Quality Indicators for Continuous Renal Replacement Therapy in Critically Ill Patients

by

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ABSTRACT

Critical care nephrology is a rapidly growing and developing field within critical care medicine. It encompasses the entire spectrum of mild acute kidney injury (AKI), usually represented by a change in biochemical markers (i.e., serum creatinine and urea) or alterations in clinical parameters (i.e., urine output). There currently exists no specific treatment for AKI; therapy consists of supportive care and prevention of further kidney insults. However, despite these measures, kidney injury can at times progress to overt kidney failure. When this occurs, kidney dialysis is often necessary, occurring in the form of renal replacement therapy (RRT).

RRT may take many different forms, from intermittent RRT (IRRT) to continuous RRT (CRRT), Each form may be more or less appropriate, depending on the severity of illness and complexity of the patient. For our sickest patients, therapy is delivered in a continuous fashion, analogous to our own intrinsic kidney function. This provides a more gradual form of RRT, which may be better tolerated by more critically ill patients.

CRRT is a complex, costly and highly specialized form of life-sustaining therapy, reserved for our most advanced intensive care units (ICUs) and our most critically ill patients. CRRT must be delivered with utmost care, to ensure the safe and high quality delivery of this life-sustaining therapy. However, there currently exist no routine markers to measure the quality of the delivery and performance of CRRT, nor to benchmark its delivery. This is an important gap in the field of critical care nephrology, and one that this research program sought to address.

The first objective of this program was to review the current state of evidence for quality and safety within critical care nephrology. To accomplish this, I conducted a review of the literature to evaluate what quality and safety measures have already been developed and evaluated. I identified that while there have been advances in better defining AKI and that numerous

organizations exist to continue to advance quality within critical care nephrology, the quality of care received by patients either at risk of or who have developed AKI remains suboptimal. Additionally, I found that evidence-informed quality indicators (QIs) for CRRT care have not been rigorously evaluated. The results of this review informed the second objective of my research program, which was to identify which QIs currently exist in the literature.

To identify potential QIs for CRRT care, I performed a systematic review. I initially screened 8,374 citations from five citation databases as well as from the grey literature. Ultimately 133 studies fulfilled eligibility, and a total of 18 potential QIs across the Donabedian framework of measures of quality were identified. However, these QIs where characterized by heterogeneous definitions, varying quality of derivation and limited evaluation. I concluded that further study was needed in order to develop a concise inventory of QIs that may be applied to CRRT care. This, in turn, informed the third objective of my research program, which was to develop a prioritized list of the most important of these QIs which may be utilized across any CRRT program.

To develop this prioritized list, I embarked on a modified Delphi process. A Delphi process is a structured communication method which relies on a panel of experts, consisting of several rounds where experts respond to questions and then have anonymized summary of responses from previous rounds, with the purpose of converging on the 'correct' answer. I conducted two internet-based rounds and a third in-person meeting for my modified Delphi process, and ultimately arrived at a prioritized list of 13 QIs for CRRT care. These 13 QIs consisted of two QIs relating to CRRT structure (filter life and specialized care team), seven QIs relating to CRRT processes (delivered dose, downtime, fluid management, medication adjustment, time from prescription to therapy, therapy prescription and small solute clearance) and four QIs of CRRT

outcomes (adverse events, bleeding, catheter dysfunction, catheter line-associated bloodstream infections). However, there was disagreement on the precise definitions of these QIs, and uncertainty on which of these may be most easily operationalized in clinical and educational practices.

In summary, this research program first evaluated the current state of quality within critical care nephrology, and then developed a prioritized list of 13 QIs for CRRT care. While consensus existed on the importance of these 13 QIs, future work will be required to better define the QIs, to establish benchmarks for bedside care and to operationalize these QIs into our healthcare data management systems. This will in turn create a CRRT Quality Dashboard that may be used to ensure the safe and high-quality delivery of CRRT care to critically ill patients.

PREFACE

This thesis is an original work by Oleksa G. Rewa. The research project, of which this thesis is a part, received ethics approval from the University of Alberta Research Ethics Board, Project Name "A Modified Delphi Process to Identify, Rank and Prioritize Quality Indicators for Continuous Renal Replacement Therapy (CRRT) Care in Critically Ill Patients," No. Pro00064315, May 19, 2016.

Some of the research conducted for this thesis forms part of an international research collaboration, led by Dr. Sean M Bagshaw at the University of Alberta. Excerpts of Chapter 1 of this thesis have been in part published as O.G. Rewa and S.M. Bagshaw, "Acute Kidney Injury – Epidemiology, Outcomes and Economics," in *Nature Reviews Nephrology* vol. 10, issue 4, 193-207 and in press as O.G. Rewa and S.M. Bagshaw, "Continuous Renal Replacement Therapy," in the textbook of *Critical Care Medicine: Principles of Diagnosis and Management in the Adult – 5th Ed.,* published by Elsevier. I was responsible for manuscript composition. S.M. Bagshaw was the supervisory author and was involved with manuscript composition and edits. Chapter 2 of this thesis has been published as O.G. Rewa, T. Mottes and S.M. Bagshaw, "Quality Measures for Acute for Acute Kidney Injury and Continuous Renal Replacement Therapy," in *Current Opinion Critical Care* vol. 21, issue 6, 490-499. I was responsible for the manuscript composition and submission. T. Mottes contributed to manuscript content and edits. S.M. Bagshaw was the supervisory author and was involved with concept formation and manuscript composition. Chapter 3 of this thesis has been published in protocol for as O.G. Rewa, P.M. Villeneuve, P. Lachance, D.T. Eurich, H.T. Stelfox, R.T.N. Gibney, L. Hartling, R. Featherstone, S.M. Bagshaw, "Quality Indicators of Continuous Renal Replacement Therapy (CRRT) care in Critically Ill Patients: Protocol for a Systematic Review," in *Systematic Reviews*, vol 4, 102-108 and in completed form as O.G. Rewa, P.M. Villeneuve, P. Lachance, D.T. Eurich, H.T. Stelfox, R.T.N. Gibney, L. Hartling, R. Featherstone, S.M. Bagshaw, "Quality Indicators of Continuous Renal Replacement Therapy (CRRT) care in Critically Ill Patients: A Systematic Review," in *Intensive Care Medicine*, vol 43, issues 6, 750-763. I was responsible for data abstraction,

analysis, manuscript composition and submission. P.M. Villeneuve assisted with data abstraction and manuscript edits. P. Lachance, D.T. Eurich, H.T. Stelfox, R.T.N Gibney and L. Hartling assisted with manuscript edits. R. Featherstone assisted with literature search. S.M. Bagshaw was the supervisory author and was involved with concept formation and manuscript composition.

