to measure urine flow rate in order to assess kidney function.

In principle, oliguria (as defined by the criteria for AKI) can occur without a decrease in GFR. For example, low intake of fluid and solute could lead to urine volume of less than 0.5 ml/kg/h for 6 hours or 0.3 ml/kg/h for 24 hours. On the other hand, severe GFR reduction in CKD usually does not lead to oliguria until after the initiation of dialysis.

As described in Chapter 2.1, the thresholds for urine flow for the definition of AKI have been derived empirically and are less well substantiated than the thresholds for increase in SCr. Urinary diagnostic indices, such as the urinary concentrations of sodium and creatinine and the fractional reabsorption of sodium and urea, remain helpful to distinguish among causes of AKI, but are not used in the definition (see Appendix D).

Kidney damage

Table 13 describes measures of kidney damage in AKD and CKD. Kidney damage is most commonly ascertained by urinary markers and imaging studies. Most markers and abnormal images can indicate AKD or CKD, based on the duration of abnormality. One notable exception is small kidneys, either bilateral or unilateral, indicating CKD, which are discussed separately below. Kidney damage is not a criterion for AKI; however, it may be present. Renal tubular epithelial cells and coarse granular casts, often pigmented and described as "muddy brown", remain helpful in distinguishing the cause of AKI, but are not part of the definition.

Small kidneys as a marker of kidney damage

Loss of renal cortex is considered a feature of CKD, and is often sought as a specific diagnostic sign of CKD. Kidney size is most often evaluated by ultrasound. In a study of 665 normal volunteers,[69] median renal lengths were 11.2 cm on the left side and 10.9 cm on the right side. Renal size decreased with age, almost entirely because of parenchymal reduction. The lowest 10th percentiles for length of the left and right kidney were approximately 10.5 and 10.0 cm, respectively, at age 30 years, and 9.5 and 9.0 cm, respectively, at age 70 years.

Table 13 | Markers of kidney damage in AKD and CKD

Markers	AKD	CKD
Pathology	X	X
Urinary markers		
RBC/casts	X	X
WBC/casts	X	X
RTE/casts	X	X
Fine and coarse granular casts	X	X
Proteinuria	X	X
Blood markers (tubular syndromes)	X	X
Imaging		
Large kidneys	X	X
Small kidneys	—	X
Size discrepancy	—	X
Hydronephrosis	X	X
Cysts	X	X
Stones	X	X
History of kidney transplantation	—	X

Kidney damage is not required for diagnosis of AKI. In the presence of AKI, findings of kidney damage do not indicate a separate diagnosis of AKD.
AKD, acute kidney diseases and disorders; CKD, chronic kidney disease; RBC, red blood cells; RTE, renal tubular epithelial cells; WBC, white blood cells.

Table 14 | Integrated approach to interpret measures of kidney function and structure for diagnosis of AKI, AKD, and CKD

	Measures			
Diagnosis	GFR/SCr	Oliguria	Kidney damage	Small kidneys
AKI	X	X		
AKD	X		X	
CKD	X	X	X	X

X indicates that the measures can contribute to the diagnosis indicated.
AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease.

Integrated approach to AKI, AKD, and CKD

Clinical evaluation is necessary for all patients with alterations in kidney function or structure. The expectation of the Work Group is that the diagnostic approach will usually begin with assessment of GFR and SCr. However, evaluation of kidney function and structure is not complete unless markers of kidney damage—including urinalysis, examination of the urinary sediment, and imaging studies—have been performed. Table 14 shows a summary of the diagnostic approach using measures for kidney function and structure. Based on interpretation of each measure separately, the clinical diagnosis indicated by an "X" can be reached.

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SUPPLEMENTARY MATERIAL

Appendix D: Evaluation and General Management Guidelines for Patients with AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Section 3: Prevention and Treatment of AKI

Kidney International Supplements (2012) **2,** 37–68; doi:10.1038/kisup.2011.33

Chapter 3.1: Hemodynamic monitoring and support for prevention and management of AKI

As discussed in Chapters 2.3 and Appendix D, patients with AKI and at increased risk for AKI require careful attention to be paid to their hemodynamic status. This is first because hypotension results in decreased renal perfusion and, if severe or sustained, may result in kidney injury. Second, the injured kidney loses autoregulation of blood flow, a mechanism that maintains relatively constant flow despite changes in pressure above a certain point (roughly, a mean of 65 mm Hg).

Management of blood pressure and cardiac output require careful titration of fluids and vasoactive medication. Vasopressors can further reduce blood flow to the tissues if there is insufficient circulating blood volume. Conversely, patients with AKI are also at increased risk for fluid overload (see Chapter 3.2) and continued fluid resuscitation despite increased intravascular volume can cause harm. Fluids and vasoactive medications should be managed carefully and in concert with hemodynamic monitoring. Hemodynamic evaluation and monitoring are discussed in Appendix D.

In this chapter therapies aimed at correcting hemodynamic instability will be discussed. Available therapies to manage hypotension include fluids, vasopressors and protocols which integrate these therapies with hemodynamic goals. There is an extensive body of literature in this field and for a broader as well as more in depth review the reader is directed to the various reviews and textbooks devoted to critical care and nephrology.[70–81]

FLUIDS

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

RATIONALE

Despite the recognition of volume depletion as an important risk factor for AKI, there are no randomized controlled trials (RCTs) that have directly evaluated the role of fluids vs. placebo in the prevention of AKI, except in the field of contrast-induced acute kidney injury (CI-AKI) (see Chapter 4.4). It is accepted that optimization of the hemodynamic status and correction of any volume deficit will have a salutary effect on kidney function, will help minimize further extension of the kidney injury, and will potentially facilitate recovery from AKI with minimization of any residual functional impairment. AKI is characterized by a continuum of volume responsiveness through unresponsiveness (Figure 8),[78,82] and large multicenter studies have shown that a positive fluid balance is an important factor associated with increased 60-day mortality.[78,83,84]

The amount and selection of the type of fluid that should be used in the resuscitation of critically ill patients is still controversial. This guideline focuses on the selection of the fluid (colloid vs. crystalloid fluid in the prevention and early management of AKI). The three main end-points of the studies explored were the effects on mortality, need for RRT, and—if possible—the incidence of AKI. Although many trials have been conducted to compare fluid types for resuscitation, studies without AKI outcomes were not systematically reviewed for this Guideline. Suppl Table 1 summarizes the RCTs examining the effect of starch for the prevention of AKI.

Albumin vs. Saline

The role of albumin physiology in critically ill patients, and the pros and cons for administering albumin to hypoalbuminemic patients, have recently been discussed.[85] Results of the Saline vs. Albumin Fluid Evaluation (SAFE) study, a RCT comparing 4% human albumin in 0.9% saline with isotonic saline in ICU patients, seem to indicate that albumin is safe, albeit no more effective than isotonic saline (the standard of care choice of isotonic sodium chloride in most centers) for fluid resuscitation. SAFE demonstrated further no difference in renal outcomes, at least based on the need for and duration of RRT.[86] The SAFE study was a double-blind study and it was noted that patients in the albumin arm received 27% less study fluid compared to the saline arm (2247 vs. 3096 ml) and were approximately 1 l less positive in overall fluid balance.[86] Furthermore, very few patients in the trial received large volume fluid resuscitation (>5 l) and thus the results may not be applicable to all patients. The Work Group noted that while isotonic crystalloids may be appropriate for initial management of intravascular fluid deficits, colloids may still have a role in patients requiring additional fluid.

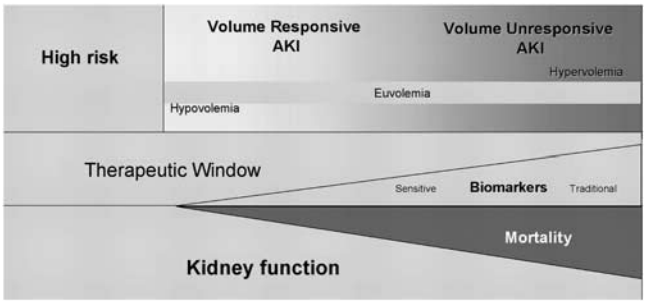

Figure 8 | Conceptual model for development and clinical course of AKI. The concept of AKI includes both volume-responsive and volume-unresponsive conditions. These conditions are not mutually exclusive, and a given patient may progress from one to the other. Time runs along the x-axis, and the figure depicts a closing "therapeutic window" as injury evolves and kidney function worsens. Biomarkers of injury and function will begin to manifest as the condition worsens, but traditional markers of function (e.g., urea nitrogen and creatinine) will lag behind hypothetical "sensitive" markers of kidney injury. Mortality increases as kidney function declines. AKI, acute kidney injury. Reproduced from Himmelfarb J, Joannidis M, Molitoris B, *et al*. Evaluation and initial management of acute kidney injury. Clin J Am Soc Nephrol 2008; 3: 962–967 with permission from American Society of Nephrology[82] conveyed through Copyright Clearance Center, Inc; accessed http://cjasn.asnjournals.org/content/3/4/962.long

Hydroxyethylstarch vs. Saline

Hydroxyethylstarch (HES) is a widely used, relatively inexpensive alternative to human albumin for correcting hypovolemia. Different HES preparations are available that vary with regard to concentration, mean molecular weight (MW), molar substitution, and substitution of hydroxyethyl for hydroxyl groups. The mean MW of the different HES preparations ranges between 70 000 and 670 000 Da. The colloid osmotic pressure effect is strongly dependent upon the concentration of colloid in the solution; e.g., 6% HES is iso-oncotic, whereas 10% HES is hyperoncotic. The number of hydroxyethyl groups per glucose molecule is specified by the molar substitution, ranging between 0.4 (tetrastarch) and 0.7 (heptastarch). Accordingly, HES solutions with a molar substitution of 0.5 or 0.6 are referred to as "pentastarch" or "hexastarch", respectively. More recently, tetrastarches (HES 130/0.4 and HES 130/0.42) have also been introduced.[87] High molecular substitution starch may impair coagulation by reducing the concentration of factor VIII: VIIIc and von Willebrand factor. Platelet activity may also be affected by blockade of the platelet fibrinogen receptor glycoprotein IIb/IIIa. Smaller starch molecules and those with less molecular substitution produce negligible coagulation defects.[88]

Aside from these negative effects on coagulation, development of renal dysfunction has been a concern associated with the use of mainly hypertonic HES. Hypertonic HES may induce a pathological entity known as "osmotic nephrosis" with potential impairment of renal function.[89] It has even been recommended that "HES should be avoided in ICUs and during the perioperative period" (for a summary of this controversy, see de Saint-Aurin *et al.*[90] and Vincent[91]).

The first major randomized trial in patients with sepsis compared HES 200/0.60 to 0.66 with gelatin and showed a greater incidence of AKI in the HES group, but no effect on survival.[92] Criticisms of this study include a higher baseline SCr level in the HES group, small sample size, and short follow-up duration of 34 days. In the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study,[93] patients with severe sepsis were randomly assigned to receive a hypertonic (10%) solution of low MW HES (HES 200/0.5), or an isotonic modified Ringer's lactate solution. Patients in the HES group received a median cumulative dose of 70.4 ml per kilogram of body weight. The mortality was not significantly different, although showing a trend toward greater mortality at 90 days. However, the hypertonic HES group had a significantly higher rate of AKI (34.9% vs. 22.8%) and more days on which RRT was required (Suppl Table 1). Also, this study has been criticized for: i) using a hyperoncotic colloid solution with potentially harmful renal effects as shown in experimental research;[94] ii) markedly exceeding the pharmaceutically recommended daily dose limit for 10% HES 200/0.5 by more than 10% in $>38\%$ of patients; and iii) pre-existing renal dysfunction in 10% of study patients, which represents a contra-indication for infusion of 10% HES 200/0.5.[95] Posthoc analyses of the VISEP study showed the cumulative dose of HES to be a significant independent predictor for both mortality and RRT at 90 days. The median cumulative dose of HES in the VISEP Study was 70 ml/kg compared to 31 ml/kg in the study by Schortgen *et al.*[92]

A systematic review of RCTs on the use of HES for fluid management in patients with sepsis totaling 1062 patients, including 537 patients from the VISEP study, showed an almost two-fold increased risk of AKI with HES compared to crystalloids.[96] Given these limitations, the results of these studies should be interpreted with caution. Furthermore, a large, prospective observational study found that HES infusion of any type (median volume 555 ml/d; intraquartile range 500–1000) did not represent an independent risk factor for renal impairment.[97]; however, recently in a large cohort of critically ill patients (approximately 8000 subjects), infusion of 10% HES 200/0.5 instead of HES 130/0.4 appeared to be an independent risk factor for RRT.[87] Finally, a recent comprehensive Cochrane review[98] concluded that there is no evidence from RCTs that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma, burns, or following surgery.

The mechanisms of colloid-induced renal injury are incompletely understood, but may involve both direct molecular effects and effects of elevated oncotic pressure.[99] These concerns have led to the widespread adoption of lower MW starches as iso-oncotic solution, as resuscitation fluids. Theoretically, such solutions may have lower nephrotoxicity; however, as yet, no appropriately powered prospective randomized studies have reported the clinical benefit and

safety of such solutions in comparison with crystalloids. A recent study by Magder *et al.* compared 10% 250/0.45 HES to isotonic saline in 262 patients who underwent cardiac surgery.[100] These investigators tested whether fewer patients required catecholamines the morning after cardiac surgery (a chief determinant of ICU discharge) with HES compared to saline, and found indeed this was the case (10.9% vs. 28.8%; $P = 0.001$). Importantly, the study found no evidence of nephrotoxicity: no difference in the daily creatinine, development of AKI by RIFLE criteria during hospital stay (16% in both groups), or need for RRT (1% in each group). Importantly, patients in the saline group received nearly 60% more volume for fluid resuscitation in the ICU compared to HES (887 vs. 1397 ml; $P < 0.0001$). While overall volumes were small, advocates for colloid resuscitation will note that this is exactly the reason colloids are preferred for patients requiring large-volume resuscitation.

The tonicity of colloid preparations may also vary by agent. A recent meta-analysis[101] described 11 randomized trials with a total of 1220 patients: seven evaluating hyperoncotic albumin and four evaluating hyperoncotic starch. Hyperoncotic albumin decreased the odds of AKI by 76% while hyperoncotic starch increased those odds by 92% (odds ratio [OR] 1.92; CI 1.31–2.81; $P = 0.0008$). Parallel effects on mortality were observed. This meta-analysis concluded that the renal effects of hyperoncotic colloid solutions appear to be colloid-specific, with albumin displaying renoprotection and hyperoncotic starch showing nephrotoxicity. A 7000-patient study comparing 6% HES 130/0.4 in saline with saline alone was scheduled to begin in Australia and New Zealand in 2010. This study will provide further high-quality data to help guide clinical practice.[102]

Thus, the use of isotonic saline as the standard of care for intravascular volume expansion to prevent or treat AKI is based upon the lack of clear evidence that colloids are superior for this purpose, along with some evidence that specific colloids may cause AKI, in addition to higher costs. It is acknowledged that colloids may be chosen in some patients to aid in reaching resuscitation goals, or to avoid excessive fluid administration in patients requiring large volume resuscitation, or in specific patient subsets (e.g., a cirrhotic patient with spontaneous peritonitis, or in burns). Similarly, although hypotonic or hypertonic crystalloids may be used in specific clinical scenarios, the choice of crystalloid with altered tonicity is generally dictated by goals other than intravascular volume expansion (e.g., hypernatremia or hyponatremia). One of the concerns with isotonic saline is that this solution contains 154 mmol/l chloride and that administration in large volumes will result in relative or absolute hyperchloremia (for a review, see Kaplan *et al.*[103]). Although direct proof of harm arising from saline-induced hyperchloremia is lacking, buffered salt solutions approximate physiological chloride concentrations and their administration is less likely to cause acid-base disturbances. Whether use of buffered solutions results in better outcomes is, however, uncertain.

VASOPRESSORS

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

RATIONALE

Sepsis and septic shock are major contributing factors to AKI[7] and vasopressor requirement appears to be highly associated with AKI in this population. Despite the high prevalence of AKI during critical illness in general, and severe sepsis specifically, success has been limited in improving the outcome of this complication.[104] Septic shock is the prototype of a high output–low resistance condition, although severe pancreatitis, anaphylaxis, burns, and liver failure share similar physiologic alterations. Persistent hypotension, despite ongoing aggressive fluid resuscitation or after optimization of intravascular volume in patients with shock, places patients at risk for development of AKI. In the setting of vasomotor paralysis, preservation or improvement of renal perfusion can only be achieved through use of systemic vasopressors once intravascular volume has been restored.[105]

It is not known which vasopressor agent is most effective for prevention or treatment of patients with AKI and septic shock. Most studies have focused on norepinephrine, dopamine, or vasopressin. Small open-label studies have shown improvement in creatinine clearance (CrCl) following a 6- to 8-hour infusion of norepinephrine[106] or terlipressin,[107] while vasopressin reduced the need for norepinephrine and increased urine output and CrCl.[108] A large RCT[109] comparing dopamine to norepinephrine as initial vasopressor in patients with shock showed no significant differences between groups with regard to renal function or mortality. However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine, and a subgroup analysis showed that dopamine was associated with an increased rate of death at 28 days among the patients with cardiogenic shock, but not among the patients with septic shock or those with hypovolemic shock. Thus, although there was no difference in primary outcome with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events.[109]

Vasopressin is gaining popularity in the treatment of shock refractory to norepinephrine.[110] Compared to norepinephrine, it increases blood pressure and enhances dieresis, but has not as yet been proven to enhance survival nor to reduce the need for RRT.[111] A recent posthoc analysis of the above mentioned RCT used the RIFLE criteria for AKI to compare the effects of vasopressin vs. norepinephrine.[112] In patients in the RIFLE-R category, vasopressin as compared to norepinephrine was associated with a trend to a lower rate of progression to F or L categories respectively, and a lower

rate of use of RRT. Mortality rates in the R category patients treated with vasopressin compared to norepinephrine were 30.8 vs. 54.7%, $P = 0.01$, but this did not reach significance in a multiple logistic regression analysis. This study suggests thus that vasopressin may reduce progression to renal failure and mortality in patients at risk of kidney injury who have septic shock. The Work Group concluded that current clinical data are insufficient to conclude that one vasoactive agent is superior to another in preventing AKI, but emphasized that vasoactive agents should not be withheld from patients with vasomotor shock over concern for kidney perfusion. Indeed, appropriate use of vasoactive agents can improve kidney perfusion in volume-resuscitated patients with vasomotor shock.

PROTOCOLIZED HEMODYNAMIC MANAGEMENT

3.1.3: We suggest using protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (*2C*) or in patients with septic shock (*2C*).

RATIONALE

A resuscitation strategy devised for patients with hypotension from septic shock that is based upon achieving specific physiologic end-points within 6 hours of hospital admission has been termed Early Goal-Directed Therapy (EGDT). This approach has been endorsed by the "Surviving Sepsis Campaign"[113] and has gained considerable acceptance despite only one, single-center, RCT evaluating its effectiveness. This protocolized strategy, consisting of fluids, vasoactive medication, and blood transfusions targeting physiological parameters, is recommended by many experts for the prevention of organ injury in septic-shock patients.

Similarly, protocolized care strategies in surgical patients at high risk for postoperative AKI have been extensively studied in an effort to provide optimal oxygen delivery to tissues in the perioperative period. In these patients, goal-directed therapy is defined as hemodynamic monitoring with defined target values and with a time limit to reach these stated goals. Together these protocols with bundled, hemodynamic, and tissue-support measures have the potential to reduce the risk of AKI following major surgical procedures in high-risk patients (e.g., age >60 years, emergent surgery, elevated American Society of Anesthesiologists score, preoperative comorbid illnesses).

Protocolized hemodynamic management strategies in septic shock

Early fluid resuscitation in the management of hypotensive patients with septic shock has been a standard treatment paradigm for decades.[93,113,114] What has not been clear, however, is how much fluid to give, for how long, or what type of fluid therapy is optimal in the physiologic support of septic shock.[93,113,114] In 2001, Rivers *et al.*[115] published the results of a small ($n = 263$), open-label, single-center study that compared a treatment protocol that the authors referred to as EGDT in the emergency management of septic shock. EGDT is predicated upon the premise that an early, protocolized resuscitation program with predefined physiologic end-points will prevent organ failure and improve the outcome of patients presenting with septic shock.

Hypotensive patients with severe infection are rapidly assessed for evidence of tissue hypoperfusion and microcirculatory dysfunction by mean arterial blood pressure measurement and plasma lactate levels.[115] Blood lactate levels are neither sensitive nor specific but are readily available measures of tissue hypoperfusion and do correlate with adverse outcomes in sepsis.[116,117] Early recognition of septic shock then initiates a protocol of resuscitation with the goal of reestablishing tissue perfusion in patients within 6 hours of diagnosis. The physiologic goals are: i) return of mean arterial blood pressure to $\geqslant 65$ mm Hg; ii) central venous pressure between 8–12 mm Hg; iii) improvement in blood lactate levels; iv) central venous oxygen saturation ($ScvO_2$) $>70\%$; and v) a urine output of $\geqslant 0.5$ ml/kg/h.

In the study by Rivers *et al.* the protocol-driven process resulted in more rapid use of fluids, more blood transfusions, and in a small number of patients, earlier use of dobutamine over the 6-hour time period than standard emergency care. The in-hospital mortality rate in the control group was 46.5% vs. 30.5% in the EGDT group ($P < 0.01$).[115] Follow-up, predominantly observational studies, have found less dramatic but generally similar effects,[118–122] though not without exception.[123]

The Rivers study did not specifically look at AKI outcomes, but multiple-organ function-scoring systems (i.e., APACHE II and SAPS 2) both showed significant improvements with EGDT. In a subsequent study, prevention of AKI was significantly improved in patients randomized to a modified EGDT strategy (without measurement of $ScvO_2$) compared to a standard-care group.[119] Criticisms of the Rivers study include: i) a complex, multistep protocol for which individual interventions have not been validated; ii) the use of a treatment team in the active-therapy arm, thus risking a Hawthorn effect; iii) high mortality in the standard-care arm; and iv) the study was a small single-center study. Three large multicenter clinical trials in the USA, UK, and Australia are currently underway to definitively evaluate this promising therapy.

Goal-directed therapy for hemodynamic support during the perioperative period in high-risk surgical patients

Efforts to improve tissue oxygen delivery by optimizing hemodynamic support in high-risk surgical patients to prevent AKI and other adverse patient outcomes have been investigated for many years.[124–126] A recent meta-analysis of these studies by Brienza *et al.*[127] concluded that protocolized therapies (regardless of the protocol) with specific physiological goals can significantly reduce postoperative AKI.

A major problem in interpreting these studies is the lack of standardized hemodynamic and tissue oxygenation targets and management strategies used to verify the efficacy of these measures over standard perioperative care. A heterogeneous collection of study populations, types of surgical procedures, monitoring methods, and treatment strategies comprise this recent meta-analysis.[127] The basic strategy of goal-directed therapy to prevent AKI in the perioperative period is based on protocols that avoid hypotension, optimize oxygen delivery, and include careful fluid management, vasopressors when indicated, and inotropic agents and blood products if needed.[127]

The relative merits and risk:benefit ratio of each discrete element of EGDT in the successful resuscitation of patients with septic shock requires further study. Given the limitations of the current studies and lack of comparative effectiveness studies comparing individual protocols, we can only conclude that protocols for resuscitation in the setting of septic shock and high-risk surgery appear to be superior to no protocol.

RESEARCH RECOMMENDATIONS

- Randomized trials of isotonic crystalloid vs. colloid therapy for intravascular volume expansion to prevent or treat AKI should be conducted in a variety of settings (critical illness, high-risk surgery, sepsis), including patient subsets. In particular, colloids may improve efficiency of fluid resuscitation but some (starch) also carry some concerns regarding effects on the kidneys. If colloid results in less volume overload, it may lead to improved outcomes.
- Comparisons of specific solutions, with specific electrolyte composition or colloid type, for effectiveness in preventing AKI should be conducted. Specifically, there is a need to examine physiologic electrolyte solutions vs. saline.
- Studies are needed that compare different types of vasopressors for prevention and treatment of AKI in hemodynamically unstable patients. Some evidence suggests that certain vasopressors may preserve renal function better than others (e.g., vasopressin analogues vs. catecholamines) and studies are needed to compare them in this setting.
- The choice of a target mean arterial perfusion pressure range of 65–90 mm Hg as a component of resuscitation (perhaps in the context of age, chronic blood pressure, or other comorbidities) also needs further study.
- The specific components of goal-directed therapy that accrue benefits for patients at risk for AKI need to be determined. Is it the timing of protocolized hemodynamic management that is beneficial: prophylactically in high-risk surgical patients, or early in the course of severe sepsis? In contrast to the benefits of prophylactic or EGDT, protocolized use of inotropes to normalize mixed venous oxygen saturation or supranormalize oxygen delivery in "late" critical illness did not result in decreased AKI[128] or improved outcomes.[128,129] Alternatively, is it attention to hemodynamic monitoring, the protocol itself that standardizes supportive care to achieve the stated goals, or a single or combination of the multiple possible interventions that improves outcome? Thus, further research is required to determine the specific components of goal-directed therapy that accrue benefits for patients at risk for AKI, if such benefits actually occur.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Summary table of RCTs examining the effect of starch for the prevention of AKI.

Appendix D: Evaluation and General Management Guidelines for Patients with AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 3.2: General supportive management of patients with AKI, including management of complications

Supportive management to prevent AKI was discussed in the previous chapter and, for many patients, many of the supportive therapies will continue even if AKI develops. Furthermore, an important goal of early management of AKI is to prevent further injury and to facilitate recovery of renal function. These goals can often best be achieved by strict attention to supportive therapy. However, as renal function deteriorates, complications arise that require different management. Some of these issues have been discussed in Chapter 2.3 and several books have been devoted, in large part, to management of the many complications that arise from AKI[130–133]; the reader is referred to these sources. Particular attention should be given to the assessment of the circulating volume and fluid administration, the prevention and/or treatment of hyperkalemia and metabolic acidosis, the knowledge of the changes in pharmacokinetics of many drugs with discontinuation of all potentially nephrotoxic drugs, and dose adaptation of drugs excreted by the kidneys to the patient's renal function. Finally, many of the other chapters in this section of the guideline deal with supportive measures (e.g., diuretics for fluid management).

Chapter 3.3: Glycemic control and nutritional support

GLYCEMIC CONTROL IN CRITICAL ILLNESS: RENAL EFFECTS AND OUTCOMES

3.3.1: In critically ill patients, we suggest insulin therapy targeting plasma glucose 110–149 mg/dl (6.1–8.3 mmol/l). (*2C*)

RATIONALE

As outlined in a recent review,[134] stress hyperglycemia is a distinctive clinical feature of critical illness. Stress mediators, and central and peripheral insulin resistance appears pivotal to the occurrence of stress hyperglycemia. Inflammatory mediators and counter-regulatory hormones have been shown to impede crucial elements of the insulin-signaling pathway. Still, exogenous insulin administration normalizes blood glucose levels in this setting. Insulin treatment may counteract hepatic insulin resistance during acute critical illness. Extensive observational data have shown a consistent, almost linear, relationship between blood glucose levels in patients hospitalized with MI and adverse clinical outcomes, even in patients without established diabetes.[135,136]

It has never been entirely clear, however, whether glycemia serves as a mediator of these outcomes or merely as a marker of the sickest patients, who present with the well-known counter-regulatory stress response to illness.[137] Interestingly, Kosiborod *et al.*[135] recently showed, in a population with MI, that while hypoglycemia was associated with increased mortality, this risk was confined to patients who developed spontaneous hypoglycemia. In contrast, iatrogenic hypoglycemia after insulin therapy was not associated with higher mortality risk.

Tight glycemic control is frequently used in patients at risk of AKI, and in the management of those who develop AKI. It has been proposed that tight glycemic control can reduce the incidence and severity of AKI. Since the landmark trial of Van den Berghe *et al.*,[138] additional studies provided initial confirmation of the benefits (reduced morbidity and mortality), and some additional mechanistic insights of tight glycemic control in critically ill patients.[139] Further secondary analysis of the original trial, which was conducted in 1548 mechanically ventilated surgical ICU patients, found that intensive insulin therapy (IIT) target plasma glucose 80–110 mg/dl (4.44–6.11 mmol/l) was associated with substantial cost savings compared to conventional insulin therapy (CIT) target plasma glucose 180–200 mg/dl (9.99–11.1 mmol/l).[140] However, when Van den Berghe *et al.* repeated their original study in a different population of critically ill patients (medical rather than surgical ICU patients), the primary end-point of in-hospital mortality did not differ between groups (40% CIT group vs. 37.3% IIT group; $P = 0.33$).[141] As in the original surgical ICU study, a variety of secondary end-points were improved in this study, including a lower incidence of AKI and need for RRT. In the original surgical ICU study, severe AKI (peak SCr >2.5 mg/dl [>221 μmol/l]) developed in 7.2% of the IIT group, compared to 11.2% of the CIT group ($P = 0.04$); the incidence of RRT was also lower in the IIT group than the CIT group (4.8% vs. 8.2%, respectively; $P = 0.007$).[138] In the medical ICU study, the IIT group similarly had a significantly lower rate of AKI (doubling of SCr, 5.4%) than the CIT group (8.9%, $P = 0.04$), although RRT incidence was not decreased.[141] In a recent analysis, Schetz *et al.*[142] combined the renal end-points of both of these trials and used a modified version of the RIFLE classification of AKI to demonstrate that tight glycemic control reduced the incidence of severe AKI (peak SCr increments two- or three-fold increased from baseline) from 7.6% to 4.5% ($P = 0.0006$) in a combined patient population of 2707. The need for RRT was not decreased in the overall population or the medical ICU population, but was significantly lower in the surgical ICU patients managed with IIT (4% vs. 7.4%, $P = 0.008$).

Several newer studies have provided additional insight concerning the efficacy and safety of tight glycemic control in critically ill patients.[93,95,143–146] Thomas *et al.*[145] conducted a systematic review of randomized trials of tight glycemic control in 2864 critically ill patients, and found a 38% risk reduction of AKI with IIT, and a nonsignificant trend towards less acute dialysis requirement. However, IIT was also associated with a greater than four-fold increase in the risk of hypoglycemia. A body of literature demonstrating that uncontrolled hyperglycemia was associated with increased AKI following cardiac surgery led to the conduct of a 400-patient, single-center RCT of tight vs. conventional intraoperative glucose control.[143,144] The investigators found that this approach did not decrease perioperative morbidity or mortality (included in a composite end-point that included AKI within 30 days of surgery): the composite end-point occurred in 44% of the IIT group vs. 46% of the CIT group. Although the incidence of hypoglycemia was similar in the groups, there was a significantly higher incidence of stroke in the IIT group (4.3%) compared to the CIT group (0.54%), as well as trends towards higher mortality and more postoperative heart block in the IIT group, raising concerns about the safety of this approach.

Further prospective comparison of IIT vs. CIT in critically ill septic patients was provided in the VISEP trial, which also incorporated a comparison on crystalloid vs. colloid

infusions in a 2×2 factorial design.[93] Patients with severe sepsis or septic shock in 18 ICUs were randomized to IIT (target glycemia 80–110 mg/dl [4.44–6.11 mmol/l]; n = 247) or CIT (target glycemia 180–200 mg/dl [9.99–11.1 mmol/l]; n = 290) (Suppl Tables 2 and 3). There were no significant differences in 28-day or 90-day mortality, Sequential Organ Failure Assessment scores, or AKI rates between the groups. However, hypoglycemia (blood glucose level <40 mg/dl [<2.22 mmol/l]) was more frequent in the IIT group (12% vs. 2%; $P<0.001$) and led to early termination of the IIT study arm. Following publication of this study, Thomas *et al.*, updated the meta-analysis (discussed above) to include these data, and reported that, with the addition of the VISEP data, the analysis of a 3397-patient group found a 36% risk reduction of AKI with IIT, but this pooled estimate was no longer statistically significant (relative risk [RR] 0.74; 95% CI 0.47–1.17).[95] In a detailed review of the VISEP trial, Thomas *et al.*, also noted that another multicenter mixed ICU trial of intensive insulin therapy (the GLUCOCONTROL Study: Comparing the effects of two glucose control regimens by insulin in intensive care unit patients; available at: http://www.clinicaltrials.gov/ct/show/NCT00107601) was stopped after 1101 patients were enrolled because of greater rates of hypoglycemia with IIT.[95] Such data have raised significant concerns regarding the effectiveness and safety of using IIT with tight glycemic control to prevent or ameliorate morbidity and mortality in patients at high risk of AKI and other forms of organ injury.

The recent meta-analysis of IIT vs. CIT by Wiener *et al.*[146] continued to find a greater incidence of hypoglycemia with IIT, but the balance of evidence now suggests no improvement in survival with this approach. Twenty-nine RCTs totaling 8432 patients contributed data for this meta-analysis. Twenty-seven studies reported no difference in hospital mortality (21.6% in IIT vs 23.3% in CIT) with a pooled RR of 0.93 (95% CI 0.85–1.03; P = NS). Nine studies reported no difference in incidence of new RRT. There was a significant benefit of tight glycemic control in reducing the incidence of septicemia but this was associated with a significantly increased risk of hypoglycemia (blood glucose <40 mg/dl [<2.22 mmol/l]) in patients randomized to IIT with a pooled RR of 5.13 (95% CI 4.09–6.43; $P<0.05$).

In summary, pooled analysis of early multicenter studies has failed to confirm the early observations of beneficial effects of IIT on renal function; the risk of hypoglycemia with this approach is significant, and even the survival benefits of IIT are in doubt. More recently, the international Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, with a targeted enrolment of 6100 patients, set out to definitively determine the risk-benefit comparison of tight glycemic control in critically ill patients (Suppl Table 3).[147,148] In this trial, adult patients were randomized within 24 hours after admission to an ICU to receive either intensive glucose control (target blood glucose range of 81–108 mg/dl [4.50–5.99 mmol/l]), or conventional glucose control (target of $\leqslant 180$ mg/dl [$\leqslant 9.99$ mmol/l]).[148] The primary outcome was mortality from any cause within 90 days after randomization. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (OR for intensive control, 1.14; 95% CI 1.02–1.28; $P = 0.02$). The treatment effect did not differ significantly between surgical patients and medical patients. There was no significant difference between the two treatment groups in incidence of new RRT (15.4% vs. 14.5%), respectively. Severe hypoglycemia (blood glucose level $\leqslant 40$ mg/dl [$\leqslant 2.22$ mmol/l]) was reported in 6.8% in the intensive-control group and in 0.5% in the conventional-control group ($P<0.001$). In summary, the largest randomized trial of intensive vs. conventional insulin therapy found that intensive glucose control actually increased mortality among adults in the ICU: a blood glucose target of $\leqslant 180$ mg/dl ($\leqslant 9.99$ mmol/l) resulted in lower mortality than did a target of 81–108 mg/dl (4.50–5.99 mmol/l). Furthermore, this trial confirmed the consistent finding of an increased incidence of hypoglycemia associated with IIT, without any proven benefit in reducing mortality, organ dysfunction, or bacteremia.

There were some methodological differences between the Leuven and NICE-SUGAR studies, possibly explaining the different outcomes.[149] These comprised different target ranges for blood glucose in control and intervention groups, different routes for insulin administration and types of infusion pumps, different sampling sites, and different accuracies of glucometers, as well as different nutritional strategies and varying levels of expertise. Finally, Griesdale *et al.*[150] performed a meta-analysis of trials of intensive vs. conventional glycemic control that included most of the studies in the Wiener meta-analysis, in addition to some newer studies, including data supplied by the NICE-SUGAR investigators. All 26 trials that reported mortality found a pooled RR of death with IIT compared to CIT of 0.93 (95% CI 0.83–1.04). Among the 14 trials reporting hypoglycemia, the pooled RR with IIT was 6.0 (95% CI 4.5–8.0). However, in subset analysis, patients in surgical ICUs appeared to benefit from IIT while patients in the other ICU settings (medical or mixed) did not. Although results from the early trials were better in studies that included surgical[138] rather than purely medical ICU patients[141], and this latest meta-analysis appears to confirm that trend, it should be noted that no such phenomenon was noted in the NICE-SUGAR trial. Overall, the data do not support the use of IIT aiming to control plasma glucose below 110 mg/dl (6.11 mmol/l) in critically ill patients, although subset analyses suggest that further trials may disclose benefits in perioperative patients, and perhaps through the use of less-intensive glucose control targets.

Considering the balance between potential benefits and harm (see Suppl Table 2), the Work Group suggests using insulin for preventing severe hyperglycemia in critically ill patients, but in view of the danger of potentially serious hypoglycemia, we recommend that the average blood glucose should not exceed 150 mg/dl (8.33 mmol/l), but that insulin

therapy should not be used to lower blood glucose to less than 110 mg/dl (6.11 mmol/l). The Work Group recognizes that these proposed thresholds have never directly been examined in RCTs but are interpolated from the comparisons tested in the trials so far.

NUTRITIONAL ASPECTS IN THE PREVENTION AND TREATMENT OF CRITICALLY ILL PATIENTS WITH AKI

Protein-calorie malnutrition is an important independent predictor of in-hospital mortality in patients with AKI. In a prospective study of 300 AKI patients, 42% presented with signs of severe malnutrition on admission.[151]

The nutritional management of AKI patients must consider the metabolic derangements and proinflammatory state associated with renal failure, the underlying disease process and comorbidities, as well as the derangements in nutrient balance caused by RRT. Very few systematic studies have assessed the impact of nutrition on clinical end-points used in these guidelines (i.e., mortality, need for RRT, and incidence of AKI). Recommendations are therefore largely based on expert opinion. Several expert panels have developed clinical practice guidelines for the nutritional management of patients with AKI, whether treated with or without RRT.[152–156] A recent narrative review has also provided updated information on this topic.[157]

3.3.2: We suggest achieving a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI. (*2C*)

RATIONALE

Carbohydrate metabolism in AKI is characterized by hyperglycemia due to peripheral insulin resistance[158,159] and accelerated hepatic gluconeogenesis, mainly from conversion of amino acids released during protein catabolism that cannot be suppressed by exogenous glucose infusions.[160] In addition, hypertriglyceridemia commonly occurs due to inhibition of lipolysis. The clearance of exogenously administered lipids can be reduced.[161] The modifications of energy metabolism are usually not caused by AKI *per se* but related to acute comorbidities and complications.[162] Energy consumption is not increased by AKI. Even in multiple-organ failure, the energy expenditure of critically ill patients amounts to not more than 130% of resting energy expenditure. The optimal energy-to-nitrogen ratio during AKI has not been clearly determined. In a retrospective study of AKI patients undergoing continuous venovenous hemofiltration (CVVH), less negative or weakly positive nitrogen balance was associated with an energy intake of approximately 25 kcal/kg/d.[163] In a randomized trial in AKI patients comparing 30 and 40 kcal/kg/d energy provision, the higher energy prescription did not induce a more positive nitrogen balance but was associated with a higher incidence of hyperglycemia and hypertriglyceridemia and a more positive fluid balance.[164] These observations provide a rationale to maintain a total energy intake of at least 20, but not more than 25–30 kcal/kg/d, equivalent to 100–130% of resting energy expenditure. Energy provision should be composed of 3–5 (maximum 7) g per kilogram body weight carbohydrates and 0.8–1.0 g per kilogram body weight fat.

3.3.3: We suggest to avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT. (*2D*)

3.3.4: We suggest administering 0.8–1.0 g/kg/d of protein in noncatabolic AKI patients without need for dialysis (*2D*), 1.0–1.5 g/kg/d in patients with AKI on RRT (*2D*), and up to a maximum of 1.7 g/kg/d in patients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients. (*2D*)

RATIONALE

Protein hypercatabolism driven by inflammation, stress, and acidosis is a common finding in critically ill patients.[157,165,166] The optimal amount of protein supplementation in AKI patients is unknown. Patients with AKI are at high risk of malnutrition. Since malnutrition is associated with increased mortality in critically ill patients, nutritional management should aim at supplying sufficient protein to maintain metabolic balance. Hence, nutritional protein administration should not be restricted as a means to attenuate the rise in BUN associated with declining GFR. On the other hand, there is little evidence that hypercatabolism can be overcome simply by increasing protein intake to supraphysiologic levels. While, in a crossover study of AKI patients, nitrogen balance was related to protein intake and was more likely to be positive with intakes larger than 2 g/kg/d,[167] only 35% of patients achieved a positive nitrogen balance in a study applying a nutrient intake as high as 2.5 g/kg/d protein.[168] No outcome data are currently available concerning the clinical efficacy and the safety of such high protein intakes, which may contribute to acidosis and azotemia, and increase dialysis dose requirements.

Due to their continuous nature and the high filtration rates, CRRT techniques can better control azotemia and fluid overload associated with nutritional support but may also result in additional losses of water-soluble, low-molecular-weight substances, including nutrients.[169] Normalized protein catabolic rates of 1.4 to 1.8 g/kg/d have been reported in patients with AKI receiving CRRT.[170–172] In a recent study in critically ill cancer patients with AKI and treated with sustained low-efficiency dialysis (SLED), those with higher BUN and serum albumin levels, which were associated with infusion of higher amount of total parenteral nutrition, had a lower mortality risk.[173]

In CRRT, about 0.2 g amino acids are lost per liter of filtrate, amounting to a total daily loss of 10–15 g amino acids. In addition, 5–10 g of protein are lost per day, depending on the type of therapy and dialyzer membrane. Similar amounts of protein and amino acids are typically lost by peritoneal dialysis (PD). Nutritional support should

account for the losses related to CRRT, including PD, by providing a maximum of 1.7 g amino acids/kg/d.

3.3.5: We suggest providing nutrition preferentially via the enteral route in patients with AKI. (*2C*)

RATIONALE

Enteral feeding may be more difficult in patients with AKI because of impaired gastrointestinal motility and decreased absorption of nutrients secondary to bowel edema.[174] Moreover, multiple factors negatively affect gastrointestinal function in critically ill patients, e.g., medications (sedatives, opiates, catecholamines, etc.), glucose and electrolyte disorders, diabetes, or mechanical ventilation. However, the provision of nutrients via the gut lumen helps maintain gut integrity, decreases gut atrophy, and decreases bacterial and endotoxin translocation. Furthermore, AKI is a major risk factor for gastrointestinal hemorrhage.[175] Enteral nutrition should exert protective effects on the risk of stress ulcers or bleeding. Clinical studies have suggested that enteral feeding is associated with improved outcome/survival in ICU patients.[176,177] Hence, enteral nutrition is the recommended form of nutritional support for patients with AKI. If oral feeding is not possible, then enteral feeding (tube feeding) should be initiated within 24 hours, and has been shown to be safe and effective.[178]

Pediatric considerations

In children with AKI, physiological macronutrient requirements are age-dependent, reflecting the developmental dynamics of growth and metabolism. Research exploring nutritional requirements in children with critical illness and AKI is limited to observational studies. With respect to calorie provision, it is generally agreed that critically ill children, like adults, should receive 100–130% of the basal energy expenditure, which can be estimated with acceptable precision and accuracy by the Caldwell-Kennedy equation[179]: (resting energy expenditure [kcal/kg/d] $= 22 + 31.05 \times$ weight [kg] $+ 1.16 \times$ age [years]).

In a recent survey of the nutritional management of 195 children with AKI on CRRT, the maximal calorie prescription in the course of treatment averaged 53, 31, and 21 kcal/kg/d, and that for protein intake 2.4, 1.9, and 1.3 g/kg/d in children aged <1, 1–13, and >13 years, respectively.[180] Although not validated by outcome studies, these figures provide an orientation for the macronutrient supply typically achieved in and tolerated by children with AKI receiving CRRT.