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LIST OF ABBREVIATIONS

ACG – Anticoagulation

ADQI – Acute dialysis quality initiative

AKI – Acute kidney injury

AKIN – Acute kidney injury network

APACHE – Acute physiology and chronic health evaluation

ARF – Acute renal failure

CCMD – Critical care medical doctor

CCN – Critical care nurse

CHF – Congestive heart failure

CIHI – Canadian institute for health information

CKD – Chronic kidney disease

CPG – Clinical practice guidelines

CLABSI – Catheter-line associated bloodstream infection

CRBSI – Catheter-related bloodstream infection

CRRT – Continuous renal replacement therapy

CVVH – Continuous veno-venous hemofiltration

CVVHD – Continuous veno-venous hemodialysis

CVVHDF – Continuous veno-venous hemodialfiltration

DBP – Diastolic blood pressure

DM – Diabetes mellitus

ECMO – extracorporeal membrane oxygenation

EHR – Electronic health record

eGFR – Estimated glomerular filtration rate

ESKD – End-stage kidney disease

FADE – Focus, analyze, develop, evaluate

Hb – Hemoglobin

ICU – Intensive care unit

IOM – Institute of Medicine

IHD – Intermittent hemodialysis

IRRT – Intermittent renal replacement therapy

KDIGO – Kidney disease: improving global outcomes

MD – Medical doctor

NSAIDs – Non-steroidal anti-inflammatory drugs

NCEPOD – National Confidential Enquiry into Patient Outcome and Death

NQF – National quality forum

NICE – National institute for health and care evidence

OR – Operating room

PD – Peritoneal dialysis

PDSA – Plan, study, do, act

PRBC – Packed red blood cell

QI – Quality indicator

RCA – Regional citrate anticoagulation

RCT – Randomized controlled trial

RIFLE – Risk, injury, failure, loss, end-stage renal disease

RRT – Renal replacement therapy

SBP – Systolic blood pressure

sCr – Serum creatinine

SCT – Specialized care team

SLED – Sustained low efficiency dialysis

TMP – Transmembrane pressure

TPE – Therapeutic plasma exchange

VTE – Venous thromboembolism

1. CHAPTER 1: INTRODUCTION

1.1 Statement of the problem

Acute kidney injury (AKI), previously termed acute renal failure (ARF), is a common and increasingly encountered complication among patients hospitalized for acute illness.[1-3] AKI is generally characterized by an abrupt deterioration in kidney function that disrupts metabolic, electrolyte and fluid homeostasis over a period of hours to days. The spectrum of AKI is broad, encompassing mild changes to biochemical markers or clinical parameters of kidney function, to overt kidney failure requiring initiation of renal replacement therapy (RRT). The significance of AKI is clearly exemplified by consistent data showing its association with increased risk for long-term poor outcome including death, incident chronic kidney disease (CKD) and greater health resource utilization.[4] Trends from observational data provide compelling evidence that the incidence of AKI is growing, and while mortality is concomitantly decreasing, more patients are ultimately suffering the long-term sequelae of AKI.[5,6] The reality is more alarming considering there are essentially no effective interventions to prevent AKI after identifying those at-risk or therapies to mitigate kidney damage once established, beyond usual supportive measures such as initiation of RRT.[7]

Once the decision is made to initiate acute RRT, there exist an array of modalities that may be undertaken: intermittent hemodialysis (IHD), slow low efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT). CRRT is typically reserved for our sickest and most complex patients, as it is the most homeostatic form of therapy; it is meant to function 24 hours a day, analogous to our own kidneys. However, while understood to be an advanced form of life support technology, there exist much variability in its prescription and delivery, leading to inconsistencies in its provision to critically ill patients, which in turn may lead to the delivery of suboptimal quality of healthcare. As there have been significant advancements in the pursuits to delivery consistent high-quality healthcare to all patients, this has led to a gap in the delivery of CRRT which needs to be addressed.

1.2 Acute kidney injury

1.2.1 Definition

The literature has been plagued by a wide array of operational definitions for AKI. A systematic review of clinical studies focused on cardiac surgery found over 35 different definitions were used to ascertain AKI.[8] This has created huge challenges for optimally estimating the burden of illness and outcomes attributable to AKI. In response to growing urgency for consistency and standardization in the diagnostic classification of AKI, consensus criteria were developed (i.e., RIFLE criteria, AKIN criteria).[9-11]

These proposed classification schemes have since been harmonized in the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI.[12] (Table 1-1) The KDIGO criteria still utilize conventional surrogates of kidney function (i.e., serum creatinine [sCr] and urine output) to define the presence and severity of kidney function loss.[12] Numerous studies have evaluated these classification schemes (or prior iterations) and have shown gradient-response relationships between severity of AKI and risk of poor outcome.[13] While the development of consensus definitions for AKI has been a monumental step for improving the scientific understanding of AKI. The role of these consensus definitions at the bedside to guide the clinical care of patients are still being evaluated, and future refinement of these classification schemes is likely to continue.[12]

1.2.2 Epidemiology

AKI occurs in approximately 1 in 5 hospitalized adults, and 1 in 3 hospitalized children. Accumulated evidence strongly suggests the true incidence of AKI is growing.[14,15] Several large cohort studies have focused on describing the incidence of AKI occurring in intensive care settings, with incidence rates 60-70%.[16-20] The incidence of AKI treated with RRT among critically ill patients is between 11-19 cases per 100,000, which represents 4-8% of all critically ill patients.[21,22] The incidence of AKI is increasing; a cohort study of more than

90,000 ICU admissions to 20 centres across Australia and New Zealand over 10 years demonstrated that the incidence of AKI increased by 2.8% per year.[23]

A wide array of patient and context specific factors have been shown to modify the risk of AKI. Older age, pre-existing proteinuria and CKD has consistently been shown to increase the risk of AKI, non-recovery of function and progression to ESKD.[24,25]. Similarly, the burden of non-renal comorbid disease also modifies the risk for AKI.[14,15] Diabetes mellitus, hypertension, cardiovascular disease (i.e., coronary artery disease, heart failure), peripheral vascular disease, chronic liver disease (i.e., cirrhosis, portal hypertension), chronic obstructive pulmonary disease, have all been implicated as important susceptibilities for development of AKI.[26-31] (Table 1-2) Acute conditions may also increase the risk of AKI. AKI in the intensive care unit (ICU) appears most commonly in association with sepsis and portends a marked increased risk for adverse outcome.[32,33]

Following acute illness, exposure to certain commonly prescribed medications may increase the risk of AKI.[34-40] (Table 1-3) Similarly, risk of AKI has been increasingly associated with adverse drug interactions, toxicity, inappropriate prescriptions, failure to adjust for kidney function, and among at-risk patients with continued nephrotoxin exposure during AKI.[41,42]. Contrast media exposure also represents one of the most commonly associated precipitants of AKI in hospitalized patients.[43] Finally, the choice and amounts of intravenous fluids utilized during resuscitation may impact the incidence of AKI. Randomized trials of fluid resuscitation with the synthetic colloid hydroxyethyl starch or administration of chloride rich solutions (i.e., 0.9% saline) have been associated with increased risk of AKI and greater utilization of RRT in surgical and critically ill patients.[44-47]

1.2.3 Outcomes

An episode of AKI has consistently portended an increased risk for immediate and long-term adverse consequences. The mortality risk associated with AKI is unequivocal and consistent across numerous clinical contexts and remains unacceptably high. The estimated unadjusted

mortality associated with an episode of AKI was recently estimated at 23.9% in adults and 13.8% in children.[2,5,6]

The adjusted risk of in-hospital death shows near linear increases with worsening severity of AKI.[19] Mortality is highest among patients with severe AKI treated with RRT, in particular in the setting of critical illness with in-hospital estimates approaching 60%.[48,49] In hospital, 90-day and 6-month mortality rates among RRT treated patients have recently been described at 35%, 45% and 49%, respectively.[50] Fluid overload in critically ill patients with AKI has shown consistent association with mortality across a number of observational studies.[51-53]

Recovery of Kidney Function

The downstream economic impact of AKI may be profound, in particular among survivors who fail to recover kidney function and remain dialysis dependent. Non-recovery of kidney function following an episode of AKI is a major morbid event with long-term patient-centered and health resource implications. Until recently, there has been no consensus on the definition for renal recovery; however, a recent consensus report by the Acute Disease Quality Initiative (ADQI) 16 workgroup has attempted to address this shortcoming by defining recovery as reduction from peak AKI stage.[54] Other studies have defined non-recovery as dialysis dependence among survivors. In large observational cohort studies of critically ill patients with severe AKI treated with RRT, the rate of dialysis dependence at hospital discharge is between 13-29%.[55-57]

Several patient-level susceptibilities modify the likelihood of non-recovery and rapid progression to ESKD, especially in older age and severity of baseline CKD, as well as the severity, magnitude and number of AKI episodes.[58] Recently, there has been renewed interest on the impact of the initial RRT modality applied to critically ill patients and recovery of kidney function. Initial renal support with continuous RRT (CRRT), compared with intermittent RRT (IRRT), has shown association with higher likelihood of recovery to dialysis independence.[59-61]

1.2.4 Modalities of Acute Renal Replacement Therapies

AKI requiring RRT occurs in approximately 4-8% of patients admitted to the ICU.[62] The incidence of dialysis-requiring AKI has steadily increased.[59] Among those critically ill patients with more severe AKI treated with RRT, CRRT remains the most common modality prescribed in ICU settings worldwide.[19]

The clinical presentation and circumstances may favor either intermittent or continuous therapies (Table 1-3). There are many theoretical benefits that may favor the use of CRRT over intermittent forms of therapy, such as improved hemodynamic stability, faster resolution of fluid overload, increased time-averaged dialysis dose delivery and improved long-term renal recovery (Table 1-4). Selected non-renal indications favoring use of CRRT include fulminant hepatic failure, brain injury with risk of cerebral edema and hyperammonemia (Table 1-5).

The most important short-term advantage to CRRT over intermittent RRT is the preservation and maintenance of hemodynamic stability. CRRT enables slower removal of solute and fluid from the intravascular space permitting adequate time for vascular refilling from the interstitial and intracellular space, theoretically minimizing iatrogenic episodes of hypotension. There are longer term implications for renal recovery, with IHD-related instability potentially exacerbating or predisposing to recurrent episodes of kidney injury and disrupting repair and recovery. Data from rigorous, comparative studies; however, have shown variable conclusions.[63]

Robust data in support of the many of the theoretical advantages of CRRT are still lacking. In the absence of a robust evidence base to guide clinical decision making, clinicians must adopt a patient-centric view to provide the most effective and safe RRT option for a given patient at a given point during their critical illness. The fundamental indications for delivering renal support remain unchanged and range from the most frequent request for

volume homeostasis to more esoteric indications such as immunomodulation. Common considerations in choosing to apply intermittent or continuous support are listed in Table 1-3, being mindful of numerous relative advantages and disadvantages of each (Table 1-4). A final consideration relates to timeliness and feasibility. CRRT can often be prescribed in collaboration with ICU and nephrology, can be started any day of the week at any time of day, and can be started and managed solely by an ICU nurse; whereas this may not always be possible with intermittent RRT. Finally, recent data have suggested critically ill patients receiving RRT can be safely mobilized and receive physiotherapy, including those with catheters in the femoral position.[64-66]