RESEARCH RECOMMENDATIONS

- The risk-benefit ratio of diets with low, medium, and high protein contents in different stages of AKI should be addressed in RCTs.
- Given gastrointestinal tract dysfunction in AKI, the possible benefit of enteral vs. parenteral feeding in AKI patients should be further evaluated in prospective RCTs.

SUPPLEMENTARY MATERIAL

Supplementary Table 2: Evidence profile of RCTs examining insulin vs. conventional glucose therapy for the prevention of AKI.
Supplementary Table 3: Summary table of RCTs examining the effect of insulin for the prevention of AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 3.4: The use of diuretics in AKI

Diuretics are frequently used in patients at risk of AKI, and in the management of those who develop AKI. Since fluid overload is one of the major symptoms of AKI, diuretics are often used for patients with AKI to facilitate fluid management. Recent observational studies showed that 59–70% of patients with AKI were given diuretics at the time of nephrology consultation or before the start of RRT.[181,182] In addition, oliguric AKI has a worse prognosis than nonoliguric AKI and physicians often prescribe diuretics to convert oliguric to nonoliguric AKI.[183] Diuretics are also used to control fluid balance and permit administration of nutrition and medications. Furthermore, several diuretics have potentially renoprotective effects that might prevent development of AKI and hasten its recovery. However, diuretics can also be harmful, by reducing the circulating volume excessively and adding a prerenal insult, worsening established AKI. Therefore, it is essential to evaluate usefulness of diuretics to improve outcome of patients with AKI, not just for fluid management.

3.4.1: We recommend not using diuretics to prevent AKI. (*1B*)

3.4.2: We suggest not using diuretics to treat AKI, except in the management of volume overload. (*2C*)

RATIONALE

Loop diuretics have several effects that may protect against AKI. They may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, thus potentially lessening ischemic injury. Loop diuretics act at the luminal surface of the thick ascending limb of the loop of Henle and inhibit the Na-K-2Cl cotransporter,[184,185] resulting in a loss of the high medullary osmolality and decreased ability to reabsorb water. Inhibition of active sodium transport also reduces renal tubular oxygen consumption, potentially decreasing ischemic damage of the most vulnerable outer medullary tubular segments;[183] therefore, furosemide might protect kidneys against ischemic injury.[186] Furosemide also might hasten recovery of AKI by washing out necrotic debris blocking tubules, and by inhibiting prostaglandin dehydrogenase, which reduces renovascular resistance and increases renal blood flow.[186,187] Based on these properties, loop diuretics might be expected to prevent or ameliorate AKI. However, there are only minimal data to support this theory, and there is some evidence of harm associated with loop diuretic use to prevent or treat AKI.[188–191] Furosemide is the most commonly prescribed diuretic in the acute-care setting,[183–185] and a number of RCTs have tested whether furosemide is beneficial for prevention or treatment of AKI. Specifically, prophylactic furosemide was found to be ineffective or harmful when used to prevent AKI after cardiac surgery,[189,190] and to increase the risk of AKI when given to prevent CI-AKI.[191] Epidemiologic data have suggested that the use of loop diuretics may increase mortality in patients with critical illness and AKI,[181] along with conflicting data that suggest no harm in AKI.[182] Finally, furosemide therapy was also ineffective and possibly harmful when used to treat AKI.[188,192]

There is no evidence that the use of diuretics reduces the incidence or severity of AKI. Ho *et al.*[192,193] conducted two comprehensive systematic reviews on the use of the loop diuretic frusemide (furosemide) to prevent or treat AKI. Furosemide had no significant effect on in-hospital mortality, risk for requiring RRT, number of dialysis sessions, or even the proportion of patients with persistent oliguria. Results from the most recent review[193] are shown in Figure 9 and Figure 10. The primary prevention studies included patients who underwent cardiac surgery,[189] coronary angiography,[191] and major general or vascular surgery.[194] In two of these studies, all participants had mild pre-existing renal impairment. Two of the three studies reported mortality in patients randomized to furosemide (n = 103) vs. placebo (n = 99), with a pooled RR of 2.67 (95% CI 0.75–7.25; $P = 0.15$). All three studies reported RRT incidence in patients randomized to furosemide (n = 128) vs. placebo (n = 127), with a pooled RR of 4.08 (95% CI 0.46–35.96; $P = 0.21$). Thus, subanalysis to separate primary and secondary prevention trials did not alter the conclusion that, within the sample size limitations of this study, furosemide is not effective for the prevention of AKI.

The systematic review and meta-analysis by Ho and Power[193] also included six studies that used furosemide to treat AKI, with doses ranging from 600 to 3400 mg/d (Figure 9 and Figure 10).[192] No significant reduction was found for in-hospital mortality or for RRT requirement. The largest single study of furosemide for treating AKI was conducted by Cantarovich *et al.*,[188] which included 338 patients with AKI requiring dialysis. Patients were randomly assigned to the administration of either furosemide (25 mg/kg/d i.v. or 35 mg/kg/d orally) or placebo. Although time to reach 2 l/d of diuresis was shorter with furosemide (5.7 days) than placebo (7.8 days, $P = 0.004$), there was no difference in survival and number of dialysis sessions. At present, the current evidence does not suggest that furosemide can reduce mortality in patients with AKI.

Furosemide may, however, be useful in achieving fluid balance to facilitate mechanical ventilation according to the

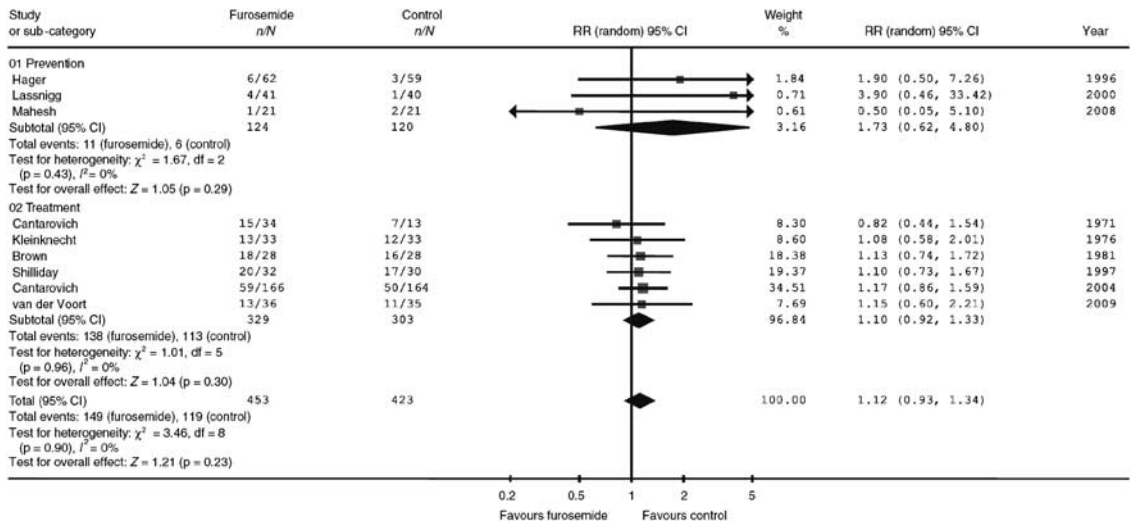

Figure 9 | Effect of furosemide vs. control on all-cause mortality. Reprinted from Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. Anaesthesia 2010; 65: 283–293 with permission from John Wiley and Sons[193]; accessed http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2044.2009.06228.x/full

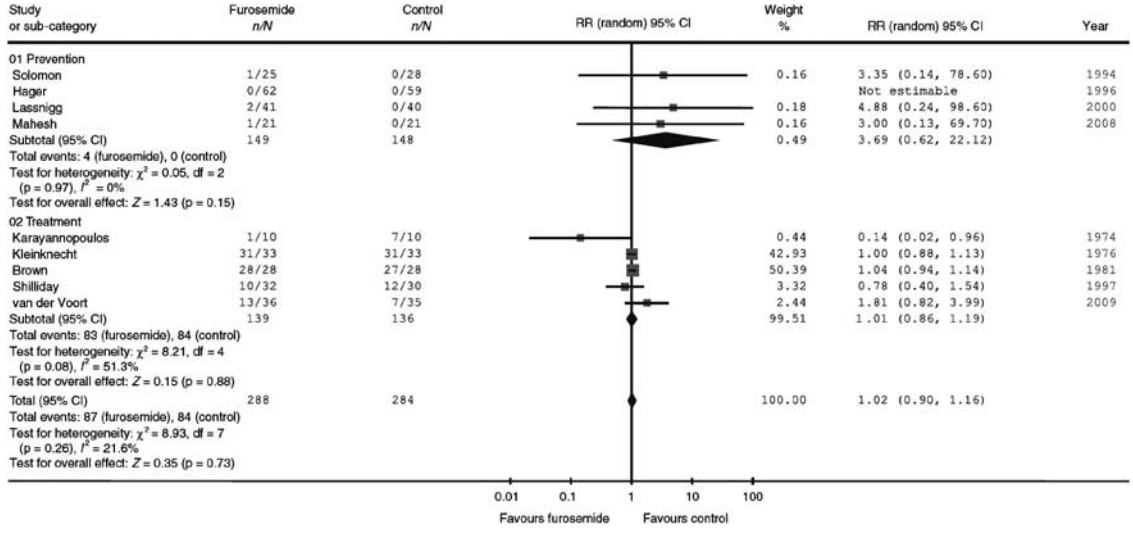

Figure 10 | Effect of furosemide vs. control on need for RRT. Reprinted from Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. Anaesthesia 2010; 65: 283–293 with permission from John Wiley and Sons[193]; accessed http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2044.2009.06228.x/full

lung-protective ventilation strategy in hemodynamically stable patients with acute lung injury. On the other hand, the literature also suggests that high-dose furosemide (>1 g/d) may cause ototoxicity. In the first meta-analysis by Ho and Sheridan,[192] high doses of furosemide (range 1–3.4 g/d) caused deafness or tinnitus more frequently than the control (RR 3.97; 95% CI 1.00–15.78; $P = 0.05$). When administered as continuous infusion a dose of 0.5 mg/kg/hour was not associated with ototoxicity.[195] Taken together with several small studies showing that the prophylactic use of diuretics to prevent AKI actually increased AKI incidence, these data raise significant concerns regarding use of loop diuretics to prevent or treat AKI in any setting. We similarly conclude that there is no evidence that the use of loop diuretics reduces the severity of AKI, or improves outcomes in this syndrome. Although the use of loop diuretics in early or established AKI facilitates management of fluid balance, hyperkalemia, and hypercalcemia, and is indicated for these clinical purposes, any putative role in the prevention or amelioration of AKI course is unproven.

Two recent studies have investigated whether the administration of furosemide to patients treated with CVVH could be associated with a more rapid discontinuation of the dialysis therapy. van der Voort *et al.*, observed, as expected, an increased urinary volume and sodium excretion, but this intervention did not lead to a shorter duration of renal failure

or more frequent renal recovery.[195] The second study by Uchino *et al.*,[196] analyzed data from the B.E.S.T. kidney and found that, from a total of 529 critically ill patients who survived during CRRT, 313 patients were removed successfully from CRRT while 216 patients needed "repeat RRT" after temporary discontinuation. Urine output (during the 24 hours before stopping CRRT) was identified as a significant predictor of successful cessation, but the predictive ability of urine output was negatively affected by the use of diuretics. Thus, a beneficial role for loop diuretics in facilitating discontinuation of RRT in AKI is not evident.

Mannitol

Mannitol has been frequently used in the past for prevention of AKI; however, most of the studies are retrospective, underpowered, and, overall, the studies did not meet the criteria of the Work Group to be included in formulation of recommendations. Prophylactic mannitol has been promoted in patients undergoing surgery. While in most of these instances mannitol increases urine flow, it is highly probable that mannitol does not convey additional beneficial effects beyond adequate hydration on the incidence of AKI.

In radiocontrast-induced nephropathy, loop diuretics and mannitol in one study have been shown to exacerbate ARF.[191] Weisberg *et al.*,[197] randomized patients undergoing contrast-medium investigations to receive saline or one of three renal vasodilator/diuretic drugs (dopamine [2 μg/kg/min], mannitol [15 g/dl in a one-half isotonic saline solution given at 100 ml/h] or atrial natriuretic peptide). Dopamine, mannitol, and atrial natriuretic peptide were associated with a much higher incidence of renal dysfunction in diabetic subjects compared to patients receiving saline alone.

Mannitol is often added to the priming fluid of the cardiopulmonary bypass system to reduce the incidence of renal dysfunction, but the results of these studies are not very convincing.[198] Two small randomized trials—one in patients with pre-existing normal renal function,[199] the second in patients with established renal dysfunction[200]—did not find differences for any measured variable of renal function. More convincing are the results obtained with the preventive administration of mannitol, just before clamp release, during renal transplantation.[201,202] The sparse controlled data available have shown that 250 ml of mannitol 20% given immediately before vessel clamp removal reduces the incidence of post-transplant AKI, as indicated by a lower requirement of post-transplant dialysis. However, 3 months after transplantation, no difference is found in kidney function compared to patients who did not receive mannitol.[203]

It has also been suggested that mannitol is beneficial in rhabdomyolysis by stimulating osmotic diuresis and by lowering the intracompartmental pressure in the affected crushed limbs[204–206]; again, these studies were either not randomized or underpowered. A separate guideline on crush injury associated with disasters, mainly earthquake victims, is under preparation by the ISN Renal Disaster Relief Task Force.

In summary, despite experimental animal data and the anecdotal human evidence for the beneficial effects of mannitol, there are no adequately powered prospective RCTs comparing mannitol vs. other strategies. Based on these considerations, the Work Group concludes that mannitol is not scientifically justified in the prevention of AKI.

RESEARCH RECOMMENDATION

- Given the potential to mitigate fluid overload but also to worsen renal function and possibly cause kidney injury, further study is required to clarify the safety of loop diuretics in the management of patients with AKI.

Chapter 3.5: Vasodilator therapy: dopamine, fenoldopam, and natriuretic peptides

DOPAMINE FOR THE PREVENTION OR TREATMENT OF AKI

Dopamine was once commonly used for renal protection in the critically ill. However, with multiple negative studies, including a randomized, double-blind, placebo-controlled trial of adequate size and power,[207] its use has been abandoned by most. Low-dose dopamine administration (1–3 μg/kg/min) to healthy individuals causes renal vasodilation, natriuresis, and increased GFR; because of these effects, it has been given as prophylaxis for AKI associated with radiocontrast administration, repair of aortic aneurysms, orthotopic liver transplantation, unilateral nephrectomy, renal transplantation, and chemotherapy with interferon.[208] The majority of prevention trials with low-dose dopamine have been small, inadequately randomized, of limited statistical power, and with end-points of questionable clinical significance. Furthermore, recent data suggest that the renal vasodilatory effect of dopamine found in healthy populations is not preserved in patients with AKI. Using Doppler ultrasound, Lauschke *et al.*[209] found that dopamine significantly increased renal vascular resistance in AKI patients. Kellum and Decker[210] found no benefit of dopamine for prevention or therapy of AKI in an adequately-powered meta-analysis, and Marik[211] found no benefit in a systematic review.

There is also limited evidence that the use of dopamine to prevent or treat AKI causes harm. Although the meta-analysis by Friedrich *et al.*,[212] found no significant increase in adverse events or evidence of harm from low-dose dopamine, there is significant literature demonstrating adverse effects of dopamine, even at low doses. It can trigger tachyarrhythmias and myocardial ischemia, decrease intestinal blood flow, cause hypopituitarism, and suppress T-cell function.[208] Taken together with the lack of positive trials to support the use of dopamine for AKI prevention or therapy, the aforementioned potential deleterious effects of this drug provide additional arguments for abandoning its use entirely for the prevention and therapy of AKI.

3.5.1: We recommend not using low-dose dopamine to prevent or treat AKI. (*1A*)

RATIONALE

In their meta-analysis, Friedrich *et al.*,[212] did not specifically separate prophylactic trials from trials where dopamine was used therapeutically in patients with established AKI, because many of the original trials failed to do so.[210] The authors analyzed 61 randomized or quasi-randomized controlled trials of low-dose dopamine, and found no improvement of survival (Figure 11), no decrease in dialysis requirement (Figure 12), no improvement in renal function, and improved urine output only on the first day of dopamine therapy.[212] Similarly, although there were trends towards transiently greater urine output, lower SCr, and higher GFR in dopamine-treated patients on day 1 of therapy (but not days 2 and 3), there was no evidence of a sustained beneficial effect on renal function. In an earlier systematic review, Kellum *et al.*,[210] performed an analysis of studies that reported incidence of AKI as an outcome, which developed in 15.3% in the dopamine arms and 19.5% in the control arms (RR 0.79 [0.54–1.13]). Similar to the earlier analysis by Kellum *et al.*, restriction of the Work Group's analysis to prevention trials did not disclose any benefit of dopamine vs. placebo therapy. Similarly, analysis of adequate trials restricted to patients treated for AKI does not suggest a benefit of dopamine therapy. Specifically, a relatively large randomized, placebo-controlled trial in 328 critically ill patients with early AKI sufficiently powered to detect a small benefit was reported.[207] There was no effect of low-dose dopamine on renal function, need for dialysis, ICU or hospital length of stay (LOS), or mortality (Suppl Table 4). Taken together, these analyses found no evidence that dopamine therapy is effective in the prevention or treatment of AKI.

FENOLDOPAM FOR THE PREVENTION OR TREATMENT OF AKI

Fenoldopam mesylate is a pure dopamine type-1 receptor agonist that has similar hemodynamic renal effects as low-dose dopamine, without systemic α- or β-adrenergic stimulation.[213]

3.5.2: We suggest not using fenoldopam to prevent or treat AKI. (*2C*)

RATIONALE

The results of animal experiments and small human studies measuring perioperative GFR in patients undergoing coronary artery bypass graft and aortic cross-clamp surgery suggested that fenoldopam might prevent or ameliorate the course of AKI.[139] Cogliati *et al.*,[214] conducted a double-blind, randomized trial of fenoldopam infusion for renal protection in 193 high-risk cardiac surgery patients, who were randomized to receive a continuous infusion of fenoldopam,

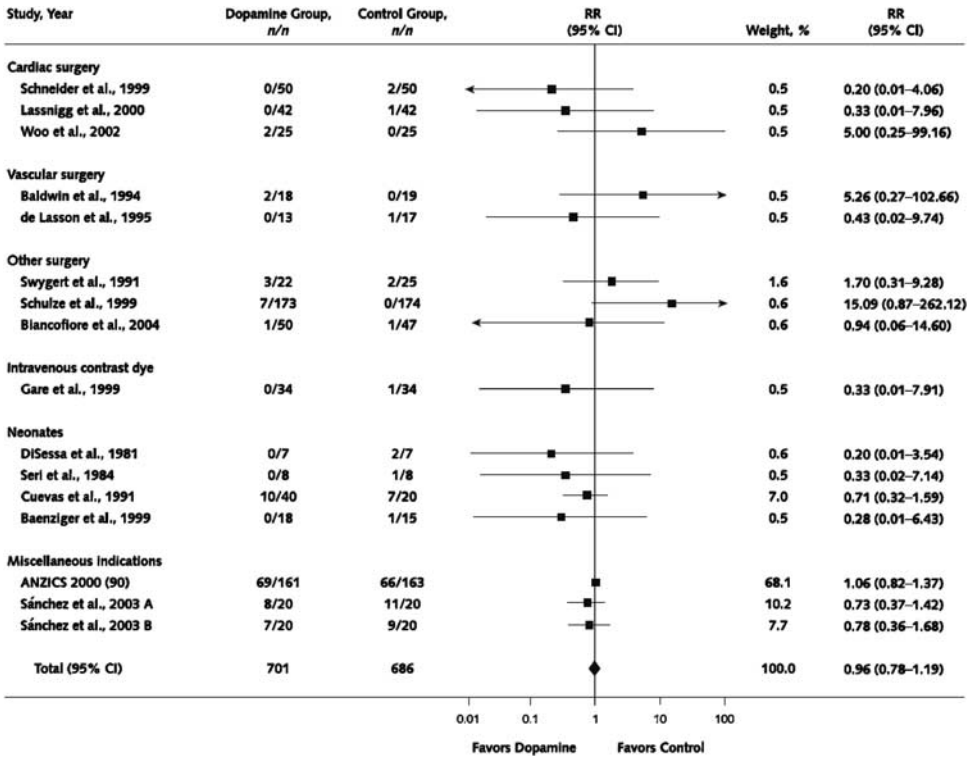

Figure 11 | Effect of low-dose dopamine on mortality. Reprinted from Friedrich JO, Adhikari N, Herridge MS *et al*. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005; 142: 510–524 with permission from American College of Physicians[212]; accessed http://www.annals.org/content/142/7/510.full

0.1 μg/kg/min (95 patients) or placebo (98 patients) for 24 hours. AKI was defined as a postoperative SCr level of $\geqslant$2 mg/dl ($\geqslant$177 μmol/l) with an increase in SCr level of $\geqslant$0.7 mg/dl ($\geqslant$61.9 μmol/l) from preoperative to maximum postoperative values. AKI developed in 12 of 95 (12.6%) patients receiving fenoldopam and in 27 of 98 (27.6%) patients receiving placebo ($P = 0.02$), and RRT was started in 0 of 95 and 8 of 98 (8.2%) patients, respectively ($P = 0.004$). These results suggested that a 24-hour infusion of 0.1 μg/kg/min of fenoldopam prevented AKI in a high-risk population undergoing cardiac surgery. A meta-analysis of 1059 patients in 13 studies that included this trial found that fenoldopam reduces the need for RRT and in-hospital death in cardiovascular surgery patients.[215] However, the pooled studies included both prophylactic and early therapeutic studies, as well as propensity-adjusted case-matched studies (rather than purely randomized trials). A 1000-patient RCT of fenoldopam to prevent the need for RRT after cardiac surgery is currently underway (ClinicalTrials.gov identifier: NCT00621790); meanwhile, this remains an unproven indication for fenoldopam therapy.

Finally, Morelli *et al*.,[216] in a prospective, double-blind trial, randomized 300 septic patients without renal dysfunction to receive infusions of fenoldopam (0.09 μg/kg/min) and compared these individuals to a placebo group; the treatment continued as long as the patient was in the ICU. The fenoldopam group had a significantly lower rate of AKI (29 vs. 51 patients, $P = 0.006$; OR of 0.47, $P = 0.005$), and shorter ICU stays, without any increase in complications. The incidence of severe AKI, dialysis, and death were not different between the groups. This study requires a larger confirmatory trial, which should be powered to test effectiveness in improving dialysis-free survival.

Emerging data from experimental AKI models suggest that fenoldopam may have multiple protective effects in AKI, including anti-inflammatory effects independent of any vasodilatory action.[217,218] Further large studies will be required to determine if fenoldopam is an effective renoprotective agent.[213,219] As discussed elsewhere in this guideline (Section 4), despite promising pilot study findings, fenoldopam was ultimately found to be ineffective for the prevention of CI-AKI,[220] and as a potent antihypertensive (the only approved indication for the drug), fenoldapam carries a significant risk of hypotension.

Fenoldopam mesylate has also been studied for early treatment of AKI. Tumlin *et al*.,[221] conducted a randomized, placebo-controlled pilot trial of low-dose fenoldopam mesylate in ICU patients with early AKI and found no benefit, though they did show a trend towards lower 21-day mortality and decreased need for dialysis in fenoldopam-treated patients (11% difference in dialysis-free survival). In secondary analyses, fenoldopam tended to reduce the

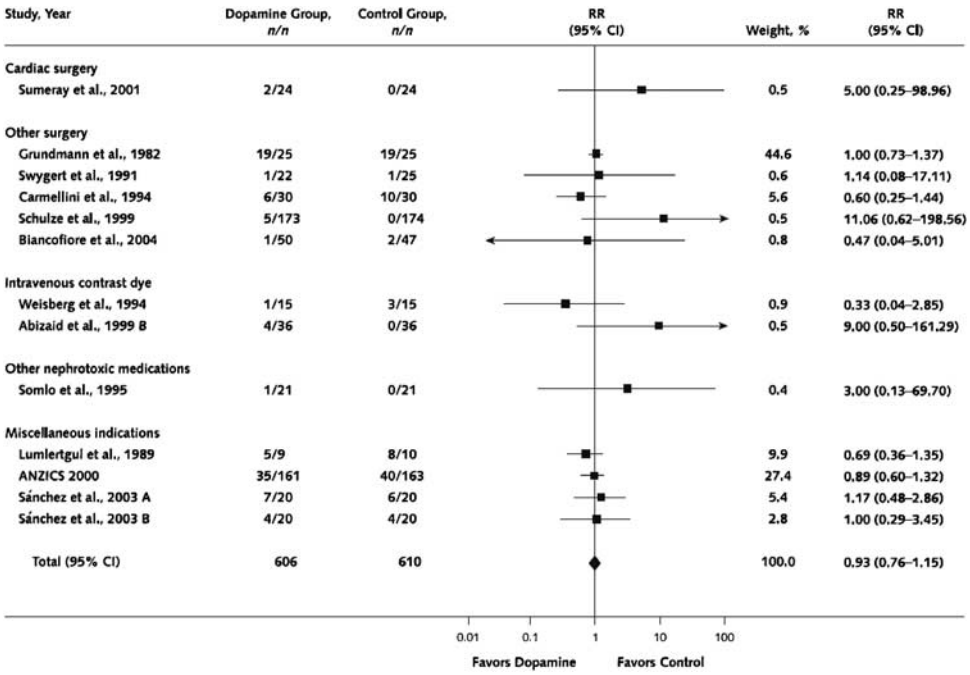

Figure 12 | Effect of low-dose dopamine on need for RRT. Reprinted from Friedrich JO, Adhikari N, Herridge MS *et al*. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005; 142: 510–524 with permission from American College of Physicians[212]; accessed http://www.annals.org/content/142/7/510.full

primary end-point in patients without diabetes and post-operative cardiothoracic surgery patients with early ATN.

Brienza *et al*.,[222] conducted a prospective, multicenter, RCT of fenoldopam therapy for early AKI in critically ill patients. The study included hemodynamically stable adults with renal dysfunction. This 100- subject study compared 4-day infusions of fenoldopam (0.1 μg/kg/min) or dopamine (2 μg/kg/min); there was no placebo arm. The primary end-point of the study was a between-group comparison of the maximum change of SCr over time during the 4-day study period. The peak SCr values and maximum increments during the study did not differ between the fenoldopam and dopamine groups; however, in the fenoldopam group at the end of infusion, SCr had decreased by 0.29 ± 0.77 mg/dl (25.6 ± 68.1 μmol/l), a value significantly different from the dopamine group (0.09 ± 0.94 mg/dl [7.96 ± 83.1 μmol/l]; $P = 0.05$). Also, the maximum decreases of SCr levels from study entry were significantly larger in the fenoldopam group. There was no difference in heart rate, blood pressure, incidence of hypotension, or urinary output (apart from a transiently higher value within the first study day in the dopamine group). The authors concluded that, for critically ill patients with impaired renal function, a continuous infusion of fenoldopam 0.1 μg/kg/min improves renal function when compared to renal-dose dopamine, without significant adverse effects. The study has, however, a number of deficiencies, including the lack of a true control, unblinding of the investigators, and an unorthodox AKI definition, among other limitations, but taken together with other positive trends in the literature, these results add to the discourse around fenoldopam's use to treat early AKI in critically ill patients. Similarly, Landoni *et al*.,[223] in a recently published meta-analysis found that fenoldopam decreased the risk of requiring acute RRT and resulted in a lower all-cause, in-hospital mortality (15.1%) compared to controls (18.9%; OR 0.64; 95% CI 0.4–0.91), along with a non-significant trend towards more hypotension or pressor use in the fenoldopam group.

Our analysis revealed three suitable prophylactic studies of adequate size and study design (Suppl Tables 5 and 6) that reported AKI incidence in patients randomized to fenoldopam (n = 1790) vs. placebo (n = 1839). The pooled RR and 95% CI was 0.96 (0.76–1.2), P = NS. Only one study reported mortality (8-day) in sepsis patients randomized to fenoldopam (35%, n = 150) vs. placebo (44%, n = 150), with a RR of 0.79 (95% CI 0.59–1.05; $P = 0.1$).

In our analysis of the two suitable studies of fenoldopam therapy for AKI, only one study[221] reported (21-day) mortality in critically ill patients with early AKI randomized to fenoldopam (11/80; 13.8%) vs. placebo (n = 19/75, 25.3%; $P = 0.068$) (Suppl Tables 7 and 8). The other study[222] reported the change in renal function in AKI patients randomized to fenoldopam (n = 50) vs. dopamine (n = 50), defined by the absolute SCr change between the beginning and end of the study drug infusion and maximum decrease from study entry, which were significantly larger in the fenoldopam group with a pooled RR of 0.96 (95% CI 0.76–1.2; P = NS). These two studies reported new RRT

incidence in patients with AKI randomized to fenoldopam (n = 130) vs. placebo (n = 125). In the study by Tumlin *et al.*, no difference in requirement of RRT was found (with fenoldopam, 13 of 80 patients; 16.25%); with placebo (19 of 75 patients; 25.3%; $P = 0.163$). Requirement of RRT was very rare in the study of Brienza *et al.*, and was prescribed in a total of only five patients; three in the dopamine group and two in fenoldopam group (P = NS). Overall, no data from adequately powered multicenter trials with clinically significant end-points and adequate safety are available to recommend fenoldopam to either prevent or treat AKI. The guideline recommendation against using fenoldopam places a high value on avoiding potential hypotension and harm associated with the use of this vasodilator in high-risk perioperative and ICU patients, and a low value on potential benefit, which is currently only suggested by relatively low-quality single-center trials.

RESEARCH RECOMMENDATION

- While randomized trials of fenoldopam to treat AKI in a variety of settings (critical illness, high-risk surgery—particular cardiac, sepsis) may be considered, the pharmacologic strategy of renal vasodilatation has not been successful to date and different approaches are likely needed.

NATRIURETIC PEPTIDES FOR THE PREVENTION OR TREATMENT OF AKI

Several natriuretic peptides are in clinical use or in development for treatment of congestive heart failure (CHF) or renal dysfunction, and could potentially be useful to prevent or treat AKI.

Atrial natriuretic peptide (ANP) is a 28-amino-acid peptide with diuretic, natriuretic, and vasodilatory activity.[224] ANP is mainly produced in atrial myocytes, and the rate of release from the atrium increases in response to atrial stretch.[225] Early animal studies showed that ANP decreases preglomerular vascular resistance and increases postglomerular vascular resistance, leading to increased GFR.[226] It also inhibits renal tubular sodium reabsorption. Increases in GFR and diuresis have also been confirmed in clinical studies.[227] It could thus be expected that ANP might be useful for treatment of AKI, and several RCTs have been conducted to test this hypothesis.

3.5.3: We suggest not using atrial natriuretic peptide (ANP) to prevent (*2C*) or treat (*2B*) AKI.

RATIONALE

There have been several negative studies of prophylactic ANP therapy; for example, ANP failed in two studies to prevent primary renal transplant dysfunction[228,229] and ANP prophylaxis also failed to prevent CI-AKI.[230] Based on the positive results of small clinical studies using ANP to treat AKI, a randomized placebo-controlled trial in 504 critically ill patients with AKI was conducted.[231] Patients received 24-hour i.v. infusion of either ANP (0.2 μg/kg/min) or placebo. The primary outcome was dialysis-free survival for 21 days after treatment. Despite the large size of the trial, ANP administration had no effect on 21-day dialysis-free survival, mortality, or change in plasma creatinine concentration. Of note, the mean SCr at enrollment (anaritide group: 4.4 mg/dl [389 μmol/l]; placebo group: 5.0 mg/dl [442 μmol/l]) in this study confirms that intervention in this trial was extremely late in the course of AKI. In subgroup analysis, dialysis-free survival was higher in the treatment group for patients with oliguria (< 400 ml/d; ANP 27%, placebo 7%, $P = 0.008$). A subsequent trial in 222 patients with oliguric renal failure, however, failed to demonstrate any benefit of ANP.[232] The dose and duration of ANP treatment and primary outcome were the same as the previous study. The dose of ANP might have been too high (0.2 μg/kg/min) in both studies: hypotension (systolic blood pressure < 90 mm Hg) occurred more frequently in the ANP groups of both trials (in the first study, 46% vs. 18%, $P < 0.001$; and in the second study, 97% vs. 58%, $P < 0.001$), and this may have negated any potential benefit of renal vasodilation in these patients. In addition to an excessive dose, the failure of these large studies has also been attributed in subsequent analyses to the late initiation of the drug to patients with severe AKI and an inadequate duration of infusion (only 24 hours).

A promising, but underpowered, study of ANP to treat AKI immediately following cardiac surgery showed a decreased rate of postoperative RRT compared to placebo-treated patients.[233] In this study, Sward *et al.* randomized 61 patients with AKI following cardiac surgery (defined as a SCr increase ⩾50% from a baseline < 1.8 mg/dl [< 159 μmol/l]) to receive infusion of ANP or placebo until the SCr decreased below the baseline value at enrollment, the patient died, or one of four prespecified dialysis criteria was reached. Of note, all patients received infusions of furosemide (20–40 mg/h) and oliguria, defined as a urine output ⩽0.5 ml/kg/h for 3 hours, was an exclusion criterion and an automatic dialysis indication. The primary end-point was the rate of dialysis within 21 days of enrollment. CrCl was significantly higher on the third study day in ANP-treated subjects ($P = 0.04$). Using prespecified dialysis criteria, 21% of patients in the ANP group and 47% in the placebo group were dialyzed within 21 days (hazard ratio [HR] 0.28; 95% CI 0.10–0.73; $P = 0.009$). The combined secondary end-point of death-or-dialysis was similarly improved in the ANP group (28%) compared to placebo (57%; HR 0.35; 95% CI 0.14–0.82; $P = 0.017$). The incidence of hypotension during the first 24 hours was 59% in the ANP group and 52% in controls (P = NS).

It is intriguing to speculate on the potential reasons for the positive outcome of this trial, compared to larger prior studies of ANP for AKI prevention and therapy. Apart from the possibility that this is a false-positive, underpowered study, possible explanations include the use of ANP earlier in the course of AKI (the mean SCr in the prior ANP studies

was much higher), and at lower doses (50 ng/kg/min vs. 200 ng/kg/min) that avoided the significant rate of hypotension observed in prior trials. The use of prespecified dialysis criteria was another strength of this trial. More recently, Sward *et al.*,[234] compared the renal hemodynamic effects of ANP and furosemide in 19 mechanically ventilated post–cardiac surgery patients with normal renal function, measuring renal blood flow, GFR, and renal oxygen extraction. ANP infusion (25–50 ng/kg/min) increased GFR, filtration fraction, fractional excretion of sodium, and urine output, accompanied by a 9% increase in tubular sodium absorption and a 26% increase in renal oxygen consumption. Furosemide infusion (0.5 mg/kg/h) increased urine output 10-fold and fractional excretion of sodium 15-fold, while decreasing tubular sodium absorption by 28% and lowering renal oxygen consumption by 23%. Furosemide also lowered GFR by 12% and filtration fraction by 7%. Thus, although the balance of renal hemodynamic and tubular effects of the two drugs appears to favor furosemide for improving renal oxygen delivery-consumption balance, ANP is more likely to acutely improve GFR. One might speculate that the use of furosemide infusion in all of the subjects in the successful ANP trial may have provided an important protection against renal ischemia by reducing tubular sodium absorption and associated oxygen consumption, despite an increase in GFR in the ANP group. A larger prospective trial of ANP to improve dialysis-free survival in this setting is required, perhaps with and without furosemide infusion.

Pooled analysis of 11 studies involving 818 participants in the prevention cohort showed a trend toward reduction in the need for RRT in the ANP group (OR 0.45; 95% CI 0.21–0.99; $P = 0.05$). Restricting the analysis to studies that used low-dose ANP preparations did not change the overall effect for this outcome. There was no significant difference noted between the ANP and control groups for mortality in the prevention category (OR 0.67; 95% CI 0.19–2.35; $P = 0.53$), and this effect was unchanged by restricting the analysis to studies that used low-dose ANP preparations. However, these studies were generally of poor quality, several without reported baseline SCr values or clear definitions of AKI or RRT indications (Suppl Tables 10 and 11), and only one was of adequate quality.

Nigwekar *et al.*, recently conducted a systematic review and meta-analysis of ANP for management of AKI.[235] They found 19 relevant studies, among which 11 studies were for prevention and eight were for treatment of AKI. Pooled analysis of the eight treatment studies, involving 1043 participants, did not show significant difference for RRT requirement between the ANP and control groups (OR 0.59; 95% CI 0.32–1.08; $P = 0.12$). There was also no significant difference for mortality (OR 1.01; 95% CI 0.72–1.43; $P = 0.89$). However, low-dose ANP preparations were associated with significant reduction in RRT requirement (OR 0.34; 95% CI 0.12–0.96; $P = 0.04$). The incidence of hypotension was not different between the ANP and control groups for low-dose studies (OR 1.55; 95% CI 0.84–2.87), whereas it was significantly higher in the ANP group in the high-dose ANP studies (OR 4.13; 95% CI 1.38–12.41). Finally, a pooled analysis of studies that examined oliguric AKI did not show any significant benefit from ANP for RRT requirement (OR 0.46; 95% CI 0.19–1.12; $P = 0.09$) or mortality (OR 0.94; 95% CI 0.62–1.43; $P = 0.79$). Only two of the treatment studies included in the Nigwekar analysis[231,232] were of adequate size and quality to meet the criteria for our systematic review (Suppl Tables 12 and 13), which found no significant inconsistencies in the findings of both trials that (combined) included 720 subjects (351 treated with ANP) (Suppl Table 12). Thus, although subset analyses separating low-dose from high-dose ANP trials suggest potential benefits, the preponderance of the literature suggests no benefit of ANP therapy for AKI. Therefore, the Work Group suggests that these agents not be used to prevent or treat AKI. This conclusion is based on placing a high value on avoiding potential hypotension and harm associated with the use of a vasodilator in high-risk perioperative and ICU patients, and a low value on potential benefit which is supported by relatively low-quality evidence from retrospective subset analyses from negative multicenter trials.

Urodilatin is another natriuretic peptide that is produced by renal tubular cells, and was found to have the same renal hemodynamic effect as ANP without systemic hypotensive effects.[236] Limited data suggest that urodilatin improves the course of established postoperative AKI.[237] Fifty-one patients who received orthotopic heart transplants received urodilatin (6–20 ng/kg/min) up to 96 hours postoperatively. AKI occurred in 6% of these patients, compared to 20% in a historical control group that did not receive urodilatin.[237] However, in another small, placebo-controlled study of 24 patients who underwent orthotopic heart transplants, the incidence of AKI was unchanged,[238] although duration of hemofiltration (HF) was significantly shorter and the frequency of intermittent hemodialysis (IHD) less in those who received urodilatin. Taken together, these data suggest that natriuretic peptides may have a role in the therapy of early AKI following cardiac surgery, but further prospective trials are needed to confirm this potential indication.

Nesiritide (brain natriuretic peptide) is the latest natriuretic peptide introduced for clinical use, and is approved by the Food and Drug Administration (FDA) only for the therapy of acute, decompensated CHF. Meta-analysis of outcome data from these and some other nesiritide CHF trials has generated some controversy.[239–241] Sackner-Bernstein *et al.*,[239] analyzed mortality data from 12 randomized trials; in three trials that provided 30-day mortality data, they found a trend towards an increased risk of death in nesiritide-treated subjects. In another meta-analysis of five randomized trials that included 1269 subjects,[240] the same investigators also found that there was a relationship between nesiritide use and worsening renal function, defined as a SCr increase > 0.5 mg/dl (> 44.2 μmol/l). Nesiritide doses $\leqslant 0.03$ μg/kg/min significantly increased the risk of renal dysfunction compared to non–inotrope-based controls or

compared to all control groups (including inotropes). Even at doses $\leqslant 0.015$ μg/kg/min, nesiritide was associated with increased renal dysfunction compared to controls. There was no difference in dialysis rates between the groups. Another retrospective study determined independent risk factors for 60-day mortality by multivariate analysis in a cohort of 682 elderly heart-failure patients treated with nesiritide vs. those who were not.[242] When patients were stratified according to nesiritide usage, AKI emerged as an independent risk factor for mortality only among patients who received the drug. Strikingly, among these heart-failure patients who developed AKI, nesiritide usage emerged as the only independent predictor of mortality.

The manufacturers of nesiritide convened an expert panel, which concluded that further trial data are needed to discern the effects of nesiritide therapy on renal function and survival in patients with decompensated CHF. The panel also re-emphasized that the indication for nesiritide therapy is acute decompensated CHF, not chronic intermittent therapy or other uses, and in particular noted that the drug should not be used to improve renal function or in place of diuretic therapy in CHF patients, as there is no proof of the utility of the drug for these purposes. A 7000-patient multicenter RCT in acute decompensated heart failure is currently in progress to determine the clinical effectiveness of nesiritide therapy for acute decompensated heart failure (the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; Clinicaltrials.gov identifier NCT00475852). Meanwhile, nesiritide is approved for treatment of symptomatic acute decompensated heart failure.

Uncontrolled studies using nesiritide for cardiovascular support of patients with CHF undergoing cardiac surgery have suggested beneficial effects on renal function. Mentzer *et al.*,[243] conducted a 303-patient, multicenter, randomized, double-blind trial of a 24- to 96-hour infusion of 0.01 μg/kg/min of nesiritide vs. placebo in patients with chronic left ventricular dysfunction (ejection fraction $\leqslant 40\%$) undergoing cardiac surgery using cardiopulmonary bypass. The Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery trial was an exploratory, safety-oriented study with five primary end-points, including three renal end-points and two hemodynamic end-points. There were no significant differences between the groups in baseline patient characteristics; SCr values were ~ 1.1 mg/dl (97.2 μmol/l), with eGFR ~ 80 ml/min per 1.73 m^2. The mean duration of study drug infusion was ~ 40 hours in both groups. Perioperative renal function quantified by the three renal primary end-points was better in the nesiritide group (peak SCr increase of 0.15 mg/dl [13.3 μmol/l] vs. placebo group 0.34 mg/dl [30.1 μmol/l]; $P < 0.001$; eGFR decrease of -10.2 ml/min per 1.73 m^2 vs. placebo -17.8 ml/min per 1.73 m^2, $P = 0.001$; initial 24-hour urinary output 2.9 $\pm$ 1.2 l vs. placebo 2.3 $\pm$ 1 l; $P < 0.001$). The RR of AKI in the nesiritide group compared to placebo was 0.58 (0.27–1.21); the 180-day mortality was also reduced in the nesiritide group (RR 0.48 [0.22–1.05]; $P = 0.046$) (Suppl Table 9). These trends were more pronounced in the small, 62-patient subset with preoperative SCr values > 1.2 mg/dl (> 106 μmol/l). Although SCr increased postoperatively in both groups, it returned to baseline within 12 hours in the nesiritide group, and remained elevated throughout hospitalization in the placebo group. Use of vasoactive drugs and hemodynamic parameters did not differ significantly between the groups. Adverse events also were similar between the groups, as was 30-day and 180-day mortality (although capture of mortality data was incomplete). Thus, it appears that administration of nesiritide infusion during and after cardiac surgery with cardiopulmonary bypass in patients with preoperative left ventricular dysfunction has favorable short-term effects on renal function, with short-term adverse effects comparable to placebo infusion; however, as mentioned earlier, this is not an FDA-approved indication for this drug. It is interesting to speculate that, based upon these results, any renoprotective effect of this vasoactive drug during and after cardiopulmonary bypass is not mediated by effects on systemic perfusion (similar in both groups), but rather suggesting an effect on regional perfusion or a pleiotropic phenomenon. Unfortunately, these promising pilot study findings have not been followed up with a confirmatory prospective clinical trial.