1.2.5 Continuous Renal Replacement Therapy

The establishment of CRRT evolved as a treatment of hemodynamically unstable patients unable to tolerate or achieve adequate therapy with conventional intermittent RRT (IRRT) or peritoneal dialysis (PD). In general, CRRT offers many theoretical advantages over IRRT in ICU settings, including better hemodynamic tolerance, enhanced fluid balance and uremic solute homeostasis and renal recovery. CRRT technology has undergone marked advances over time to improve efficiency, safety and bedside simplicity.[67]

The various modalities of CRRT are depicted in Table 1-6 and Figure 1-1. Continuous veno-venous hemofiltration (CVVH) is a form of CRRT where solute is cleared by convection and where the ultrafiltrate is either completely or partially replaced before (i.e., pre-dilution) and/or (i.e., post-dilution) to the hemofilter. Continuous venous-venous hemodialysis (CVVHD) is characterized by slow countercurrent dialysate flow into the dialysate compartment of the hemodialyzer, similar to traditional IHD. The main mechanism of solute removal is diffusion. Continuous veno-venous hemodiafiltration (CVVHDF) combines hemofiltration and hemodialysis modalities. Solute clearance is achieved by both convective and diffusion mechanisms. Slow, continuous ultrafiltration (SCUF) is based on the slow removal of plasma water (i.e., ultrafiltrate) only; there is no clearance of solutes. Studies evaluating the efficacy and outcomes between the various modalities of solute clearance with

CRRT (i.e., CVVH vs. CVVHD vs. CVVHDF) have shown equipoise, and prescription remains institutional specific.[68,69]

Regardless of institutional specific practices, to ensure effective, safe and timely CRRT, programs should ideally measure and review their own CRRT data. Selected quality indicators (QI) should be routinely captured for all patients receiving CRRT to monitor and benchmark performance and identify areas for improvement.[70] Programs should establish regional committees to review data and engage in quality improvement initiatives to continuously aim to provide high-quality CRRT care.[71] The purpose of these committees should be to review metrics collected by QIs in place, and ensure that established benchmarks are being achieved, and when not, to evaluate and examine underlying reasons for missing these targets so as to ensure the ongoing delivery of safe, effective and high-quality CRRT care.

1.3 Quality in Healthcare

1.3.1 Historical Perspective

Health care quality is, "the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[72] While the delivery of high quality, safe and efficacious medical care may seem like an obvious goal, it hasn't always been the focus of healthcare providers. It was not until 1999 when the Institute of Medicine released its report, "To Err is Human," that strong focus was placed on delivering high quality of care.[73] This report further defined quality across 6 domains: effectiveness, efficiency, equity, patient-centeredness, safety and timeliness (Table 1-7). A fundamental aspect of delivering high quality of health care centers upon means to measure health care delivery. The Donabedian model presents a framework for developing such measures, focused on three different categories of structure, processes and outcomes for examining health services and evaluating quality of health care.[74,75] Structure includes all physical or personal attributes relating to health care delivery.

This may include buildings, equipment and staff. Process is the sum of all actions that make up health care and summarizes how structure is put into place. Finally, outcome refers to the results of processes, essentially containing all the effects of healthcare on patients or populations, including changes to health status, behaviour or knowledge as well as patient satisfaction and health-related quality of life.[76] While other quality of care frameworks exist, such as the World Health Organization Recommended Quality of Care Framework, the Donabedian Model continues to be the dominant form for assessing the quality of healthcare.[77]

1.3.2 Current Practices

Numerous organizations exist today to ensure the delivery of high quality healthcare. In the United States, the Agency for Healthcare Research & Quality and the National Quality Forum both strive to produce evidence and guidelines to make health care delivery safer, higher quality, more accessible, equitable and affordable.[72,78] The National Quality Forum has particular focus on developing measures that fit within the Donabedian model to improve healthcare, and they have developed measures for chronic kidney disease.[79] However, measures for AKI are still lacking. In the United Kingdom, the National Institute for Health and Care Evidence (NICE) exists to provide guidance, recommendations and to develop quality standards for health, public health and social care. They also have a strong focus to relay resources to help maximize the use of evidence and guidance.[80] Furthermore, NICE has developed specific quality standards that cover preventing, detecting and managing acute kidney injury in adults, young people and children as well as for adults with kidney failure.[81,82] However, in their document for RRT services for adults, the focus is primarily for patients with longstanding RRT, rather than for patients requiring acute RRT or for patients in the ICU. Finally, in Canada, the Canadian Institute for Health Information (CIHI) has a strong focus on quality of care and outcomes. The CIHI contributes to patient safety and health outcome evaluation, and considers how well services are provided to patients by addressing four important questions: do health services measure up to health care evidence; are they patient-centered; do they produce desired health outcomes; and to they contribute to patient safety?[83] Locally, the Health Quality Council of Alberta utilizes this framework and

provides an Alberta Quality Matrix for Health. The purpose of this Matrix is to set a framework of organizing information and thinking about the complexity of the health system along the six dimensions of quality as per the Institute of Medicine.[84] While there has been specific work on QIs at the CIHI, there has not been any focus on measures relating to AKI or acute RRT, of which CRRT is the most common modality utilized worldwide.[19] This is an important gap in our evaluation of healthcare, and will be the focus of this research program.

1.4 Summary

AKI is a global health concern with a growing incidence and prevalence amongst critically ill patients. Treatment is either supportive consisting of mitigating inciting circumstances and ensuring no further kidney insults, but when AKI progressive to renal failure, RRT is necessary. Acute RRT can occur in many forms, intermittent or continuous, but CRRT remains the most widely form of acute RRT utilized worldwide. It is a complex life-sustaining technology, reserved for our most acutely ill patients. As such, it is important to ensure the delivery of high quality, safe and effective CRRT as per the framework set forth by the Institute of Medicine. To ensure that this occurs, QIs are necessary to monitor, benchmark and provide continuous feedback on the delivery of CRRT. To date, there exists no rigorously defined QIs for CRRT care, and this is a significant knowledge gap. This research program will target this knowledge gap and will develop a set of QIs that may be adapted to any CRRT program to ensure the delivery of safe and high quality CRRT care.

1.5 Objectives

The objectives of this program are the following:

1. To evaluate what quality and safety measures have been developed and evaluated in critical care nephrology.
2. To identify potential existing quality indicators for CRRT care currently available in the literature.

3. To rank, prioritize and define quality indicators for CRRT care that may be utilized across any clinical or educational CRRT program.

Table 1-1 KDIGO definition and classification of AKI

AKI definition	is defined as any of the following: • Increase in SCr by 26.5 μmol/L (0.3 mg/dL) within 48 hours; or • Increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or • Urine volume <0.5 mL/kg/hr for 6 hours	
AKI Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥26.5 μmol/L (0.3 mg/dL)	<0.5 mL/kg/hr for 6-12 hours
2	2.0-2.9 times baseline	<0.5 mL/kg/hr for ≥12 hours
3	3.0 time baseline OR Increase in SCr to ≥353 μmol/L (4.0 mg/dL) OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to < 35 mL/kg/min per 1.73m^2	<0.3 mL/kg/hr for ≥24 hours

Abbreviations: AKI - acute kidney injury; sCr - serum creatinine; eGFR - estimated glomerular filtration rate

Table 1-2 Summary of risk factors for AKI

Susceptibilities (non-modifiable)
Older Age
Male sex
Black race
Chronic kidney disease
Proteinuria or elevated albumin-to-creatinine ratio
Hypertension
Diabetes mellitus
Chronic liver disease and/or complications of portal hypertension
Heart failure, decreased ejection fraction
Coronary artery disease and/or recent myocardial infarction
Chronic obstructive pulmonary disease
Peripheral vascular disease
Malignancy
Modifiable risk factors
Anemia
Critical illness
Sepsis
Trauma
Prior cardiac surgery, cardiac surgery with cardiopulmonary bypass
Major non-cardiac surgery
Radiocontrast media
Fluid overload
Synthetic colloid (i.e., hydroxyethyl starch)
Chloride rich solutions (i.e. 0.9% saline)
Drug toxicity, drug interaction or nephrotoxic medication
High risk or emergency procedure

Non-modifiable risk factors are patient specific characteristics, while modifiable risk factors are those which may be acted on by healthcare providers.

Table 1-3 Clinical considerations for CRRT versus IHD in the ICU

Condition/Feature	Method of Delivery	
	Intermittent	Continuous
Hemodynamic instability	No/yes	Yes
High fluid requirements	No/yes	Yes
High potassium generation	Yes	No
High catabolism	Yes	Yes/no
Peripheral vascular disease	Yes	Yes/no
Global cardiac dysfunction	No/yes	Yes
Septic shock	No/yes	Yes
APACHE II score >25	No/yes	Yes

Abbreviations: APACHE – Acute Physiology and Chronic Health Evaluation

Table 1-4 Intermittent and continuous forms of RRT

Feature	Modality		
	IHD	SLED	CRRT
Setting	Hemodynamically stable	Hemodynamically unstable	Hemodynamically unstable Increased intracranial pressure
Advantages	Rapid removal of low-molecular-weight substances and toxins Time when not receiving treatment may be used for diagnostic or therapeutic procedures Reduced anticoagulation exposure Low cost	Hemodynamic stability Time when not receiving treatment may be used for diagnostic or therapeutic procedures Decreased anticoagulation requirements	Easy control of fluid balance Hemodynamic stability Continuous removal of toxins Improved long-term renal recovery
Disadvantages	Hypotension with rapid fluid removal Dialysis disequilibrium with risk of cerebral edema Technically complex	Slower clearance of toxins Technically complex	Slower clearance of toxins May require anticoagulation Patient immobilization Hypothermia Increased costs

Abbreviations: CRRT - continuous renal replacement therapy; IHD - intermittent hemodialysis; SLED - sustained low-efficiency hemodialysis

Table 1-5 Indications for RRT

Absolute	Relative	Theoretical
Pulmonary edema	Volume overload	Immunomodulation
Hyperkalemia	Electrolyte imbalance[a]	
Metabolic acidosis	Acid-base imbalance[b]	
Uremia	Myoglobinemia	
Toxin removal	Tumour lysis syndrome	
	Temperature control	
	Hyperammonemia	
	Nutritional support	

[a]hyponatremia, hyperphosphatemia and hypermagnesemia. [b]metabolic acidosis, mixed acidosis/alkalosis.

Table 1-6 Modalities of CRRT

Feature	SCUF	CVVH	CVVHD	CVVHDF
Method of clearance	Convection	Convection	Diffusion	Convection and diffusion
Middle molecular size clearance	+	+++	+	+++
Replacement fluid	None	Present	None	Present
Dialysate	None	None	Present	Present
Effluent composition	Ultrafiltrate	Ultrafiltrate	Dialysate + ultrafiltrate	Dialysate + ultrafiltrate