A prospective, randomized clinical trial (the Nesiritide Study), found no benefit of nesiritide for 21-day dialysis and/or death in patients undergoing high-risk cardiovascular surgery.[244] However, the study did demonstrate that the prophylactic use of nesiritide was associated with reduced incidence of AKI, the latter defined by the AKIN Group, in the immediate postoperative period (nesiritide 6.6% vs. placebo 28.5%, $P = 0.004$). Recently, Lingegowda *et al.*[245] investigated whether the observed renal benefits of nesiritide had any long-term impact on cumulative patient survival and renal outcomes. Data on all 94 patients from the Nesiritide Study were obtained with a mean follow-up period of 20.8 $\pm$ 10.4 months. No differences in cumulative survival between the groups were noted, but patients with in-hospital incidence of AKI had a higher rate of mortality than those with no AKI (41.4% vs. 10.7%; $P = 0.002$). It seemed, thus, that the possible renoprotection provided by nesiritide in the immediate postoperative period was not associated with improved long-term survival in patients undergoing high-risk cardiovascular surgery.

In summary, although evidence from a variety of small studies suggests the potential for therapy with natriuretic peptides to be useful for the prevention or treatment of AKI in a variety of settings, there are no definitive trials to support the use of ANP, BNP, or nesiritide for these purposes. Thus, the Work Group suggests that these agents not be used for prevention or treatment of AKI.

RESEARCH RECOMMENDATION

- We recommend further trials of ANP at doses below 0.1 μg/kg/min, for the prevention or treatment of AKI. There is a possibility that ANP might be effective if it is

given at a lower dose (0.01–0.05 μg/kg/min) in patients prophylactically or with early AKI, and during a longer period than in previous large studies.

SUPPLEMENTARY MATERIAL

Supplementary Table 4: Summary table of RCTs examining the effect of dopamine vs. placebo for the treatment of AKI.
Supplementary Table 5: Evidence profile of RCTs examining fenoldopam vs. control for the prevention of AKI.
Supplementary Table 6: Summary table of RCTs examining the effect of fenoldopam for the prevention of AKI.
Supplementary Table 7: Evidence profile of RCTs of fenoldopam vs. placebo for the treatment of AKI.
Supplementary Table 8: Summary table of RCTs of examining the effect of fenoldopam for the treatment of AKI.
Supplementary Table 9: Summary table of RCTs of nesiritide vs. control for the prevention of AKI.
Supplementary Table 10: Evidence profile of RCTs examining anaritide vs. control for the prevention of AKI.
Supplementary Table 11: Summary table of RCTs examining the effect of anaritide vs. control for the prevention of AKI.
Supplementary Table 12: Evidence profile of RCTs examining anaritide vs. placebo for the treatment of AKI.
Supplementary Table 13: Summary table of RCTs examining the effect of ANP vs. placebo for the treatment of AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 3.6: Growth factor intervention

Recovery from AKI involves increased expression of various growth factors acting via autocrine, paracrine, and endocrine mechanisms. The advent of recombinant growth factors has stimulated research exploring their therapeutic potential in AKI. Experimental studies have yielded promising results with individual growth factors[246] including insulin-like growth factor-1 (IGF-1), hepatic growth factor, and, more recently, erythropoietin. The physiological basis for the use of erythropoietin in the prevention of AKI has recently been described.[247]

3.6.1: We recommend not using recombinant human (rh)IGF-1 to prevent or treat AKI. (*1B*)

RATIONALE

IGF-1 is a peptide with renal vasodilatory, mitogenic and anabolic properties. rhIGF-1 has been demonstrated to accelerate the recovery of renal function in several animal models of AKI.[248–251] Three double-blind, placebo-controlled RCTs have addressed the usefulness of IGF-1 in adults with imminent or established AKI.[252–254] Franklin *et al.*,[252] administered rhIGF-1 every 12 hours for 3 days post-operatively to 54 patients undergoing abdominal aortic surgery. While no patient developed ARF, a smaller proportion of IGF-1–treated patients showed a decline in GFR as compared to the placebo group (22% vs. 33%). Hladunewich *et al.*,[254] administered rhIGF-1 or placebo in 43 patients undergoing cadaveric renal transplantation at high risk of delayed graft function. Treatment was started within 5 hours of transplantation and continued for 6 days. On day 7, neither inulin clearance, nor urine flow or fractional sodium excretion differed between the treatment arms, nor did the nadir SCr after 6 weeks or the proportion of patients require post-transplantation dialysis. Hirschberg *et al.*,[253] treated 72 patients suffering from AKI mainly due to sepsis or hemodynamic shock with either rhIGF-1 or placebo for a mean of 10.6 days. No differences were observed with respect to changes in GFR, urine output, need for RRT, and mortality. Hence, despite its therapeutic efficacy in various animal models of ARF, rhIGF-1 largely failed to prevent or accelerate recovery from established AKI in humans. In addition, the high cost of this treatment should be mentioned.

Based on an analysis of the three RCTs with rhIGF-1 that are currently available and which were overall negative or at least equivocal, and considering that there is no benefit and the concern over potential harm and cost associated with this drug, the Work Group recommends against its use in patients with AKI.

Erythropoietin

A small pilot trial evaluated the effectiveness of erythropoietin in the prevention of AKI after elective coronary artery bypass graft.[255] Patients received either 300 U/kg of erythropoietin or saline i.v. before surgery. AKI was defined as a 50% increase in SCr levels over baseline within the first five postoperative days. Of 71 patients, 13 developed postoperative AKI: three of the 36 patients in the erythropoietin group (8%) and 10 of the 35 patients in the placebo group (29%; $P = 0.035$). The increase in postoperative SCr concentration and the decline in postoperative eGFR were significantly lower in the erythropoietin group than in the placebo group.

More recently, Endre *et al.*,[256] performed a prospective randomized trial with erythropoietin in the primary prevention of AKI in ICU patients at risk for AKI (Suppl Table 14). As a guide for choosing the patients for treatment the urinary levels of two biomarkers, the proximal tubular brush border enzymes c-glutamyl transpeptidase and alkaline phosphatase were measured. Randomization to either placebo or two doses of erythropoietin was triggered by an increase in the biomarker concentration product to levels above 46.3. The primary outcome was the relative average SCr increase from baseline over 4–7 days. The triggering biomarker concentration product selected patients with more severe illness and at greater risk of AKI, dialysis, or death; however, the urinary marker elevations were transient. The use of the biomarkers allowed randomization within an average of 3.5 hours of a positive sample. There was no difference in the incidence of erythropoietin-specific adverse events; however, there was also no difference in the primary outcome between the placebo and treatment groups.

RESEARCH RECOMMENDATION

- Recent animal studies suggest a potential clinical benefit of erythropoietin in AKI. In various rodent models of AKI, erythropoietin consistently improved functional recovery. The renoprotective action of erythropoietin may be related to pleomorphic properties including antiapoptotic and antioxidative effects, stimulation of cell

proliferation, and stem-cell mobilization.[247] Although one recent RCT in the prevention of human AKI was negative, the usefulness of erythropoietin in human AKI should be further tested in RCTs.

SUPPLEMENTARY MATERIAL

Supplementary Table 14: Summary table of RCTs examining the effect of erythropoietin vs. placebo for the prevention of AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 3.7: Adenosine receptor antagonists

The activation of tubuloglomerular feedback in response to elevated luminal chloride concentrations in the distal renal tubules is an early event in ischemic AKI. Adenosine released as part of the tubuloglomerular feedback loop binds to glomerular adenosine A1 receptor, causing vasoconstriction of the afferent arteriole, decreased renal blood flow and GFR, and sodium and water retention. This well-known role of adenosine in this phenomenon has stimulated a body of research seeking to prevent or treat AKI with adenosine receptor antagonists, primarily in three clinical syndromes with increased risk of AKI: perinatal asphyxia, radiocontrast exposure, and cardiorenal syndrome. Theophylline is a nonselective adenosine receptor antagonist.

3.7.1: We suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI. (*2B*)

RATIONALE

AKI occurs in 60% of neonates suffering from perinatal asphyxia.[257] Experimental studies indicated an important role of adenosine-mediated vasoconstriction in neonatal kidneys exposed to normocapnic hypoxemia.[258] A potential renoprotective effect of theophylline in perinatal asphyxia has been assessed in three randomized, placebo-controlled clinical trials,[259–261] including a total of 171 term neonates. Theophylline was uniformly administered in the first hour of life as a single i.v. bolus at a dose of 5 mg/kg[259,261] or 8 mg/kg.[260] The three studies all observed significantly higher GFR, higher urine output with more negative fluid balance, and lower urinary β2-microglobulin excretion, with theophylline as compared to placebo during the first 3–5 days of life. In each study, theophylline treatment was associated with a significantly reduced risk of severe renal dysfunction (17–25% vs. 55–60% in placebo group, RR 0.3–0.41). The beneficial effect was selective for kidney function, whereas the incidence of central nervous system, cardiac, pulmonary, and gastrointestinal complications was unaltered. Patient survival was not affected by treatment. In line with these studies in mature neonates, a similar improvement of GFR and urine output was observed during the first 2 days of life by administration of 1 mg/kg theophylline vs. placebo in 50 very preterm neonates with respiratory distress syndrome.[262] The further evolution of renal function was followed throughout the first year of life by Bhat *et al.*,[260] who found equally normal glomerular and tubular function in both groups from 6 weeks of age onward. Hence, while theophylline clearly improves renal function in the first week of life in postasphyctic neonates, the overall benefit from this intervention in neonatal intensive care is less evident in view of the complete long-term recovery of renal function in the placebo-treated controls and the absence of an effect on patient survival.

In recent years, the advent of selective adenosine A1 receptor antagonists has prompted the conduct of some interesting clinical trials, which to date have focused on the prevention and treatment of cardiorenal syndrome. In a double-blind placebo-controlled trial of 63 patients with CHF, single doses of the adenosine A1 antagonist BG9719 had a marked stimulatory effect on diuresis and increased GFR.[263] When coadministered with furosemide, BG9719 showed a synergistic diuretic effect and prevented the decrease in GFR associated with the loop diuretic.

Rolofylline, another adenosine A1 receptor antagonist, was tested in two double-blind placebo-controlled RCTs in patients with acute decompensated heart failure. In the first study, rolofylline or placebo was administered either concomitantly with furosemide for 3 days (146 patients), or as a single infusion in 35 diuretic resistant patients.[264] In both substudies, rolofylline improved urine output and CrCl compared to placebo. The second trial involved 301 patients hospitalized for acute heart failure with renal impairment who received either placebo or one of three doses of rolofylline for 3 days.[265] Rolofylline administration dose-dependently attenuated the rise in SCr observed in the placebo group within 14 days, and tended to reduce 60-day mortality or readmission for cardiovascular or renal causes.

Three pivotal phase III trials in a total of 2500 patients were recently completed, aiming to corroborate the renoprotective effects of rolofylline in patients with cardiorenal syndrome, and to establish drug safety. The final results of the PROTECT trial have recently been published.[266] Rolofylline, as compared to placebo, did not provide a benefit with respect to the three primary end-points: survival, heart-failure status, and changes in renal function. Persistent renal impairment developed in 15.0% of patients in the rolofylline group and in 13.7% of patients in the placebo group ($P = 0.44$). By 60 days, death or readmission for cardiovascular or renal causes had occurred in similar proportions of patients assigned to rolofylline and placebo (30.7% and 31.9%, respectively; $P = 0.86$). Adverse-event rates were similar overall; however, only patients in the rolofylline group had seizures, a known potential adverse effect of A1-receptor antagonists. Thus, rolofylline does not appear to be effective for treatment of cardiorenal AKI.

RESEARCH RECOMMENDATION

- It appears that if there are benefits of using adenosine receptor antagonists to decrease tubuloglomerular

feedback-mediated vasoconstriction and increase renal blood flow and GFR in AKI, they may be limited to very specific populations (e. g., asphyctic neonates). These benefits must be balanced against potential adverse drug effects: both renal (increased renal blood flow and distal salt delivery might harmfully increase tubular oxygen consumption in the presence of ATN), and nonrenal (lower seizure threshold). Thus, further studies are still needed to clarify the role for theophylline in neonates.

Chapter 3.8: Prevention of aminoglycoside- and amphotericin-related AKI

AMINOGLYCOSIDE NEPHROTOXICITY

Aminoglycoside antimicrobial agents are highly potent, bactericidal antibiotics effective against multiple Gram-negative, and selected Gram-positive bacterial pathogens when administered with beta-lactams and other cell-wall active antimicrobial agents.[267–269] Progressive antimicrobial resistance to other antimicrobial agents and lack of new alternatives to aminoglycoside antibiotics have caused a recent increase in their use. Aminoglycosides have many favorable attributes, including their remarkable stability, predictable pharmacokinetics, low incidence of immunologically mediated side-effects, and lack of hematologic or hepatic toxicity. Nephrotoxicity, and to a lesser degree ototoxicity and neuromuscular blockade, continue to be the major dose-limiting toxicities of the aminoglycosides. Careful dosing and therapeutic drug monitoring of aminoglycosides using pharmacokinetic and pharmacodynamic principles can mitigate the risk of AKI with these clinically useful, yet nephrotoxic antibiotics.[270] A number of meta-analyses and treatment guidelines have been published recently indicating that the risk of AKI attributable to aminoglycosides is sufficiently frequent that they should no longer be added to other standard antimicrobial agents for the empirical or directed treatment of a number of severe Gram-positive or Gram-negative bacterial infections.[271–276] The intrinsic risk of AKI with the administration of aminoglycosides has led some authors to call for elimination of aminoglycosides as a therapeutic option in current clinical management of infectious diseases.[277] The anticipated demise of aminoglycosides from our therapeutic armamentarium has not occurred, however, in light of recent developments with progressive antimicrobial resistance to beta-lactams, quinolones, and a number of other classes of antimicrobial agents.

3.8.1: We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (*2A*)

RATIONALE

Aminoglycosides exhibit a number of favorable pharmacokinetic and pharmacodynamic advantages, but a major dose-limiting toxicity of the aminoglycosides remains the risk of drug-induced AKI.[270] The risk of AKI attributable to aminoglycosides is sufficiently high (up to 25% in some series, depending upon the definition of AKI used and the population studied)[271–276,278] that they should no longer be used for standard empirical or directed treatment, unless no other suitable alternatives exist. The intrinsic risk of AKI with the administration of aminoglycosides has led some authors to recommend the elimination of aminoglycosides as a clinical treatment option.[277] Certainly their use should be restricted to treat severe infections where aminoglycosides are the best, or only, therapeutic option.

Aminoglycosides should be used for as short a period of time as possible. Repeated administration of aminoglycosides over several days or weeks can result in accumulation of aminoglycosides within the renal interstitium and within the tubular epithelial cells.[279] This can result in a higher incidence of nephrotoxicity with repeated exposure to aminoglycosides over time. Older patients (>65 years), patients with pre-existing renal dysfunction, and septic patients with intravascular volume depletion and rapid alterations in fluid dynamics may be at greater risk for aminoglycoside nephrotoxicity. Other risk factors for aminoglycoside-induced AKI are diabetes mellitus, concomitant use of other nephrotoxic drugs, prolonged use, excessive blood levels, or repeated exposure to separate courses of aminoglycoside therapy over a short time interval.[267–279]

3.8.2: We suggest that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single dose daily rather than multiple-dose daily treatment regimens. (*2B*)

RATIONALE

Aminoglycoside demonstrates concentration-dependent bactericidal activity, with a prolonged "postantibiotic effect", thereby permitting extended interval dosing in an effort to optimize efficacy and minimize toxicity. This dosing strategy and a number of other measures to limit aminoglycoside uptake in renal tubular cells, prevent apoptosis, limit oxygen injury, and protect mitochondrial function have all been recommended to minimize the risk of AKI and preserve the therapeutic value of these important antimicrobial agents.[280–296] Single-dose daily or extended-interval dosing of aminoglycosides offer a number of theoretical and practical advantages to maintain antimicrobial activity while limiting possible nephrotoxicity. This convenient and inexpensive aminoglycoside dosing strategy has been widely adopted at many centers when using this potentially toxic, yet highly effective, class of antibiotics.

When feasible in patients with normal and stable kidney function, once-daily (often referred to as extended-interval) dosing of aminoglycosides should be used to limit aminoglycoside nephrotoxicity. The pharmacokinetic and pharmacodynamic properties of aminoglycosides favor high dosing strategies with extended intervals between doses. The key therapeutic parameter for efficacy is peak blood level divided by minimum inhibitory concentration (MIC) of the infecting organism (C_{max}/MIC) in an effort to obtain >10-fold C_{max}/MIC. Aminoglycosides induce a prolonged postantibiotic effect (inhibition of bacterial growth after blood levels have fallen below the MIC of the organism). The length of the postantibiotic effect is directly related to the peak blood levels. These pharmacokinetic/pharmacodynamic parameters make single-dose daily strategies an attractive option when using aminoglycosides.

The nephrotoxicity of aminoglycosides has been very well studied[280–282,284–293,295,296] and is primarily related to uptake of aminoglycosides through a receptor known as megalin, expressed on epithelial cells along the proximal convoluted tubule.[293] Aminoglycosides are concentrated in the proximal convoluted tubules, where they bind avidly to polyanionic, phospholipid-containing membranes. Aminoglycosides induce myeloid body formation, impair protein synthesis, degrade mitochondrial function, and culminate in apoptosis and eventual necrosis of renal tubular epithelial cells. Direct glomerular injury can occur[288] but is usually a secondary consequence of aminoglycoside-induced tubular impairment. As the receptor uptake of aminoglycosides is saturable, high-level intermittent doses of aminoglycosides actually reduced the daily uptake and accumulation of aminoglycosides when compared to multiple-daily dosing strategies. This should limit the risk of nephrotoxicity, at least in principle.

The potential efficacy of single-dose daily regimens (or other extended dosing treatment programs) of aminoglycosides vs. multiple-daily dosing strategies has been extensively studied in numerous controlled and uncontrolled clinical studies over many years[297–308], and the subject has been the focus of a number of formal meta-analyses.[309–314] These investigations include pediatric populations, elderly populations, empirical therapy, targeted therapy, treatment directed towards Gram-negative bacterial pathogens and Gram-positive bacterial pathogens.

The cumulative results of this evidence-based review and numerous meta-analyses indicate that once-daily dosing strategies generally tend to result in less AKI when compared to multiple-dose dosing strategies, although the benefit accrued by the single-daily dose strategy is modest and inconsistent across a number of these studies. For this reason, a level 2 recommendation is suggested in support of the use of single-daily dose strategies over multiple-dose daily strategies. It should be noted that multiple-daily dosing strategies continue to be the standard of care for enterococcal endocarditis; no detailed, randomized trials have been reported comparing single-daily vs. multiple-daily regimens for enterococcal endocarditis.[272,315–317]

The use of single-daily dosing of aminoglycosides is generally well-tolerated but bolus infusions of aminoglycosides should be avoided. The high-dose, once-daily aminoglycoside regimens should be administered over 60 minutes to avoid untoward events such as neuromuscular blockade. This recommendation is particularly important when patients are receiving other potential neuromuscular blocking agents, or have underlying disorders affecting neuromuscular transmission (e.g., myasthenia gravis).

3.8.3: We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 hours. (*1A*)

RATIONALE

Therapeutic drug monitoring has been the standard of care when administering aminoglycosides for many years. Aminoglycoside levels are variable among individuals, and subtle changes in the volume distribution, renal blood flow, and filtration rate can affect renal handling of aminoglycosides and alter the risk of nephrotoxicity. For these reasons, therapeutic drug monitoring, in combination with or independent from, single-dose daily treatment regimens is recommended.[318–321] When using therapeutic drug monitoring in single-dose or extended-dose treatment strategies, the C_{max} should be at least 10-fold greater than the MIC of the infecting microorganism. This C_{min} (trough level) should be undetectable by 18–24 hours to limit accumulation of aminoglycosides in renal tubular cells and to minimize the risk of AKI. The usual dosing strategy for once-daily aminoglycosides is 5 mg/kg/d for gentamicin and tobramycin (with normal renal function); 6 mg/kg/d for netilmicin; and 15 mg/kg/d for amikacin. The multiple-dose daily regimen for gentamicin and tobramycin is usually 1.7 mg/kg every 8 hours with peak blood levels at 8 ± 2 μg/ml (17 ± 4 μmol/l) and trough of 1–2 μg/ml (2–4 μmol/l). Amikacin levels with the multiple-dose daily dosing strategy should be a peak of 20 ± 5 μg/ml (34 ± 9 μmol/l) and a trough of 5–8 μg/ml (9–14 μmol/l). We recommend therapeutic drug monitoring when using prolonged courses of aminoglycosides to limit the risk of nephrotoxicity when using multiple-daily dosing, and suggest therapeutic drug monitoring when using single-daily dosing strategies.

3.8.4: We suggest monitoring aminoglycoside drug levels when treatment with single-daily dosing is used for more than 48 hours. (*2C*)

RATIONALE

The timing of measurement of peak doses of aminoglycosides with single-daily dosing strategies is not standardized and remains somewhat controversial. Some investigators do not measure therapeutic drug levels at all in patients receiving this dosing strategy. Others recommend at least a single peak measurement to ensure that the blood levels are 10-fold

greater than the MIC of the infecting organism. Many investigators recommend at least one or at least a weekly C_{min} level obtained at either 12, 18, or 24 hours after the aminoglycoside dose.[267–270] The C_{min} level should be below the limits of detection of the assay ($<1\,\mu g/ml$) at these time intervals.

Measuring aminoglycoside levels with multiple-daily dosing strategies have been standardized for C_{max} to be obtained 30 minutes after a 30-minute infusion, and C_{min} right before the next dose for trough levels. The aminoglycosides should be administered in patients who are volume-replete; volume depletion increases the risk of nephrotoxicity in experimental studies and is suggested in clinical studies. Additionally, potassium repletion has been shown experimentally and clinically to diminish the risk of AKI related to aminoglycoside administration.

Single-dose daily regimens are difficult to apply in patients with pre-existing kidney disease, and patients with vacillating eGFR and hemodynamics, such as critically ill patients in the ICU setting. The changing pharmacokinetics and pharmacodynamics of antibiotics in general and aminoglycosides in particular, in the critically ill patient, are such that the avoidance of single-daily dosing and application of frequent therapeutic drug monitoring is indicated.[322]

3.8.5: We suggest using topical or local applications of aminoglycosides (e.g., respiratory aerosols, instilled antibiotic beads), rather than i.v. application, when feasible and suitable. (*2B*)

RATIONALE

Local instillation of aminoglycosides for a variety of indications is gaining more widespread use in a selected set of clinical situations where aminoglycoside levels can be concentrated at specific tissue sites. The use of aminoglycoside-loaded beads for the prevention and treatment of bone and joint infections have become commonplace as a strategy to limit nephrotoxicity, while providing antimicrobial activity of aminoglycosides at the tissue level.[323] Local concentrations of aminoglycoside are achieved for prolonged periods when administered by this route. Aminoglycoside aerosol delivery systems are now in use to provide high intrapulmonary antibiotic levels with minimal systemic and kidney concentrations of the antibiotic. This strategy has been used successfully in cystic fibrosis patients for the management of difficult-to-treat Gram-negative bacillary pneumonia.[324,325] However, significant nephrotoxicity with the use of inhaled tobramycin has been described in at least two cases.[326,327]

RESEARCH RECOMMENDATIONS

- No standard method exists for therapeutic drug monitoring of aminoglycosides by single daily dosing. Uniform guidance, based upon carefully performed pharmacokinetic/pharmacodynamic studies on the optimal timing and method of therapeutic drug monitoring with single-daily dosing regimens, would be of great assistance.[319]
- It is generally recommended that patients receiving extended-dosing interval aminoglycosides should have aminoglycosides administered at even greater dosing intervals if mild or moderate degrees of underlying renal impairment exist. Optimal therapeutic monitoring in the setting of infrequent dosing intervals for patients with underlying CKD needs to be standardized and uniform recommendations need to be provided by careful pharmacokinetic/pharmacodynamic observational studies.
- The impact of IHD and high-flux CRRT upon the efficacy and toxicity of extended-duration dosing of aminoglycosides needs further study. As membranes with greater sieving coefficients come into greater use, the impact on aminoglycoside elimination needs to be carefully considered. This could be investigated by RCTs using standard dosing intervals vs. individualized dosing regimens, with frequent drug-level monitoring and the use of efficacy measures and kidney injury markers as outcomes.
- The interaction between aminoglycosides and other antimicrobial agents, and other therapeutic agents with nephrotoxic potential needs to be more carefully quantified. The degree of aminoglycoside-induced nephrotoxicity alone vs. combination effects with such drugs as vancomycin, amphotericin B, cephalosporins, extended-spectrum penicillins, colistin, loop diuretics, clindamycin, cisplatin, and nonsteroidal anti-inflammatory agents needs to be more carefully examined in observational studies.

AMPHOTERICIN B NEPHROTOXICITY

Amphotericin B has been the standard of treatment for life-threatening systemic mycoses for over 50 years. This polyene antifungal agent is insoluble in water and needs to be solubilized with deoxycholate and given i.v. in the absence of electrolyte solutions to maintain solubility. Despite its broad-spectrum fungicidal activity against a large number of invasive systemic mycoses, drug-induced nephrotoxicity is common and remains the principal dose-limiting toxicity of amphotericin B.[328–330] Amphotericin B has numerous other significant toxicities, including thrombophlebitis, electrolyte disturbances, hypoplastic anemia, and systemic toxicity associated with fever, chills, hypotension, and cytokine release.[331,332] AKI related to amphotericin B is clinically significant and is associated with higher mortality rates, increased LOS, and increased total costs of health care when managing patients with systemic fungal infection.[328,330]

Over the past two decades, three major advances in antifungal therapy have become clinically available: i) the lipid formulations of amphotericin B; ii) the introduction of the echinocandin class of antifungal agents; and iii) an expanding number of azoles with extended activity against a variety of fungal pathogens. Therapeutic alternatives to

amphotericin B have been a welcome addition in the management of systemic mycoses and selected, protozoan, parasitic infections, but their incremental costs and tradeoffs in spectrum of activity against fungal pathogens need to be considered, in addition to their favorable toxicity profiles and reduced potential for nephrotoxicity. A number of therapeutic options are now available to the clinician when deciding upon the choice for empiric or directed antifungal therapy. Avoidance of risk of nephrotoxicity is one of the major, but not the only, determinants when selecting antifungal therapy at present.

3.8.6: We suggest using lipid formulations of amphotericin B rather than conventional formulations of amphotericin B. *(2A)*

RATIONALE

The broad-spectrum, polyene, antifungal agent amphotericin B deoxycholate has been the mainstay of treatment for systemic mycoses for decades. Despite its well-known toxicity profile, the potent antifungal activity of amphotericin B, in addition to its activity against certain protozoan parasites (*Plasmodium* spp., *Leishmania* spp., *Naegleria* spp.), indicates that this therapy will remain a standard agent in clinical medicine for the foreseeable future.

Amphotericin B–induced nephrotoxicity is related to multiple mechanisms, including ischemic injury and direct tubular- and glomerular-cell membrane toxicity. Amphotericin causes vasoconstriction of the afferent renal arteriole along with a systemic inflammatory response that may reduce renal blood flow. Amphotericin B also directly inserts into human cellular membranes, where it disrupts membrane permeability and physiology.[331,332] Tubular epithelial cells residing in the deep medullary regions of the kidney are particularly susceptible to injury where considerable osmotic stress exists across cell membranes even under physiologic conditions. The end result is enzymuria, loss of renal tubular concentrating ability, renal tubular acidosis, increasing urinary losses of potassium and magnesium, and decreased glomerular function, resulting in azotemia and decreased synthesis of erythropoietin. Amphotericin B–induced nephrotoxicity is often accompanied by concomitant administration of other potentially nephrotoxic agents such as cyclosporine A, aminoglycosides, chemotherapeutic agents, and a number of other potentially nephrotoxic agents.[328,329,333]

Considerable efforts have been undertaken to try to limit nephrotoxicity and permit the continued use of amphotericin B deoxycholate for the management of systemic mycoses. Simple maneuvers, such as salt repletion and provision of adequate amounts of potassium, are beneficial in animal models in the prevention of amphotericin B nephrotoxicity. These measures have a mixed record in clinical practice, and their capacity to prevent AKI when treating severe fungal infections remain unclear. The relative ease and simple logic of volume repletion and potassium supplementation during amphotericin B therapy supports their routine use, despite the relative lack of compelling clinical evidence to recommend these maneuvers.

Various dosing strategies have also been instituted in an attempt to limit amphotericin B–induced nephrotoxicity. One strategy is to give amphotericin B as a continuous infusion rather than a 2- to 4-hour infusion to limit nephrotoxicity.[329,334] While there is some suggestion that a continuous infusion may limit nephrotoxicity, enthusiasm for this strategy is tempered by the potential loss of some antifungal activity. Amphotericin B exhibits concentration-dependent antifungal activity, and continuous infusion of low-doses of amphotericin B could result in suboptimal protection for some patients with invasive fungal infections.[334]

Another common strategy is the administration of alternate-day doses of amphotericin B, rather than daily doses.[335,336] This strategy is better tolerated and might reduce nephrotoxicity without sacrificing efficacy in stable patients. However, clear evidence that this strategy reduces nephrotoxicity is not supported by large, adequately controlled clinical trials as yet.

One of the major innovations in amphotericin B therapy over the last 15 years has been the introduction of lipid formulations of amphotericin to limit the problem of nephrotoxicity associated with conventional amphotericin B deoxycholate. Three lipid formulations are available including: amphotericin B colloidal dispersion, amphotericin B lipid complex, and liposomal amphotericin B. Amphotericin B colloidal dispersion is formulated by amphotericin B complexed with cholesteryl sulfate. Amphotericin B lipid complex is composed of amphotericin B complexed with dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol. Liposomal amphotericin consists of amphotericin B complexed with hydrogenated soy phosphatidylcholine, distearoylphosphatidylcholine, and cholesterol.[337–340] Other formulations that might further reduce the risk of AKI from amphotericin B include nanoparticle packaging in micelles with polyaspartic acid.[340]

The safety and efficacy (in incidence of nephrotoxicity) of lipid formulations of amphotericin have been studied in numerous experimental and clinical trials with conventional amphotericin B deoxycholate as the comparator.[337–339,341–350] A detailed analysis of these various trials, and a number of meta-analyses that have analyzed this clinical question, concluded that the lipid formulations are less nephrotoxic than amphotericin B deoxycholate.[344,346] When feasible, we recommend that lipid formulations supplant the use of conventional amphotericin B deoxycholate to reduce the risk of nephrotoxicity.

The incremental costs associated with the lipid formulations and their relative efficacy for systemic mycoses remains the subject of considerable debate. The existing evidence would suggest that the overall risk-benefit ratio and cost-effectiveness with these lipid formulations is essentially

cost-neutral with amphotericin B deoxycholate.[337,339] Attempts to increase the doses of lipid formulations of amphotericin further to improve efficacy have resulted in mixed results and are not recommended at present.[342,343]

Lipid formulations of amphotericin are less nephrotoxic but require different dosing strategies (three- to five-fold higher doses than deoxycholate formulations of amphotericin B). Some of these agents continue to induce general systemic toxicity reactions similar to those observed with the deoxycholate formulation (e.g., amphotericin B colloidal dispersion).

3.8.7: In the treatment of systemic mycoses or parasitic infections, we recommend using azole antifungal agents and/or the echinocandins rather than conventional amphotericin B, if equal therapeutic efficacy can be assumed. (*1A*)

RATIONALE

Another approach to prevent amphotericin B nephrotoxicity is to avoid polyene antifungal agents entirely and use alternative agents, such as the azoles and echinocandins.[351–355] Azole antifungal agents inhibit sterol synthesis in fungal cell membranes by blocking the activity of the 14-demethylase enzyme essential for ergosterol synthesis. Nephrotoxicity is an unusual event following the use of azole compounds. The echinocandins are beta-glucan inhibitors that interfere with cell-wall synthesis of fungal elements, and have an entirely different mechanism of action from that of amphotericin B. Both the azole compounds (voriconazole, fluconazole, itraconazole, and posaconazole) and the echinocandins (caspofungin, anidulafungin, and micafungin) compare favorably to amphotericin B with respect to their efficacy against a variety of the systemic mycoses. Both classes of antifungal agents have the advantage of lacking the intrinsic nephrotoxicity associated with amphotericin B deoxycholate. Both the azole compounds and echinocandins have proven to be less nephrotoxic than conventional amphotericin B deoxycholate in observational studies, historical control studies, and in small comparative trials.[355]

An important consideration in using these antifungal agents is their relative efficacy with respect to the likely pathogen that is targeted for treatment. *Candida krusei* is intrinsically resistant to the azoles and *Candida parapsilosis* is frequently resistant to the echinocandins. Amphotericin B-resistant strains of selected *Aspergillus* spp. and *Pseudallescheria boydii* are well described and require alternative therapies.

There is currently insufficient evidence as to whether the echinocandins, the azoles, or the lipid formulations of amphotericin B differ significantly from each other with respect to the risk of nephrotoxicity. No adequately controlled, large, randomized studies have been reported to date comparing the relative risk of nephrotoxicity amphotericin B lipid formulations with either azole or echinocandin antifungal agents. Such studies face the difficulty of recruiting sufficient numbers of patients with similar baseline risk for drug-induced AKI, and with a balance of exposure to other potentially nephrotoxic agents. Until such time as these studies are completed, no evidence-based recommendations can be given about the relative risk of AKI attributable directly to these antifungal agents.

RESEARCH RECOMMENDATIONS

- Some studies indicate that the liposomal form of amphotericin B is less nephrotoxic than amphotericin B lipid complex or amphotericin B colloidal dispersion. RCTs in patients with systemic mycosis, with the rate of AKI as a primary or secondary end-point, should be conducted to answer this question.
- Innovative strategies to formulate amphotericin B in microvesicles, nanoparticles, or micelles should be undertaken to limit nephrotoxicity in treating fungal infections. Clinical trials should compare existing formulations to these novel formulations, and could generate cost-effective, yet non-nephrotoxic derivatives of amphotericin B.
- Carefully selected combinations of antifungal therapies to enhance efficacy and shorten duration of therapy may limit toxicity and reduce costs in the treatment of fungal infections. Investigations need to be carried out in the laboratory and in clinical studies to improve the care of patients with severe fungal infections. The costs and complication rates of AKI, and other toxicities of short-course combination treatment, should be compared to standard dosing regimens of antifungal therapy.
- Markers of early nephrotoxicity and mechanisms to avoid nephrotoxicity with amphotericin B formulations need to be studied further in clinical investigations. These antifungal agents are given for prolonged periods, and should allow ample opportunity to test the validity of novel biomarkers of drug-induced nephrotoxicity. A group monitored with novel AKI biomarkers should be compared to conventional monitoring of AKI, to determine if one or more early biomarkers of kidney injury add to standard clinical care in the prevention of drug-induced AKI.

Chapter 3.9: Other methods of prevention of AKI in the critically ill

ON-PUMP VS. OFF-PUMP CORONARY ARTERY BYPASS SURGERY

The type of cardiac surgery is important in the discussion on risk for kidney problems associated with this surgery. Valvular procedures or aorta surgery are associated with a higher risk. One of the most controversial risk factors is on-pump vs. off-pump coronary artery bypass surgery. Off-pump coronary artery bypass obviously removes the bypass circuit but can be associated with greater hemodynamic instability secondary to ventricular compression as the heart is manipulated to access the coronary arteries.[356] It is possible, with standard operative techniques, to perform coronary artery bypass surgery (but not valve surgery) without using cardiopulmonary bypass. This technique is known as "off-pump" coronary artery bypass surgery.

It has been hypothesized that preservation of physiologic renal perfusion by avoidance of cardiopulmonary bypass would partially nullify the risk of AKI in patients receiving coronary artery bypass surgery. Potential benefits that have been posited for off-pump coronary artery bypass (compared to on-pump procedures) are reduced mortality, reduction of AKI risk (and in particular, acute dialysis, which is associated with a perioperative mortality of 42% in the Society of Thoracic Surgeons database), reduced risk of cerebral dysfunction (due to stroke and neurocognitive dysfunction, the latter sometimes referred to as "pump head"), reduction in ICU stay and days in hospital, and reduction in atrial fibrillation. As in other areas covered by these guidelines only mortality, risk for RRT, and AKI risk are addressed as end-point measures. It must, however, be remembered that the potential benefits of off-pump coronary artery bypass might be predominantly outside these areas of focus.

3.9.1: We suggest that off-pump coronary artery bypass graft surgery not be selected solely for the purpose of reducing perioperative AKI or need for RRT. (*2C*)

RATIONALE

As detailed in Suppl Tables 15 and 16, which summarize RCTs, the balance of the potential benefit and harms is uncertain and the quality of the evidence is weak, that off-pump surgery is associated with better outcomes of the three end-points used in these guidelines: incidence of AKI, need for RRT, or mortality.

A recent good-quality RCT[357] was performed in 2203 patients (only $\sim$8% of patients with SCr $>$1.5 mg/dl [$>$133 μmol/l]) (Suppl Table 16). There was no significant difference between off-pump and on-pump coronary artery bypass graft in the rate of the 30-day composite outcome. The rate of the 1-year composite outcome was higher for off-pump than for on-pump coronary artery bypass graft. Follow-up angiograms in the majority of the patients revealed that the overall rate of graft patency was lower in the off-pump group than in the on-pump group (82.6% vs. 87.8%, $P<0.01$).

A comprehensive meta-analysis including RCTs, and abstracts from the proceedings of scientific meetings through February 2010, was recently published.[358] AKI was defined by a mixture of criteria, including biochemical parameter, urine output, and dialysis requirement. Mortality was evaluated among the studies that reported kidney-related outcomes. This analysis compared off-pump with the more traditional on-pump technique. Off-pump coronary artery bypass graft was associated with a statistically significant 40% lower odds of postoperative AKI and a nonsignificant 33% lower odds for dialysis requirement. Within the selected trials, off-pump coronary artery bypass graft surgery was not associated with a significant decrease in mortality. It is apparent from this meta-analysis that the trials were clinically heterogeneous, particularly in regards to their definitions of kidney outcomes, and mostly were of poor to fair quality (based on the Jadad score). The very low event rates (often 0–1 patients) make the estimates suspect and highly imprecise. There is also a question of publication bias. There are several large trials in progress that are likely to generate more definitive data. In chronic dialysis patients, there are observational US Renal Data Systems data to weakly support the use of off-pump technique (slightly lower mortality). However, with any technical advance that is introduced in certain centers, institutional familiarity with the technique, operator experience, and characteristics of the population referred to the center are likely to be important modulators of outcomes. In conclusion, based on the analysis of the RCTs and the recent meta-analysis, the Work Group found that there was not enough evidence to recommend off-pump coronary artery bypass for reducing AKI or the need for RRT.

RESEARCH RECOMMENDATION

- Further studies are needed to clarify the role of off-pump coronary artery bypass in patients with increased risk for AKI.

N-ACETYLCYSTEINE (NAC)

3.9.2: We suggest not using NAC to prevent AKI in critically ill patients with hypotension. (*2D*)

RATIONALE

NAC has been most frequently applied in the prevention of CI-AKI, and this topic is discussed in more detail in Chapter 4.4.

NAC is a modified form of L-cysteine, an amino acid that is a precursor to reduced glutathione that can regenerate glutathione stores. It is known to be a potent antioxidant that scavenges oxygen-free radicals in the body. It also has vasodilatory properties derived from enhanced nitric oxide availability.[359] NAC has been shown to attenuate ischemic and nephrotoxic ARF in a number of animal studies,[360–363] and the pharmacological characteristics of NAC that could play a role in the prevention of AKI have recently been summarized.[364] NAC undergoes extensive first-pass metabolization in the gastric mucosa and liver. This results in a very low oral bioavailability, with substantial intrapatient variability (3–20%), as well as inconsistency between available oral products. The plasma half-life of acetylcysteine after i.v. injection is approximately 6–40 minutes, and there is extensive binding to plasma and tissue proteins through the sulfhydryl group. Virtually no acetylcysteine can be detected in the systemic circulation after i.v. or oral administration, suggesting that any potential therapeutic benefit must be due to secondary effects such as the induction of glutathione synthesis, rather than due to direct effects. As these secondary effects are not directly measurable, the determination of the optimal dosage schedule has been necessarily empirical.[365]

A particularly important problem with NAC is whether it can alter SCr independent of a change in GFR. NAC has been reported to decrease SCr levels in subjects with normal kidney function. This reduction in SCr was not accompanied by a change in serum cystatin C levels. This suggests an effect independent of a change in GFR, such as an increase in tubular secretion of creatinine or a decrease in creatinine production.[366] By contrast, *in vitro* analysis on the effect of NAC on SCr[367] showed no analytical interference with the measurement of SCr by any of the commonly used analytical methods. Haase *et al.*,[368] studied 30 patients with normal kidney function who received i.v. NAC for 24 hours in association with cardiac surgery. No change in the ratio of SCr to cystatin C, compared to baseline values, was observed at the end of the 24-hour infusion or 48 hours after the cessation of the infusion. In addition, there was no effect on urinary creatinine excretion during the infusion. However, in clinical practice, NAC is generally recommended for patients with CKD, with an eGFR <60 ml/min per 1.73 m^2. Mainra *et al.*,[369] observed no change in SCr or cystatin C at 4, 24, or 48 hours after administration of a single 600-mg dose of NAC to 30 patients with CKD Stage 3. Finally, Rehman *et al.*,[370] tested the potentially confounding effect of NAC in a CKD population (Stages 3–5) following doses of NAC currently recommended for prophylaxis of AKI. There was no effect of NAC on either SCr or cystatin C levels.

It is thus safe to conclude that NAC, in doses currently recommended for prophylaxis of AKI, has—by itself—no effect on SCr or cystatin C levels. In addition, NAC is inexpensive and appears to be safe, although it may have some detrimental effects on myocardial and coagulation function.[371–373] The "safety" of NAC should further be amended, particularly when high i.v. doses are used, as in some of the RCTs in CI-AKI. When prospectively studied in acetaminophen poisoning, i.v. NAC produced anaphylactoid reactions in up to 48% of participants.[374] Although most of these reactions were mild, at least one death has been reported in a patient with asthma.[375] It should also be noted that the doses of acetaminophen used are still much higher than in the "high doses" used, particularly in AKI trials. Besides the prevention of CI-AKI, NAC has also been tested in the setting of cardiothoracic surgery and liver transplantation, and in hypotensive critically ill patients.

NAC IN CRITICALLY ILL PATIENTS

3.9.3: We recommend not using oral or i.v. NAC for prevention of postsurgical AKI. (*1A*)

RATIONALE

The above recommendation is based on an evaluation of the available literature on prevention studies with NAC in cardiovascular and abdominal vascular surgery, and liver transplantation.