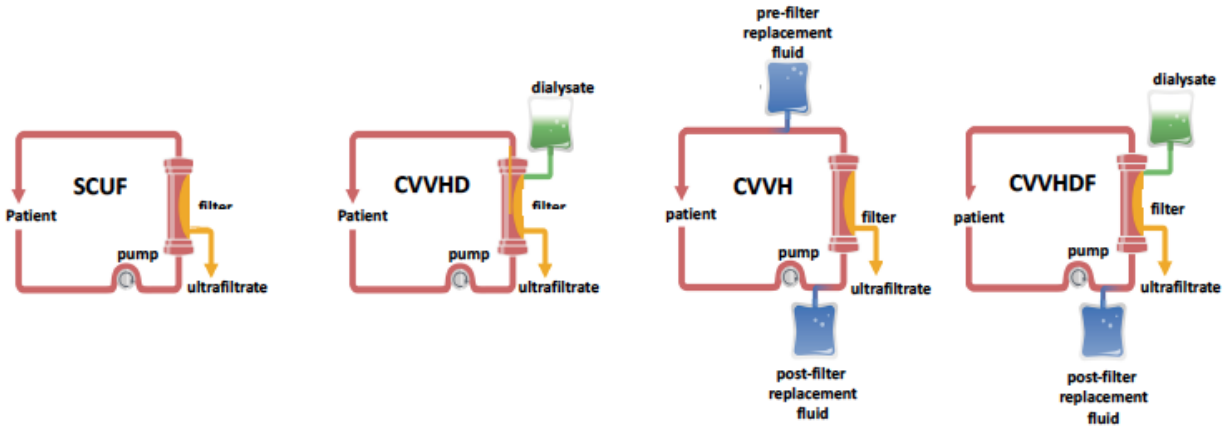
Abbreviations: CVVH - continuous venovenous hemofiltration; CVVHD - continuous venovenous hemodialysis; CVVHDF - continuous venovenous hemodiafiltration; SCUF - slow continuous ultrafiltration.

Table 1-7 Quality Domains

Quality Domain	Definition
Effectiveness	Providing care processes and achieving outcomes as supported by scientific evidence
Efficiency	Maximizing the quality of a comparable unit of health care delivered or unit of health benefit achieved for a given unit of health care resources used
Equity	Proving health care of equal quality to those who may differ in personal characteristics other than their clinical condition or preferences for care
Patient-centeredness	Meeting patients' needs and preferences and providing education and support
Safety	Minimizing actual or potential bodily harm
Timeliness	Obtaining needed care within a reasonable time frame and minimizing delays

Above are the 6 quality domains as per the institute of medicine along with their operational definitions.

Figure 1-1 CRRT Modalities



The four primary CRRT modalities are depicted above, along with their fluid requirement. SCUF only serves for ultrafitration; there is no solute clearance. CVVHD provides solute clearance through a dialyzer, similar to traditional dialysis. CVVH provides solute clearance through filtration, and requires replacement fluid which may be delivered both pre- and post-filter. Finally, CVVHDF combines elements of both CVVH and CVVHDF for solute clearance. Adapted from Fresenius Medical Care.[85]

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CHAPTER 2: QUALITY INDICATORS FOR CRITICAL CARE NEPHROLOGY

2.1 Introduction

Quality and safety have long been important ideals to achieve in medicine. However, recently there has been emphasis on the application of formalized mechanisms to implement measures to monitor and evaluate the quality and safety of care delivered to patients. This was first publicized in 1999 by the Institute of Medicine (IOM) and then further characterized by their 2001 report, "Crossing the Quality Chasm: A New Health System for the 21st Century."[1,2] Since the publication of these reports there have been a few notable quality improvement initiatives focused on acute kidney injury (AKI) and continuous renal replacement therapy (CRRT).[3-6] These have contributed to the development of a consensus classification scheme for the diagnosis for AKI, clinical practice guidelines for AKI, and initiatives for the effective and safe application of CRRT in critically ill patients. However, recent literature suggests that the quality of care received by patients with AKI is generally poor, suffers from numerous deficiencies, and has an attributable morbidity and mortality due to iatrogenic complications and sub-optimal quality of care.[7]

CRRT is generally delivered to the most severely ill patients with AKI, often characterized by multi-organ dysfunction and receiving complex multi-modality support. Due to the complexity and sheer number of interventions routinely received by these patients, they are not only more susceptible to medical errors and adverse events but are also likely to have diminished capacity to withstand and recover.[8,9] Accordingly, the delivery of high quality and safe care is particularly important for these patients, where small lapses or inadvertent omissions in care may have far more significant consequences. In this review, we provide a high-level overview of the history of the development of the quality and safety culture in medicine. Next, we will discuss the current quality of care and quality initiatives proposed for AKI and CRRT. We then present quality and safety development methodologies used in health care before finally presenting the evidence for quality and safety in AKI and CRRT along with future avenues for improvement.

2.2 Summary of Quality and Safety Culture in Medicine

Healthcare is not as safe as it should be. The 1999 IOM "To Err is Human" revealed that between 44,000 and 98,000 die each year in the United States from preventable medical errors.[1] A subsequent Canadian study found that adverse events in hospitalized patients occur frequently – an estimated 185,000 occur yearly, and nearly 70,000 of these are potentially preventable.[10] The 1999 IOM report advocated for a comprehensive approach to improve patient safety.[11] A follow up IOM publication, "Crossing the Quality Chasm" identified six specific aims for improvement of care: safety, effectiveness, patient-centered, timely, efficient and equitable.[1] Since its publication, there has been an increase in patient safety initiatives, patient safety publications and a significant growth in the funding for patient quality and safety initiatives and research and has led to the establishment of numerous health quality organizations.[11] Healthcare systems are investing considerable resources to improve workplace and patient safety, are promoting and cultivating a culture of safety to help anticipate and prevent such errors and also to document and investigate these events if they should occur.[12] These initiatives have led to continuous quality improvement initiatives to enhance of quality of care in hospitals, and in the patient safety climate to improve care processes and patient outcomes, including in AKI and CRRT.[13]

2.3 Current Quality of Care Offered in AKI and CRRT

The National Confidential Enquire in Patient Outcome and Death (NCEPOD) in the United Kingdom published an audit of the quality and processes of care provided to hospitalized patients that had died with AKI.[14] They identified 1518 patients from 215 hospitals, of which 700 cases had detailed documentation for evaluation. It was determined that only in 50% of cases care provided to patients with AKI was considered good. There were also significant issues in the recognition and management of AKI – in 43% of cases there were unacceptable delays in the recognition of AKI, 21% of episodes of AKI were both predictable and avoidable, in 13% of cases complications of AKI were missed, avoidable in 17% and

managed badly in 22% of cases. Additionally, 33% of patients had inadequate investigations relating to their AKI and 29% of patients had poor clinical management of their AKI, including physiological monitoring. Finally, they determined that referrals to nephrologists only occurred in 31% of patients, and may have been warranted in up to 20% of patients who were not referred. This report highlighted numerous "systematic failings" and quality care gaps in the recognition and management of hospitalized patients with AKI. Unfortunately, only a few years following the NCEPOD report, another study found that the management of hospitalized patients with AKI remained poor.[7] Aitken et al. evaluated a large cohort and found that AKI still remained common, occurring in 14.9% of hospitalized patients, and was associated with poor outcomes (increased mortality, 19% vs. 3.8%, $p<0.001$), and increased length of hospital stay (11.5 vs. 4.9 days, $p<0.001$). This study also highlighted, that despite the NCEPOD report, there still exists significant delays and failure of recognition of AKI. A more recent report has also echoed these results, finding that in a retrospective audit of 170 hospitalized patients who developed AKI during admission, 30% of these episodes could have been avoided if physicians had taken appropriate preventive actions.[15] These observations reinforce the concerns regarding gaps in the recognition, care process and quality of care received by patients with AKI and imply that a significant proportion of the morbidity and mortality observed in AKI may be iatrogenic and attributable to poor quality of care.

The quality of care in AKI and CRRT has been recognized as a priority issue, a fact reinforced by the above mentioned NCEPOD audit and Aitken study.[16] There currently exist several organizations that strive to deliver high quality evidence-based therapy in AKI and CRRT care. These include the Acute Dialysis Quality Initiative (ADQI), the Acute Kidney Injury Network (AKIN), the Kidney Disease: Improve Global Outcomes Initiative (KDIGO) and the National Institute for Health and Care Excellence (NICE).[17-19] These organizations aim to comprehensively evaluate the scientific literature focused on AKI and acute RRT, to identify existing knowledge gaps, and to inform best practice standards for risk identification, diagnosis, monitoring, investigation and management of patients with AKI and receiving renal support. KDIGO has published comprehensive evidence-based clinical practice guidelines for AKI that includes a harmonized consensus definition and

classification scheme for AKI. The long-desired intent of a consensus definition has been to facilitate more rigorous and applicable scientific inquiry for how to prevent, diagnose and manage AKI.[20,21] Yet, AKI remains exceedingly common among hospitalized patients, particularly in the ICU, is often predictable and/or even avoidable and is frequently mismanaged. This may be especially true during off-peak hour admissions (i.e., weekend and night-time). This was shown in a recent large American cohort study that found increased in-hospital mortality (7.3 vs. 6.7%, $p<0.05$) for patients admitted with AKI during the weekend.[22] This mortality difference may be multi-factorial and, similarly to the findings of previously published reports, may stem from delayed recognition of AKI, delayed referral for nephrology consultation and/or delayed initiation of RRT.

When RRT is initiated in the ICU, CRRT is the most often utilized modality.[23,24] However, the quality of care of delivered CRRT, as with AKI, remains suboptimal. This may stem from the wide variations in practice associated with the care of patients with AKI and receiving CRRT. The factors contributing to this variation are likely related to a combination of center-specific, provider-specific and therapy-specific variations.

Center specific education standards

When considering measures of AKI and CRRT quality of care, there are a number of center-specific considerations. First, regional health regions or jurisdictions often independently establish unique CRRT protocols and/or preferentially utilize selected operating parameters and technologies to suit local practice (i.e., specific CRRT mode such as CVVH, CVVHD or CVVHDF, anticoagulation strategy or CRRT dose).[23-25] Whether this contributes to observed site-specific variation in the utilization of RRT and associated patient outcome remains uncertain.[26] Second, centers may also have a particular practice with referral patterns to critical care or nephrology for investigation and management of patients with AKI or needing CRRT. Non-specialist management of AKI has been associated with omission of key assessments in the management of patients with AKI.[27] Delayed nephrologist consultation ($\geq$ 48 hours after development of AKI) has been associated with increased hospital mortality in ICU patients.[28] These data would suggest early and appropriate specialist consultation and a team management approach are important aspects for delivery of high quality AKI

management. Third, quality of care associated with AKI and CRRT may also follow a volume-outcome relationship. Theoretically, high-volume CRRT centers, where large numbers of patients routinely receive treatment, may have more developed infrastructure (i.e., educational/training/certification programs) or more experienced and knowledgeable providers. Similarly, low-volume centers may have limited opportunity for providers to perform and refine the technical and non-technical skill necessary to develop sustainable expertise.[29] Volume-outcome relationships have been shown with other technologies applied to critically ill patients, such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in acute respiratory distress syndrome (ARDS), where high-volume centers (and referral to regional centers of excellence) are associated with improved outcomes.[30] The care model, along with the infrastructure and process demands for CRRT programs, may also be variably impacted in institutions that provide additional complex extracorporeal support therapies (i.e., therapeutic plasma exchange [TPE], extracorporeal membrane oxygenation [ECMO]) or perform complex cardiothoracic and solid organ transplantation. In these settings, CRRT is often run in parallel with one or more other complex life support therapies. In these circumstances, greater infrastructure and provider support may exist, enabling greater opportunity for continuous quality assurance activities to improve care delivery.[31,32]

Provider-specific factors

The decision on when to initiate CRRT is influenced by institutional standards as well as the clinician experience and training. The provider's training and background, intensivist versus nephrologist, likely contributes, in part, to some of the observed variation in CRRT prescription and delivery. In addition, numerous aspects of CRRT care lack standardization and therefore are susceptible to variation in practice. When to start and stop therapy, when to safely transition from CRRT to intermittent forms of RRT (and vice versa), the optimal methods and techniques for monitoring fluid removal and temperature management during CRRT are some of the treatment decisions most susceptible to practice variation due to an uncertain evidence base.[33-35] Accordingly, in the absence of a clear evidence base to guide these decisions regarding CRRT, centers and providers adopt their own practices as

standards. This individualized practice has the potential to systematically bias in how to best provide care for AKI patients receiving CRRT.[29]