The tables summarize the RCTs where either oral or i.v. NAC was compared to placebo; only studies containing a minimum of 50 patients in each study arm have been included. In addition, a recent meta-analysis is available,[376] containing 10 studies involving a total of 1193 adult patients undergoing major surgery. Seven studies (1003 patients) evaluated the effects of NAC in patients undergoing cardiac surgery, and three of these (508 patients) exclusively studied patients with pre-existing renal impairment. Two studies (111 patients) evaluated the effects of NAC on patients undergoing abdominal aneurysm repair surgery and one study (79 patients) was of patients undergoing major abdominal cancer surgery. End-points in most of the studies were mortality, need for RRT, or varying increases in postoperative SCr concentrations compared to preoperative SCr values.

Suppl Tables 17 and 18 summarize the five studies where NAC was compared to placebo in patients undergoing cardiac surgery and who were not exposed to radiocontrast media.[377–381] All five studies analyzed the effects of NAC in patients with moderate, pre-existing renal functional impairment. Surgery included elective or emergency coronary artery bypass graft operations or heart valve surgery. NAC was given

i.v. in most of the studies; mortality was evaluated at different follow-up times; either in-hospital or at 30 or 90 days. Only one study found a significantly lower mortality at 30 days.[377] None of the studies found either a difference in need for RRT, or in AKI defined as variable changes in SCr after surgery. All studies were of A-level quality. Two relatively small studies evaluated the effects of NAC on patients undergoing abdominal aneurysm repair surgery[382,383] and did not find any protective effect on renal function.

Further, one meta-analysis[376] did not find evidence that NAC used perioperatively can alter mortality or renal outcomes after major cardiovascular or abdominal cancer surgery when radiocontrast agents are not used. In none of the studies were significant treatment-related adverse effects of NAC reported. These reports suggest that NAC, in the context of cardiovascular surgery, is not associated with increased risk of mortality, surgical re-exploration, or allogeneic transfusion.

Only one single study has compared NAC to placebo in critically ill patients (Suppl Table 18).[384] One hundred and forty-two ICU patients with new-onset (within 12 hours) of at least $\geqslant 30$ consecutive minutes of hypotension and/or vasopressor requirement were randomized to receive either oral NAC or placebo for 7 days, in addition to standard supportive therapy. AKI was defined as $\geqslant 0.5$ mg/dl ($\geqslant 44$ μmol/l) increase in SCr. Patients who received NAC had an incidence of AKI of 15.5%, compared to 16.9% in those receiving placebo (NS). There were no significant differences between treatment arms in any of the secondary outcomes examined, including incidence of a 50% increase in SCr, maximal rise in creatinine, recovery of renal function, length of ICU and hospital stay, and requirement for RRT. Mortality in both arms was 10%. Based on this single study, which is underpowered but did not show any beneficial effect on incidence of AKI, need for RRT, or patient mortality, we suggest not using NAC to prevent AKI in critically ill patients with hypotension.

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SUPPLEMENTARY MATERIAL

Supplementary Table 15: Evidence profile of RCT examining on vs. off pump cardiothoracic surgery.
Supplementary Table 16: Summary table of RCTs examining the effect of on vs. off pump CABG for the prevention of AKI.
Supplementary Table 17: Evidence profile of RCTs examining NAC vs. placebo in the prevention of AKI.
Supplementary Table 18: Summary table of RCTs examining the effect of NAC vs. placebo in the prevention of AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Section 4: Contrast-induced AKI

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Chapter 4.1: Contrast-induced AKI: definition, epidemiology, and prognosis

BACKGROUND

Contrast-related acute kidney problems are frequent and occur in both ambulatory and hospitalized patients. Since there is accumulating evidence that many risk factors, preventive measures, and the immediate and long-term prognosis of these problems are common to the other causes of AKI, the Work Group believes that there is a need for a unifying definition for all forms of AKI and therefore proposes that the term contrast-induced acute kidney injury (CI-AKI) be used for patients developing AKI secondary to intravascular radiocontrast media exposure.

The literature on CI-AKI is predominantly related to AKI following iodinated contrast-media administration. As will be discussed in Appendix E, non–iodine contrast media—notably Gd-containing contrast media—may also occasionally induce AKI.

4.1: Define and stage AKI after administration of intravascular contrast media as per Recommendations 2.1.1–2.1.2. (*Not Graded*)

4.1.1: In individuals who develop changes in kidney function after administration of intravascular contrast media, evaluate for CI-AKI as well as for other possible causes of AKI. (*Not Graded*)

RATIONALE

Pending the validation of future biomarkers which would allow a more straightforward comparison and integration of CI-AKI in the overall framework of AKI, we suggest that the same criteria, using the changes in SCr concentrations and urine output be used as for the other forms of AKI. The Work Group is not aware of any pathophysiological or epidemiological reason why the definition and staging of CI-AKI should be different from the RIFLE/AKIN criteria. It should, however, be stressed that for the development of this guideline, the term contrast-induced nephropathy is widely used in the literature and usually defined as a rise in SCr of $\geqslant$0.5 mg/dl ($\geqslant$44 μmol/l) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure. This definition also consistently predicted major adverse cardiovascular events after percutaneous coronary intervention.[385] The Society of Urogenital Radiology used the same definition, but the creatinine changes were said to occur within 3 days after intravascular administration of contrast media without an alternative etiology.[386] It should be recognized that, in a minority of cases, the peak increase of SCr may occur up until 5 days after contrast exposure. However, a recent prospective study[387] showed that the percentage change of SCr 12 h after contrast vs. the basal value was the best predictor of CI-AKI ($P<0.001$). A 5% increase of its value yielded 75% sensitivity and 72% specificity, with an area under the curve (AUC) of 0.80 and an OR of 7.37 (95% CI 3.34–16.23) for early detection. Furthermore, this 12-hour basal value strongly correlated with the development of renal impairment at 30 days ($P=0.002$; sensitivity 87%, specificity 70%; AUC 0.85; OR 13.29; 95% CI 2.91–60.64).

It has been shown that substantial variation in SCr may occur from day to day in hospitalized patients who do not receive contrast-media injections.[388] Depending on the threshold criterion for CI-AKI chosen, this variation can lead to rates of 6–35% of inpatients, not exposed to contrast media, who would be labeled as having CI-AKI had they received contrast media. The exact cause of this "hospital-induced nephropathy"[389] is not known, but other studies have shown that AKI (various etiologies) is common in hospitalized patients.

The magnitude of the impact of the "background fluctuation of kidney function" in patients receiving iodinated contrast has not been prospectively studied, but a recent retrospective study compared the incidence of AKI among patients undergoing enhanced computed tomography (CT) with i.v. low-osmolar (iohexol) or iso-osmolar (iodixanol) contrast media to the AKI incidence among patients undergoing CT without contrast-media administration.[390] The incidence of AKI (defined as an increase of SCr of 0.5 mg/dl [44 μmol/l] or a $\geqslant$25% decrease in eGFR within 3 days after CT) was similar in all three groups (two receiving contrast agents and one not) up to a baseline SCr level of 1.8 mg/dl (159 μmol/l). A high incidence of "AKI" among control subjects undergoing noncontrast CT was thus identified. Given the results of this retrospective study, it is clear that AKI after i.v. administration

of iodine contrast media cannot be automatically attributed to the contrast agent, but may, in fact, reflect AKI from other causes, such as worsening underlying disease or drug toxicity. Therefore, the Work Group strongly recommends that individuals showing increases of SCr compatible with the definition of AKI after administration of intravascular contrast media be also evaluated for other possible causes of AKI.

In a study using cystatin C as an early marker for AKI, a cut-off cystatin C increase concentration of $\geqslant 10\%$ at 24 hours after contrast-media exposure was detected in 87 patients (21.2%), and was the best cut-off value for the early identification of patients at risk for CI-AKI with a negative predictive value of 100% and a positive predictive value of 39%. As in other cases of AKI, it appears that, in patients with CKD, cystatin C may be a useful marker for the early diagnosis of CI-AKI.

Epidemiology of CI-AKI

Keeping the above-mentioned problems of definition in mind, it is not surprising that the reported incidence of CI-AKI varies widely across the literature, depending on the definitions used, the patient population, and the baseline risk factors.

The. impact of different definitions on the incidence of CI-AKI can be illustrated by the recent results of the Oxilan Registry.[391] In this registry, CI-AKI was defined as either a SCr increase >0.5 mg/dl (>44 μmol/l), or a SCr increase $>25\%$, or a decrease $>25\%$ of eGFR, or the composite of all three definitions. The baseline SCr was 1.12 ± 0.3 mg/dl (99 ± 26.5 μmol/l) and 24% had an eGFR <60 ml/min. CI-AKI rates were 3.3% (SCr increase >0.5 mg/dl [>44 μmol/l]), 10.2% (SCr increase $>25\%$), 7.6% (eGFR decrease $>25\%$), and 10.5% (composite), respectively.

It is accepted that, in patients with normal renal function—even in the presence of diabetes—the risk for CI-AKI is low (1–2%).[392] However, the incidence may be as high as 25% in patients with pre-existing renal impairment or in presence of certain risk factors, such as the combination of CKD and diabetes, CHF, advanced age, and concurrent administration of nephrotoxic drugs.[393] CI-AKI was described as the third most common cause of new AKI in hospitalized patients (after decreased renal perfusion and nephrotoxic medications) and was responsible for 11% of cases.[394]

The epidemiology of *de novo* CI-AKI in critically ill patients is not known. In a group of 75 ICU patients with a normal baseline SCr who were exposed to CT scans with an i.v. low-osmolar contrast medium, an increase in SCr $>25\%$ was recorded in 18% of the patients. There was no change of the SCr in a control group of patients undergoing CT scans but not receiving contrast media.[395] This rather small study shows that in critically ill patients, even with an apparently "normal" renal function, i.v. administration of iodinated contrast media is associated with a significant incidence of CI-AKI.

It could be expected that radiological procedures performed in an emergency would be associated with an increased risk of CI-AKI but, as recently summarized,[396] the published evidence to support this premise is rather scarce.[397]

Prognosis of CI-AKI

Many studies have now shown that patients who develop CI-AKI have a greater risk for death or prolonged hospitalization, as well as for other adverse outcomes, including early or late cardiovascular events. The latter are more common after, for example, percutaneous coronary interventions (for review, see McCullough[398]). In a retrospective analysis including 27 608 patients who underwent coronary angiography at the University of Pittsburgh Medical Center during a 12-year period, discrete proportional odds models were used to examine the association between increases in SCr and 30-day in-hospital mortality and LOS, respectively. It appeared that small absolute (0.25–0.5 mg/dl [22–44 μmol/l]) and relative (25–50%) increases in SCr were associated with risk-adjusted OR for in-hospital mortality of 1.83 and 1.39, respectively; larger increases in SCr generally were associated with greater risks for these clinical outcomes.[399] Moreover, when patients with CI-AKI require dialysis, the mortality is higher compared to those not requiring dialysis. For example, in the study by McCullough *et al.*,[400] the hospital mortality was 7.1% in CI-AKI and 35.7% in patients who required dialysis. By 2 years, the mortality rate in patients who required dialysis was 81.2%.

The more recent Cardiac Angiography in Renally Impaired Patients study[401]—a large, multicenter, prospective, double-blind RCT of patients who had moderate to severe CKD and were undergoing cardiac angiography—also showed that the adjusted incidence rate ratio for adverse events was twice as high in those with CI-AKI. However, these data demonstrating a temporal association between CI-AKI and short or long-term prognosis do not establish a causal relationship, since most of the patients in these observational studies have underlying risk factors that, in addition to increasing the patient's risk of CI-AKI, can directly increase their overall risk for the complications studied. Finally, many of the retrospective studies may also have introduced selection bias for patients who presumably had a clinical reason for having their SCr concentration followed.

Data on the association between risk of ESRD and CI-AKI are scarce. In contemporary studies, CI-AKI requiring dialysis developed in almost 4% of patients with underlying renal impairment and 3% of patients undergoing primary percutaneous coronary interventions for acute coronary syndrome. However, only a small proportion of patients continued on chronic dialysis.[402,403] Although CI-AKI requiring dialysis is relatively rare, the impact on patient prognosis is considerable, with high hospital and 1-year mortality rates (for a review, see McCullough[398]). Only one study[404] reported the incidence of new CKD Stage 4–5 (eGFR <30 ml/min) following percutaneous coronary interventions and found that this occurred in 0.3% of patients

with an eGFR >30 ml/min at baseline and newly diagnosed kidney disease within 6 months after the procedure, and in 0.9% of patients with an eGFR >60 ml/min at baseline. These percentages are higher than the estimated annual incidence of CKD at 0.17% that was found in a British general population cohort over a 5.5-year period of follow-up.[405] Thus, careful long-term follow-up of SCr following contrast exposure is warranted.

RESEARCH RECOMMENDATION

- Large prospective RCTs examining the epidemiology of CI-AKI are needed, especially on long-term outcomes, with attention to controlling for confounders.

SUPPLEMENTARY MATERIAL

Appendix E: Risks with Gadolinium-Based Contrast Agents.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.2: Assessment of the population at risk for CI-AKI

At present, millions of doses of intravascular contrast media are being administered worldwide.[406,407] Most of these radiological examinations are performed in ambulatory populations who do not need special preventive measures. However, contrast media are also increasingly used in an elderly population, many of whom have CKD and diabetes—the principal risk factors for CI-AKI. It is, thus, of utmost importance to screen the population at risk for CI-AKI.

4.2.1: Assess the risk for CI-AKI and, in particular, screen for pre-existing impairment of kidney function in all patients who are considered for a procedure that requires intravascular (i.v. or i.a.) administration of iodinated contrast medium. (*Not Graded*)

RATIONALE

Screening for pre-existing impairment of kidney function

Pre-existing renal functional impairment is the most important risk factor above all other risk factors for developing CI-AKI[408] and screening for both acute and chronic kidney disease is highly recommended. There is no sharp GFR threshold below which the risk for CI-AKI is clearly increasing. Both the KDOQI guideline and KDIGO recommend that, in stable patients, an eGFR should be used.[409]

A CI-AKI Consensus Working Panel[410] agreed that the risk of CI-AKI becomes clinically important when the baseline SCr concentration is $\geqslant 1.3$ mg/dl ($\geqslant 115$ μmol/l) in men and $\geqslant 1.0$ mg/dl ($\geqslant 88.4$ μmol/l) in women, equivalent to an eGFR < 60 ml/min per 1.73 m^2. However, Bruce *et al.*[390] showed that the incidence of "true" AKI became significant only between controls and contrast-media administered patients from a baseline SCr concentration of > 1.8 mg/dl (> 159 μmol/l) onward. The CI-AKI Consensus Working Panel[410] recommended that precautions to reduce the risk should be implemented in patients with a baseline eGFR < 60 ml/min per 1.73 m^2. In light of more recent information, this threshold could probably be lowered to 45 ml/min per 1.73 m^2.

In many institutions, point-of-care SCr testing is present, and the results can be available quite fast. In places without point-of-care laboratories, the appropriate blood tests should be requested, but an emergent imaging/intervention, where the benefit of very early imaging outweighs the risk of waiting, should not be delayed.

For its relative simplicity, only SCr is used at many hospitals to determine whether a patient is a candidate for intravascular contrast-media administration, but the thresholds used and the acceptable time between the determined SCr value and administration of contrast media to perform the radiology examination differs among radiology departments.

Risk-factor questionnaire

For outpatient radiological studies where renal function data are unavailable, a simple survey or questionnaire may be used to identify outpatients at higher risk for AKI in whom appropriate precautions should be taken.

Choyke *et al.*[411] (Figure 13) used a questionnaire and could identify a high proportion of patients with normal SCr concentrations, and reduced by 67% the number of patients in whom SCr measurement was necessary before imaging studies.

The European Society of Urogenital Radiology[386] recommends a risk-factor analysis based on the Choyke questionnaire to identify patients with a higher risk of abnormal renal function. The CI-AKI Consensus Working Panel[410] considered that a survey or questionnaire may be a useful guide for identifying patients at higher risk for CI-AKI compared to the general population.

Urinary protein screening

The CI-AKI Consensus Working Panel also supported the use of dipstick testing for urine protein as a rapid screen to identify patients who can undergo studies requiring contrast media without SCr measurement.[410] Of 310 patients with a negative urine protein test and no history of diseases potentially associated with renal impairment, none had a SCr level > 2.0 mg/dl (> 177 μmol/l), and only 1% had a level > 1.7 mg/dl (> 150 μmol/l).

Thus, the Work Group recommends that, when a recent SCr is not available, a simple questionnaire or a dipstick testing for urine protein may be useful for identifying pre-existing kidney disease. Risk stratification hinges on age, baseline kidney function, other comorbidities, and other risk factors.

In the past 3 months have you been told there may have been a change in your kidney function? Y/N

In the past 3 months have you been on any medications? Please list:

Have you used any over-the-counter pain relievers within the last 10 days? Y/N Please list:

In the past 3 months have you had any surgery? Y/N

Describe:

Do you feel dry or thirsty? Y/N

Circle one

*Have you ever been told you have kidney disease of any type? Please describe:	Y	N
*Have you had kidney surgery?	Y	N
*Do you have diabetes? Do you use insulin? Do you use metformin or glucophage?	Y Y Y	N N N
*Do you have hypertension, heart disease, or vascular disease?	Y	N
*Do you have gout?	Y	N
Do you have multiple myeloma?	Y	N
Have you ever had x-ray contrast media (dye) for CT, angiography, or IVP? Have you had contrast media within the last 3 days? Do you have any allergies to x-ray contrast media (dye)? Please describe:	Y Y Y	N N N
Have you received pretreatment with medication for this study?	Y	N
Do you have any allergies or asthma? Please describe:	Y	N

Figure 13 | Sample questionnaire. Asterisks denote questions with the highest association with abnormal renal function. Adapted from Choyke PL, Cady J, DePollar SL *et al*. Determination of serum creatinine prior to iodinated contrast media: is it necessary in all patients? Tech Urol 1998; 4: 65–69 with permission.[411]

Other risk factors of CI-AKI

Besides pre-existing kidney disease with renal function impairment, other risk factors for developing CI-AKI include diabetes, hypertension, CHF, advanced age, volume depletion, hemodynamic instability, use of concurrent nephrotoxic medications, and large volume or high osmolality of the contrast agent.[408,412] Although there is doubt that diabetes by itself is an independent risk factor, in a patient with CKD it acts as a risk multiplier.[398] Metabolic syndrome, prediabetes, and hyperuricemia have been identified as new risk factors for CI-AKI, while the use of ACE-I and angiotensin-receptor blockers (ARB), renal transplantation, diabetes mellitus with normal renal function, low-osmolar contrast media, multiple myeloma, female gender, and cirrhosis have been classified as conflicting risk factors for CI-AKI.[413] There are conflicting data on the impact of ACE-I or ARB but, overall, there is currently insufficient evidence to recommend discontinuation of these medications prior to contrast-media administration.

When possible, the administration of contrast media should be delayed in patients with circulatory collapse or CHF until their hemodynamic status is corrected. Repeated exposure should be delayed for 48 hours in patients without risk factors for CI-AKI, and for 72 hours in those with diabetes mellitus or pre-existing chronic renal dysfunction. If acute renal dysfunction develops after contrast-media administration, repeated exposure should preferably be delayed until the SCr level has returned to baseline levels.[414]

Concurrent nephrotoxic medication—including, in particular, NSAIDs, aminoglycosides, amphotericin B, high doses of loop diuretics, and antiviral drugs like acyclovir and foscarnet—should preferably be stopped. A recent study using a so-called forced euvolemic diuresis protocol including mannitol and furosemide led to a significantly increased risk of CI-AKI.[415] It can be advised that such strategy should be abandoned, and that furosemide therapy should preferably be stopped before angiography.

Table 15 | CI-AKI risk-scoring model for percutaneous coronary intervention

Risk factors	Integer score (calculate)
Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast-media volume	1 per 100 ml
SCr >1.5 mg/dl (>132.6 μmol/l) *or* eGFR <60 ml/min per 1.73 m^2	4 2 for 40–60 4 for 20–39 6 for <20

Note: Low risk: cumulative score <5; high risk: cumulative score >16.
CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; SCr, serum creatinine. Reprinted from Mehran R, Aymong ED, Nikolsky E *et al*. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393–1399 *et al*.,[418] copyright 2004, with permission from American College of Cardiology Foundation; accessed http://content.onlinejacc.org/cgi/content/full/44/7/1393

Risk models of CI-AKI

Most risk factors for CI-AKI can be detected by history-taking and physical examination, and the risk rises exponentially with the number of risk factors present.[416] Validated risk-prediction models using patient and procedural risk factors to assess for CI-AKI have been developed for patients undergoing percutaneous coronary intervention.[417,418] For example, the Mehran risk model[418] is given in Table 15. The overall occurrence of CI-AKI in the development set of the score was 13.1% (range 7.5% to 57.3% for a low [$\leqslant 5$] and high [$\geqslant 16$] risk score, respectively); the rate of CI-AKI increased exponentially with increasing risk score. In the validation dataset, the increasing risk score was again strongly associated with CI-AKI (range 8.4% to 55.9% for the low and high risk score, respectively). These models can help in counseling about the risks of the procedure, selecting prophylactic interventions, and can also be used to characterize patients in studies of CI-AKI.

4.2.2: Consider alternative imaging methods in patients at increased risk for CI-AKI. (*Not Graded*)

RATIONALE

The selection and advantages and disadvantages of non-iodinated contrast media are beyond the scope of these guidelines. Detailed discussions of all these techniques can be found in radiology textbooks and the radiology literature. The Work Group suggests that, in patients at increased risk for CI-AKI, the risks and benefits of iodinated contrast-media administration should be discussed with the radiologist.

Because of the great relevance for the nephrologist, radiologist, and cardiologist of the side-effects of Gd chelates used in magnetic resonance imaging (MRI), a short overview of their nephrotoxicity is given here.

Nephrotoxicity of Gd chelates

Gd chelates are widely used as MRI contrast agents, and are considered to have a good overall safety profile. Early on, phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity, although it is not clear whether it approaches the incidence of AKI associated with iodine-containing contrast media. Gd-related AKI appears to be a risk in patients with advanced kidney disease, especially those with diabetic nephropathy.[419,420] Perazella *et al.*[420] have summarized studies showing Gd-induced nephrotoxic AKI compared to CI-AKI.[421–425] Studies in patients with underlying kidney disease demonstrate the importance of renal clearance in determining the pharmacokinetic profile of Gd chelates.[426] More details on the pharmacokinetics of Gd chelates and their dialyzability are provided in Appendix E.

Nephrogenic systemic fibrosis (NSF)

The risk of developing NSF with Gd, particularly in patients with severe AKI and CKD, is reviewed in detail in Appendix E. It should be noted here that the European Medicines Agency stated a contraindication for use of gadodiamide in patients with a GFR <30 ml/min per 1.73 m^2, and issued a warning for its use in patients who have a GFR between 30 and 60 ml/min per 1.73 m^2 (EMEA Public assessment report. http://www.esur.org/fileadmin/NSF/Public_Assessment_Report_NSF_Gadolinium_26_June_2007.pdf; last accessed January 5, 2012). The US FDA requested that vendors add warnings about the risk for developing NSF to the full prescribing information on the packaging for all Gd-containing contrast agents (gadopentetate dimeglumine, gadodiamide, gadoversetamide, gadoteridol, gadobenate dimeglumine).[427] New labeling describes the risk for NSF following exposure to Gd in patients with a GFR <30 ml/min per 1.73 m^2 and in patients with AKI of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period. Additional recommendations were recently proposed by Perazella[420] and were endorsed by the Work Group:

(a) Use of a macrocyclic chelate (gadoteridol in the USA), is preferred over linear chelates. The risk associated with the various Gd-containing agents is likely different. Gadodiamide, the linear nonionic chelate–based formulation, maintains the highest risk on the basis of epidemiologic data and animal studies. Gadopentetate, the linear ionic chelate–based product probably has a medium risk, less than the linear nonionic chelates but more than the macrocyclic chelates. Gadoteridol, the only FDA-approved macrocyclic chelate, maintains less risk. Clearly, high dosages and large cumulative dosages of all these agents will increase risk for NSF.

(b) Demonstration of significant quantities of insoluble Gd in the skin of NSF patients, months after exposure to Gd-based contrast material and after extensive tissue processing, suggests that Gd might have undergone transmetallation *in vivo*. Supporting the importance of transmetallation, all NSF cases reported before 2009 have been associated with linear MRI contrast agents (for a review, see Kay[428]) that have inferior thermodynamic stability and a kinetic or conditional stability that favors transmetallation. However, a recent case of NSF in a dialysis patient after exposure to a macrocyclic chelate has been described,[429] and at least two additional cases are known.[430]

(c) Use the lowest dosage of the agent possible to achieve the image.

(d) Avoid repeat exposures with Gd.

(e) Consider performing IHD after the exposure (and the next 2 days) in patients who are already maintained on IHD, recognizing that there are no data that support prevention of NSF with this modality.

This recommendation is based on the pharmacokinetics of Gd and the theoretical benefit of removing it with IHD (>95% plasma clearance). PD clears these agents rather poorly.

SUPPLEMENTARY MATERIAL

Appendix E: Risks with Gadolinium-Based Contrast Agents.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.3: Nonpharmacological prevention strategies of CI-AKI

There have been a large number of strategies/agents evaluated to prevent CI-AKI. Sterling *et al.*[431] have recently summarized most of these strategies and classified them as having either definitive, possible, or doubtful value. From the many strategies, these authors only retain parenteral volume expansion, minimizing contrast-media volume, use of low-osmolar and iso-osmolar contrast media, and administration of non-iodinated contrast media as strategies with definitive value. A recent comprehensive meta-analysis by Kelly *et al.*[432]—including RCTs that administered NAC, theophylline, fenoldopam, dopamine, iloprost, statins, furosemide, or mannitol, and covering studies up to November 2006—provides an excellent overview.

DOSE/VOLUME OF CONTRAST-MEDIA ADMINISTRATION

4.3.1: Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. (*Not Graded*)

RATIONALE

The correlation between the volume of contrast media administered and the risk of CI-AKI has been recognized. [433] In the vast majority of papers dealing with CI-AKI after coronary procedures, contrast-media doses are only expressed in volumes. The Work Group feels that such expression can be misleading, since commercially available contrast-media concentrations range from 140 to 400 milligrams of iodine per milliliter, a difference with almost a factor of 3. The Work Group recommends, therefore, that the dose of contrast medium should be better expressed in relation to both volume and concentration, e.g., grams iodine, which also directly relates to the diagnostic capacity, the primary purpose of the contrast medium. Such "double" expression would also facilitate the comparison between different studies on epidemiology and prognosis of CI-AKI.

It is well known that, when measuring the plasma clearance of a GFR marker (e.g., with the contrast medium iohexol), the AUC is directly related to the dose of iohexol and inversely related to the GFR. Thus, by mathematically estimating the AUC and knowing the injected iodine dose, the GFR can be calculated by dose $\div$ AUC. Thus, AUC = dose $\div$ GFR, and AUC is directly related to the systemic exposure of a drug, including the contrast medium, which, in turn, is mostly correlated with its efficacy and toxicity.[434] An interesting experimental study[435] investigated the correlation between the calculated dose to CrCl ratio and the experimentally measured AUC for the contrast agent iodixanol. The experimentally determined AUC data correlated highly with the dose:CrCl ratio. This ratio could thus be a rapid and accurate way to estimate AUC for an iodinated contrast medium, without the need for multiple blood samples.

A recent study by Nyman *et al.*[436] in patients undergoing coronary angioplasty calculated the probability of CI-AKI (SCr rise >0.5 mg/dl [>44.2 μmol/l] or oliguria/anuria) at various eGFR levels based on g-I (grams iodine)/eGFR ratios of 1:2, 1:1, 2:1, and 3:1. At a ratio <1, the risk of CI-AKI was 3%, while it was 25% at a ratio $\geqslant 1$. This, and other preliminary studies, indicate that a g-I/GFR ratio <1 may be relatively safe in a patient without multiple risk factors.[436–438]

Finally, the association between absolute and body weight- and SCr-adjusted contrast-media volume, CI-AKI incidence ($\geqslant$25% SCr increase), and clinical outcome was prospectively investigated in patients with acute MI.[439] For each patient, the maximum contrast-medium dose was calculated according to the formula (5 $\times$ body weight [kg]) $\div$ SCr, and the contrast-medium ratio—defined as the ratio between the contrast-medium volume administered and the maximum dose calculated—was assessed. Development of CI-AKI was associated with both contrast-medium volume and ratio. Additional radiological measures to reduce CI-AKI can be found in Table 16.

Route of administration of contrast media

The risk of CI-AKI appears to be greater after arterial compared to venous administration of contrast media. Indeed, in the rare studies where an appropriate control group without contrast media was included, no significant difference was observed in the rate of CI-AKI between the patients who received i.v. iodinated contrast media and the control subjects who did not.[440–442] Thus, the risk of CI-AKI with i.v. contrast medium is probably very low. CI-AKI reportedly occurs after i.v. contrast-medium injection for CT in only 4% of patients with CKD.[443] Katzberg and Lamba[444] summarized the six studies on CI-AKI after i.v. contrast-medium administration in patients at risk and all suffering from moderate CKD. The overall incidence of CI-AKI in these studies, using the current generation of low-osmolar contrast media, was about 5%.

Given the logistic challenges in the outpatient setting, the use of specific prophylactic measures prior to administration of i.v. contrast media could be limited to those subjects who are at higher levels of baseline risk than they would be when an i.a. procedure was planned.[445] This conclusion, may

Table 16 | Additional radiological measures to reduce CI-AKI

Some CT strategies in patients at risk of CI-AKI

- Perform CT, when possible, without contrast media; scrutinize the examination and discuss with the referral physician-surgeon before deciding on the need for contrast media.
- Dosing per kilogram body weight to reduce the amount of contrast media is needed in thin patients.
- Adapt injection duration to scan duration when performing CT-angiography, so that the injection is not still running when the scan is finished.
- Use a saline chaser to decrease the amount of contrast media, by using the contrast medium that otherwise would remain in the dead space of the arm veins; this may save 10–20 ml of contrast media.
- Use 80 kVp; contrast-medium dose may be reduced by a factor of 1.5–1.7 compared to the dose used at 120 kVp since iodine attenuation increases, and combine with increased tube loading (mAs) to maintain signal-to-noise ratio.
- Further reduction of contrast media may be instituted in patients with known decreased cardiac output (not unusual in patients with renal impairment) undergoing CT-angiographic studies.

Some angiographic strategies in patients at risk of CI-AKI

- Use biplane when appropriate.
- Avoid test injections; the same amount may be enough for a diagnostic digital-subtraction angiography run.
- Scrutinize each series before performing the next; avoid unnecessary projections.
- Decrease kilovoltage in a thin patient; a lower iodine concentration may be used.
- Assess the physiologic significance of a stenosis by measurement of translesional pressure gradient and fractional flow reserve, a technique well accepted and validated for the coronary circulation. For different arterial beds, perform manometry of a questionable stenosis instead of multiple projections.
- Avoid ventriculography: echocardiography (and ''echo contrast'') is always a reasonable alternative.
- Use plasma isotonic contrast-media concentrations for renal artery injections.
- When renal artery stenosis is suspected, map the origin of major renal arteries with noninvasive procedures (e.g., CT without contrast media) for proper initial renal angiographic projections to avoid unnecessary runs, or perform primary manometry.
- CO_2 may be used as contrast medium in venous examinations and below the diaphragm for arterial examinations or alternatively use iodinated contrast media with the same contrast effect, i.e., about 40 mg iodine per milliliter.
- Since the contrast effect of 0.5 M Gd-contrast media has been regarded as diagnostic by many investigators (coronary, renal, aortofemoral arteriography, etc.), iodinated contrast media may be diluted to the same density, i.e., about 75 mg iodine per milliliter.
- Use selective or superselective catheterizations when appropriate, e.g., ''single leg run-off''.
- Reduce aortic flow and amount of contrast medium by temporal occlusion of femoral arteries with tourniquets when performing aortography.

Gd, gadolinium; kVp, peak kilovoltage.

however, be too optimistic when applied to critically ill patients undergoing emergency CT scans.[395]

The majority of the literature covering CI-AKI and its prevention involves i.a. iodinated contrast-medium administration.[445,446] The higher risk of CI-AKI after i.a. administration is probably due to the more direct exposure of the kidneys to contrast media,[447] or to the fact that, in general, i.a. contrast-media examinations are performed in patients who carry a higher risk.

RESEARCH RECOMMENDATIONS

- Randomized trials should explore whether there is need for discontinuation of ACE-I and/or ARBs in patients at risk for CI-AKI.
- Additional studies are needed to better determine the exact relationship between the dose of contrast media and the risk for CI-AKI.

SELECTION OF A CONTRAST AGENT

4.3.2: We recommend using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media in patients at increased risk of CI-AKI. (*1B*)

RATIONALE

This recommendation is supported by the summary tables of the different RCTs and on the evidence profile tables (Suppl Tables 19–21).

High-osmolar vs. iso-osmolar or low-osmolar contrast media

The recommendation to avoid high-osmolar contrast media is based on older literature, since recent RCTs comparing high- vs. low- and iso-osmolar iodine-based contrast media are not available. In addition, high-osmolar contrast media have virtually been abandoned in modern radiological units. Both the review of Goldfarb *et al.*,[448] and the meta-analysis of Barrett and Carlisle combining 24 randomized studies[449] suggest that the risk of CI-AKI is similarly low with high-osmolar and low-osmolar agents among otherwise stable patients with normal renal function, but that in contrast to high-osmolar contrast media, low-osmolar contrast media are less nephrotoxic in patients with pre-existing kidney function impairment.

Low-osmolar vs. iso-osmolar contrast media

The present hotly debated question is whether iso-osmolar contrast media are safer than low-osmolar contrast media in high-risk patients. This question has been the subject of a number of randomized trials as well as systematic reviews and meta-analyses (Suppl Tables 19–21).

We separated studies meeting our inclusion criteria (see Chapter 1.2) into those administering i.a. or i.v. contrast media. We used the general definitions of CI-AKI provided in the studies (an increase in SCr by $>25\%$ or 0.5 mg/dl [44.2 μmol/l]) occurring within 72 hours after contrast-medium administration, in the absence of an alternative etiology for the decrease in kidney function.

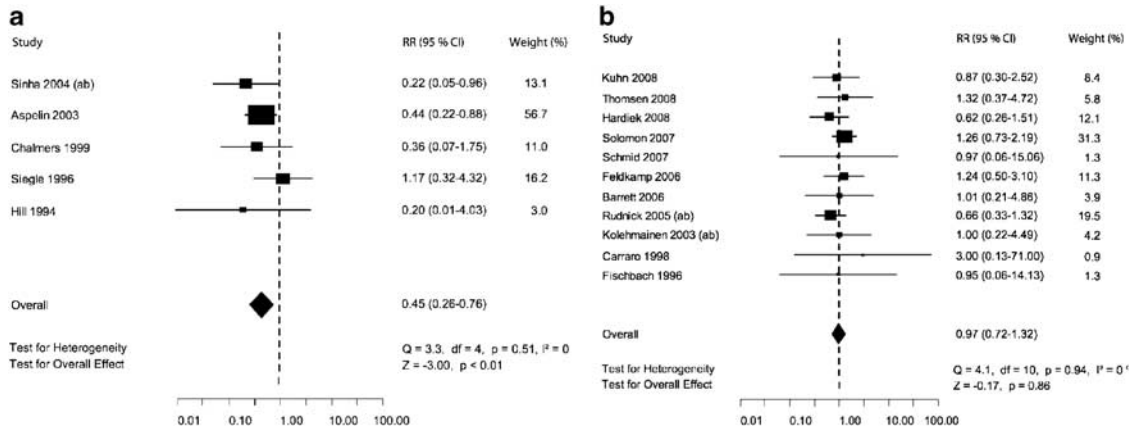

Figure 14 | Risk for contrast-induced nephropathy. (**a**) Iodixanol vs. iohexol and risk for contrast-induced nephropathy; (**b**) iodixanol vs. nonionic low-osmolar contrast media other than iohexol and risk for contrast-induced nephropathy. Reprinted from Heinrich MC, Haberle L, Muller V *et al*. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low osmolar contrast media: meta-analysis of randomized controlled trials. Radiology 2009; 250: 68–86 with permission, copyright 2009, from Radiological Society of North America[457]; accessed http://radiology.rsna.org/content/250/1/68.long

In total, 14 RCTs fulfilling the search criteria were found. Ten RCTs were found with i.a. and four RCTs with i.v. injection, respectively (Suppl Tables 19–21). There is only moderate quality of evidence and overall, no benefit—or, at least, no consistent benefit—was found of nonionic iso-osmolar (iodixanol) contrast media compared to low-osmolar ionic or nonionic contrast media. In eight studies comparing contrast media given i.a.[401,450–456] some showed superiority of iso-osmolar contrast media (iodixanol), compared to iohexol[450] and iopromide.[455] There was no difference when iodixanol was compared to iopamidol,[401,452] iopromide,[451,453] and ioversal.[456]

The most recent prospective, multicenter, randomized, double-blind study compared the renal effects of iodixanol to the nonionic, low-osmolar agent iopamidol, in 526 subjects with CKD and diabetes mellitus undergoing diagnostic and/or therapeutic coronary angiography.[454] The overall CI-AKI incidence was 10.5% (11.2% % in the iodixanol arm and 9.8% in the iopamidol arm, NS). The volume of contrast medium, volume of saline administered, frequency of coronary interventional procedures, and severity of baseline kidney disease and of diabetes mellitus were similar between treatments.

Finally, a recent meta-analysis[457] (Figure 14) analyzed studies comparing iodixanol with low-osmolar contrast media. The pooled RR was 0.68 (95% CI 0.46–1.01; $P = 0.06$). In studies that included patients with normal renal function after i.a. contrast-media administration, the RR was 0.82 (95% CI 0.45–1.51; $P = 0.53$). In the studies that included only patients with decreased kidney function after i.a. contrast-media administration, the RR was 0.59 (95% CI 0.33–1.07; $P = 0.08$). However, in all three studies in which iohexol was the low-osmolar contrast medium used, the risk of CI-AKI was significantly lower with iodixanol (RR 0.38; 95% CI 0.21–0.68; $P < 0.01$). In contrast, the risk of CI-AKI did not significantly differ in the two studies in which iodixanol was compared to other low-osmolar contrast agents (RR 0.95; 95% CI 0.50–1.78; $P = 0.86$). Iodixanol is thus not associated with a significantly reduced risk of CI-AKI compared to the low-osmolar contrast media pooled together. However, in patients with decreased kidney function, iodixanol is associated with a reduced risk of CI-AKI compared to iohexol.

The clinical heterogeneity between all these studies, as far as basal kidney function and prevalence of diabetes mellitus are concerned, hampers the ability to compare the results across studies, but can widen the applicability of consistent findings across different risk groups provided the mechanisms of contrast-induced nephrotoxicity are the same. One should note, also, that in all these studies different definitions of CI-AKI have been used and that the timing of SCr measurements after contrast-media injection was not uniform. It has been shown that different time-points for the measurement of CI-AKI can give different results.[458] One may expect that those studies with a standardized and simultaneous measurement of renal function between the two arms are probably the most conclusive. Finally, different types and amounts of volume expansion and different pharmacological preventive strategies have been used throughout the studies, making conclusive comparisons virtually impossible.

i.a. Iodixanol vs. ioxaglate

Two studies fulfilled our inclusion criteria; one study[459] showed a superiority of iodixanol vs. ioxaglate, but this was not confirmed in the study by Mehran *et al.*,[460] who found no difference between these two contrast agents. Although overall the number of patients is substantial, there is heterogeneity among the comparators with which iodixanol has been compared. In addition, the cost of iodixanol is probably higher than the cost of most of the low-osmolar contrast agents. No studies comparing a possible difference

among low-osmolar contrast media have been performed. Based on evidence profiles (Suppl Tables 19 and 20) and the most recent meta-analysis[457] (Figure 14) of the studies comparing i.a. administration of iso- vs. low-osmolar contrast media, the Work Group found no evidence to recommend a preference for either type of agent.

i.v. Administration

There are four studies following i.v. injections fulfilling our inclusion criteria: Barrett *et al.*,[443] Kuhn *et al.*,[461] Thomsen *et al.*,[462] and Nguyen *et al.*[463] The overall conclusion, based on the evidence profile summarized in Suppl Table 20 comparing i.v. iso- vs. low-osmolar contrast media, is that there is no benefit for the nonionic iso-osmolar agent (iodixanol); the overall quality of the evidence is moderate. This conclusion is supported by the above-mentioned recent meta-analysis[457] which, in seven studies comparing i.v. contrast-media administration with iodixanol vs. low-osmolar contrast media, showed no statistically significant difference for CI-AKI (RR 1.08; 95% CI 0.62–1.89; $P = 0.79$). Subgroup analysis did not show superiority of any agent in studies of individuals with normal kidney function (RR 1.12; 95% CI 0.35–3.65; $P = 0.85$) or in studies of individuals with reduced kidney function (RR 1.07; 95% CI 0.56–2.02; $P = 0.84$).

In head-to-head comparisons with different low-osmolar agents, iodixanol has been shown to be superior to iopromide, but not to iopamidol and iomeprol. It is, however, difficult to determine whether this is simply due to spurious findings in a smaller number of comparisons, or due to true differences between low-osmolar agents. Until better head-to-head comparative studies among the different contrast media agents are available, the Work Group is unable to draw definite conclusions on the selection of iso-osmolar vs. low-osmolar contrast media.

RESEARCH RECOMMENDATION

- Additional studies with head-to-head comparisons among the different contrast media should be performed in order to draw definite conclusions on the selection of iso-osmolar vs. low-osmolar contrast media. A more uniform definition of CI-AKI, as suggested in this guideline, should be used as the end-point.

SUPPLEMENTARY MATERIAL

Supplementary Table 19: Evidence profile of RCTs examining the effect of intrarterial isosmolar vs. low osmolar contrast agent on the prevention of CI-AKI.

Supplementary Table 20: Evidence profile of RCTs examining the effect of intravenous isosmolar vs. low osmolar contrast agent on the prevention of CI-AKI.

Supplementary Table 21: Summary table of RCTs examining the effect of isosmolar vs. low osmolar contrast agent on the prevention of CI-AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.4: Pharmacological prevention strategies of CI-AKI

FLUID ADMINISTRATION

Extracellular volume expansion at the time of radiocontrast-media administration may serve to counteract both the intrarenal hemodynamic alterations and the direct tubulotoxic effects that play a role in the pathophysiology of CI-AKI. Neurohumoral effects of volume expansion that may attenuate radiocontrast-induced medullary hypoxia include suppression of vasopressin as well as inhibition of the renin-angiotensin axis; but an increased synthesis of vasodilatory renal prostaglandins may also play a role.[464]

Volume expansion may also directly reduce cellular damage by dilution of the contrast medium, particularly in the medullary tubular segments. Likewise, an effect of radiocontrast media to increase tubular fluid viscosity may be diminished by intravascular volume expansion.[465] It is important to note that these potentially attenuating effects of volume expansion are speculative, and the precise mechanisms by which volume expansion protects against CI-AKI remain unknown.

4.4.1: We recommend i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no i.v. volume expansion, in patients at increased risk for CI-AKI. (*1A*)

RATIONALE

Despite the recognition of volume depletion as an important risk factor for AKI, there are no RCTs that have directly evaluated the role of fluids vs. placebo in the prevention of AKI. However, RCTs have compared different fluids and have combined fluids with other interventions.[191] Furthermore, comparisons between outcomes seen in these trials[191] and historical untreated control subjects[466] suggest a large benefit from fluids. In particular, volume expansion and treatment of dehydration are well-established interventions in the prevention of CI-AKI. A recent propensity analysis, however, noted that strategies to prevent CI-AKI are implemented rather nonuniformly.[467] Pre– and post–contrast-media administration i.v. fluids were given to only 264 of 660 study patients (40.0%), more commonly with coronary angiography than with CT (91.2% vs. 16.6%). Other preventive measures, such as administration of NAC or discontinuation of NSAIDs, were equally rarely applied. Only 39.2% of patients received NAC, while only 6.8% of patients were instructed to discontinue NSAIDs. In a propensity analysis, the use of i.v. fluids was associated with a reduced rate of CI-AKI. The incidence of CI-AKI was lowest following CT (range, 0.0–10.9%) and was highest following noncoronary angiography (range, 1.9–34.0%).

The fluids that have been tested in the prevention of CI-AKI are hypotonic saline (0.45%), isotonic saline (0.9%) and isotonic sodium bicarbonate. The interpretation of all these studies is hampered by the fact that not all other risk factors (susceptibilities) for CI-AKI were excluded or considered in every study (i.e., age of the patient, presence of CKD and/or diabetes prior to contrast-media administration, type and dose of contrast agent, associated therapy with NAC, and other risk factors [see Chapter 2.2]).

There is no clear evidence from the literature to guide the choice of the optimal rate and duration of fluid infusion in CI-AKI prevention, but most studies suggest that the fluids should be started at least 1 h before and continued for 3–6 hours after contrast-media administration. A "good" urine output (>150 ml/h) in the 6 hours after the radiological procedure has been associated with reduced rates of AKI in one study.[468] Since not all of i.v. administered isotonic crystalloid remains in the vascular space, in order to achieve a urine flow rate of at least 150 ml/h, $\geqslant 1.0$–1.5 ml/kg/h of i.v. fluid has to be administered for 3–12 hours before and 6–12 hours after contrast-media exposure.

Mueller *et al.*[469] found that i.v. 0.9% saline solution, compared to 0.45% saline solution in dextrose, in 1620 patients undergoing coronary angiography significantly reduced CI-AKI. The sustained administration of isotonic saline before and after radiocontrast injection seems, thus, to be more protective than equivalent volumes of hypotonic saline.[464] Although the mechanism by which sodium bicarbonate, beyond its volume-expanding effects, might further reduce CI-AKI remains poorly defined, it has been postulated that sodium bicarbonate infusion may decrease generation of free radicals mediated by the Haber-Weiss reaction by increasing tubular pH. The Haber-Weiss reaction is most active at lower pH levels.[470] Sodium bicarbonate infusion may also scavenge the potent oxidant peroxynitrate, produced via a nitric oxide–mediated pathway.[471] Reactive oxygen species activate cytokine-induced inflammatory mediators, resulting in damage to proximal tubular cells,[472] and it is likely that the activation of these mediators is influenced by tissue hypoxia and intracellular medullary acidosis.[473]

It is worth noting that, compared to i.v. bicarbonate, the combination of oral azetazolamide inducing an alkaline urine, plus i.v. saline, was more effective for the prevention of

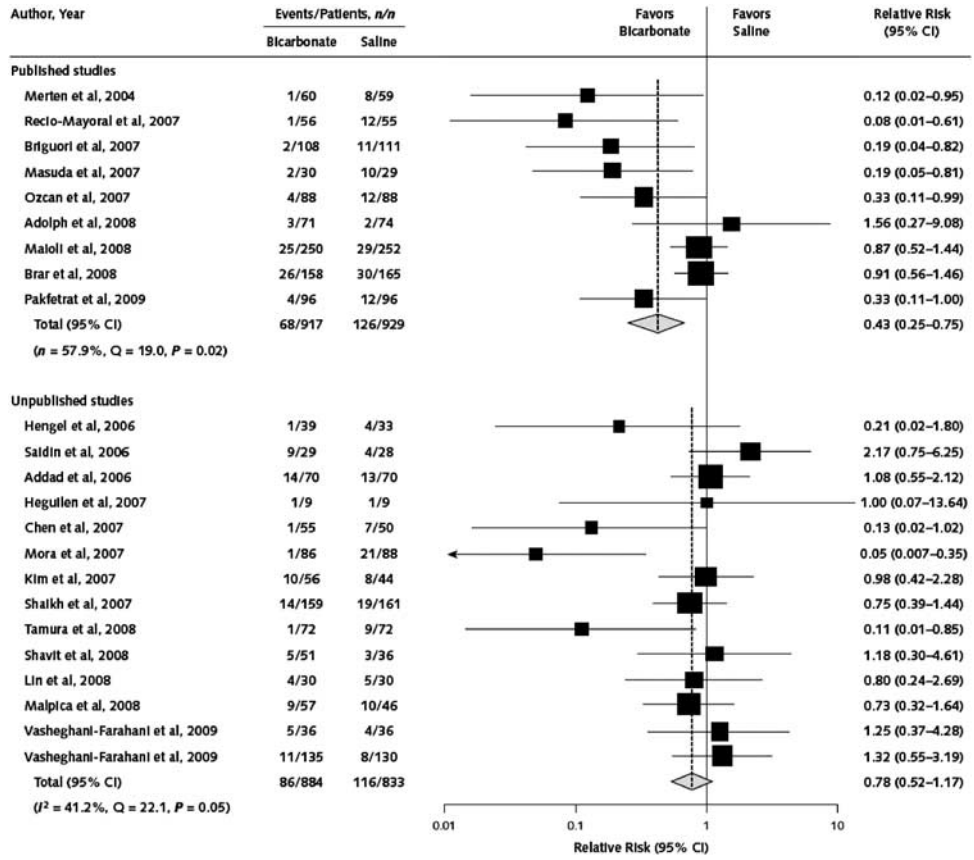

Figure 15 | Bicarbonate vs. saline and risk of CI-AKI. Reprinted from Zoungas S, Ninomiya T, Huxley R *et al*. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med 2009; 151: 631–638 with permission from American College of Physicians[481]; accessed http://www.annals.org/content/151/9/631.full

CI-AKI than saline alone, in a relatively small study in children with stable chronic renal failure (CRF).[474] It could also be hypothesized that sodium bicarbonate has a stronger impact in lowering the intratubular viscosity caused by the contrast medium, compared to isotonic saline, because it causes less tubular sodium reabsorption than saline.

Sodium bicarbonate solutions have been tested in the prevention of CI-AKI in comparison with isotonic saline, either with or without NAC. A number of systematic reviews on the role of sodium bicarbonate compared to isotonic saline in the prevention of CI-AKI are available.[475–481]

The most recent and probably the most complete systematic review[481] analyzed MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from 1950 to December 2008; conference proceedings; and ClinicalTrials.gov, without language restriction (Figure 15). This systematic review included RCTs of i.v. sodium bicarbonate that prespecified the outcome of CI-AKI as a 25% increase in baseline SCr concentration or an absolute increase of 0.5 mg/dl (44.2 μmol/l) after contrast-media administration. Twenty-three published and unpublished trials with information on 3563 patients and 396 CI-AKI events were included. The pooled RR was 0.62 (95% CI 0.45–0.86), with evidence of significant heterogeneity across studies. Some heterogeneity was due to the difference in the estimates between published and unpublished studies: RR 0.43 (95% CI 0.25–0.75) vs. 0.78 (95% CI 0.52–1.17), respectively. Meta-regression showed that small, poor-quality studies that assessed outcomes soon after contrast-media administration were more likely to suggest the benefit of bicarbonate ($P < 0.05$ for all). No clear effects of treatment on the risk for dialysis, heart failure, and total mortality were identified.

Suppl Tables 22 and 23 summarize the evidence from RCTs where isotonic bicarbonate was compared to isotonic saline alone, without concomitant other "preventive" interventions. In all studies, a minimum of 50 patients in both arms and publication as full paper were required for inclusion in the tables. Only three studies directly compared isotonic bicarbonate to isotonic saline.[470,482,483] In a fourth study by Brar *et al.*,[484] NAC was included in 47% and 46% of the patients in both arms of the study (bicarbonate vs. saline), respectively. The first study was a small single-center RCT[470] enrolling 119 patients with stable SCr of at least 1.1 mg/dl (97.2 μmol/l), randomized to either infusion of isotonic saline or isotonic sodium bicarbonate before and after contrast-media administration. CI-AKI (defined as an increase of 25% in SCr from baseline within 48 hours)

developed in 1.7% in the bicarbonate group, compared to 13.6% in the saline solution group.

Ozcan *et al.*[483] included three prophylactic regimens: infusion of sodium bicarbonate, sodium chloride, and sodium chloride plus oral NAC (600 mg b.i.d.). The incidence of CI-AKI, defined as an increase in SCr level >25% or 0.5 mg/dl (44.2 μmol/l) after 48 hours was significantly lower in the sodium bicarbonate group (4.5%) compared to sodium chloride alone (13.6%, $P = 0.036$). After adjusting for the Mehran nephropathy risk score, the risk of CI-AKI significantly reduced with sodium bicarbonate compared to sodium chloride alone (adjusted risk ratio 0.29; $P = 0.043$).

By contrast, Adolph *et al.*[482] did not find differences in CI-AKI between the two fluid regimens on day 1 after angiography; even on day 2, most parameters were similar in both groups. In none of the above-mentioned studies was there need for RRT.

Finally, a recent but retrospective study[485] defined CI-AKI as an increase in SCr ⩾25% within 48 hours of receiving contrast media, and compared sodium bicarbonate to normal saline in patients exposed to cardiac angiography. One group of patients (n = 89) received prophylactic bicarbonate; a second group, normal saline (n = 98). The patients in the bicarbonate group had more severe renal disease with higher baseline SCr (1.58 ± 0.5 mg/dl; 140 ± 44.2 μmol/l) vs. (1.28 ± 0.3 mg/dl; 113 ± 26.5 μmol/l), $P = 0.001$ and a lower eGFR, compared to the normal saline group. After contrast-media exposure, there was significant drop in eGFR (6.4%) and increase in SCr (11.3%) in the normal saline group and no significant change in the bicarbonate group. Three patients (3.4%) in the bicarbonate group, as opposed to 14 patients (14.3%) in the normal saline group, developed CI-AKI ($P = 0.011$). Two patients in the normal saline group and none in the bicarbonate group needed dialysis. This study suggests that the use of i.v. sodium bicarbonate is more effective than normal saline in preventing CI-AKI.

Three studies compared bicarbonate and saline solutions associated with the administration of NAC in both study arms.[486–488] Recio-Mayoral *et al.*[488] conducted a prospective single-center RCT in 111 consecutive patients with acute coronary syndrome undergoing emergency angioplasty. One group of patients received an infusion of sodium bicarbonate plus NAC started just before contrast-media injection and continued for 12 hours after angioplasty. The second (control) group received the standard fluid protocol consisting of i.v. isotonic saline for 12 hours after angioplasty. In both groups, two doses of oral NAC were administered the next day. A SCr concentration >0.5 mg/dl (>44.2 μmol/l) from baseline after emergency angioplasty was observed in 1.8% in the bicarbonate group and in 21.8% of the saline group. Mortality and need for RRT were not significantly different between both groups. Briguori *et al.*[486] randomized 326 CKD patients (SCr ⩾2 mg/dl [⩾177 μmol/l] and/or eGFR <40 ml/min per 1.73 m^2), and referred for coronary and/or peripheral procedures to three different protocols: prophylactic administration of 0.9% saline infusion plus NAC (n = 111), sodium bicarbonate infusion plus NAC (n = 108), and 0.9% saline plus ascorbic acid plus NAC (n = 107). CI-AKI was defined as an increase of ⩾25% in the SCr concentration 48 hours after the procedure. CI-AKI occurred in 9.9% of the saline plus NAC group, in 1.9% of the bicarbonate/NAC group ($P = 0.019$ vs. saline plus NAC group), and in 10.3% of the saline plus ascorbic acid plus NAC group ($P = 1.00$ vs. saline plus NAC group). There was no difference in mortality nor in need for RRT among the different groups. While these two studies suggest that isotonic bicarbonate may provide greater benefit than isotonic saline, either in association with NAC or not, neither study can be considered conclusive.

Maioli *et al.*[487] prospectively compared the efficacy of sodium bicarbonate vs. isotonic saline in addition to NAC in a larger population of 502 patients with an estimated CrCl <60 ml/min, and undergoing coronary angiography or intervention. CI-AKI was defined as an absolute increase of SCr ⩾0.5 mg/dl (⩾44.2 μmol/l) measured within 5 days. CI-AKI occurred in 10.8%; 10% were treated with sodium bicarbonate and 11.5% with saline. In patients with CI-AKI, the mean increase in creatinine was not significantly different in the two study groups. Based on this last prospective study, bicarbonate does not seem to be more efficient than saline. Furthermore, a retrospective cohort study at the Mayo Clinic assessed the risk of CI-AKI associated with the use of sodium bicarbonate, NAC, or the combination. Surprisingly, i.v. sodium bicarbonate was associated with an increased incidence of CI-AKI.[489]

While one might take the position that, if in doubt, one should choose the regimen that is potentially superior, the Work Group also considered the potential harm. In addition, isotonic bicarbonate solutions are usually composed by adding 154 ml of 8.4% sodium bicarbonate (i.e., 1 mmol/ml) to 846 ml of 5% glucose solution, resulting in a final sodium and bicarbonate concentration of 154 mmol/l each. Since this mixing of the solution is often done at the bedside or in the hospital pharmacy, there is the possibility for errors leading to the infusion of a hypertonic bicarbonate solution. The potential for harm from dosing errors, and the added burden from preparation of the bicarbonate solution, has to be taken into account in clinical practice when making a choice between using bicarbonate rather than standard isotonic saline solutions. Taken together, the Work Group concluded that there is a possible but inconsistent benefit of bicarbonate solutions based on overall moderate-quality evidence (Suppl Table 22). As discussed above, the potential of harm and the additional burden for preparing the bicarbonate solutions led the Work Group not to express a preference for or against one solution (isotonic saline or isotonic bicarbonate). Thus, either can be used for the prevention of CI-AKI.

4.4.2: We recommend not using oral fluids alone in patients at increased risk of CI-AKI. (*1C*)

RATIONALE

Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as i.v. volume expansion.[490] One small RCT of 53 patients[491] who underwent nonemergent cardiac catheterization found that i.v. volume expansion with saline was more effective than unrestricted oral fluid intake. A more recent trial[492] examined the effects of oral volume intake on renal function in 180 patients with preserved renal function referred for coronary CT angiography. The patients were divided into two groups: 106 subjects with an increase in SCr after coronary CT angiography; and 74 without. Significant correlations were observed between the amount of oral fluid intake and the percentage changes in SCr as well as the absolute changes in eGFR. In multiple regression analysis, the amount of oral fluid intake was the only independent predictor for an increase in SCr. However, a recent study compared oral fluids (water with or without bicarbonate) to i.v. fluids (isotonic saline or bicarbonate) and did not find differences in incidence of CI-AKI patients with mild CKD. If confirmed in larger studies, this regimen could offer an equivalent and more practical approach in preventing a decline in renal function after contrast exposure, without accruing additional delay in hospital days or in-hospital mortality.[493]

ROLE OF NAC IN THE PREVENTION OF CI-AKI

4.4.3: We suggest using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (*2D*)

RATIONALE

NAC—in many, but not all, studies—has been shown to have a protective effect on CI-AKI when administered before the onset of renal insult; for a review, see McCullough.[494] In addition, NAC is inexpensive and appears to be safe, although it may have some detrimental effects on myocardial and coagulation function.[371–373] The "safety" of NAC should further be amended, particularly when high i.v. doses are used, as in some of the RCTs in CI-AKI. When prospectively studied in acetaminophen poisoning, i.v. NAC produced anaphylactoid reactions in up to 48% of participants.[374] Although most of these reactions were mild, at least one death has been reported in a patient with asthma.[375] It should be noted that the doses used in acetaminophen intoxication are still much higher than in the "high doses" used in CI-AKI prevention trials. In a recent review,[495] doses of NAC 300 mg/kg i.v. over 21 hours, 980 mg/kg i.v. over 48 hours, and 1330 mg/kg p.o. over 72 hours were mentioned to have been all comparably effective at preventing hepatotoxicity in most uncomplicated early-presenting acute acetaminophen overdoses. Although a variety of doses of NAC has been administered in the prevention of CI-AKI, the i.v. "high doses" used in one study[496] are mostly 2×1200 mg NAC per day for 2–3 days, far below the doses used in acetaminophen intoxication. A meta-analysis[497] of studies using high doses of NAC defined the latter as a daily dose greater than 1200 mg or a single periprocedural dose greater than 600 mg (periprocedural being described as immediately or within 4 hours of the planned contrast exposure). It should also be remembered that no FDA label is available for NAC as a preventive drug of AKI.

Suppl Tables 24 and 25 summarize the quite numerous RCTs where NAC has been compared to placebo on the impact of patient mortality, need for RRT, or prevention of CI-AKI. In most of the studies, i.v. fluids, either with isotonic saline or with isotonic bicarbonate, was used in both arms. Moreover, the impact of NAC on important "hard" patient outcomes, such as all-cause mortality, need for RRT, or doubling of SCr level has only rarely been studied. At present, there is no current evidence that either oral or i.v. NAC can alter mortality or need for RRT after contrast-media administration to patients at risk for CI-AKI. The only study showing a significant decrease in hospital mortality is the three-arm study of Marenzi *et al.*[498] in patients undergoing primary angioplasty. Overall in-hospital mortality was higher in patients with CI-AKI, defined as a 25% increase in SCr, than in those without CI-AKI (26 % vs. 1 %; $P<0.001$). Thirteen patients (11%) in the control group died, as did five (4%) in the standard-dose NAC and three (3%) in the high-dose NAC group ($P=0.02$). All other studies did not show a beneficial effect on mortality (Suppl Table 25). Overall, this evidence was deemed to be of moderate quality and the possible positive effect on mortality dubious.

The effect of NAC on the incidence of CI-AKI is quite variable. As is shown in the evidence profile (Suppl Table 24), the evidence that NAC reduces CI-AKI, as defined in the different trials, comes from studies with rather heterogeneous results; most of the studies were of either high or modest quality. In one study, a protective—even dose-dependent—effect was observed.[498] In that study, the risk for CI-AKI was reduced by 54.5% in the standard-dose NAC group and by 75.8% in the high-dose NAC group. These findings are in sharp contrast to many other studies showing no effect and, in particular, with the large study of Webb *et al.*,[499] which was terminated early after enrollment of 487 patients because of a determination of futility by the Data Safety Monitoring Committee. As mentioned earlier, combination studies of NAC with bicarbonate administration[486] have found a moderate benefit for this combination, compared to the combination of NAC-saline.

As recently remarked by Fishbane,[364] most of the studies published on NAC for the prevention of CI-AKI are quite small in size, and meta-analyses have been performed to increase the probability of explaining the full spectrum of utility for NAC. To date, seven out of the 11 meta-analyses that have been published on this subject found a net benefit for NAC in the prevention of CI-AKI.[364] However, as pointed out before, marked heterogeneity in the studies, and publication bias must lead to the conclusion that "pooling of data to arrive at a summary estimate for treatment efficacy

should generally be avoided in situations where the trials exhibit significant statistical and/or clinical heterogeneity".[500,501] A recent prospective RCT[502] was performed in patients with decreased kidney function (CrCl $\leqslant$60 ml/min and/or SCr level of $\geqslant$1.1 mg/dl [$\geqslant$97.2 μmol/l]), comparing a high oral dose of NAC with high doses of vitamin C. All patients underwent a coronary angiography. The primary end-point was the maximum increase of SCr level, and the secondary end-point was the incidence of CI-AKI, defined as a relative increase in baseline SCr level of $\geqslant$25% and/or an absolute increase of $\geqslant$0.5 mg/dl ($\geqslant$44.2 μmol/l) within 48 hours after contrast-media administration. The maximum increase of SCr level was significantly lower in the NAC group than in the ascorbic acid group (-0.03 ± 0.18 mg/dl [-2.65 ± 15.9 μmol/l] vs. 0.04 ± 0.20 mg/dl [3.54 ± 17.7 μmol/l]), respectively ($P = 0.026$). The incidence of CI-AKI tended to be in favor of NAC rather than ascorbic acid, 1.2% vs. 4.4%, respectively, although this difference was not significant ($P = 0.370$). It was concluded that an oral high dose of NAC seemed to be more beneficial than ascorbic acid in preventing CI-AKI, particularly in diabetic patients with pre-existing CKD.

Finally, a randomized, single-blind, controlled trial was recently published to assess NAC effects on CI-AKI and reperfusion injury in ST-segment elevation myocardial infarction (MI) patients undergoing primary angioplasty with moderate contrast-media volumes (between 120–230 ml of an iso-osmolar contrast medium).[496] The patients undergoing primary angioplasty were randomized to either high-dose NAC (two times 1200 mg/d for 48 hours; or placebo plus fluids). CI-AKI occurred in 14% of the NAC group and in 20% of the placebo group ($P = 0.28$). The myocardial salvage index was also not different between both treatment groups. Activated oxygen protein products and oxidized low-density lipoprotein as markers for oxidative stress were reduced by as much as 20% in the NAC group, whereas no change was evident in the placebo group.

Thus, despite high-dose i.v. NAC reducing oxidative stress, it does not provide an additional clinical benefit, compared to placebo, with respect to CI-AKI and myocardial reperfusion injury in nonselected patients undergoing angioplasty. A recent meta-analysis of all prospective trials of individuals randomized to either orally or i.v. administered high doses of NAC, defined as a daily dose greater than 1200 mg or a single periprocedural dose (within 4 hours of contrast-media exposure) $>$600 mg, was published by Trivedi *et al.*[497] The overall effect size, assuming a common OR, was 0.46 (95% CI 0.33–0.63) for the occurrence of CI-AKI with the use of high-dose NAC. The results of the more conservative random-effects approach were similar (OR 0.52; 95% CI 0.34–0.78).

Another recently published meta-analysis of RCTs included published trials and conference abstracts (Figure 16).[503] The primary and secondary outcomes of interest were CI-AKI, and renal failure requiring dialysis, respectively. Ten RCTs met the inclusion criteria. Nine studies compared combination treatment (bicarbonate and NAC) to NAC and normal saline; one study compared combination therapy to NAC alone; one study compared combination therapy to NAC with normal saline, and a separate arm with NAC and ascorbic acid. Collectively, combination treatment of NAC with i.v. sodium bicarbonate reduced CI-AKI by 35% compared to the other above-mentioned combinations (RR 0.65; 95% CI 0.40–1.05). However, the combination of NAC plus sodium bicarbonate did not significantly reduce renal failure requiring dialysis (RR 0.47; 95% CI 0.16–1.41). It was concluded that combination prophylaxis with NAC and sodium bicarbonate substantially reduced the occurrence of CI-AKI overall, but not dialysis-dependent renal failure. This paper suggests that combination prophylaxis should be incorporated for all high-risk patients (emergent cases or patients with pre-existing CKD). Most of the studies administered NAC orally; some studies used the i.v. route or even a combination of oral and i.v. There was also a substantial variation in doses and timing of NAC administration.

One additional study was recently published and was thus not included in the meta-analysis discussed above. Koc *et al.*,[504] investigated the efficacy of prophylactic i.v. NAC and fluids for the prevention of CI-AKI in patients with mild to moderate renal dysfunction (SCr $\geqslant$1.1 mg/dl [$\geqslant$97.2 μmol/l] or a CrCl $\leqslant$60 ml/min) who were undergoing coronary angiography. A group of patients was assigned to i.v. NAC (bolus of 600 mg twice daily before and on the day of the procedure) plus high-dose normal saline, a second group to only high-dose saline, and a third (control) group received standard saline. Patients in the NAC plus high-dose saline group received an i.v. bolus of 600 mg of NAC twice daily before and on the day of the coronary procedure (total 2.4 g) plus i.v. 0.9% saline 1 ml/kg/h before, on, and after the day of the coronary procedure. Patients in the high-dose arm received the same amount of isotonic saline, while patients in the control group received an i.v. dose of 0.9% saline 1 ml/kg/h for 12 hours before and 12 hours after the coronary procedure. The rate of CI-AKI in the NAC plus high-dose saline group was lower than in the high-dose saline group without NAC. No significant differences in the primary and secondary end-points were found between the high-dose saline and control groups.

In conclusion, based on the evidence tables and even taking the last recent study into account, the overall benefit of NAC is not consistent or overwhelming. On the other hand, oral NAC has a low risk of adverse events and usually a low cost.

THEOPHYLLINE AND FENOLDOPAM IN PREVENTION OF CI-AKI

Theophylline

4.4.4: We suggest not using theophylline to prevent CI-AKI. (*2C*)

RATIONALE

A rationale for the prophylactic use of adenosine antagonists in patients undergoing radiocontrast procedures was

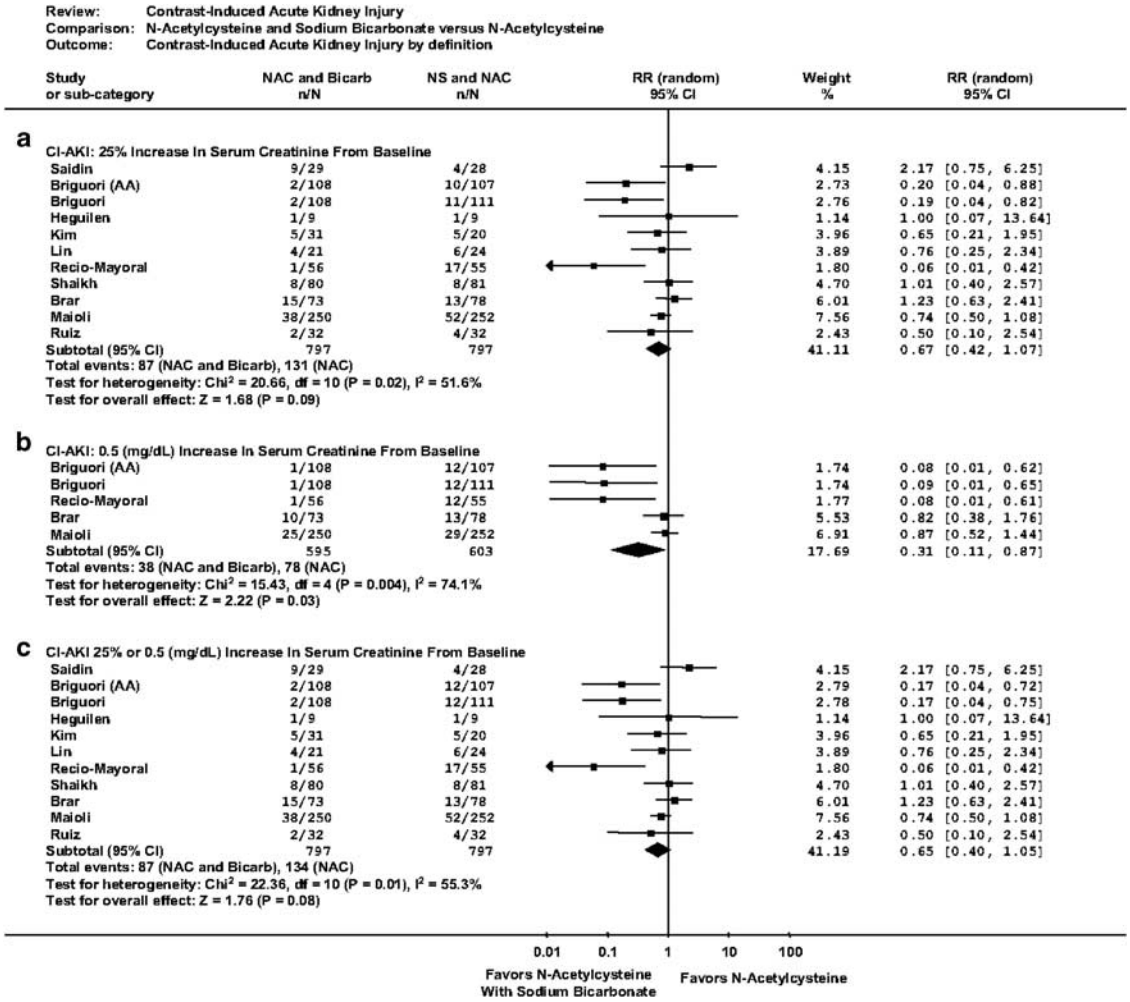

Figure 16 | NAC and bicarbonate vs. NAC for risk of CI-AKI. Reprinted from Brown, JR, Block CA, Malenka DJ *et al*. Sodium bicarbonate plus N-acetylcysteine prophylaxis: a meta-analysis. JACC Cardiovasc Interv 2009; 2: 1116–1124,[503] copyright 2009, with permission from American College of Cardiology Foundation; accessed http://interventions.onlinejacc.org/cgi/content/full/2/11/1116

suggested by results showing increased serum levels and urinary excretion of adenosine occurring after intravascular administration of contrast media.[505] The efficacy of theophylline in preventing CI-AKI has been addressed by a systematic review and meta-analysis in 2005 (nine RCTs, 585 patients),[506] and another meta-analysis in 2008 (six RCTs, 629 patients).[432] Both meta-analyses indicated a nonsignificant trend toward a renoprotective effect of theophylline prophylaxis. The incidence of CI-AKI tended to be lower (Bagshaw: OR 0.4, CI 0.14–1.16, $P = 0.09$; Kelly: OR 0.49, CI 0.23–1.06, $P = 0.14$), SCr concentrations 48 hours after intervention were significantly lower (-0.17 mg/dl; 95% CI -0.2 to -0.06 mg/dl [-15.0 µmol/l, CI -17.7 to -5.30 µmol/l]; $P = 0.002$) with theophylline compared to control therapies. However, the overall benefit was small and findings were inconsistent across studies. The benefit attributable to the use of theophylline tended to be less marked in patients receiving iso-osmolar, nonionic contrast media, and in patients undergoing a predefined saline protocol.

Neither meta-analysis included a RCT published in 2006 in 150 contrast-media examinations in 91 patients, in which the renoprotective effects of theophylline, NAC, and the combination of both were directly compared.[507] All patients had at least one risk factor for developing CI-AKI, and received more than 100 ml of low-osmolar radiocontrast agent. The incidence of CI-AKI was significantly lower with theophylline as compared to NAC pretreatment (2% vs. 12%; $P = 0.045$), and did not differ between theophylline monotherapy and the combination treatment. The renoprotective superiority of theophylline, which was given as a single i.v. 200 mg dose 30 minutes prior to the procedure, was even more significant in patients with pre-existing renal damage as indicated by an SCr > 1.5 mg/dl (> 133 µmol/l) ($P = 0.008$). Moreover, a recent study[508] randomized 217 patients with eGFR between 30 and 60 ml/min who were undergoing coronary angiography to one of three prophylactic treatments: i.v. isotonic saline (1 ml/kg/h for 12 hours before and after contrast media (group 1, n = 72); isotonic saline as in group 1 together with NAC (600 mg p.o. twice daily the

preceding day and the day of angiography (group 2, n = 73); or isotonic saline and NAC as in group 2 together with 200 mg theophylline orally twice daily for the preceding day and the day of angiography (group 3, n = 72). The incidence of CI-AKI (0.5 mg/dl or 44.2 μmol/l SCr increase within 48 hours of intravascular contrast-media injection) was 6.9% in group 1, 9.6% in group 2, and 0% in group 3 ($P < 0.03$), suggesting a beneficial effect of adding theophylline to a standard regimen in the prevention of CI-AKI. Notably, at least in this study, NAC administration had no additive protective effect compared to isotonic saline alone.

A very recent study[509] randomly assigned patients to prophylactic administration of saline with sodium bicarbonate plus theophylline (either orally or i.v.) or sodium bicarbonate only. Theophylline plus bicarbonate prophylaxis significantly reduced the incidence of CI-AKI (1.6% vs. 7.9%; $P = 0.015$) compared to bicarbonate alone. Theophylline was administered either orally (200 mg b.i.d. starting the day before the contrast administration and continuing for 24 hours thereafter) or i.v. 200 mg in a short infusion before contrast administration and continuing orally at 200 mg b.i.d. for 48 hours. Theophylline prophylaxis significantly reduced the incidence of CI-AKI in moderate and high-risk patients (0% vs. 8.8%; $P = 0.022$ and 9.1% vs. 42.1%; $P = 0.014$, respectively). This study did not mention side-effects of theophylline.

Although these data suggest that preinterventional theophylline administration might be helpful in patients at increased risk for CI-AKI, the possibility of cardiovascular side-effects and the interactions with numerous drugs associated with theophylline[510,511] should be recognized (Suppl Tables 26 and 27). As can be noted from the evidence profile tables, the evidence is low and the balance of benefits vs. harm is uncertain. In view of the low evidence and the uncertain balance of benefits vs. harm, the Work Group does not support the use of theophylline for prevention of CI-AKI.

Fenoldopam

4.4.5: We recommend not using fenoldopam to prevent CI-AKI. (*1B*)

RATIONALE

Fenoldopam is a selective dopamine A1 receptor agonist that might theoretically increase blood flow, especially to the renal medulla. Several uncontrolled studies (historical controls, retrospective review) suggested that it is effective in reducing the risk for contrast-induced nephropathy, and the results of a pilot trial were promising (for review, see Stacul *et al.*[512]). However, two prospective randomized trials showed negative results.[220,513] In the first trial,[513] patients were randomized to saline alone or with fenoldopam (0.1 μg/kg per minute for 4 hours before and after the procedure); a third arm was treated with NAC. The incidence of CI-AKI was similar in the fenoldopam (15.7%) and control (15.3%) groups, and there was no benefit over saline alone. A second, larger trial[220] also confirmed the lack of benefit with fenoldopam. In this double-blind trial of 315 patients, all with saline 0.45%, were randomized to fenoldopam (0.05 μg/kg per minute titrated to 0.1 μg/kg per minute) or placebo starting 1 h before the procedure and continuing for 12 hours afterward. There was no significant difference in the incidence of CI-AKI within 96 hours in the two groups (fenoldopam, 33.6%; placebo, 30.1%) or in the rates of dialysis, rehospitalization, or death at 30 days.

Statins in the prevention of CI-AKI

Two recent studies examined the use of statins in the prevention of CI-AKI patients with CKD. In the first study,[514] 31 patients were prospectively randomized to receive atorvastatin 80 mg/d or placebo for 48 hours before and 48 hours after contrast-medium administration. All patients received i.v. saline and oral NAC. CI-AKI occurred in 16 patients (11%) in the placebo group and 15 patients (10%) in the atorvastatin group. Persistent kidney injury, defined as 1-month increase from baseline creatinine value >25%, was observed in 30% in the placebo group and in 31% in the atorvastatin group. The second study[515] followed 431 patients, 194 of whom were receiving pravastatin treatment for hypercholesterolemia. SCr levels were measured at baseline (preprocedure) and within 48 hours after contrast-medium exposure (peak postprocedure). Logistic regression analysis revealed that pravastatin treatment, preprocedure SCr, and contrast volume were independently related to the decreased risk of CI-AKI. However, such studies are susceptible to the so-called "healthy user effect" where certain groups may have reduced risk, not because of the drug but because of healthier lifestyles, for which use of the medication is a marker. For example, patients taking statins may also be more compliant with other medical-care regimens that may reduce adverse events.

SUPPLEMENTARY MATERIAL

Supplementary Table 22: Evidence profile of RCTs examining effect of i.v. sodium bicarbonate vs. control for the prevention of CI-AKI.
Supplementary Table 23: Summary table of RCTs examining the effect of i.v. sodium bicarbonate on the prevention of CI-AKI.
Supplementary Table 24: Evidence profile of RCTs examining the effect of NAC vs. placebo on the prevention of CI-AKI.
Supplementary Table 25: Summary table of RCTs examining the effect of NAC vs. placebo on the prevention of CI-AKI.
Supplementary Table 26: Evidence profile of RCTs examining the effect of theophylline vs. placebo on the prevention of CI-AKI.
Supplementary Table 27: Summary table of RCTs examining the effect of theophylline vs. placebo on the prevention of CI-AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 4.5: Effects of hemodialysis or hemofiltration

4.5.1: We suggest not using prophylactic intermittent hemodialysis (IHD) or hemofiltration (HF) for contrast-media removal in patients at increased risk for CI-AKI. (*2C*)

RATIONALE

Contrast media are excreted mainly by glomerular filtration and there is a significant correlation between both total body and renal clearances of contrast media and GFR; the renal excretion of contrast media will thus be delayed in patients with renal failure (for review, see Deray).[516] Contrast media can be efficiently removed from blood by IHD and a single session effectively removes 60–90% of contrast media.[516,517] On the basis of these observations, several studies have explored the prophylactic value of IHD in patients at high risk, but most of these studies have not demonstrated a reduced incidence of CI-AKI.[516,518] For example, Vogt *et al.*[518] recorded renal function and other parameters, IHD requirements, and relevant clinical events before and during 6 days after administration of contrast media in 113 patients with a baseline SCr >2.3 mg/dl (>203 μmol/l). Eight out of 55 patients in the prophylactic IHD group and three in the non-IHD group ($P=0.12$), required IHD after contrast-media examination. Reinecke *et al.*[519] performed a prospective single-center trial in 424 consecutive patients with SCr concentrations between 1.3–3.5 mg/dl (115–309 μmol/l) who underwent elective coronary angiography. Patients were randomized to one of three treatment strategies with all patients receiving pre- and postprocedural fluids: one group received no additional therapy, patients in the second group were hemodialyzed once, and the third group received oral NAC. The frequency of CI-AKI (defined as an increase in SCr $\geqslant 0.5$ mg/dl or $\geqslant 44.2$ μmol/l) from 48 to 72 hours after catheterization was 6.1% in the fluids-only group, 15.9% with IHD treatment, and 5.3% in the NAC group (intention-to-treat analysis; $P=0.008$). There were no differences between the treatment groups with regard to increased SCr $\geqslant 0.5$ mg/dl ($\geqslant 44.2$ μmol/l) after 30–60 days (4.8%, 5.1%, and 3.1%, respectively; $P=0.700$). Analyses of long-term follow-up (range 63–1316 days) by Cox regressions models of the study groups found quite similar survival rates ($P=0.500$). This large study concluded that IHD, in addition to fluids, for the prevention of CI-AKI provided no evidence for any outcome benefit but showed evidence for probable harm.

A retrospective but important cohort study of 391 patients (age 69 ± 8 years, with chronic renal insufficiency [SCr $\geqslant 1.3$ mg/dl; $\geqslant 115$ μmol/l]) who underwent cardiac catheterization, also did not find any beneficial preventive effect.[520] By contrast, Lee *et al.*[521] presented a prospective RCT indicating that prophylactic IHD might be useful in patients scheduled for coronary angiography or coronary intervention with severely impaired renal function (baseline CrCl of 13 ml/min per 1.73 m^2). Patients were treated with normal saline at 1 ml/kg/h for 6 hours before and 12 hours after contrast-media administration and randomized to receive IHD for 4 hours as soon as possible after angiography or control treatment. Four days after angiography, SCr concentrations were lower in the IHD group compared to the control group. Out of 42 patients, one patient (2%) in the IHD group but 14 (35%) out of 40 patients in the control group required temporary IHD after coronary angiography. Furthermore, none of the 42 patients in the IHD group, but five (13%) out of 40 patients in the control group, required maintenance IHD after discharge from the hospital ($P<0.05$).

A recent meta-analysis of studies using periprocedural extracorporeal blood purification techniques[517] concluded that such treatments did not decrease the incidence of CI-AKI. It could theoretically be anticipated that high-flux membranes used in HF or hemodiafiltration (HDF) modalities should be able to remove contrast media more efficiently than low-flux membranes used in routine IHD. However, recent publications on this topic have added to the controversy about the role of IHD or HF to prevent CI-AKI (Suppl Tables 28 and 29). Marenzi *et al.*[522] studied 114 consecutive patients with CRF (SCr concentration >2 mg/dl or >177 μmol/l) who were undergoing coronary interventions. Fifty-eight patients were assigned to either HF starting before the contrast-medium administration and continuing for up to 24 hours after, while 56 patients were treated with isotonic saline at a rate of 1 ml per kilogram of body weight per hour, given in a step-down unit over the same time interval. In-hospital mortality was 2% in the HF group and 14% in the control group ($P=0.02$), and the cumulative 1-year mortality was 10% and 30%, respectively ($P=0.01$). Temporary RRT was required in 25% of the control group and in only 3% of the patients in the HF group. An increase in the SCr concentration of $>25\%$ from the baseline value after the coronary intervention occurred less frequently among patients in the HF group than among the control patients (5% vs. 50%, $P<0.001$). The effective removal of creatinine during HF or IHD makes it difficult to be certain that an observed lower incidence of CI-AKI is not related to the transport removal of creatinine during the procedure.

In a subsequent study, the same authors[523] randomized 92 patients with CKD (CrCl $\leqslant 30$ ml/min) to three different prophylactic treatments: i.v. isotonic saline (control group); i.v. saline for 12 hours before contrast-media exposure,

followed by HF for 18–24 hours after contrast-media exposure; and a third group where HF was performed for 6 hours before and for 18–24 hours after contrast-media exposure. The incidence of CI-AKI (>25% increase in SCr) and the in-hospital clinical course were compared in the three groups. In-hospital mortality was 20%, 10%, and 0%, respectively, in the three groups; IHD was required in nine (30%), 3 (10%), and zero (0%) patients, respectively ($P = 0.002$). According to these results, pre-HF is required to obtain the full clinical benefit, suggesting that among different mechanisms possibly involved, high-volume controlled volume expansion before contrast-media exposure plays a major role in prevention. This study further suggests that bicarbonate exposure with HF may ultimately have been the mechanism for the lower CI-AKI incidence (Suppl Table 29). In summary, the evidence profile for IHD vs. HF showed low-quality evidence and an uncertain benefit vs. harm balance of HF/IHD in preventing CI-AKI in patients with severe CKD. Given the costs and logistical difficulties, the use of HF modalities for CI-AKI prevention can only be advocated if future studies will convincingly show clear benefit.

SPONSORSHIP

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SUPPLEMENTARY MATERIAL

Supplementary Table 28: Evidence profile of RCTs examining the effect of hemodialysis or hemofiltration on the prevention of CI-AKI.

Supplementary Table 29: Summary table of RCTs examining the effect of hemodialysis or hemofiltration on the prevention of CI-AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Section 5: Dialysis Interventions for Treatment of AKI

Kidney International Supplements (2012) **2,** 89–115; doi:10.1038/kisup.2011.35

Chapter 5.1: Timing of renal replacement therapy in AKI

Whether or not to provide RRT, and when to start, are two of the fundamental questions facing nephrologists and intensive-care practitioners in most cases of severe AKI. In recent publications, the timing of initiation of RRT was listed as one of the top priorities in research on AKI.[524] However, this dimension has not been included as a factor in any of the large RCTs in this area. The optimal timing of dialysis for AKI is not defined. In current practice, the decision to start RRT is based most often on clinical features of volume overload and biochemical features of solute imbalance (azotemia, hyperkalemia, severe acidosis). However, in the absence of these factors there is generally a tendency to avoid dialysis as long as possible, a thought process that reflects the decisions made for patients with CKD Stage 5.

Clinicians tend to delay RRT when they suspect that patients may recover on their own, and because of concern for the well-known risks associated with the RRT procedure, including hypotension, arrhythmia, membrane bioincompatibility, and complications of vascular access and anticoagulant administration. There is also some concern that RRT may compromise recovery of renal function, and increase the progression of CKD.[525] Whether these risks outweigh the potential benefits of earlier initiation of RRT is still unclear.

5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (*Not Graded*)

5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (*Not Graded*)

RATIONALE

While no RCTs exist for dialysis for life-threatening indications, it is widely accepted that patients with severe hyperkalemia, severe acidosis, pulmonary edema, and uremic complications should be dialyzed emergently. In the absence of kidney function, and when therapeutic measures that promote the intracellular shift of potassium (such as correction of acidosis with bicarbonate, glucose and insulin infusion, and beta-2 agonists) are exhausted, an excess of potassium can only be eliminated with RRT. On the other hand, when intermittent dialysis is used after these therapeutic interventions, the extracorporeal removal of potassium will be reduced and the post-treatment rebound of serum potassium will be more pronounced.[526]

Metabolic acidosis is a frequent clinical problem in patients with severe AKI. Although the discussion as to when metabolic acidosis in critically ill patients should be corrected is outside the scope of this guideline, metabolic acidosis associated with AKI can usually be corrected with bicarbonate and should rarely require urgent dialysis if not accompanied by volume overload or uremia.[527] As the pH and bicarbonate values to initiate dialysis for metabolic acidosis are not supported by evidence, no standard criteria for initiating dialysis for acidosis exist. A variety of poisons, drug overdoses, and toxic compounds (e.g., salicylates, ethylene glycol, methanol, metformin) can contribute to acid-base problems and also lead to AKI. In these circumstances, RRT may also facilitate removal of the offending drug.[528–530]

Only one RCT has evaluated the effect of timing of initiation of RRT on outcome. Bouman *et al.*[531] randomized 106 critically ill patients with AKI to early vs. late initiation of RRT. The early initiation group started RRT within 12 hours of oliguria (<30 ml/h for 6 hours, not responding to diuretics or hemodynamic optimization), or CrCl <20 ml/min. The late-initiation group started RRT when classic indications were met. The study did not find differences in ICU or hospital mortality, or in renal recovery among survivors, but was clearly too small to allow for definitive conclusions (Suppl Table 30).

The remaining data come from observational studies. The association of early initiation of dialysis with survival benefit was first suggested by case series with historical controls conducted in the 1960 s and 1970 s.[532–535] In these studies, levels of blood urea or BUN were used to distinguish early vs. late start of dialysis. However, these studies mostly combined early start with more-intensive dialysis and late start with less-intensive dialysis. More recent studies have continued the trend focusing on BUN as a biomarker for starting RRT. Single-center observational studies that were restricted to AKI after trauma[536] and coronary artery bypass surgery[537,538]

suggested a benefit to RRT initiation at lower BUN concentrations. A prospective multicenter observational cohort study performed by the Program to Improve Care in Acute Renal Disease (PICARD) analyzed dialysis initiation—as inferred by BUN concentration—in 243 patients from five geographically and ethnically diverse clinical sites. Adjusting for age, hepatic failure, sepsis, thrombocytopenia, and SCr, and stratified by site and initial dialysis modality, initiation of RRT at higher BUN (>76 mg/dl [blood urea >27.1 mmol/l]) was associated with an increased risk of death (RR 1.85; 95% CI 1.16–2.96).[539] In a prospective multicenter observational study conducted at 54 ICUs in 23 countries, timing of RRT was stratified into "early" or "late" by median urea at the time RRT started (24.2 mmol/l [BUN 67.8 mg/dl]), and also categorized temporally from ICU admission into early (less than 2 days), delayed (between 2–5 days), or late (more than 5 days). Timing by serum urea showed no significant difference in mortality. However, when timing was analyzed in relation to ICU admission, late RRT was associated with greater crude mortality (72.8% late vs. 62.3% delayed vs. 59% early, $P=0.001$) and covariate-adjusted mortality (OR 1.95; 95% CI 1.30–2.92; $P=0.001$). Overall, late RRT was associated with a longer duration of RRT and stay in hospital, and greater dialysis dependence.[540] It is, however, not clear whether AKI occurring later in the course of ICU stay has the same pathophysiology and prognosis than AKI present on or early after admission. The most recent study on this subject is the analysis of surgical ICU patients with AKI, showing that late initiation of RRT (defined as RIFLE-I or -F) was an independent predictor of mortality (HR 1.846; CI 1.07–3.18).[541]

Traditional indications for RRT, developed for patients with advanced CKD, are not necessarily valid in the context of AKI. For instance, massive volume overload resulting from volume resuscitation may be an indication for RRT even in the absence of significant elevations in BUN or SCr. In this instance, it may be more appropriate to consider dialytic intervention in the ICU patient as a form of renal support rather than renal replacement. Indeed, some of the traditional indications for dialysis (e.g., uremic pericarditis, pleuritis, encephalopathy, coagulopathy) would be considered "complications" of AKI rather than indications for RRT. Additionally, the decision to start RRT should recognize the goals of therapy, keeping in mind the therapeutic potential of dialysis in general, and each dialysis modality in particular. The treatment of AKI with RRT has the following goals: i) to maintain fluid and electrolyte, acid-base, and solute homeostasis; ii) to prevent further insults to the kidney; iii) to permit renal recovery; and iv) to allow other supportive measures (e.g., antibiotics, nutrition support) to proceed without limitation or complication. Ideally, therapeutic interventions should be designed to achieve the above goals and a systematic assessment of all these factors is key to determining the optimal timing for initiating dialysis (Table 17).

There is increasing evidence that fluid overload in critical illness and AKI is associated with adverse outcomes, especially in the pediatric setting.[83,84,542–549] Whether this is a causal relationship remains to be proven, although a randomized trial in hemodynamically stable patients with acute respiratory distress syndrome seems to suggest that it is.[549] Randomizing patients according to RRT initiation on the basis of fluid status would allow this question to be answered. A secondary analysis of a randomized trial comparing IHD to CRRT showed that patients receiving RRT predominantly for solute control experienced better outcomes than those predominantly treated for volume overload. Patients dialyzed for control of both azotemia and volume overload experienced the worst outcome.[550] Analysis of a multicenter observational cohort showed that mean daily fluid balance in AKI patients was significantly more positive among nonsurvivors than survivors.[84] Data from the PICARD group examining 396 ICU patients with AKI requiring RRT further supports these findings. Survivors had lower fluid accumulation at dialysis initiation compared to nonsurvivors (8.8% vs. 14.2% of baseline body weight; $P=0.01$ adjusted for dialysis modality and severity score). The adjusted OR for death associated with fluid overload at dialysis initiation was 2.07 (95% CI 1.27–3.37).[83] These data suggest that fluid overload should be further evaluated as parameter to guide the initiation of RRT (see also *Pediatric Considerations*).

Other factors that might influence the decision of when to start RRT are the severity of the underlying disease (affecting the likelihood of recovery of kidney function), the degree of dysfunction in other organs (affecting the tolerance to e.g., fluid overload), the prevalent or expected solute burden (e.g., in tumor lysis syndrome), and the need for fluid input related to nutrition or drug therapy (Table 17). Early detection and accurate prediction of patients that ultimately will require RRT may allow earlier initiation in those who need it and, at the same time, prevent harm in those who do not. Recent evidence suggests a potential role for biomarkers in this field. Plasma neutrophil gelatinase-associated lipocalin was shown to have an area under the receiver operating characteristic curve of 0.82 for the prediction of RRT requirement.[551]

Pediatric considerations

Provision of acute RRT to children requires special considerations. Pediatric and adolescent patients range in age from the premature neonate to 25 years of age, with a size range of 1.5–200 kg. In addition, the epidemiology of the pediatric AKI has changed from primary kidney disease in the 1980 s to injury resulting from another systemic illness or its treatment (e.g., sepsis and nephrotoxic medications).[552,553] Newborns with inborn errors of metabolism who do not respond to dietary and pharmacologic management require expeditious dialytic removal of ammonia to decrease the risk of death and long-term neurologic dysfunction,[554] and infants who receive surgical correction of congenital heart disease, often receive PD early after cardiopulmonary bypass to prevent fluid overload and/or minimize the proinflammatory response. Finally, children develop multiorgan dysfunction very rapidly in their ICU course, with the maximal organ dysfunction

Table 17 | Potential applications for RRT

Applications	Comments
Renal replacement	This is the traditional, prevailing approach based on utilization of RRT when there is little or no residual kidney function.
Life-threatening indications	No trials to validate these criteria.
Hyperkalemia	Dialysis for hyperkalemia is effective in removing potassium; however, it requires frequent monitoring of potassium levels and adjustment of concurrent medical management to prevent relapses.
Acidemia	Metabolic acidosis due to AKI is often aggravated by the underlying condition. Correction of metabolic acidosis with RRT in these conditions depends on the underlying disease process.
Pulmonary edema	RRT is often utilized to prevent the need for ventilatory support; however, it is equally important to manage pulmonary edema in ventilated patients.
Uremic complications (pericarditis, bleeding, etc.)	In contemporary practice it is rare to wait to initiate RRT in AKI patients until there are uremic complications.
Nonemergent indications	
Solute control	BUN reflects factors not directly associated with kidney function, such as catabolic rate and volume status. SCr is influenced by age, race, muscle mass, and catabolic rate, and by changes in its volume of distribution due to fluid administration or withdrawal.
Fluid removal	Fluid overload is an important determinant of the timing of RRT initiation.
Correction of acid-base abnormalities	No standard criteria for initiating dialysis exist.
Renal support	This approach is based on the utilization of RRT techniques as an adjunct to enhance kidney function, modify fluid balance, and control solute levels.
Volume control	Fluid overload is emerging as an important factor associated with, and possibly contributing to, adverse outcomes in AKI. Recent studies have shown potential benefits from extracorporeal fluid removal in CHF. Intraoperative fluid removal using modified ultrafiltration has been shown to improve outcomes in pediatric cardiac surgery patients.
Nutrition	Restricting volume administration in the setting of oliguric AKI may result in limited nutritional support and RRT allows better nutritional supplementation.
Drug delivery	RRT support can enhances the ability to administer drugs without concerns about concurrent fluid accumulation.
Regulation of acid-base and electrolyte status	Permissive hypercapnic acidosis in patients with lung injury can be corrected with RRT, without inducing fluid overload and hypernatremia.
Solute modulation	Changes in solute burden should be anticipated (e.g., tumor lysis syndrome). Although current evidence is unclear, studies are ongoing to assess the efficacy of RRT for cytokine manipulation in sepsis.

AKI, acute kidney injury; BUN, blood urea nitrogen; CHF, congestive heart failure; SCr, serum creatinine; RRT, renal replacement therapy.

Table 18 | Fluid overload and outcome in critically ill children with AKI

Author	Cohort (N)	Outcome	*P*
Goldstein 2001[545]	Single-center (22)	Survivors 16% FO Nonsurvivors 34% FO	0.03
Gillespie 2004[544]	Single-center (77)	% FO >10% with OR death 3.02	0.002
Foland 2004[543]	Single-center (113)	3 organ MODS patients Survivors 9% FO Nonsurvivors 16% FO 1.78 OR death for each 10% FO increase	0.01
Goldstein 2005[546]	Multicenter (116)	2+ organ MODS patients Survivors 14% FO Nonsurvivors 25% FO <20% FO: 58% survival >20% FO: 40% survival	0.002
Hayes 2009[547]	Single-center (76)	Survivors 7% FO Nonsurvivors 22% FO OR death 6.1 for >20% FO	0.001
Sutherland 2010[548]	Multicenter (297)	<10% FO: 70% survival 10–20% FO: 57% survival >20% FO: 34% survival OR 1.03 (1.01–1.05) per % FO	0.001

AKI, acute kidney injury; FO, fluid overload; MODS, multiple-organ dysfunction syndrome; OR, odds ratio.
Reprinted from Goldstein SL. Advances in pediatric renal replacement therapy for acute kidney injury. Semin Dial 2011; 24: 187–191 with permission from John Wiley and Sons[560]; accessed http://onlinelibrary.wiley.com/doi/10.1111/j.1525-139X.2011.00834.x/full

occurring with 72 hours and mortality occurring within 7 days of ICU admission, respectively.[555,556] Thus, the issue of timing of dialysis initiation is critically important in children.

Both recommendations in this section of the guideline are applicable to pediatric patients. A detailed discussion of the specific pediatric clinical situations is beyond the scope of

this guideline, and the reader is referred to in-depth reviews.[557,558]

Importantly, fluid overload has emerged as a significant factor associated with mortality in children with AKI requiring CRRT (Table 18), although the physiological link between increasing percent volume overload and mortality is not completely clear.[543–548,559] The largest trial to assess this relationship in children is a multicenter prospective study showing that the percentage fluid accumulation at CRRT initiation is significantly lower in survivors vs. non-survivors ($14.2 \pm 15.9\%$ vs. $25.4 \pm 32.9\%$; $P<0.03$) even after adjustment for severity of illness. This study also found a significantly higher mortality in patient with $>20\%$ fluid overload (58%) vs. $<20\%$ fluid overload (40%) at CRRT initiation.[546] One retrospective study, in pediatric patients who received stem-cell transplantation and developed AKI, suggested that survival may be improved by an aggressive use of diuretics and early initiation of RRT. All survivors ($n=11$) maintained or remained with percentage fluid accumulation $<10\%$, with diuretics and RRT. Among the 15 nonsurvivors, only 6 (40%) had percentage fluid accumulation $<10\%$ at the time of death.[559] The latest analysis on this issue confirmed increased mortality with increasing fluid overload in 297 children treated with RRT: 29.6% mortality with less than 10% fluid overload, 43.1% with 10–20% fluid overload, and 65.6% with $>20\%$ fluid overload.[548] However, strong evidence to suggest that preventing this fluid overload with earlier RRT will improve outcome remains absent.

RESEARCH RECOMMENDATIONS

- Determine reproducible criteria (e.g., fluid overload, biomarker level, severity score) to inform the decision to start RRT in adult and pediatric AKI patients. Such criteria may also permit the identification of patients who will ultimately require RRT and hence limit uncertainty around whether to begin therapy.
- Determine whether early vs. late start of RRT, based on the above-mentioned criteria, results in improved clinical outcomes (e.g., mortality, evolution to CKD Stage 5) of AKI patients.

SUPPLEMENTARY MATERIAL

Supplementary Table 30: Summary table of RCTs examining the effect of early vs. late CVVH in the treatment of AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 5.2: Criteria for stopping renal replacement therapy in AKI

Although many patients with AKI recover kidney function sufficiently to be independent of RRT, discontinuation of RRT in AKI has received little attention in the literature. The decision whether or when to stop RRT in a patient with AKI needs to consider an improvement in kidney function adequate to meet demand, an improvement in the disorder that prompted kidney support or futility. It is evident that each of these events is influenced by the initial indication for starting RRT and is subject to individual variation. The strategy for stopping RRT requires consideration of additional factors and often involves a modality transition.

5.2.1: Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (*Not Graded*)

RATIONALE

Many, but not all, patients requiring RRT will recover enough function not to require long-term RRT. [21,394,561] The mean duration of RRT in two recent large RCTs was 12–13 days.[562,563] Thus, daily assessment of both intrinsic kidney function and the ongoing appropriateness of RRT consistent with the goals of therapy for the patient are required. More than 50% of patients with severe AKI will not improve, despite appropriate therapy. The incidence of withdrawal of life-support treatments in critically ill patients with multiorgan failure has increased over the last decade.[564] In addition to vasoactive medication, mechanical ventilation, and artificial nutrition, RRT is one of the therapies most likely to be discontinued during withdrawal of life support. In general, decisions to withdraw therapy occur in 10% of all patients from general ICUs, and are responsible for roughly 40% of all deaths. Analysis of a database of 383 AKI patients shows withdrawal of life support in 72% of deaths.[565] In another single-center retrospective study involving 179 AKI patients requiring RRT, therapy was withheld or withdrawn in 21.2%.[566] A posthoc analysis of the BEST KIDNEY database showed that CRRT was withdrawn in 13% of the patients, representing 29% of those who died while on CRRT and 21% of all nonsurvivors.[196]

Assessment of kidney function during RRT is not easy and will depend on the modality used. In IHD, the fluctuations of solute levels prevent achieving a steady state and thus exclude the use of clearance measurements. Native kidney function can only be assessed during the interdialytic period by evaluating urine volume, urinary excretion of creatinine, and changes in SCr and/or BUN values. However, one must realize that intermittent treatment will be associated with post-treatment rebound in solute levels, and that changes in BUN and creatinine levels can also be modified by nonrenal factors, such as volume status and catabolic rate. In CRRT, continuous solute clearance of 25–35 ml/min will stabilize serum markers after 48 hours. This allows more reliable measurements of CrCl by the native kidneys during CRRT.

Very few investigators have looked at urine CrCl values as a guide for CRRT withdrawal. One small retrospective study (published as abstract) demonstrated that a CrCl (measured over 24 hours) >15 ml/min was associated with successful termination of CRRT, defined as the absence of CRRT requirement for at least 14 days following cessation.[567] Further prospective trials will be needed to support these findings. A large prospective observational study showed that, in 529 patients who survived the initial period of CRRT, 313 were successfully removed from RRT, whereas 216 patients needed "repeat CRRT" within 7 days of discontinuation. Multivariate logistic regression identified urine output as the most significant predictor of successful termination (OR 1.078 per 100 ml/d). Not surprisingly, the predictive ability of urine output was negatively affected by the use of diuretics.[196] Another retrospective observational analysis showed that, of a total of 304 patients with postoperative AKI requiring RRT (IHD), 31% could be weaned for more than 5 days and 21% were successfully weaned for at least 30 days. Independent predictors for restarting RRT within 30 days were longer duration of RRT, a higher Sequential Organ Failure Assessment score, oliguria, and age >65 years.[568] In other words, urine output seems to be a very important predictor of successful discontinuation of RRT. Whether too-early discontinuation of RRT, requiring reinstitution, is by itself harmful has not been properly investigated. The above-mentioned observational studies found a higher mortality in patients who needed to be retreated with RRT (42.7% vs. 28.5%[196] and 79.7% vs. 40%[568]). It is, however, not clear whether failure to wean is simply a marker of illness severity or contributed by itself to the adverse outcome.

The process of stopping RRT may consist of simple discontinuation of RRT, or may include a change in the

modality, frequency, or duration of RRT. For example, switching from CRRT to IHD, or decreasing the frequency of IHD from daily to every other day, represents different methods of testing the ability of the patient's own kidney to take over. No specific guidance can be provided for how to manage the transition of RRT from continuous to intermittent. Evidence from large observational studies suggests that large variation in practice exists.[196]

5.2.2: We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT. (*2B*)

RATIONALE

The role of diuretics in the prevention and treatment of AKI has already been discussed in Chapter 3.4. Only one RCT has evaluated the potential role of diuretics in resolving AKI in patients receiving RRT. After the end of the CVVH session, the urine of the first 4 hours was collected for measuring CrCl. Seventy one patients were subsequently randomized to receive furosemide (0.5 mg/kg/h) or placebo by continuous infusion, continued until CrCl reached 30 ml/min. Urinary fluid losses were compensated by i.v. infusion. The primary end-point was renal recovery (CrCl >30 ml/min or stable SCr without RRT) in the ICU and in the hospital. CVVH was restarted based on predefined criteria. Patients treated with furosemide ($n=36$) had a significantly increased urinary volume and greater sodium excretion compared to placebo-treated patients ($n=35$). However, there were no differences in need for repeated CVVH, or renal recovery during ICU or hospital stay.[195] An observational study of discontinuation of RRT also found no difference in diuretic use between patents with successful or unsuccessful discontinuation of IHD.[568] In summary, diuretics may improve urine volume after RRT, but do not appear to have any significant benefit in reducing the need for RRT or promoting renal recovery from AKI.

Pediatric considerations

The medical indications guiding discontinuation of RRT in children do not differ from adults, except in those instances where RRT is initiated for pediatric-specific disease, such as inborn errors of metabolism to treat hyperammonemia[557] or immediately after surgical correction of congenital heart disease to maintain euvolemia, and/or possibly mitigate the postbypass proinflammatory response.[558]

Prognosis in children who survive an AKI episode is significantly better than in adults, and many children may have several decades of life expectancy. Askenazi demonstrated nearly 80% 3- to 5-year survival for children discharged after an AKI episode from a tertiary center,[569] yet two-thirds of deaths occurred in the first 2 years after discharge, suggesting a high probability of greater life expectancy after that period. In addition, no data exist to define a maximal RRT duration; even data from the Prospective Pediatric CRRT Registry show 35% survival in children receiving CRRT for >28 days.[570] Finally, since pediatric AKI now results more often as a secondary phenomenon from another systemic illness or its treatment,[552,553] determination of the overall goals of therapy for children, as in for adults, must take into consideration local standards, patient and family wishes, as well as the probability of recovery of the underlying illness leading to AKI and the need for RRT.

RESEARCH RECOMMENDATIONS

- Determine clinical parameters (e.g., parameters of kidney function, fluid overload, hypercatabolism) that predict successful discontinuation of RRT in AKI patients.
- Determine biomarkers that may indicate renal recovery, and whether their levels can be used to guide discontinuation of RRT.
- Determine more reliable predictors of long-term outcomes (e.g., mortality, quality of life) in AKI patients (including clinical severity scores, biomarkers, machine learning techniques, or combinations of these), that—after validation in large cohorts—could be helpful adjuncts in the decision to withdraw treatment.

Chapter 5.3: Anticoagulation

In patients with AKI requiring RRT, the contact of blood with the foreign surface of the extracorporeal circuit results in activation of both the intrinsic and the extrinsic pathway of plasmatic coagulation and activation of platelets.[571] Prevention of dialyzer/hemofilter clotting often requires some form of anticoagulation, which may represent a particular challenge in patients with AKI. The need for continuous anticoagulation represents a potential drawback of CRRT.

5.3.1: In a patient with AKI requiring RRT, base the decision to use anticoagulation for RRT on assessment of the patient's potential risks and benefits from anticoagulation (see Figure 17). (*Not Graded*)

5.3.1.1: We recommend using anticoagulation during RRT in AKI if a patient does not have an increased bleeding risk or impaired coagulation and is not already receiving systemic anticoagulation. (*1B*)

RATIONALE

The goal of anticoagulation with RRT is to prevent clotting of the filter and/or reduction in membrane permeability, and thus to achieve adequate RRT and to prevent blood loss in the clotted filter. These benefits have to be weighed against the risk of bleeding, and economic issues, such as workload and costs.

Patients with impaired coagulation (e.g., thrombocytopenia, or prolonged prothrombin time or activated partial thromboplastin time [aPTT]), due to underlying diseases such as liver failure or dilution coagulopathy, may not benefit from additional anticoagulation for RRT. In two recent large trials 50–60% of AKI patients requiring RRT were treated without anticoagulant.[562,563] While filter performance was not assessed, adequate CRRT filter survival without anticoagulation has mostly been described in patients with coagulopathies.[572–575] However, no specific cut-off points have been determined for platelet count, aPTT, International Normalized Ratio, fibrinogen, or other coagulation factors that would indicate the possibility to perform RRT without anticoagulation. On the other hand, prolonged clotting times can also point to a consumptive coagulopathy based on the presence of an activated coagulation. In these patients, frequent filter clotting will occur and necessitate a switch to some form of anticoagulation.[576]

In patients that are treated without anticoagulation, special attention is required to non-anticoagulant strategies to prolong filter survival. These include a good functioning vascular access, the reduction of blood viscosity and hemoconcentration by saline flushes, predilution, high blood flow rates, diffusive treatment, the reduction of blood-air contact in the bubble trap, and assuring prompt reaction to alarms.[577,578]

Many patients with AKI require systemic anticoagulation for their underlying diseases (e.g., artificial heart valve, acute coronary syndrome, atrial fibrillation). It is evident that, in most instances, these patients will not require additional anticoagulation for RRT; however, this should be assessed on a case-by-case basis.

5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:

5.3.2.1: For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. *(1C)*

5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. *(2B)*

5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. *(2C)*

RATIONALE

Worldwide, unfractionated heparin is still the most widely used anticoagulant. Many European centers, however, have switched from unfractionated to low-molecular-weight heparin for routine anticoagulation during IHD.[579] Advantages and disadvantages of each type of heparin are summarized in Table 19.

A recent meta-analysis of 11 RCTs comparing unfractionated to low-molecular-weight heparin in chronic IHD concluded that both are equally safe in terms of bleeding complications (RR 0.96; CI 0.27–3.43) and as effective in preventing extracorporeal thrombosis (RR 1.15; CI 0.7–1.91).[586] Mainly because of the convenience of using a single bolus injection at the start of IHD, the reduced risk of heparin-induced thrombocytopenia (HIT), and of long-term side-effects such as abnormal serum lipids, osteoporosis, and hypoaldosteronism, the European practice guideline for prevention of dialyzer clotting suggests using low-molecular-weight rather than unfractionated heparin in chronic dialysis patients.[587] Many European centers have extrapolated

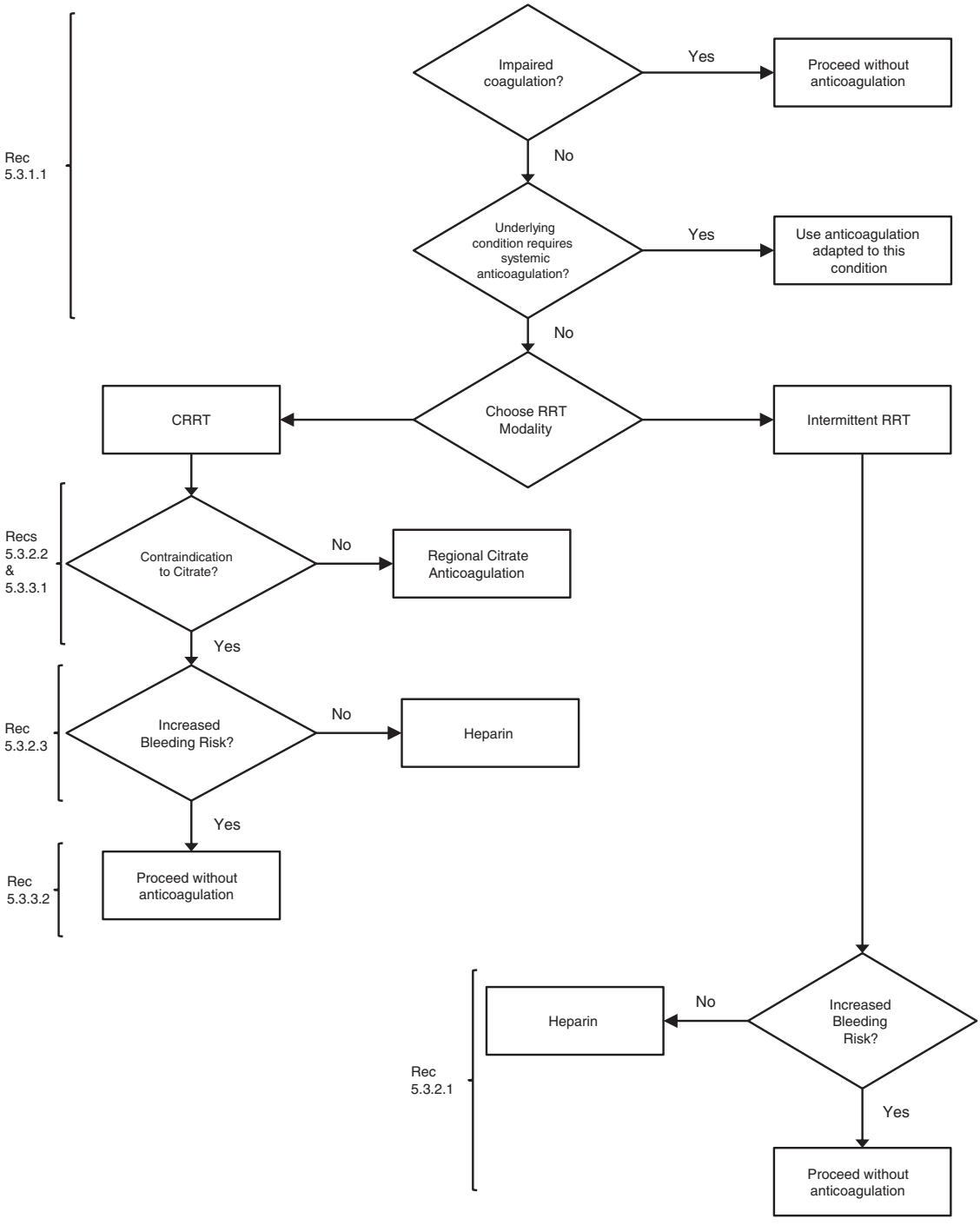

Figure 17 | Flow-chart summary of recommendations. Heparin includes low-molecular-weight or unfractionated heparin. CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

this to IHD for AKI, although studies in this setting are lacking. In patients with AKI, the dose of heparin for IHD and the target aPTT should be individualized according to the presence or absence of coagulation abnormalities and/or risk of bleeding.[588,589] Monitoring should also include platelet count, allowing timely detection of HIT.[581] Since low-molecular-weight heparins rely on the kidney as primary route of elimination, patients with kidney injury are at risk of accumulation and bleeding complications, depending on the degree of kidney injury, and the dose and type of low-molecular-weight heparin.[590] The American College of Chest Physicians (ACCP) guidelines for antithrombotic and thrombolytic therapy therefore suggest using unfractionated instead of low-molecular-weight heparin in patients with severe renal insufficiency (CrCl <30 ml/min) who require therapeutic anticoagulation, or to reduce the dose of low-molecular-weight heparin by 50%.[580] The doses of low-molecular-weight heparin that are required for IHD are

Table 19 | Overview of the advantages and disadvantages of different anticoagulants in AKI patients

Anticoagulant	Advantage	Disadvantage	References
Heparin (unfractionated)	Wide availability Large experience Short half-life Antagonist available Monitoring with routine tests (aPTT or ACT) Low costs	Narrow therapeutic index – risk of bleeding Unpredictable kinetics – monitoring required HIT Heparin resistance	580,581
Low-molecular-weight heparin	More predictable kinetics – Weight-based dosing possible More reliable anticoagulant response – No monitoring required Single predialysis dose may be sufficient in IHD Reduced risk of HIT	Risk of accumulation in kidney failure Monitoring requires nonroutine test (anti–Factor Xa) Different drugs not interchangeable Incomplete reversal by protamine In most countries more expensive than unfractionated heparin	580,582–584
Citrate	Strict regional anticoagulation – reduced bleeding risk	Risk of accidental overdose with potentially fatal consequences Insufficient citrate metabolism in patients with reduced liver function and shock states resulting in accumulation with metabolic acidosis and hypocalcemia Other metabolic complication (acidosis, alkalosis, hypernatremia, hypocalcemia, hypercalcemia) Increased complexity Requires strict protocol	585

aPTT, activated partial thromboplastin time; ACT, activated clotting time; HIT, heparin-induced thrombocytopenia; IHD, intermittent hemodialysis

lower than those required for therapeutic anticoagulation. The doses of low-molecular-weight heparin, as provided by the manufacturers, should be adapted to the bleeding risk of the individual patient. Dose reduction may also be required in patients receiving daily dialysis, which increases the risk of accumulation. Since many patients with AKI require prophylaxis for deep-vein thrombosis, scheduling this prophylactic (or a slightly higher) dose at the beginning of the dialysis session may serve the two purposes. Periodic measurement of anti–Factor Xa levels may be useful with prolonged use.

Alternative anticoagulants for IHD include protease inhibitors such as nafamostate and platelet inhibitors such as prostacyclin or its analogues. Randomized trials comparing these anticoagulants/antiaggregants with heparin in the setting of IHD for AKI are not available, and their use in clinical practice is limited. Nafamostat is a protease inhibitor that is mainly used in Japan and not available in the USA or Europe. Small observational trials in chronic dialysis patients with increased bleeding risk suggest a reduced bleeding incidence.[591–593] Concerns with nafamostat include the absence of an antidote, and side-effects such as anaphylaxis, hyperkalemia, and bone marrow suppression.[594–596] Crossover comparisons of prostacyclin with low-molecular-weight heparin in chronic dialysis patients show reduced efficiency.[597] A small trial showed reduced bleeding complications compared to low-dose heparin; however, at the expense of slightly more premature terminations.[598] Additional drawbacks are systemic hypotension and the high costs. Therefore, the routine use of alternative anticoagulants can not be recommended in patients with AKI.

The anticoagulant effect of sodium citrate relies on forming a complex with ionized calcium, thus removing an essential component of the coagulation cascade. Part of the citrate is removed in the extracorporeal circuit. Citrate reaching the systemic circulation is rapidly metabolized in the liver, muscle, and kidney, liberating the calcium and producing bicarbonate. The buffering effect of sodium citrate is proportional to the sodium ions it contains: a mole of trisodium citrate produces the same buffering effect as 3 moles of sodium bicarbonate; whereas preparations of citrate, including hydrogen citrate, have proportionally less buffering effect. Extracorporeal losses of calcium have to be compensated by an exogenous infusion. Additional complications of citrate are summarized in Table 19. Regional citrate anticoagulation requires a strict protocol, adapted to the local treatment modality and flow settings. The protocol should include instructions for the infusion of citrate and calcium, for the composition of the dialysate/replacement fluid, and for intensive metabolic monitoring, including acid-base status, sodium, and total and ionized calcium levels.

Five randomized trials have compared citrate to heparins during CRRT (Suppl Tables 31 and 32). For ethical reasons, these trials were performed in patients without increased bleeding risk. The first trial by Monchi *et al.* used a crossover design to compare anticoagulation with unfractionated heparin or citrate in 20 patients treated with postdilution CVVH. Patients with high bleeding risk, liver cirrhosis, and sensitivity to heparin were excluded. Forty-nine filters were evaluated. Citrate was titrated to achieve a postfilter ionized calcium level below 1.20 mg/dl (0.3 mmol/l). The dosing regimen of heparin consisted of a bolus of 2000 to 5000 U,

followed by a continuous infusion of 500–2000 U/h, aiming at an aPTT of 60–80 seconds. Despite this rather high heparin dose, the citrate group had a longer filter lifetime and less spontaneous filter failure. Fewer patients in the citrate group required transfusion, and the number of transfused units was also lower. One patient in the heparin group experienced bleeding and one patient in the citrate group had metabolic alkalosis.[599]

The second trial randomized 30 patients with AKI undergoing predilution continuous venovenous hemodiafiltration (CVVHDF) to anticoagulation with citrate or unfractionated heparin. Patients with contra-indications to one of the two anticoagulants (mainly high bleeding risk/severe coagulopathy or metabolic problems that might be aggravated by citrate) or who required systemic anticoagulation for medical reasons were excluded. Heparin was titrated to achieve an aPTT of 45–65 seconds. Citrate was titrated to a postfilter ionized calcium between 1.0–1.40 mg/dl (0.25–0.35 mmol/l). Two patients in each group crossed over to the other anticoagulant and these filters were not included in the analysis. The trial was stopped early after 79 filters because of an advantage using citrate, which resulted in a significantly improved filter survival (124.5 hours vs. 38.3 hours; $P<0.001$). In addition, significantly less citrate-anticoagulated filters were terminated for clotting (16.7% vs. 53.5%). The incidence of bleeding also tended to be lower with citrate (RR 0.17; CI 0.03–1.04; $P=0.06$), but transfusion requirement was not significantly different. Three patients in the citrate group had metabolic alkalosis and two had hypocalcemia.[600]

The third trial randomized 48 patients with AKI, treated with CVVH, to citrate or unfractionated heparin. Patients requiring systemic anticoagulation for medical reasons and patients with high bleeding risk, severe coagulopathy, circulatory failure, liver failure, or hypocalcemia were excluded (n = 12). A total of 142 circuits was analyzed. Heparin was administered as a bolus of 3000–5000 U followed by a continuous infusion of 1500 U/h adjusted to achieve an aPTT of 50–70 seconds. Citrate (500 mmol/l) was titrated to a postfilter ionized calcium between 1.0–1.20 mg/dl (0.25–0.30 mmol/l). Neither circuit survival nor the reasons for disconnecting the CVVH circuit differed significantly between the two groups. However, the number of major bleedings and the need for transfusion was significantly greater in the heparin group. Two cases of metabolic alkalosis were noted in the heparin group and two episodes of hypocalcemia in the citrate group.[601] Findings from two studies published after the cut-off date for our literature review are consistent with recommendation 5.3.2.2.[601a,601b]

A small randomized crossover study compared citrate anticoagulation to regional heparinization in 10 CVVH patients. Both treatment arms had a relatively short filter life (13 hours for regional heparinization and 17 hours for citrate) that did not differ significantly. No bleeding occurred in either group.[602]

In the largest and most recent randomized trial, 200 patients treated with postdilution CVVH were randomized to citrate or the low-molecular-weight heparin, nadroparin. Again, patients with bleeding risk or liver cirrhosis were excluded. Nadroparin was started with a bolus of 2850 U followed by 380 U/h without further monitoring. Citrate (500 mmol/l) was administered at a dose of 3 mmol per liter blood flow, without monitoring of postfilter ionized calcium. The primary outcomes were safety, defined as the absence of adverse events necessitating discontinuation of the study anticoagulant, and efficacy, defined as circuit survival. Safety was significantly better in the citrate group with only two patients requiring a change in anticoagulation regimen vs. 20 patients in the nadroparin group ($P>0.001$). Adverse events were citrate accumulation (n = 1) and early clotting due to protocol violation (n = 1) in the citrate group, and bleeding (n = 16) or severe thrombocytopenia (n = 4) in the nadroparin group. Circuit survival did not significantly differ. A computer-driven combination of buffered and nonbuffered replacement fluids was used in the citrate group, explaining why metabolic alkalosis occurred more frequently in the nadroparin group. Rather surprisingly, the authors also found an improved renal recovery and an improved hospital survival in the citrate group. This could not be attributed to differences in severity of illness, nor in bleeding or transfusion requirement, and requires further investigation.[603]

Metabolic complications were infrequent in these randomized trials. In observational trials, the most frequent metabolic complication is metabolic alkalosis, occurring in up to 50% of the patients.[604–606] In recently published surveys or large clinical trials, the use of regional citrate anticoagulation is still limited to 0–20% of the patients/treatments.[562,563,607]

A major contra-indication for the use of citrate anticoagulation is severely impaired liver function or shock with muscle hypoperfusion, both representing a risk of citrate accumulation. Markedly reduced citrate clearances and lower ionized calcium levels have been found in patients with acute liver failure or with severe liver cirrhosis.[608–610] These patients were excluded in all the randomized trials. In patients at risk, intensified monitoring is recommendable. The ratio of total to ionized calcium appears to be the best parameter to detect citrate accumulation[611,612] with an optimal cutoff at 2.1.[613] Another important drawback of citrate anticoagulation, that might influence the decision to implement it in routine clinical practice, is the increased complexity of the procedure, with risk of metabolic complications and the need for a strict protocol adapted to the local RRT modality. We, therefore, only recommend the use of citrate for anticoagulation during CRRT in patients that do not have shock or severe liver failure, and in centers that have an established protocol for citrate anticoagulation.

Unfractionated heparin still remains the most widely used anticoagulant during CRRT,[562,563,607] mostly administered as a prefilter infusion, with large variability in the administered doses. When choosing a dose of heparin, the clinician should realize that the relationship among heparin dose, aPTT, filter survival, and bleeding complications is not straightforward,[574,614–619] but it is common practice to measure aPTT

for safety reasons and to adapt the target to the bleeding risk of the patient.

Only two small prospective RCTs have compared unfractionated to low-molecular-weight heparin for anticoagulation during CRRT in patients with AKI and, thus, no firm recommendations can be made. The first trial randomized 47 patients with AKI or systemic inflammatory response syndrome undergoing CVVHDF to heparin, starting with a bolus of 2000–5000 U followed by an infusion of 10 U/kg/h titrated to an aPTT of 70–80 seconds, or to dalteparin administered as bolus of 20 U/kg followed by an infusion of 10 U/kg/h. The mean aPTT in the heparin group was 79 seconds. The mean anti–Factor Xa level, determined in six patients in the dalteparin group, was 0.49 U/ml. Only 37 of the 82 tested filters were stopped for coagulation. There was no difference in filter survival (with electively discontinued filters being censored). The mean time to filter failure was 46.8 hours in the dalteparin group and 51.7 hours in the heparin group (NS). Three patients in each group had bleeding, with no difference in transfusion requirement between the two groups. Daily costs, including the coagulation assays, were 10% higher with dalteparin.[620]

The second trial used a crossover design in 40 patients with normal coagulation parameters undergoing predilution CVVH. Patients treated with unfractionated heparin received a bolus of 30 U/kg followed by a continuous infusion of 7 U/kg/h titrated to achieve an aPTT of 40–45 seconds. Enoxaparin was given as an initial bolus of 0.15 mg/kg followed by a continuous infusion of 0.05 mg/kg/h, adjusted to an anti–Factor Xa level of 0.25–0.30 U/ml. In the 37 patients that completed both treatment arms, mean filter life was 21.7 hours with heparin and 30.6 hours with enoxaparin ($P = 0.017$). A similar difference was found in the per-protocol analysis. The incidence of bleeding was low and not different between the two anticoagulants. Filter life did not correlate with aPTT or anti–Factor Xa level. Costs were similar in the two groups.[616] Interestingly, these clinical studies did not find a correlation between anti–Factor Xa levels and filter life, questioning the value of anti–Factor Xa monitoring with regard to efficacy.[616,621] However, if used for more than a few days, monitoring might be useful to detect accumulation.

Alternative anticoagulants for use during CRRT include the protease inhibitor nafamostate and the platelet inhibitors, prostacyclin and analogues. Both have a short half-life and a low MW, with the theoretical advantage of extracorporeal elimination and reduced systemic anticoagulation. Nafamostat is not available in the USA and Europe; there is no antidote and several side-effects (agranulocytosis, hyperkalemia, anaphylactoid reactions) have been described.[594–596] A few small trials showed improved filter survival during CRRT when adding prostaglandins to heparin compared to heparin alone.[622–624] However, prostaglandins appear to have a limited efficacy when used alone, induce systemic hypotension,[625,626] and are expensive. Their use during CRRT can therefore not be recommended.

5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:

5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. ***(2C)***

5.3.3.2: We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. ***(2C)***

RATIONALE

The risk of bleeding is considered high in patients with recent (within 7 days) or active bleeding, with recent trauma or surgery (especially in head trauma and neurosurgery), recent stroke, intracranial arteriovenous malformation or aneurysm, retinal hemorrhage, uncontrolled hypertension, or presence of an epidural catheter. In these patients, the benefit of anticoagulation may not outweigh the risk of bleeding, and they should (at least initially) be treated without anticoagulation, or with CRRT with regional citrate anticoagulation.

We suggest performing RRT without anticoagulation in patients with increased bleeding risk. A possible exception can be made for patients who do not have contraindications for citrate. Randomized trials comparing citrate with heparins have been performed in patients without increased bleeding risk. However, since citrate results in strictly regional anticoagulation, it seems reasonable to also suggest its use during CRRT in AKI patients with increased bleeding risk.

Another approach to achieve regional anticoagulation is regional heparinization combining a prefilter dose of heparin, aiming at a prolongation of the extracorporeal aPTT, with postfilter neutralization with protamine, aiming at normalizing the systemic aPTT. This procedure has been described in chronic dialysis and CRRT,[572,573,624,627,628] but has not been studied with much scrutiny. It is cumbersome and difficult to titrate because heparin has a much longer half-life than protamine, inducing a risk of rebound. In addition, it exposes the patient to the side-effects of both heparin (mainly the risk of HIT) and protamine (mainly anaphylaxis, platelet dysfunction, hypotension, and pulmonary vasoconstriction with right ventricular failure)[629] and is therefore not recommended.

5.3.4: In a patient with heparin-induced thrombocytopenia (HIT), all heparin must be stopped and we recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. (*1A*)

5.3.4.1: In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (*2C*)

RATIONALE

Immune-mediated HIT results from antibodies directed against the complex of heparin and platelet factor 4, and occurs in 1–3% of heparin-exposed patients. Its main clinical complication is the development of thrombocytopenia with or without thrombosis.[581] In patients with AKI undergoing CRRT, the diagnosis should therefore also be suspected in patients with repeated premature filter clotting.[630] The likelihood of having HIT can be predicted by the so-called 4 T score, that includes the degree of thrombocytopenia, the timing of onset of the fall in platelet count, the presence of thrombosis or acute systemic symptoms, and the presence of other etiologies of thrombocytopenia.[631] If HIT is likely, all heparins have to be stopped, including any "heparin lock" solutions for dialysis or other catheters.

With regard to the diagnosis and management of HIT, we refer to the recent guideline of the ACCP[581] and the European best practice guideline on chronic dialysis.[587] These guidelines recommend the use of therapeutic doses of an alternative nonheparin anticoagulant in patients with strong suspicion of HIT. Candidates are the direct thrombin inhibitors lepirudin, argatroban, or bivaluridin, or the anti-thrombin-dependent Factor Xa inhibitors, danaparoid or fondaparinix. Pharmacokinetic data and dosing guidelines for these alternative anticoagulants have been published for IHD[588,632] and CRRT.[633]

Argatroban is a direct thrombin inhibitor, is eliminated by the liver, has a short half-life, and can be monitored with aPTT.[634] A recent observational study on the use of argatroban for anticoagulation during continuous dialysis in 30 patients with AKI and HIT derived a dosing equation, based on illness severity scores or by use of indocyanine green plasma clearance.[635] Regional citrate anticoagulation has been used along with reduced doses of argatroban or other nonheparin anticoagulants in cases where bleeding occurs. However, there are no published reports on this practice.

Pediatric considerations

Standardized protocols have been well established for both heparin and regional citrate anticoagulation in children receiving dialysis. The ppCRRT Registry Group has shown that heparin- and citrate-based anticoagulation protocols have been shown to confer equitable filter survival in pediatric CRRT, and the use of either is clearly supported over the use of no anticoagulation schemes.[636] The main advantage of citrate anticoagulation was the prevention of systemic pharmacological anticoagulation of the patient, which can be an issue in patients with multiorgan failure and sepsis. Calcium is a requisite cofactor in both the intrinsic and extrinsic coagulation cascades. Citrate functions by binding free calcium, thereby inhibiting coagulation in both the intrinsic and extrinsic coagulation pathways. The most frequently studied pediatric citrate protocol[636–638] uses Anticoagulant Dextrose solution A (ACD-A, Baxter Healthcare, USA), prescribed based on the blood flow rate:

$$\text{ACD rate (ml/h)} = \text{blood pump rate (ml/ min} \times \text{min /h)} \times 1.5$$

ACD-A is infused via a stopcock at the catheter-CRRT circuit connection leading to the CRRT machine. Since our prescribed blood pump flow is 200 ml/min, the resulting ACD-A rate would be 300 ml/h. The second aspect of the citrate protocol provides prevention of citrate-induced systemic hypocalcemia by providing a calcium chloride continuous infusion (8 g calcium chloride per liter normal saline) to the patient via a central line. The calcium chloride rate is also based on the blood pump rate:

$$\text{Calcium chloride (ml/h)} = \text{blood pump rate (ml/ min} \times \text{min /h)} \times 0.6$$

The goals of regional citrate anticoagulation are to maintain the circuit ionized calcium between 0.8 and 1.6 mg/dl (0.2 and 0.4 mmol/l), and the patient's systemic ionized calcium in the normal physiologic range 4.4–5.2 mg/dl (1.1–1.3 mmol/l). The circuit ionized calcium concentration is managed by adjustment of the citrate rate, while the patient's systemic ionized calcium concentration is managed by adjustment of the calcium chloride rate.

RESEARCH RECOMMENDATIONS

- Randomized trials should compare unfractionated to low-molecular-weight heparin during IHD in patients with AKI.
- Randomized trials should compare unfractionated to low-molecular-weight heparin during CRRT in patients with AKI.
- Randomized trials should compare citrate to unfractionated to low-molecular-weight heparin during CRRT in patients with AKI.
- Future trials should compare a strategy without anticoagulation against one of anticoagulation during CRRT.
- Outcomes of interest for trials testing different anticoagulation strategies with RRT in AKI are clinical end-points, including bleeding, renal recovery, mortality, incidence of HIT, and surrogates such as circuit survival and efficiency of dialysis, metabolic complications, and effects on the coagulation system.

SUPPLEMENTARY MATERIAL

Supplementary Table 31: Evidence profile of RCTs examining the effect of citrate vs. heparin/nadroparin in CRRT for AKI.
Supplementary Table 32: Summary table of RCTs examining the effect of citrate vs. heparin/nadroparin in CRRT for AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 5.4: Vascular access for renal replacement therapy in AKI

Functional vascular access is essential for adequate RRT. Basic requirements are to ensure adequate and regular flow with low morbidity. Most studies on indwelling tunneled dialysis catheters have been performed in chronic dialysis patients. For individuals requiring acute dialysis, the evidence on dialysis catheters is more limited, but there is a body of literature on nondialysis central venous catheters (CVC) in intensive-care patients. Many of the recommendations for patients requiring acute dialysis are, therefore, based on extrapolation of evidence from tunneled dialysis catheters or from nondialysis nontunneled CVC.

5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. (*2D*)

RATIONALE

Since most early catheter-related infections have a cutaneous origin, tunneling the catheter under the skin together with a subcutaneous anchoring system, may reduce the risk of infection. Tunneling also increases mechanical stability of the catheter. On the other hand, the insertion of a tunneled cuffed catheter (TCC) is a cumbersome procedure that requires expertise (mostly performed by surgeons or interventional radiologists), time, and effort (mostly performed in the operating room or radiology department), thus potentially delaying initiation of RRT. The removal of TCCs is also technically more difficult.

A randomized trial compared the initial use of tunneled vs. nontunneled femoral catheters in 34 patients with AKI. Failure to insert the TCC occurred in four patients (12%) that were excluded from the final analysis. In the remaining 30 patients, those with tunneled catheters had an increased insertion time and more femoral hematomas, but also less dysfunction, fewer infectious and thrombotic complications, and a significantly better catheter survival.[639] The small size of this study and the absence of an intention-to-treat analysis preclude firm conclusions (Suppl Table 33). In addition, the use of tunneled catheters for starting acute dialysis is not widespread practice.

Both the Centers for Disease Control (CDC) guidelines for prevention of catheter-related infections and the KDOQI guideline for vascular access in chronic dialysis patients recommend using a cuffed catheter for dialysis if a prolonged (e.g., >1–3 weeks) period of temporary access is anticipated.[640,641] In two recent large randomized trials, the mean duration of RRT for AKI was 12–13 days.[562,563] This probably does not justify the burden of an initial tunneled catheter in all patients with AKI receiving RRT. Rather, selected use of tunneled catheters in patients who require prolonged RRT is warranted.

No recommendation can be given regarding the optimal timing to change the nontunneled-uncuffed catheter to a more permanent access. It seems reasonable to create a more permanent access when recovery of kidney function is unlikely. The optimal timing should take into account the increased risk of infection with untunneled catheters, but also the practical issues related to the insertion of a tunneled catheter.

Several configurations of dialysis catheter lumen and tip have emerged over the years with no proven advantage of one design over another. The outer diameter varies between 11 and 14 French and it is self-evident that larger sizes decrease the risk of inadequate blood flow. In order to provide an adequate blood flow and reduce the risk of recirculation, the tip of the catheter should be in a large vein (see Recommendation 5.4.2). This means that the optimal length is 12–15 cm for the right internal jugular vein, 15–20 cm for the left internal jugular vein, and 19–24 cm for the femoral vein.[642–644]

In PD, the Tenckhoff catheter, a soft, silicone rubber catheter with a polyester cuff, reduced early complications such as bowel perforation, massive bleeding, or leakage, and has become the standard for PD. Further modifications, including the use of swan-neck catheters, T-fluted catheters, curled intraperitoneal portions, dual cuffs, and insertion through the rectus muscle instead of the midline, have been made to reduce remaining complications such as peritonitis, exit/tunnel infection, cuff extrusion, obstruction, and dialysate leaks.[645,646] Blind placement has been largely replaced by surgical placement or placement guided by ultrasound/fluoroscopy, laparoscopy, or peritoneoscopy.[647–649] Continuous-flow PD dictates the need for an efficient dual-lumen catheter or two separate catheters with ports separated maximally.[646] Outside the pediatric setting, no investigations have specifically looked at peritoneal catheters in the setting of AKI.

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (*Not Graded*):

- **First choice: right jugular vein;**
- **Second choice: femoral vein;**
- **Third choice: left jugular vein;**
- **Last choice: subclavian vein with preference for the dominant side.**

RATIONALE

Although generally associated with the lowest rate of infectious complications, the CDC guideline as well as the KDOQI guideline recommend avoiding the subclavian vein for RRT access,[640,641] because this may lead to central vein stenosis and jeopardize subsequent permanent access. This recommendation is mainly derived from observational data in ESRD patients showing a higher incidence of central vein stenosis with subclavian than with jugular dialysis catheters.[650,651] On the other hand, central vein stenosis has also been described after jugular catheterization.[652,653] Contact of the catheter with the vessel wall is considered a primary initiating event for catheter-related thrombosis and stenosis. Catheters in the right internal jugular vein have a straight course into the right brachiocephalic vein and superior vena cava, and, therefore, the least contact with the vessel wall. A catheter inserted through the subclavian or the left jugular vein has one or more angulations. explaining the higher risk of vessel contact and thrombosis/stenosis with subclavian compared to jugular catheters,[650,651] and with left-sided compared to right-sided jugular catheters.[654–656] The subclavian vein should, therefore, be considered the last choice for insertion of a dialysis catheter in patients with AKI, especially when the risk of nonrecovery of kidney function is substantial. Whether this recommendation should be extended to the left jugular vein remains unclear. In patients where the subclavian vein remains the only available option, preference should be given to the dominant side in order to spare the nondominant side for eventual future permanent access.

Because the subclavian vein should be avoided, the remaining options are the jugular and femoral veins. The use of femoral catheters is thought to be associated with the highest risk of infection, and avoidance of femoral lines is part of many "central line bundles" that intend to reduce the incidence of catheter-related bloodstream infection.[657] This dogma was questioned in a concealed, randomized, multicenter, evaluator-blinded, parallel-group trial of 750 AKI patients, comparing the femoral with the jugular site for first catheter insertion for RRT. Ultrasound was seldom used, probably explaining the somewhat higher rate of failure on one side and crossover in the jugular group. The rate of hematoma formation was also higher in the jugular group. In both groups, 20% of the catheters were antiseptic-impregnated. Mean duration of catheterization was 6.2 days for the femoral and 6.9 days for the jugular group. The major reasons for catheter removal were death or "no longer required". The incidence of catheter colonization at removal (the primary end-point) was not significantly different between the femoral and jugular group. When stratified according to body mass index (BMI), those within the lowest BMI tertile had a higher incidence of colonization with the jugular site, whereas those within the highest BMI tertile had the highest colonization rate with femoral catheters. Bloodstream infection did not differ between the groups (2.3 per 1000 catheter-days for jugular and 1.5 per 1000 catheter-days for femoral) but the study was not powered for this end-point. This was also the case for thrombotic complications (Suppl Table 34).[658]

Malfunction is another issue that needs to be considered when choosing between a jugular and femoral vascular access. Observational trials show more malfunctioning and a shorter actuarial survival for femoral than for jugular dialysis catheters],[659–661] and more malfunction with left-sided jugular catheters compared to right-sided.[662] Recirculation has been shown to be more frequent in femoral than subclavian or jugular dialysis catheters, especially with shorter femoral catheters.[642,643] A secondary analysis of the French multicenter trial did not find a difference in catheter dysfunction between jugular and femoral catheters in the intention-to-treat analysis. However, a separate analysis of the right and left jugular catheters showed a trend toward more dysfunction with femoral than with right jugular catheters, but significantly more dysfunction with left jugular compared to femoral catheters.[663]

Another point to consider is that any patient who has the option of undergoing a kidney transplantation should not have a femoral catheter placed to avoid stenosis of the iliac vein, to which the transplanted kidney's vein is anatomized.[640] The presence of a femoral catheter also reduces the patient's mobilization, especially when the RRT is continuous.

In summary, the right jugular vein appears to be the best option for insertion of a dialysis catheter. Femoral catheters are preferred over left jugular catheters because of reduced malfunction, and the subclavian vein should only be considered a rescue option. It is evident that individual patient characteristics may require deviations from this order of preferences. Catheter insertion should be performed with strict adherence to infection-control policies, including maximal sterile barrier precautions (mask, sterile gown, sterile gloves, large sterile drapes) and chlorhexidine 2% skin antisepsis.[641,664,665]

5.4.3: We recommend using ultrasound guidance for dialysis catheter insertion. (*1A*)

RATIONALE

For several decades, techniques involving the use of anatomic landmarks have been the traditional mainstay of accessing the central venous system. Using the "blind" landmark technique is not without significant morbidity and mortality. Complications of central venous catheterization include arterial puncture (0.5–6%), hematoma (0.1–4.4%), hemothorax (0.4–0.6%), pneumothorax (0.1–3.1%), and up to 10–20% of insertion attempts are not successful.[666,667] In view of their large size, the risk of complications of dialysis catheters is expected to be even higher. Two meta-analyses have addressed the role of real-time two-dimensional ultrasound for central vein cannulation, and concluded that, compared to the landmark method, ultrasound-guided venous access

increases the probability of successful catheter placement and reduces the risk of complications, the need for multiple catheter placement attempts, and the time required for the procedure. The advantage appears most pronounced for the jugular vein, whereas the evidence is scarce for the subclavian and femoral vein.[668,669] Subsequent large randomized trials have confirmed the superiority of ultrasound guidance.[670,671] Trials evaluating the placement of dialysis catheters in ESRD patients, mostly with observational design, yield a similar conclusion.[672–678] The KDOQI guideline for vascular access also recommends using ultrasound-assisted insertion.[640]

5.4.4: We recommend obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter. (*1B*)

RATIONALE

Uncuffed, nontunneled dialysis catheters are semirigid. Their tip should not be in the heart, because of the risk of atrial perforation and pericardial tamponade. On the other hand, a position too high in the brachiocephalic vein, especially with subclavian and left-sided catheters, should also be avoided, because it allows a narrow contact between the catheter tip and the vessel wall, which may result in improper catheter function and vessel thrombosis.[655,679,680] The correct position of the tip of a semirigid dialysis catheter is at the junction of the superior vena cava and the right atrium, allowing the catheter to run in parallel with the long axis of the superior vena cava.[679] Tunneled catheters are usually softer and can be positioned into the right atrium, thus allowing a higher blood flow.[680]

To confirm the correct position and to assess for potential complications, a postprocedural chest radiograph is conventionally performed. Although this procedure has been debated after uneventful placement of a CVC, the high blood flows used during RRT and the administration of anticoagulants necessitate confirming the correct position before initiating dialysis therapy.[640] It should, however, be remembered that none of the radiographic landmarks (carina, right tracheobronchial angle, etc) that are used to exclude intra-atrial tip position are 100% reliable.[679,680] Echocardiography might be another tool to confirm the correct position of the catheter.[681]

5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. (*2C*)

RATIONALE

The incidence of catheter-related bloodstream infection can be reduced by implementing education-based programs and so-called central-line bundles, that emphasize the importance of hand hygiene, maximal barrier precautions upon insertion, chlorhexidine skin antisepsis, optimal catheter site selection, and daily review of line necessity.[657] For detailed instructions on catheter care, the reader is referred to published guidelines.[640,641,664,665] These guidelines also recommend not using dialysis catheters for applications other than RRT, except under emergency circumstances.[641]

A recent meta-analysis of five RCTs confirmed that topical antibiotics (mainly mupirocin) reduce the risk of bacteremia, exit-site infection, need for catheter removal, and hospitalization for infection in ESRD patients.[682] The majority of the catheters in the included studies were tunneled. However, the CDC, National Health Service, and Infectious Diseases Society of America guidelines strongly recommend against topical antibiotic ointment for the care of CVC, because of their potential to promote fungal infections and antimicrobial resistance.[641,664,665] For patients with AKI that are treated in an ICU, it seems reasonable to follow this last recommendation. No recommendations can be given for AKI patients that are treated outside an ICU.

5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. (*2C*)

RATIONALE

Four meta-analyses have evaluated the efficacy of various antibiotic lock solutions in chronic dialysis patients, and conclude that they significantly reduce catheter-related bloodstream infection. Drawbacks are the overall moderate trial quality and the short follow-up that does not allow excluding the development of resistance.[682–685] However, the CDC, National Health Service, and Infectious Diseases Society of America guidelines strongly recommend against routinely using antibiotic lock solutions in CVC, because of their potential to promote fungal infections, antimicrobial resistance, and systemic toxicity.[641,664,665] Mentioned exceptions are long-term cuffed and tunneled catheters with history of multiple catheter-related bloodstream infections despite maximal adherence to aseptic technique,[641,665] patients with limited venous access and history of recurrent catheter-related bloodstream infection, or patients with heightened risk of severe sequelae from a catheter-related bloodstream infection.[664]

Pediatric considerations

Most of the guidelines for adults are applicable to children. Functional CRRT circuit survival in children is favored by larger catheter size[686] that should be adapted to patient size (Table 20).[687] Recent data from the Prospective Pediatric CRRT Registry group shows that internal jugular catheters may be associated with longer functional CRRT circuit survival, compared to femoral and subclavian access.[686] In addition, the Prospective Pediatric CRRT Registry group showed extremely poor circuit survival with two single-lumen 5 F catheters; these catheters should therefore be avoided. Future permanent access in the form of an arteriovenous graft or fistula for patients who develop CKD may be

Table 20 | Catheter and patient sizes

Patient size	Catheter size	Site of insertion
Neonate	Double-lumen 7F	Femoral artery or vein
3–6 kg	Double- or triple-lumen 7F	Jugular, subclavian, or femoral
6–30 kg	Double-lumen 8F	Jugular, subclavian, or femoral
>15 kg	Double-lumen 9F	Jugular, subclavian, or femoral
>30 kg	Double-lumen 10F or triple-lumen 12F	Jugular, subclavian, or femoral

Reprinted from Bunchman TE, Brophy PD, Goldstein SL. Technical considerations for renal replacement therapy in children. Semin Nephrol 2008; 28: 488-492 [687], copyright 2008, with permission from Elsevier; accessed http://www.seminarsinnephrology.org/article/S0270-9295(08)00117-4/fulltext

compromised if acute access is placed in a subclavian vein. Clinicians must therefore consider the potential long-term vascular needs of patients who may be expected to develop CKD, especially children who have demonstrated excellent long-term survival with CKD and ESRD.[688]

Analysis of a pediatric database (1989–1999) showed that surgically placed Tenckhoff catheters for PD induce less complications than more stiff percutaneously placed catheters.[689] A more recent retrospective analysis with historical controls reports that, compared to the surgically placed Tenckhoff catheter, using a more flexible catheter for percutaneous insertion may achieve a comparable catheter survival and complication rate.[690]

RESEARCH RECOMMENDATIONS

- Determine whether the initial use of a tunneled vs. nontunneled catheter for RRT in AKI patients results in a beneficial effect on catheter function and catheter-related complications, including infections and number of additional access procedures.
- Develop better means of predicting the need for long-term access and better methods to select access site in individual patients by balancing various risks and benefits.

SUPPLEMENTARY MATERIAL

Supplementary Table 33: Summary table of RCTs examining the effect of access placement with tunneled versus non-tunneled catheters on AKI.

Supplementary Table 34: Summary table of RCTs examining the effect of jugular vs. femoral access placement on AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 5.5: Dialyzer membranes for renal replacement therapy in AKI

Semipermeable hollow-fiber dialyzers are used as standard of care for both solute clearance and ultrafiltration in IHD and CRRT circuits. Membrane composition and clearance characteristics vary among the commercially available dialyzers. While no RCTs exist to provide definitive recommendations for a particular dialyzer type, the characteristics and potential side-effects of each dialyzer type require consideration.

5.5.1: We suggest to use dialyzers with a biocompatible membrane for IHD and CRRT in patients with AKI. (*2C*)

RATIONALE

Semipermeable hollow-fiber dialyzers currently represent the standard of care for IHD or CRRT for patients with AKI. All dialyzer membranes induce some degree of activation of blood components, a phenomenon called bioincompatibility.[691] Earlier-generation dialyzer membranes composed of cuprophane or unmodified cellulose were more bioincompatible and had the potential to cause a "dialyzer membrane reaction", mediated by complement activation, release of proinflammatory markers, and oxidative stress, and manifested clinically by acute hypotension, vasodilatation, leucopenia, hypoxia and fever.[692–697] More recently, modified cellulosic membranes (with substitution of the hydroxyl groups) and synthetic membranes composed of polyacylnitrile, polysulfone, or poly(methyl methacrylate) have been developed. These "biocompatible membranes" (or less bioincompatible membranes) produce less complement and cytokine activation, and decrease oxidative stress.[697,698] Recent studies suggest that platelet activation might also be involved in the bioincompatibility phenomenon.[698–701] Another membrane characteristic that might have clinical importance is the flux property, with membranes generally being divided in low-flux and high-flux, the latter having larger pores and thus the potential to clear larger solutes. The question of whether membrane bioincompatibility or flux has clinical relevance in the setting of AKI has been the subject of many clinical trials. A recent meta-analysis of 10 randomized or quasi-randomized controlled trials in 1100 patients could not establish any advantage for biocompatible or high-flux membranes.[702] Of note, the authors chose to include modified cellulose membranes in the bioincompatible group, although other investigators consider modified cellulosic membranes to be biocompatible. When comparing the synthetic membranes to cuprophane, there was a trend towards reduced mortality with the synthetic membranes. This meta-analysis also did not assess the side-effects of different membrane compositions on more proximal, temporal associations, such as acute hypotension or fever. As a result, we agree with the authors' conclusion that the use of either a biocompatible or modified cellulose acetate membrane appears to be appropriate.

Recent observations reveal specific potential side-effects when using certain dialyzer membranes. Bradykinin release syndrome has been observed at the start of CRRT with uncoated AN-69 membranes.[703] Bradykinin release syndrome is characterized by acute hypotension and pulmonary vascular congestion. The syndrome is usually self-limited and is pH-dependent, and therefore more pronounced in patients with severe acidosis. Also, priming of the circuit with banked blood (that is acidotic and contains a large amount of citrate, inducing hypocalcemia) may evoke bradykinin release syndrome. Numerous measures have been published to prevent or mitigate this syndrome, including zero-balance HF to normalize the banked blood pH and calcium,[704] or a bypass maneuver in which the blood prime is given to the patient instead of the circuit, while the patient is bled on to the circuit with the saline prime discarded.[705] Finally, a form of bradykinin release syndrome has been reported in patients receiving ACE-I and IHD with AN-69 membranes,[706–708] since ACE-I prevent the conversion of bradykinin and thereby prolong the hypotensive response when acidic blood comes in contact with the AN-69 membrane. However, others have disputed this interaction.[704,705] Nevertheless, clinicians should be aware of the potential for bradykinin release syndrome if an uncoated AN-69 membrane is employed for RRT, especially in acidotic patients or in those receiving ACE-I. Neutralizing the electronegativity of the AN-69 membrane by coating with polyethyleneimine significantly reduces bradykinin generation.[709]

Whether conventional dialysis membranes are able to affect clinical outcomes in sepsis by removal of inflammatory mediators remains highly controversial. Until further evidence becomes available, the use of RRT to treat sepsis should be considered experimental.

RESEARCH RECOMMENDATIONS

- Future research should assess the impact of middle-molecule clearance by high-flux membranes and/or membrane adsorption on patient outcome in sepsis.

The comparator group should be patients with sepsis that do not receive extracorporeal treatment (if no AKI) or conventional RRT (if AKI).

- The potential impact of dialyzer membrane composition (material, flux, etc.) on outcomes in patients with AKI remains unsettled, due to the relatively small size of trials. It would be useful to conduct larger trials comparing different membranes and examining patient-centered outcomes include survival, renal recovery, and resource utilization.

Chapter 5.6: Modality of renal replacement therapy for patients with AKI

Controversy exists as to which is the optimal RRT modality for patients with AKI. In current clinical practice, the choice of the initial modality for RRT is primarily based on the availability of, and experience with, a specific treatment and on the patient's hemodynamic status. Transitions between CRRT and IHD are also frequent, mostly determined by the hemodynamic status of the patient or coagulation problems. Experience with PD in AKI is limited, except in the pediatric setting and in regions with limited resources.

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (*Not Graded*)

RATIONALE

Current modalities of RRT for AKI include IHD, CRRT, and PD. An overview of the different modalities of RRT and their commonly used settings is given in Table 21.

Since the introduction of CRRT into clinical practice in the early 1980 s, its use in critically ill patients with AKI has increased steadily.[710–712] The theoretical advantages of CRRT over IHD are the slower fluid removal, resulting in more hemodynamic stability and better control of fluid balance, the slower control of solute concentration, avoiding large fluctuations and fluid shifts (including a reduced risk [worsening] of cerebral edema), the great flexibility (allowing adaptation of the treatment to the patient's need at any time), and the ability to perform the treatment with relatively simple and user-friendly machines (allowing ICU nurses to monitor the treatment). Disadvantages include the need for immobilization, the use of continuous anticoagulation, the risk of hypothermia and, in some settings, higher costs. Major advantages of IHD over CRRT are the fast removal of toxins and the restricted treatment period, allowing down-time for diagnostic and therapeutic interventions. IHD may, therefore, be the preferred treatment in patients where immediate removal of small solutes is required, such as severe hyperkalemia, some cases of poisoning, and tumor lysis syndrome. Hybrid treatments, such as SLED, may share some of the advantages of both IHD and CRRT without having their disadvantages (Table 22).

Several RCTs have compared CRRT to IHD in AKI patients. The most inclusive meta-analysis was performed by the Cochrane Collaboration, analyzing 15 RCTs in 1550 AKI patients. This analysis concluded that outcomes were similar in critically ill AKI patients treated with CRRT and IHD for hospital mortality (RR 1.01; 95% CI 0.92–1.12; n = 1245), ICU mortality (RR 1.06; 95% CI 0.90–1.26; n = 515), length of hospitalization (mean deviation −6.1; 95% CI −26.45 to −14.25; n = 25), and renal recovery (free of dialysis on discharge) in survivors (RR 0.99; 95% CI 0.92–1.07; n = 161).[713] Comparable results have been reported by other meta-analyses.[714,715] Individual studies used different definitions of AKI and were underpowered. Most of the trials excluded patients with hypotension or maximized efforts to improve the hemodynamic tolerance of IHD. The high rate of crossover between the treatment modalities also complicates the interpretation of the results. In addition, in some of the trials, IHD patients were treated with bioincompatible membranes and studies were not standardized for treatment dose. A subsequent RCT not included in the Cochrane meta-analyses reported similar outcomes.[716] Two recent studies, confined to single geographic regions, showed reduced costs with IHD compared to CRRT.[717,718] However, an analysis of cost ranges from a multicenter, multinational observational study found considerable heterogeneity in costs related to IHD and CRRT, and concluded that either therapy might be

Table 21 | Typical setting of different RRT modalities for AKI (for 70-kg patient)

	SCUF	CVVH	CVVHD	CVVHDF	PD	SLED	IHD
Blood flow (ml/min)	100–200	150–250	150–250	150–250	N/A	100–300	200–300
Predominant solute transport principle	convection	convection	diffusion	diffusion + convection	diffusion	diffusion	diffusion
Ultrafiltrate (ml/h)	100–300	1500–2000	variable	1000–1500	variable	variable	variable
Dialysate flow (ml/h)	0	0	1500–2000	1000–1500	1–2 l per exchange	100–300 ml/min	300–500 ml/min
Effluent volume (l/d)	2–8	36–48	36–48	36–72	24–48	N/A	N/A
Replacement fluid for zero balance (ml/h)	0	1500–2000	0	1000–1500	0	0	0
Urea clearance (ml/min)	1–5	25–33	25–33	25–33	variable	80–90	variable

CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis, CVVHDF, continuous venovenous hemodialfiltration; IHD, intermittent hemodialysis; N/A, not applicable; PD, peritoneal dialysis; SCUF, slow continuous ultrafiltration; SLED, slow low-efficiency dialysis.

Table 22 | Theoretical advantages and disadvantages of CRRT, IHD, SLED, and PD

Modality	Potential setting in AKI	Advantages	Disadvantages
IHD	Hemodynamically stable	Rapid removal of toxins and low-molecular-weight substances Allows for "down time" for diagnostic and therapeutic procedures Reduced exposure to anticoagulation Lower costs than CRRT	Hypotension with rapid fluid removal Dialysis disequilibrium with risk of cerebral edema Technically more complex and demanding
CRRT	Hemodynamically unstable Patients at risk of increased intracranial pressure	Continuous removal of toxins Hemodynamic stability Easy control of fluid balance No treatment-induced increase of intracranial pressure User-friendly machines	Slower clearance of toxins Need for prolonged anticoagulation Patient immobilization Hypothermia Increased costs
SLED	Hemodynamically unstable	Slower volume and solute removal Hemodynamic stability Allows for "down time" for diagnostic and therapeutic procedures Reduced exposure to anticoagulation	Slower clearance of toxins Technically more complex and demanding
PD	Hemodynamically unstable Coagulopathy Difficult access Patients at risk of increased intracranial pressure Under-resourced region	Technically simple Hemodynamic stability No anticoagulation No need for vascular access Lower cost Gradual removal of toxins	Poor clearance in hypercatabolic patients Protein loss No control of rate of fluid removal Risk of peritonitis Hyperglycemia Requires intact peritoneal cavity Impairs diaphragmatic movement, potential for respiratory problems

CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; PD, peritoneal dialysis; SLED, sustained low-efficiency dialysis.

more or less costly depending on local practices, especially staffing.[719]

Some large observational studies, including all patients receiving RRT, suggest that CRRT is an independent predictor of renal recovery among survivors.[720–722] This evidence, however, is insufficient to fully elucidate the impact of choice of therapy on this outcome. Appropriately planned prospective trials will be required to address this issue.

In conclusion, no RRT is ideal for all patients with AKI. Clinicians should be aware of the pros and cons of different RRTs, and tailor RRT on the basis of the individual and potentially changing needs of their patients. Besides the individual patient's characteristics, the available expertise and resources may also be an important determinant of the ultimate choice.

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (*2B*)

RATIONALE

Many clinicians prefer CRRT in critically ill AKI patients with severe hemodynamic instability, because of better hemodynamic tolerance due to the slower fluid removal and the absence of fluid shifts induced by rapid solute removal. The Cochrane meta-analysis could not establish a difference in the number of patients with (however poorly defined) hemodynamic instability (RR 0.48; 95% CI 0.10–2.28; n = 205) nor with (variably defined) hypotension (RR 0.92; 95% CI 0.72–1.16; n = 514). On the other hand, the mean arterial pressure at the end of the treatment was significantly higher with CRRT than with IHD (mean deviation 5.35; 95% CI 1.41–9.29; n = 112) and the number of patients requiring escalation of vasopressor therapy was significantly lower with CRRT compared to IHD (RR 0.49; 95% CI 0.27–0.87; n = 149).[713] In general, the number of patients included in these analyses of the hemodynamic tolerance of RRT remains limited, and none of the RCTs has specifically looked at the effect of different modalities of RRT in patients with shock.

SLED has been proposed as an alternative to other forms of RRT and is used in many centers worldwide for logistical reasons. A recent review[723] summarizes the results obtained with SLED in several studies and discusses in detail the technical aspects of this dialysis method. However, randomized trials comparing IHD with SLED have not been performed. Also, clinical experience is far more limited with SLED compared to CRRT, and very few randomized studies have compared SLED to CRRT. A first small trial in 39 AKI patients did not find any difference in hemodynamics, and less need for anticoagulation with SLED compared to CRRT.[724] An (even smaller) Australian study showed similar control of urea, creatinine, and electrolytes, but a better control of acidosis and less hypotension during the first hours of the treatment with CRRT.[725,726] A recent retrospective analysis examined the mortality data from three general ICUs in different countries that have switched their predominant therapeutic dialysis approach from CRRT to SLED. This change was not associated with a change in mortality.[727] In addition, Fieghen *et al.*[728] examined the

relative hemodynamic tolerability of SLED and CRRT in critically ill patients with AKI. This study also compared the feasibility of SLED administration with that of CRRT and IHD. Relatively small cohorts of critically ill AKI patients in four critical-care units included 30 patients treated with CRRT, 13 patients with SLED, and 34 patients with IHD. Hemodynamic instability occurred during 22 (56.4%) SLED and 43 (50.0%) CRRT sessions ($P = 0.51$). In a multivariable analysis that accounted for clustering of multiple sessions within the same patient, the OR for hemodynamic instability with SLED was 1.20 (95% CI 0.58–2.47) compared to CRRT. Significant session interruptions occurred in 16 (16.3%), 30 (34.9%), and 11 (28.2%) of IHD, CRRT, and SLED therapies, respectively. This study concluded that, in critically ill patients with AKI, the administration of SLED is feasible and provides hemodynamic control comparable to CRRT.

In conclusion, in the presence of hemodynamic instability in patients with AKI, CRRT is preferable to standard IHD. SLED may also be tolerated in hemodynamically unstable patients with AKI in settings where other forms of CRRT are not available, but data on comparative efficacy and harm are limited. Once hemodynamic stability is achieved, treatment may be switched to standard IHD.

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)

RATIONALE

In a patient with acute brain injury, IHD may worsen neurological status by compromising cerebral perfusion pressure. This may be the result of a decrease of mean arterial pressure (dialysis-induced hypotension) or an increase of cerebral edema and intracranial pressure (dialysis disequilibrium), and may jeopardize the potential for neurologic recovery. Dialysis disequilibrium results from the rapid removal of solutes, resulting in intracellular fluid shifts. Both hypotension and disequilibrium can be avoided by the slow progressive removal of fluids and solutes that occurs during CRRT.[729] Small observational trials and case reports in patients with intracranial pressure monitoring indeed reported increases in intracranial pressure with IHD.[730,731] Using CT scans to measure brain density, Ronco *et al.*[732] showed an increase of brain water content after IHD, whereas no such changes were observed after CRRT.

Protocols for decreasing hemodynamic instability with intermittent RRT

Intradialytic hypotension is a major problem during RRT in AKI patients, limiting its efficacy and causing morbidity. Surprisingly, there are only a few studies assessing this highly relevant clinical problem. Paganini *et al.*[733] performed a small-sample (10 subjects) randomized crossover controlled trial in AKI patients. They evaluated two different RRT protocols: fixed dialysate sodium (140 mEq) and fixed ultrafiltration rate vs. variable dialysate sodium (160 to 140 mEq) and variable ultrafiltration rate (50% in first third of the treatment and 50% in the last two-thirds of the treatment). The variable sodium and ultrafiltration rate protocol achieved better hemodynamic stability, needed fewer interventions, and induced lesser relative blood volume changes, despite higher ultrafiltration rates.

Schortgen *et al.*[734] evaluated the effects of implementing specific guidelines aiming to improve IHD hemodynamic tolerance. The clinical practice algorithm included priming the dialysis circuit with isotonic saline, setting dialysate sodium concentration at 145 mEq/l, discontinuing vasodilator therapy, and setting dialysate temperature to below 37 °C. A total of 289 RRT sessions were performed in 76 patients and compared to a historical series of 248 sessions in 45 patients. Hemodynamic tolerance was better in the guideline patients. They developed less systolic drop at and during RRT. They also had less hypotensive episodes and the need for therapeutic interventions was less frequent. The adoption of guidelines did not influence ICU mortality, but death rate was significantly lower than predicted from illness severity in the guideline patients, but not in the historical series subjects. Length of ICU stay was also reduced for survivors in the protocol-oriented group, as compared to the historical series of patients.

Peritoneal dialysis

In the developing world, the development of CRRT techniques has resulted in a substantial decline in the expertise with, and use of, PD for treatment of AKI. The use of PD in AKI is mainly confined to pediatrics and in regions with limited resources, because of its ease of use, low cost, and minimal requirements on infrastructure. Other advantages include the lack of a need for vascular access and anticoagulation, the absence of a disequilibrium syndrome and the relatively good hemodynamic tolerance compared to IHD. Disadvantages are the overall lower effectiveness (especially in patients with splanchnic hypoperfusion or who are on vasopressors), the risk of protein loss, the unpredictability of solute and fluid removal, the need for an intact peritoneal cavity, risk of peritonitis, diaphragmatic splinting leading to ventilatory compromise and fluctuating blood glucose levels. Recent developments in the technique of PD (use of flexible and cuffed catheters, automatic cycling, and continuous flow PD) have increased its potential to become an acceptable alternative to other forms of RRT in AKI,[735–737] but direct comparative effectiveness trials are extremely limited. Earlier reports on PD in AKI are mainly uncontrolled observations. Only two relatively recent randomized trials have compared PD to other modalities of RRT in AKI. Phu randomized 70 patients with septic AKI to PD or continuous venovenous hemofiltration (CVVH) and found a better survival with CVVH. However, the PD treatment appeared not to be "up to date" with use of a rigid catheter, manual exchanges with open drainage and acetate

buffering.[738] The second trial compared daily IHD to high-volume PD (with Tenckhoff catheter and automated cycler) and showed no difference in survival or recovery of kidney function. The duration of RRT was significantly shorter in the PD group (Suppl Table 35).[739] However, this trial has not been published in a peer-reviewed journal and the randomization process is unclear. Currently indications for PD in patients with AKI may include bleeding diathesis, hemodynamic instability and difficulty in obtaining a vascular access. Extremely high catabolism, severe respiratory failure, severe ileus, intra-abdominal hypertension, recent abdominal surgery and diaphragmatic peritoneum-pleura connections are contraindications to PD.

Pediatric considerations

RRT modality choice for children with AKI is guided by many of the same principles used for adult patients. However, since severe AKI is relatively rare in children compared to adults, occurring in less than 1% of hospitalized children[740] and only 4.5% of children admitted to an intensive care unit,[741] the impact of local expertise and resource restrictions may be greater for pediatric acute RRT modality decisions. As noted below, each modality of acute RRT can be successfully provided to pediatric patients of all sizes. Thus, with rare exception driven by medical indication or contraindication, no form of acute RRT can be recommended above another at the present time. Each program should evaluate which modality is provided most optimally and feasibly in its particular setting.

Provision of RRT as IHD, PD, or CRRT is now a mainstay of treatment for the child with severe AKI. The widely varying size range of pediatric patients imparts technical considerations in selection of a modality. Given their small size and associated low blood volume, PD may provide the least technically challenging option for infants and small children. However, technological advances aimed at providing accurate ultrafiltration with volumetric control incorporated into IHD and CRRT equipment, and disposable lines, circuits, and dialyzers sized for the entire pediatric weight spectrum have made IHD and CRRT safer and feasible for children of all ages and sizes.[570,742–744] Transition from the use of adaptive CRRT equipment to production of high-flow machines with volumetric control allowing for accurate ultrafiltration flows has likewise lead to a change in pediatric RRT modality prevalence patterns in the USA. Accurate ultrafiltration and blood flow rates are crucial for pediatric RRT, since the extracorporeal circuit volume can comprise more than 15% of a small pediatric patient's total blood volume, and small ultrafiltration inaccuracies may represent a large percentage of a small pediatric patient's total body water. Polls of USA pediatric nephrologists demonstrate increased CRRT use over PD as the preferred modality for treating pediatric ARF. In 1995, 45% of pediatric centers ranked PD and 18% ranked CRRT as the most common modality used for initial ARF treatment. In 1999, 31% of centers chose PD vs. 36% of centers reported CRRT as their primary initial modality for ARF treatment.[745]

In the 1990 s, survival rates stratified by RRT modality were better for children receiving IHD (73–89%) than those receiving PD (49–64%) or CRRT (34–42%).[545,746] However, this analysis did not correct for illness severity. More recent data demonstrate much improved survival in children receiving CRRT,[543,544,546,570] with survival rates ranging from 50–70% for children with multiple-organ dysfunction who receive CRRT. While no RCT exists to assess the impact of CRRT modality on survival, convective modalities were associated with increased survival in children with stem-cell transplants in a prospective cohort study (59% vs. 27%, $P<0.05$).[747]

RESEARCH RECOMMENDATIONS

- Large RCTs should compare SLED against other forms of RRT in patients with AKI. These trials should be standardized for treatment dose, buffer, membrane, anticoagulant, and timing of treatment.
- The effects of different modalities of RRT on the long-term need for chronic dialysis, along with mortality, should be evaluated in prospective randomized trials.

SUPPLEMENTARY MATERIAL

Supplementary Table 35: Summary table of RCTs examining the effect of dialysis modality (continuous vs. intermittent RRT) in AKI.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 5.7: Buffer solutions for renal replacement therapy in patients with AKI

One goal of CRRT is to maintain normal or near-normal acid-base balance, thus preventing detrimental effects of acidosis on cardiovascular performance and hormonal response. Options for correction of metabolic acidosis include the use of acetate-, lactate-, and bicarbonate-containing replacement solutions or dialysate. Some centers use citrate anticoagulation, and the citrate load provides an adequate supply of anionic base to control metabolic acidosis. Dialysate solutions for IHD are produced on-line by the dialysis machine, by mixing specially treated municipal water with electrolytes. Dialysate or replacement solutions for CRRT are produced commercially or locally in hospital pharmacies.

5.7.1: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI. (*2C*)

5.7.2: We recommend using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and circulatory shock. (*1B*)

5.7.3: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and liver failure and/or lactic acidemia. (*2B*)

RATIONALE

Options for correction of metabolic acidosis in patients with AKI include acetate, lactate, bicarbonate, and citrate. The use of acetate has been largely abandoned in view of the associated hemodynamic instability and weight loss, probably related to excessive nitric oxide production and cytokine synthesis.[748] Citrate, used for regional anticoagulation of the extracorporeal circuit, is alkalinizing, and most patients receiving citrate anticoagulation do not need an additional buffer in the dialysate or replacement fluid.

Original HF solutions contained lactate as a buffer. Under normal circumstances, this lactate is metabolized, resulting in adequate correction of acidosis in most patients. A survey in 34 Australian ICUs concluded that 55% of the ICU patients with AKI were treated with lactate-based solutions[710] that, in most countries, are less expensive than bicarbonate solutions. In addition, bicarbonate solutions have a higher risk of bacterial contamination and the solution is unstable in the presence of calcium and magnesium. However, in recent years, bicarbonate has gained popularity because of concerns that lactate may not be rapidly metabolized in the setting of multiple-organ failure.[749] Since lactate is a strong anion, insufficient lactate conversion will result in worsening acidosis, especially since bicarbonate losses are ongoing in the extracorporeal circuit. Hyperlactatemia has also been linked to impaired cellular function and catabolism due to lowering of the cellular redox state and phosphorylation potential.[750] In addition, iatrogenic increases in lactate levels may lead to misinterpretation of the clinical situation. The risk of "lactate intolerance" is highest in patients with liver failure (impaired lactate clearance) or circulatory shock (increased endogenous lactate production).

Few adequately designed trials have compared different buffers during RRT in AKI patients, and most of them have been performed during CRRT. Barenbrock *et al.*[751] randomized 117 AKI patients to CVVH with lactate or bicarbonate replacement fluid. The use of bicarbonate resulted in better correction of acidosis and lower lactate levels. Also, the incidence of hypotension and other cardiovascular events was lower with bicarbonate. In the subgroup of patients with cardiac failure, mortality tended to be lower with bicarbonate, whereas in the subgroup of septic patents no difference in outcome was found (Suppl Table 36). A nonrandomized crossover study in 54 patients with multiple-organ dysfunction undergoing CVVHDF confirmed the superior control of acidosis and better hemodynamic tolerance with bicarbonate.[752] However, another RCT in 40 patients treated with CVVH could not find a difference in hemodynamic tolerance, despite the higher lactate levels in the lactate-buffered group.[753] Differences in the case-mix may explain these different results.

Two small prospective randomized crossover comparisons of bicarbonate- and lactate-buffered solutions in AKI patients treated with CVVH or CVVHDF found elevated serum lactate levels with lactate, an effect that was more pronounced in patients with hepatic insufficiency.[754,755] An observational trial in 27 patients found a compromised lactate tolerance in patients with coincidental liver disease, those on inotropic support, and in patients with initial blood lactate measurements of >90.1 mg/dl (>10 mmol/l) and large base deficits.[756]

In conclusion, the use of bicarbonate as a buffer in the dialysate or replacement fluid of AKI patients results in better correction of acidosis, lower lactate levels, and improved hemodynamic tolerance. This effect is most pronounced in patients with circulatory problems and in those with liver dysfunction.

Table 23 | Microbiological quality standards of different regulatory agencies

	ANSI/AAMI/ISO[763–765]	ERA-EDTA guidelines[765a]
Water for dialysis		
Bacteria (CFU/ml)	<100 (action level at 50)	<100
Endotoxin (EU/ml)	<0.5	<0.25
Dialysate		
Bacteria (CFU/ml)	<100 (action level at 50)	<100
Endotoxin (EU/ml)	<0.5	<0.25
Ultrapure dialysate		
Bacteria (CFU/ml)	<0.1	<0.1
Endotoxin (EU/ml)	<0.03	<0.03
Substitution fluid for infusion		
Bacteria (CFU/ml)	Sterile	$<10^{-6}$
Endotoxin (EU/ml)	Undetectable	<0.03

AAMI, Association for the Advancement of Medical Instrumentation; ANSI, American National Standards Institute; CFU, colony-forming units; ERA-EDTA, European Renal Association—European Dialysis and Transplant Asssociation; EU, endotoxin units; ISO, International Organization for Standardization.

5.7.4: We recommend that dialysis fluids and replacement fluids in patients with AKI, at a minimum, comply with American Association of Medical Instrumentation (AAMI) standards regarding contamination with bacteria and endotoxins. (*1B*)

RATIONALE

Replacement fluids for HF or HDF are infused directly into the patient's circulation and should be sterile. A potential major step forward in acute RRT, reducing the costs and the need for storage of fluids, is the on-line production of replacement fluids, which is achieved by passing water and/or dialysate through two or three ultrafilters before being infused.[757,758] On-line production of replacement fluids has not yet been approved by the FDA or by some regulatory authorities in Europe.

Conventional IHD uses nonsterile dialysate, as there is no direct contact between blood and dialysate. However, with the use of high-permeability membranes, the lower blood side pressures at the end of the dialyzer filter may allow back-filtration of dialysate to the blood,[759] raising the possibility of endotoxin or other contaminant exposure. Two studies confirmed microbial contamination of (locally prepared and commercial) fluids and circuitry during CRRT.[760,761] Dialysate for CRRT should preferably be ultrapure, and should at least comply with quality standards for dialysis water and dialysis fluids that may differ worldwide (Table 23).[762]

Finally, an international quality standard for dialysis fluid is in preparation by the International Society for Standardization. Until international standards are in place, we recommend that dialysis fluids and replacement fluids in patients with AKI, at a minimum, comply with AAMI standards for bacteria and endotoxins. When local standards exceed AAMI standards, local standards should be followed (Table 23).

RESEARCH RECOMMENDATION

- Further studies are required to explore the impact of on-line preparation of replacement fluid for HDF on clinical outcomes (incidence of sepsis, renal recovery, mortality) in AKI patients requiring RRT.

SUPPLEMENTARY MATERIAL

Supplementary Table 36: Summary table of RCTs examining the effect of bicarbonate vs. lactate as buffer for CVVH replacement fluid on acidosis in AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Chapter 5.8: Dose of renal replacement therapy in AKI

The first report of RRT in AKI was published in 1965.[766] Despite more than six decades of clinical experience and research, controversy remains about the best way to measure and what constitutes optimal dose of RRT for patients with AKI. Indeed, three of the top five questions considered most relevant by an international expert's panel on RRT delivery in AKI were about dose.[767]

The methods used for RRT dose quantification in AKI have several limitations, and have not been fully validated in this specific population. Earlier single-center trials assessing the effects of RRT dose in AKI provided conflicting results.[531,768–772] Considering the complexity of AKI patients, RRT dose, by itself, may have less impact on mortality both in patients with very high or very low chance of surviving, but may be most important in patients with intermediate scores of disease severity.[773] In addition, it is possible that dose and timing are closely linked factors, i.e., a high RRT dose may not work adequately if provided late, or an early RRT starting may not be able to change outcomes if the dose is not optimized. Currently, only one small RCT considered both variables at the same time.[531]

5.8.1: The dose of RRT to be delivered should be prescribed before starting each session of RRT. (*Not Graded*) We recommend frequent assessment of the actual delivered dose in order to adjust the prescription. (*1B*)

5.8.2: Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs. (*Not Graded*)

RATIONALE

The judgment and awareness of how much of a particular therapeutic procedure should be, and actually it is, delivered is essential for a good medical practice. However, recent surveys have shown a disappointingly low number of physicians that report being aware of, or calculating, RRT dose in AKI.[774]

Although widely used for evaluation of RRT in CKD, Kt/V urea has important limitations as a tool for RRT dosing in AKI. AKI patients are metabolically unstable, with variations in urea generation. In addition, their urea volume of distribution appears to exceed the patient's total body-water volume.[775] Different ways to measure Kt/V obtained significantly different results in AKI patients.[776] In the same way, the selection of a target serum urea level as an indicator of dialysis dose is highly arbitrary, as serum urea is influenced by several extrarenal factors, such as ethnicity, age, gender, nutrition, presence of liver disease, sepsis, muscle injury, drugs, etc.

Several clinical investigations have shown that the actual delivered dose of RRT in AKI patients is frequently smaller than the prescribed dose, and even smaller than the recommended minimum for CKD patients.[771,773,776–778] Impediments to adequate dose delivery were hemodynamic instability, patient size, access problems, technical problems, need for patient transportation, and early filter clotting.

Trials studying dose in CRRT have used the amount of effluent volume normalized by the patient's weight and procedure time as a parameter for dose evaluation. However, the actual effluent flow will be influenced by interruptions of CRRT, and effluent flow will exceed actual dose with use of predilution or with reductions in membrane permeability during the treatment. In summary, it is essential to check very carefully if the prescribed RRT dose is really being delivered to AKI patients. Increasing filter size, dialysis time, blood flow rate, dialysate flow rate, and/or effluent flow rate should be considered in case of dose inadequacy.

In determining a prescription of RRT it is mandatory to consider parameters other than small-solute clearance, such as patients' fluid balance, acid-base and electrolyte homeostasis, and nutrition, among others, as possible components of an optimal RRT dose. In fact, positive fluid balance appears to be an independent risk factor for mortality in AKI patients.[83]

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. (*Not Graded*)

RATIONALE

Three RCTs evaluated the dose of IHD in AKI (Suppl Tables 37 and 38). Schiffl *et al.*[771] compared daily to alternate-day IHD in 146 ICU patients with AKI. RRT was started with rather high values of SCr (over 4.5 mg/dl [398 μmol/l]) and BUN (around 90 mg/dl [32.1 mmol/l urea]). The daily arm received a weekly Kt/V approximately two times higher than the alternate-day arm (5.8 ± 0.6 vs. 3 ± 0.6, respectively). Daily IHD resulted in lower mortality (28% vs. 46%, $P = 0.01$) and faster recovery of kidney function (9 ± 2 vs. 16 ± 6 days, $P = 0.001$). Major limitations of this study were

inadequate randomization, a "very low dose" in the control group (actually less than that recommended for CKD). Also overall mortality in the study (34%) was lower than in other studies in this population, suggesting that the results may not generalize. Moreover, alternate-day IHD was associated with significant differences in fluid removal and dialysis-associated hypotension, suggesting that aspects other than solute control might modify patient outcomes.

The Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ARFTN) study[563] was a RCT assessing the effects of intensive compared to less-intensive RRT in 1124 ICU patients with AKI in 27 Veterans Affairs– and university-affiliated North-American centers. Within each randomization arm patients were switched between IHD and CRRT or SLED, based on their hemodynamic status, reflecting average clinical practice in the USA. Intermittent treatments were prescribed at a Kt/V of 1.4, with a delivered Kt/V averaging 1.3, and were performed three (less-intensive arm) or six (more-intensive arm) times per week. Consequently, the weekly Kt/V was approximately 6.5 in the intensive and 3.9 in the less-intensive arm. Mortality at 60 days was similar in both groups (53.6% and 51.5%) as was the percentage of patients recovering kidney function (15.4% and 18.4%). Limitations of this study include the predominance of males, and the nonstandardized timing for initiating RRT. In addition, a significantly higher frequency of hypotension and electrolyte disturbances were seen in the more-intensive arm. Similar to what has been reported in chronic dialysis, acute IHD results in underdosing when Kt/V is not measured. In the ARFTN study, the first session of IHD had an average delivery of 1.1 Kt/V, while the prescribed dose was 1.4.

The Hannover Dialysis Outcome Study[768] randomized 148 ICU patients with AKI to two different doses of SLED: a standard-dialysis arm dosed to maintain plasma urea levels between 120–150 mg/dl (20–25 mmol/l), or an intensified-dialysis arm dosed to maintain plasma urea levels <90 mg/dl (<15 mmol/l). Patients were included with SCr around 3 mg/dl (265 μmol/l) and plasma urea around 60 mg/dl (10 mmol/l). The mean plasma urea was kept at 68 ± 24 mg/dl (11.3 ± 4 mmol/l) in the intensified and 114 ± 36 mg/dl (19 ± 6 mmol/l) in the standard group. Mortality at 28 days was not statistically different between groups (38.7% and 44.4%) and the frequency of survivors recovering kidney function at day 28 was very similar (63% and 60%).

In CKD, the analysis by Gotch and Sargent[779] of the National Cooperative Dialysis Study showed that survival could be increased by increasing Kt/V to 1.0–1.2. Analysis of a large database of 2311 Medicare IHD patients also showed a strong association between the delivered IHD dose and mortality, with a decreased mortality risk of 7% for each 0.1 higher level of delivered Kt/V in CKD patients. However, above a Kt/V of 1.3, no further decrease in mortality was noted.[780] The HEMO study, a large RCT comparing two different dialysis doses in CKD, also could not demonstrate a further reduction of mortality with equilibrated Kt/V of 1.43 compared to 1.16.[781] If we assume that AKI patients should receive at least the same dose as CKD patients, it seems reasonable to recommend a thrice-weekly Kt/V of 1.3 or a weekly Kt/V of 3.9 (assuming at least thrice-weekly treatment), which also represents the lowest dose in the largest randomized trial in AKI (ARFTN study). Whether specific subgroups of AKI patients, such as those with hypercatabolism, may benefit from higher doses will require further investigation.

In conclusion, there are only two adequately designed and executed RCTs testing intermittent or extended RRT dose in AKI. Neither study showed improvement in mortality or renal recovery when the dialysis dose was increased, either by increasing Kt/V above 3.9 weekly or by achieving a plasma urea target below 90 mg/dl (15 mmol/l) in AKI patients. However, consistent with the data on dose of IHD in CKD, and consistent with the lower-dose arm in the ARFTN study, we recommend thrice-weekly Kt/V of 1.3 or a weekly Kt/V of 3.9 for IHD in AKI.

Seven RCTs have investigated the role of CRRT dose in AKI (Suppl Tables 37 and 38).[531,562,563,768–770,772] While earlier single-center trials showed mixed results, two large multicenter trials have reached remarkably consistent conclusions concerning the dose of CRRT that should be provided to critically ill patients with AKI.

The ARFTN study[563] compared standard-intensity predilution CVVHDF with a prescribed effluent flow of 20 ml/kg/h to high-intensity CVVHDF at 35 ml/kg/h. As discussed in Recommendation 5.8.3 rationale, there were no differences in outcomes between the two study arms. Importantly, more than 95% of the prescribed dose of CRRT was delivered in the less-intensive group. This represents a considerably greater intensity of delivered dose than is typically seen in clinical practice. As in chronic dialysis, studies in CRRT have shown that delivery usually falls substantially short of the prescribed dose.[782] Thus, it will usually be necessary to prescribe a high dose of CRRT in order to achieve a specific target. For example, in order to achieve a delivered dose of 20–25 ml/kg/h, it is likely that the prescription will need to be in the range of 25–30 ml/kg/h. The Randomized Evaluation of Normal vs. Augmented Level of RRT study was conducted in 35 centers in Australia and New Zealand.[562] It compared the effects of postdilution CVVHDF at doses of 25 and 40 ml/kg/h on 28- and 90-day mortality rates in 1464 AKI patients. The delivered dose was 88% and 84% of prescribed in the low- and high-dose groups, respectively. As in the ARFTN study, there was no difference in 28- or 90-day mortality between the two groups. Apart from a higher incidence of hypophosphatemia in the high-dose group, the complication rate was similar.[562]

In conclusion, there are now consistent data from two large multicenter trials showing no benefits of increasing CRRT doses in AKI patients above effluent flows of 20–25 ml/kg/h. In clinical practice, in order to achieve a delivered dose of 20–25 ml/kg/h, it is generally necessary to prescribe in the range of 25–30 ml/kg/h, and to minimize interruptions in CRRT.

Additional considerations

In patients who do not achieve the target dose of RRT, despite optimization of the initial modality, a switch to another modality or the combination of different modalities should be considered.

Although there are insufficient data supporting a recommendation for elevated RRT doses in patients with AKI and septic shock, limited data suggest that a higher dose might be beneficial in some patients. A small single-center RCT was conducted in 20 patients with septic shock and AKI. Patients were randomized to either high-volume (effluent flow of 65 ml/kg/h) or low-volume CVVH (effluent flow of 35 ml/kg/h). The primary end-point was vasopressor dose required to maintain mean arterial pressure at 65 mm Hg. Mean norepinephrine dose decreased more rapidly after 24 hours of high-volume as compared to low-volume CVVH treatment. Survival on day 28 was not affected.[783]

RESEARCH RECOMMENDATIONS

- Determine the *optimal dose parameter* that should be used in future trials comparing different intensities of dialysis in AKI patients. Some possible methods to explore are on-line Kt/V urea, urea reduction ratios, or application of the concept of corrected equivalent renal urea clearance for solute removal measurement and ultrafiltration effluent volume, or substitution fluid volume normalized by body weight and time for CRRT. Other aspects of intensity should also be studied, e.g., fluid control and acid-base and electrolyte balance. The comparators might be the standard ways to measure dose as Kt/V or prescribed effluent volume. Suggested outcome parameters are 60- to 90-day mortality, ICU and hospital LOS, and recovery of kidney function.
- Determine the optimal *dose of RRT in AKI in homogeneous subpopulations*, such as cardiac surgery or sepsis patients, and separately in ICU and non-ICU patients. Future RCTs should be controlled for timing of RRT initiation and, perhaps, for general care of patients (antibiotics, nutrition, kind and indication for vasoactive drugs, mode of mechanical ventilation). Studies should also assess the efficiency of RRT (since dose does not necessarily mean efficiency), assessing control of BUN, creatinine, fluid balance, and acid-base and electrolyte status. The comparators might be different efficiency targets. The suggested outcomes are 60- to 90-day mortality, need for vasopressor drugs, time on mechanical ventilation, ICU and hospital stay, and renal recovery.

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SUPPLEMENTARY MATERIAL

Supplementary Table 37: Evidence profile of RCTs examining the effect of dose of continuous and intermittent RRT on AKI.

Supplementary Table 38: Summary table of RCTs examining the effect of dose of continuous and intermittent RRT on AKI.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php

Biographic and Disclosure Information

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John A Kellum, MD, FCCM, FACP (Work Group Co-Chair), is Professor of Critical Care Medicine, Medicine, Bioengineering and Clinical and Translational Science, and Vice Chair for Research within the Department of Critical Care Medicine at the University of Pittsburgh. In addition, he is the Director of the Program on Bioengineering and Organ Support for the CRISMA (Clinical Research Investigation and Systems Modeling of Acute Illness) Center at the University of Pittsburgh.

Dr Kellum is actively involved in education, research, and administration. His research interests span various aspects of critical-care medicine, but center in critical-care nephrology, sepsis, multiorgan failure, and clinical epidemiology, including consensus development and research methodology. He has authored more than 300 publications and served as editor and contributor to recent texts including *Continuous Renal Replacement Therapy*, *Critical Care Nephrology*, and *Management of Acute Kidney Problems*. Dr Kellum has won several awards for teaching and has given more than 400 seminars and invited lectures worldwide related to his research.

Advisor/Consultant: Abbott; Alere; Astute Medical; Baxter; CytoSorbents; EBI; Eli Lilly; Fresenius; Gambro; Siemens; Spectral Diagnostics
Speaker: Baxter; Fresenius; Gambro
Grant/Research Support: Astute Medical; Baxter; CytoSorbents; Gambro

Norbert Lameire, MD, PhD (Work Group Co-Chair), is Professor of Internal Medicine and former Chief of Renal Division at the University of Ghent where he also received his medical degree and PhD. Dr Lameire's interests include basic research topics such as renal circulation in experimental ARF and peritoneal circulation, as well as clinical topics spanning clinical ARF, PD, and organizational and economic aspects of chronic RRT and transplantation. He currently oversees the worldwide continuing medical education programs of COMGAN of the International Society of Nephrology, and serves as current Editor-in-Chief for *Acta Clinica Belgica* and is emeritus Editor-in-Chief for *Nephrology Dialysis Transplantation*. For his activities in the Renal Sister Program of the International Society of Nephrology and his leadership of the Renal Disaster Relief Task Force, he was awarded Doctor Honoris Causa at the Kaunas Medical Academy in Lithuania and an honorary membership of the International Society of Nephrology (ISN). Dr Lameire also received the Garabed Eknoyan Award from the NKF (USA) in 2007 for his continuing work to improve dialysis therapy and PD, and his contributions to improving and implementing KDOQI Guidelines. He also served as the KDIGO Co-Chair from 2004 to 2007.

Dr Lameire reported no relevant financial relationships.

Peter Aspelin, MD, PhD, received his basic training in radiology at Malmö University Hospital (Lund University) and was Associate Professor there for 13 years. In 1989 he became Professor and Chairman of the Department of Radiology at Karolinska Institutet, Huddinge University Hospital. Professor Aspelin was Vice Dean of the Medical School at Karolinska Institutet from 1993 to 1995 and served as Vice President at the institution from 1995 to 2001. He was also Head of Research & Development at Huddinge University Hospital in 2002 and Vice Chairman of Research & Development at the Karolinska University Hospital. Other notable accomplishments also include his roles as President for the Scientific Board of the Swedish Council of Technology Assessment in Health Care (1999–2005); Chairman of the Swedish Society of Medical Radiology (2003–2005); and past Vice Chairman and current Chairman of the Swedish Medical Association.

Professor Aspelin has conducted research on contrast media since 1972 when he studied under the tutelage of Professor Torsten Almén. He has written more than 170 scientific publications to date and his primary research centers on the development of nonionic contrast media and the examination of their effects on medical imaging and patient safety.

Speaker: GE Healthcare
Expert witness: GE Healthcare

Rashad S Barsoum, MD, FRCP, FRCPE, is Emeritus Professor of Medicine at Cairo University and current Chairman of Cairo Kidney Center and Medical Sector Committee for Supreme Council for Egyptian Universities. He received his medical degree from Cairo University, where he also completed his fellowship in nephrology in 1967. Dr Barsoum has been a primary investigator in clinical trials involving the study of immunosuppression agents in kidney transplantation and treatment of HCV infection in dialysis patients. He has also authored more than 200 journal articles and book chapters and currently serves as Associate Editor for *Nephron Clinical Practice* and editorial board member for *American Journal of Kidney Diseases*. Dr Barsoum is also active in numerous medical societies, having served as Past President for the Arab Society of Nephrology and Renal Transplantation and Egyptian Society of Nephrology. Among

his noted achievements include the International Award from the NKF (USA), the Roscoe Robinson Award from the International Society of Nephrology, and the Distinguished Researcher Award from Cairo University.

Advisor/Consultant: Wyeth
Speaker: Amgen; B. Braun; Fresenius; Janssen Cilag; Novartis; Roche; Wyeth

Emmanuel A Burdmann, MD, PhD, is Head of Intensive Care Unit and Associate Professor, Division of Nephrology at University of São Paulo Medical School. He received his medical degree from the University of São Paulo, where he also completed his fellowship. He was the Past President of the Latin American Society of Nephrology and Hypertension and current President of Brazilian Society of Nephrology. Dr Burdmann has authored over 150 journal articles and book chapters and is currently on the editorial boards of *Clinical Journal of the American Society of Nephrology*, *Clinical Nephrology*, *Kidney International*, *Nephrology Dialysis Transplantation*, and *Nephron Clinical Practice*. He is also a member of numerous professional societies and has served on the Council of the International Society of Nephrology and KDIGO Board. In addition to his research interest in AKI, Dr Burdmann is also a coinvestigator in the TREAT study.

Dr Burdmann reported no relevant financial relationships.

Stuart L Goldstein, MD, is Professor of Pediatrics and Director, Center for Acute Care Nephrology at Cincinnati Children's Hospital Medical Center. He received his medical degree from Columbia University and completed both clinical and research fellowships in pediatric nephrology at the Children's Hospital in Boston, Massachusetts. Dr Goldstein is a member of the American Academy of Pediatrics, the American Society of Nephrology, the International Pediatric Nephrology Association, the American Society of Pediatric Nephrology, the International Society of Nephrology, and the Society for Pediatric Research. In addition, he is Chairman of the Medical Advisory Committee to the FORUM of ESRD Networks and a member of the Medical Review Board for the ESRD Networks 9 and 10, is the Pediatric Nephrologist Representative for the International Society of Nephrology Commission of Acute Renal Failure, and has been elected to the Council of the American Society of Pediatric Nephrology. Dr Goldstein has developed and validated the pediatric modified RIFLE (pRIFLE) AKI criteria, is Founder and Principal Investigator for the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry Group, and has evaluated novel urinary AKI biomarkers in the pediatric critical care setting. He has written over 110 journal articles and contributed book chapters to numerous texts including, *Critical Care Nephrology*, *Evidence-Based Nephrology*, *Handbook of Dialysis Therapy*, *Management of Acute Kidney Problems*, *Pediatric Critical Care*, *Pediatric Nephrology*, and *Pediatric Nephrology in the ICU*.

Advisor/Consultant: Baxter; Gambro
Speaker: Gambro
Grant/Research Support: Amgen; Baxter; Gambro

Charles A Herzog, MD, is Director of the Cardiovascular Special Studies Center, United States Renal Data System (USRDS). An investigator at the USRDS since 1999, Dr Herzog has been a cardiologist at Hennepin County Medical Center (HCMC) in Minneapolis and a member of the University of Minnesota faculty for 27 years. He has been a professor of medicine at the University of Minnesota since 2004 and the cardiology consultant to the ESRD program (dialysis and renal transplant) at HCMC since 1985. He founded the program in interventional cardiology and served as the director of the cardiac catheterization laboratory at HCMC from 1985 to 1991. Since 1997, Dr Herzog has been the director of the cardiac ultrasound laboratory at HCMC. He participated in the development of the National Kidney Foundation's K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients, and co-chaired the 2010 KDIGO Controversies Conference, "Cardiovascular Disease in CKD: What is it and What Can We Do About It?" The author or co-author of more than 100 published papers and reviews, Dr Herzog has served on the Editorial Board for the *American Heart Journal* since 2005 and as liaison editor (cardiology) for *Nephrology Dialysis Transplantation* since 2007. His areas of research and special interests include cardiac disease and chronic kidney disease, and echocardiography.

Advisor/Consultant: Abbott; Affymax; Amgen; CorMedix; FibroGen; Fresenius
Board of Trustees: Roche Foundation for Anemia Research
Honorarium: UpToDate
Grant/Research Support: Johnson & Johnson; National Institutes of Health
Equity Interest: Boston Scientific; Cambridge Heart; Johnson & Johnson; Merck

Michael Joannidis, MD, is Associate Professor in Medicine and serves as Director of the Medical Intensive Care Unit, Dept. Internal Medicine I at Medical University Innsbruck in Austria. He is a certified specialist in critical-care medicine, nephrology, and cardiology, and his research interests cover several aspects of critical-care medicine with a major focus on AKI, renal tubular epithelial pathophysiology, RRT, and sepsis.

Dr Joannidis currently serves as chair of the section Acute Kidney Injury of the European Society of Intensive Care Medicine (ESICM), President of the Austrian Society of Medical and General Intensive Care Medicine (OEGIAIM) and associate editor of *Intensive Care Medicine*.

Speaker: Baxter; Fresenius; Gambro

Andreas Kribben, MD, is Professor of Medicine and Head of the Department of Nephrology at the University Hospital Essen at the University of Duisburg-Essen. He received his medical degree at the Johann-Wolfgang Goethe University Frankfurt, Germany in 1983. Dr Kribben was trained in Internal Medicine and Nephrology at the Department of Nephrology of the University Hospital Klinikum Steglitz, Free University of Berlin, Germany and at the University Hospital Essen, University Duisburg-Essen, Germany. From

1990 to 1993, he was a research fellow at the Renal Division of the University of Colorado Health Sciences Centre in Denver, Colorado, USA. His major scientific interests include all aspects of AKI, CRF, as well as transplantation and hypertension.

Dr Kribben is member of numerous professional organizations, including the International Society of Nephrology, the American Society of Nephrology, the European Dialysis and Transplantation Association, and he is a member of the Board of Directors of the German Society of Nephrology. He is an editorial member of *Clinical Nephrology* and served as subject editor of *Nephrology Dialysis Transplantation*. Dr Kribben is also a member of the World Health Organization Work Group for the 11th revision of ICD.

Advisor/Consultant: Roche; Shire; Teva

Speaker: Amgen; Apherese ForschungsInstitut; Baxter; Bayer-Schering; Berlin-Chemie; Fresenius; GE Healthcare; Genzyme; Roche; Shire

Grant/Research Support: B. Braun; Biosite; Fresenius; Koehler; Roche; Teva

Andrew S Levey, MD, is Dr Gerald J. and Dorothy R. Friedman Professor of Medicine at Tufts University School of Medicine, Chief of the William B. Schwartz, MD Division of Nephrology at Tufts Medical Center, Senior Scientist at the US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, and Professor, Clinical Research at the Sackler School of Graduate Biomedical Sciences at Tufts University. His research is mainly in the areas of epidemiology of CKD and cardiovascular disease in CKD, controlled trials to slow the progression of CKD, clinical assessment of kidney function, assessment and improvement of outcomes in dialysis and transplantation, and clinical practice guideline development and implementation. Dr Levey is currently Program Director for an NIDDK-funded clinical research training program, "Clinical Trials, Epidemiology and Outcomes Research in Nephrology". He is also the Director of the Tufts Center for Guideline Development and Implementation and Editor of the *American Journal of Kidney Disease*. Dr Levey is past Chair of the NKF's Task Force on Cardiovascular Disease in Chronic Renal Disease, KDOQI Work Group on Chronic Kidney Disease: Evaluation, Classification and Stratification, and KDOQI Work Group on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.

Grant/Research Support: Amgen; National Institutes of Health; National Kidney Foundation

Alison M MacLeod, MBChB, MD, FRCP London and Edinburgh, is Professor in the Department of Medicine and Therapeutics at the University of Aberdeen Medical School, UK. She completed her fellowship at the Royal Colleges of Physicians of London and Edinburgh, and has interests in epidemiology of CKD, AKI, and evidence based medicine in nephrology. Her research group also conducts systematic literature reviews and she is a member of the Editorial Board of the Cochrane Review Group. Dr MacLeod is a current committee member of the European Renal Registry Executive Committee, Anemia Management in Chronic Kidney Disease–National Institute for Health and Clinical Excellence, Scientific Committee, and European Renal Association Congress. In addition, she is Chairman of the Scottish Intercollegiate Guidelines Network, Diagnosis and Management of Chronic Renal Failure and was a member of the Executive Committee of KDIGO.

Dr MacLeod reported no relevant financial relationships.

Ravindra L Mehta, MD, FACP, FASN, FRCP, is Professor of Medicine in the Division of Nephrology and Associate Chair for Clinical Research in the Department of Medicine at the University of California, San Diego (UCSD) where he directs the Acute Dialysis Program and the UCSD CREST and Masters in Clinical Research Program. He received the M.B.B.S. degree (1976) from the Government Medical School in Amritsar, India, and the M.D. (1979) and D.M. (1981) degrees from the Post-Graduate Institute of Medical Education and Research in Chandigarh, India. He subsequently completed a nephrology fellowship at the University of Rochester in Rochester, New York and obtained his boards in internal medicine (1986) and Nephrology (1988). He has been on the faculty at UCSD since 1988.

Dr Mehta is an internationally recognized expert in the field of ARF and has directed several clinical studies in the management of patients with kidney disease including comparing different dialytic modalities in the treatment of AKI, conducting large multicenter observational studies of AKI with the PICARD group, evaluating different predictive models for outcomes in AKI, investigating the role of cytokine removal by dialysis membranes in sepsis and AKI, and evaluating techniques for determining the amount of excess fluid in dialysis patients. In addition to his clinical and research activities, he has worked with the American Society of Nephrology, NKF, Society of Critical Care Medicine, and the International Society of Nephrology in developing courses for fellows and practicing physicians in clinical nephrology and dialysis techniques. Dr Mehta chairs the annual International Conference on CRRT that is now in its 15th year and he is also the Chair of the International Society of Nephrology Committee on AKI, founding member of the ADQI and AKIN. He has authored over 150 scientific articles, papers and book chapters, and has been actively involved in resident and scholar teaching. He won the house staff teaching award on four occasions and was awarded School of Medicine Faculty teaching award in 2003. He has been recognized as one of the Best Doctors in San Diego and the USA. In 2008, he was recognized by the American Nephrologists of Indian Origin for his achievements in nephrology. In March 2009, he was elected as a Fellow of the Royal College of Physicians in the UK. Over the course of his academic career, he has trained over 50 postdoctoral fellows

in nephrology, of whom 15 have carried out their research projects with him.

Advisor/Consultant: Astute Medical; Eli Lilly; Takeda
Speaker: Baxter; Gambro
Grant/Research Support: Eli Lilly

Patrick T Murray, MD, FASN, FRCPI, FJFICMI, is a nephrologist and clinical pharmacologist at the Mater Misericordiae University Hospital and University College Dublin, Ireland. Dr Murray received his medical education at University College Dublin, Ireland and following his internship at the Mater Misericordiae University Hospital in Dublin, he completed his residency in internal medicine at Hennepin County Medical Center in Minneapolis, Minnesota, USA and fellowship training programs in nephrology, critical care medicine, and clinical pharmacology at the University of Chicago Hospitals in Chicago, Illinois, USA.

Dr Murray is board-certified in internal medicine, nephrology, critical care medicine, and clinical pharmacology and practiced as an intensivist, nephrologist, and clinical pharmacologist at the University of Chicago Hospitals from 1996 to 2008, serving as the fellowship training program director in nephrology and also directing the Acute Dialysis Service. Since 2008, he has been the Professor of Clinical Pharmacology at University College Dublin, and a Consultant in Nephrology & Clinical Pharmacology at the Mater Misericordiae University Hospital. Dr Murray has published extensively with contributions in numerous books including, *Critical Care Nephrology*, *Evidence-Based Nephrology*, *Evidence-Based Practice of Critical Care*, and *Intensive Care in Nephrology*. He has a long-standing interest in research and education to improve the prevention, diagnosis, and therapy of AKI.

Advisor/Consultant: Abbott; Alere; AM Pharma; Argutus Medical; FAST Diagnostics; Reata; Sanofi-Aventis
Grant/Research Support: Abbott; Alere; Argutus Medical

Saraladevi Naicker, MBChB, MRCP, FRCP, FCP (SA), PhD, is currently Academic Head of the Department of Internal Medicine and Professor of Renal Medicine and head of the Division of Nephrology at the University of the Witwatersrand in Johannesburg. She completed her undergraduate and postgraduate medical training primarily at the University of Natal in Durban, South Africa and spent short periods training in nephrology at the Universities of the Witwatersrand, Johannesburg and Newcastle on Tyne in the UK. She currently chairs the Postgraduate (Higher Degrees) Committee of the Faculty of Health Sciences at the University of the Witwatersrand and is a member of the Council of the College of Physicians of the Colleges of Medicine of South Africa. She is also a Council member of the International Society of Nephrology (ISN) and chairs its Education Committee.

Dr Naicker was the recipient of the Philip Tobias/Convocation Distinguished Teachers Award at the University of the Witwatersrand in 2006, the International Distinguished Medal of NKF of the USA in 2005 and was awarded the prestigious Roscoe Robinson award for nephrology education by the ISN at its World Congress in Milan in May 2009. She has hosted the nephrology training of ISN Fellows from Ethiopia, Nigeria, Botswana, Tanzania, Rwanda, Kenya and Zambia as well as ISPD trainees from Nigeria and Tanzania. During her period as Chair of the Africa Committee of ISN COMGAN from 2000 to 2007, she made site visits and participated in continuing medical education programs in many African countries. Her research interests include areas related to HIV and kidney disease, prevention of CKD, CVD in renal disease, and medical education.

Advisor/Consultant: Amgen; Novartis; Roche

Steven M Opal, MD, is Professor of Medicine at The Warren Alpert Medical School of Brown University and Chief of the Infectious Disease Division, Memorial Hospital of Rhode Island. He received his medical degree from Albany Medical School, Albany, New York and completed his fellowship training in infectious diseases at Walter Reed Army Medical Center in Washington, DC. Dr Opal is a member of numerous national and international committees including, International Steering Committee for Sepsis Clinical Trials; Steering Committee FDA Meta-analysis Committee on Sepsis; International Endotoxin Society; and International Sepsis Forum. He has written extensively with over 300 publications and has given more than 100 invited presentations. Dr Opal currently serves on the editorial boards of *Advances in Sepsis*, *Critical Care Forum*, *Current Opinion in Critical Care*, and *Shock*. In recognition for his work, he was awarded the Brown Medical School Infectious Disease Fellowship Teacher of the Year Award in 2008 and was acknowledged in *Best Doctors in America* from 2003 to 2009.

Dr Opal reported no relevant financial relationships.

Franz Schaefer, MD, is Professor of Pediatrics and Chief of the Pediatric Nephrology Division at Heidelberg University Hospital. Dr Schaefer received his M.D. at Würzburg University Medical School and performed research scholarships at the Institute of Child Health, London, University of Virginia, and Stanford University. His research interests include topics on physiopathology of growth failure, cardiovascular and endocrine disorders in CKD and the role of genetic abnormalities in congenital kidney disorders. In clinical research, he conducted numerous collaborative clinical trials and established several international consortia such as the the European Study Group on Progressive CKD in Children, the International Pediatric Peritoneal Dialysis Network, and the PodoNet Registry for Steroid Resistant Nephrotic Syndrome. Dr Schaefer has published over 280 articles and book chapters, and co-edited the standard textbooks *Comprehensive Pediatric Nephrology* and *Pediatric Dialysis*. He received several prestigious awards for innovative research including the Recklinghausen Prize and the IBM Faculty Award. Dr Schaefer is a current council member of the International Pediatric Nephrology Association and the

International Society of Peritoneal Dialysis. He is a member of several editorial boards and serves as Section Editor for *Nephrology Dialysis Transplantation* and *Pediatric Nephrology*.

Dr Schaefer reported no relevant financial relationships.

Miet Schetz, MD, PhD, graduated from the faculty of Medicine of the Catholic University of Leuven, Belgium, after which she specialized in anesthesiology and later in intensive care medicine. Since 1981 she is staff member of the department of Intensive Care Medicine at the University Hospital Leuven (Chair: Greet Van den Berghe) and has been Associate Professor at the Catholic University Leuven since 2000. Dr Schetz completed her PhD thesis on the subject, "The Hemostatic System and Continuous Renal Replacement Therapy: Mutual Effects". Her main field of interest is AKI and its treatment, on which she published several articles.

Grant/Research Support: Gambro

Shigehiko Uchino, MD, PhD, is Associate Professor and Staff Intensivist in the Department of Anesthesiology at Jikei University School of Medicine in Tokyo, Japan. He received his medical degree from Tokyo Medical and Dental University and his PhD from Jikei University School of Medicine. Dr Uchino is a member of the Japanese Society of Intensive Care Medicine, Japanese Association for Acute Medicine, Society of Critical Care Medicine, and the European Society of Intensive Care Medicine. In addition to serving as a reviewer for numerous journals, he has written book chapters in recent texts such as *Critical Care Nephrology*, *Evidence-Based Practice of Critical Care*, and *Intensive Care in Nephrology*. Dr Uchino is also a coinvestigator in the BEST Kidney study.

Dr Uchino reported no relevant financial relationships.

KDIGO CHAIRS

Kai-Uwe Eckardt, MD, is Professor of Medicine and Chief of Nephrology and Hypertension at the University of Erlangen—Nuremberg, Germany. He received his MD from the Westfälische Wilhelms-Universität Münster, Germany. In 1993, following postgraduate training in internal medicine, pathology and physiology, he was appointed Assistant Professor of Physiology at the University of Regensburg, Germany. Subsequently, he continued his training in internal medicine and nephrology at the Charité, Humboldt University in Berlin, where he was appointed Associate Professor of Nephrology in 2000. His major scientific interests are in the molecular mechanisms and physiological/pathophysiological relevance of oxygen sensing and the management of anemia. As such, he has contributed to the development of the European Best Practice Guidelines for Anemia Management and participated in the CREATE and TREAT studies. Professor Eckardt is subject editor of *Nephrology Dialysis Transplantation* and serves on the editorial board of several other journals. He has also authored book chapters and most recently served as a Co-Editor of the text, *Studies on Renal Disorders*. Dr Eckardt is a member of the executive committee of KDIGO.

Advisor/Consultant: Affymax; Amgen; Hexal Sandoz; Johnson & Johnson; Roche
Speaker: Amgen; Janssen Cilag; Johnson & Johnson; Roche
Grant/Research Support: Roche

Bertram L Kasiske, MD, is Professor of Medicine at the University of Minnesota, USA. He received his medical degree from the University of Iowa and completed his Internal Medicine residency and fellowship training in Nephrology at Hennepin County Medical Center where he is currently Director of Nephrology.

Dr Kasiske is former Deputy Director of the United States Renal Data System and former Editor-in-Chief of *The American Journal of Kidney Diseases*. He has served as Secretary/Treasurer and on the Board of Directors of the American Society of Transplantation, and on the Organ Procurement and Transplantation Network/United Network of Organ Sharing Board of Directors, and the Scientific Advisory Board of the National Kidney Foundation. He is currently serving on the Board of Councilors of the International Society of Nephrology. He is the Principal Investigator for a National Institutes of Health-sponsored, multi-center study of long term outcomes after kidney donation. He is the Director of the Scientific Registry of Transplant Recipients. He has over 160 scientific publications in major peer reviewed journals, and 230 review articles, editorials and textbook chapters. Dr Kasiske is also a recipient of the NKF's Garabed Eknoyan Award in 2003.

Advisor/Consultant: Litholink
Grant/Research Support: Bristol-Myers Squibb; Merck-Schering Plough

EVIDENCE REVIEW TEAM

Katrin Uhlig, MD, MS, is the Director, Guideline Development at the Tufts Center for Kidney Disease Guideline Development and Implementation, Boston, MA, Associate Professor of Medicine at Tufts University School of Medicine, and a staff nephrologist at Tufts Medical Center. Dr Uhlig completed her training in internal medicine, nephrology, and rheumatology in Germany (Aachen University Hospital and Munich University Hospital) and the USA (Georgetown University Medical Center and Tufts Medical Center). Since 2001, she has been participating in or directing the evidence review for KDOQI and KDIGO guidelines. In 2005, she co-chaired the KDIGO Evidence Rating Group to develop a consensus on grading of KDIGO guidelines. From 2006 to 2007, she served as Co-Editor of the *American Journal of Kidney Diseases*. Her focus in teaching and research is in evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

Dr Uhlig reported no relevant financial relationships.

Jose Calvo-Broce, MD, MS, served as a research fellow at the Tufts Center for Kidney Disease Guideline Development and

Implementation in Boston, MA and participated in the conduct of systematic reviews and critical literature appraisals for this guideline. Dr Calvo-Broce was recently awarded a Master of Science in Clinical Research for his thesis on "Hospital-Acquired AKI: An Analysis of Nadir-to-Peak Serum Creatinine Increments Stratified by Baseline Estimated GFR".

Dr Calvo-Broce reported no relevant financial relationships.

Aneet Deo, MD, MS, served as a research fellow at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA. She participated in the conduct of systematic reviews and critical literature appraisals for this guideline. Dr Deo was awarded a Master of Science in Clinical Research for her thesis on "Loss to Analysis in Randomized Controlled Trials of Chronic Kidney Disease".

Dr Deo reported no relevant financial relationships.

Amy Earley, BS, is a project coordinator at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA. She assists in the development of clinical practice guidelines and conducts systematic reviews and critical literature appraisals.

Ms Earley reported no relevant financial relationships.

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(Ohio State University), Nestor Schor (Universidade Federal de Sao Paulo-UNIFESP), Mehmet Sukru Sever (European Renal Best Practice), Amma Sewaah-Bonsu (Nephrology Associates of Central Florida), Deepak Sharma (Mil Hospital Jalandhar, India), Justin Silver (Hadassah University Hospital), Richard Solomon (Fletcher Allen Health Care), Peter Spiro (American College of Chest Physicians), Takeshi Sugaya (St. Marianna University School of Medicine), Cem Sungur (Anadolu Medical Center), Charles Swanepoel (University of Cape Town), Seng Hoe Tan (Gleneagles Medical Centre, Singapore), Samuel A Tisherman (Society of Critical Care Medicine), Charles Tomson (Southmead Hospital), Stéphan Troyanov (Hôpital du Sacré-Coeur, Montreal), Hung-Bin Tsai (Buddhist Dalin Tzu Chi General Hospital), Hirokazu Tsukahara (Okayama University Hospital), Wim Van Biesen (University Hospital Ghent), Raymond Vanholder (University Hospital Ghent), Rowan Walker (Royal Melbourne Hospital), Michael Walsh (McMaster University), HaiYan Wang (Beijing University), Jiandong Wei (SUNY Downstate Medical Center), Colin White (University of British Columbia), Hitoshi Yokoyama (Kanazawa Medical University), Luis Yu (University of São Paulo), Elena Zakharova (Moscow City Hospital), Carmine Zoccali (CNR-IBIM Clin Research Unit Ospedali Riuniti, Italy), Kim Zuber (Metropolitan Nephrology Associates).

Participation in the review does not necessarily constitute endorsement of the content of this report by above individuals or the organization or institution they represent.

John A Kellum, MD, FCCM, FACP, Work Group Co-Chair
Norbert Lameire, MD, PhD, Work Group Co-Chair

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