The model of nursing care is potentially an important determinant of the quality of CRRT care delivered to patients that is also susceptible to practice variation. There are two basic nursing models, single versus collaborative models (Table 2-1). There is no consensus on the merit of either model, and each has distinct benefits; however, these merit further evaluation.[36-38] With the single program model, one group assumes full responsibility for all aspects of CRRT delivery.[36,38] This theoretically minimizes the potential for miscommunication between provider teams (i.e., necessity for additional sign-over). In contrast, the collaborative program model shares the responsibilities between different provider groups based on their areas of expertise.[38] The most common example of a collaborative RRT care model is a partnership between the dialysis program and the critical care program. Duties are shared and determined by discipline expertise, often with the dialysis nurse performing set-up and initiation, while the critical care nurse assumes the hour-to-hour bedside care.[37] However, given the complexity of providing care to patients receiving CRRT, an inter-professional team is ideally required.[39,40]

Therapy-specific factors

There are therapy-specific factors that importantly may be employed to measure the quality of CRRT care. For example, common measures of CRRT quality described in the literature have included the number of filters utilized or filter lifespan, hours of CRRT provided per day (i.e., unplanned downtime) and prescribed vs. delivered CRRT dose.[41] However, these are relatively limited in scope and additional measures require further development and evaluation. These may include, but are not limited to the optimal time to replace CRRT filters and the optimal type and composition of the replacement and dialysate solutions.[35] Machine complexity combined with the level of nursing knowledge can impact the quality of CRRT care. Navigating machine alarms, recognizing, and responding to the changing patient condition will be more challenging for the inexperienced user. These all have the potential to interrupt therapy and create discrepancies between the prescribed and delivered dose.[42]

However the potential to incorporate simulator devices into CRRT training may help mitigate these factors and may be topics for future research.[43]

Additional therapy-specific factors warranting consideration include the location and type of catheter and the method of circuit anticoagulation used during CRRT. The KDIGO clinical practice guidelines for AKI recommend preferential access of the right internal jugular vein over femoral vein. The principle concern with use of the femoral site was risk of catheter-related infection. This recommendation; however was ungraded. More recent data would imply the infection risk may be similar; however, is modified by use of the femoral site in obese patients.[44,45] Femoral access may be associated with prolongation of filter lifespan, reduced mechanical complications and sparing of upper extremity vascular access for long-term RRT access compared with internal jugular access.[45,46]

Selecting the ideal methods of anticoagulation to preserve filter lifespan and minimize iatrogenic complications also represent an important quality consideration for critically ill patients receiving CRRT. While use of systemic heparin (+/- regional protamine) has long been the standard method of circuit anticoagulation in CRRT; regional citrate anticoagulation (RCA) has gained significant traction supported by several clinical trials showing greater filter lifespan, reduced bleeding and cost savings relative to heparin.[47-51] There is theoretical risk of citrate toxicity in patients with liver disease and infants; however, RCA may be safe with appropriate protocols for administration and monitoring.[52-54] A recent multicenter study involving 212 patients and 857 CRRT circuits found anticoagulation with RCA improved filter lifespan while reducing adverse events when compared to heparin plus protamine.[55] While these data would support the benefits of RCA, many of its nuanced issues are yet to be resolved. There are many different RCA protocols involving variable solutions, differing calcium replacement protocols along with inconsistent monitoring techniques for efficacy that remain important knowledge gaps that require further study. This has created challenges for how to ideally monitor and benchmark use of RCA.

2.4 Quality Indicator Development Methodology

As quality and safety in medicine have become priorities, quality improvement methodologies have also become more defined. These measure development strategies provide a data decision driven structure for improving patient outcomes.[56] Two of the most important of these strategies include the PDSA and FADE models (Figure 2-1). The PDSA is a four-step (*plan, do, study, act*) model for recognizing, implementing, and evaluating change. PDSA has been used for developing interventions as well as evaluating and reporting progress on initiatives to improve the care delivery for patients with AKI.[57] The FADE (*focus, analyze, develop, evaluate*) model is characterized by four broad steps: *focus* to define and verify the process to be improved, *analyze* the data to establish baselines, identify root causes and point towards possible solution, *develop* action plans for improvement and *execute* and *evaluate* the implementation of the action plan and to monitor the system to ensure success.[58] The FADE model has been used to develop and implement educational programs in healthcare and identify areas that require further improvement.[59] Rigorously developed and validated measures of quality of care can be endorsed by the National Quality Forum (NQF), which is a gold standard for healthcare quality and a means for widespread dissemination to facilitate adoption.[60] Lean thinking has also been used to improve the efficiency of CRRT workflow, reduce CRRT-related costs, and improve job satisfaction among providers.[61] Lean is a form of quality improvement that has been adopted from the car manufacturing industry. It utilizes value-stream mapping to identify non-value added waste and inefficiencies in a system and to create solutions to avoid or eliminate waste.[62] Other methods such as checklists, Six-sigma methodology and Kaizen methods have been used in the prescription and delivery of CRRT.[56,61] These have contributed to the development of protocols and documentation for CRRT with the aim to reduce unnecessary practice variation across providers and reduce avoidance errors in CRRT prescriptions and delivery. The goals for any CRRT quality and safety initiate should be aimed at maximizing efficacy and effectiveness of prescribed/delivered therapy while minimizing the risk of adverse events. However, rigorously evaluated quality measures for CRRT to achieve these aims are currently missing.

2.5 Evidence for Quality Indicators in AKI and CRRT

Following the recent National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report and subsequent cohort study by Aiken et al. which highlighted significant shortcomings in the diagnosis and treatment of AKI in hospitalized patients, NICE has published recommendations for management of AKI and RRT.[7,14] They have generated 51 unique recommendations following a rigorous systematic process for evaluating and grading the quality and strength of the evidence base.[63] The NICE recommendations describe the current evidence base for identifying at-risk patients and prevention of AKI, along with strategies for early recognition, monitoring, investigation and management of AKI including when to consider specialist referral and when to initiate RRT.[16] (Table 2-2) Recognition and diagnosis of AKI has been shown to often be significantly delayed.[63] One potential remedy has been to integrate electronic medical record alerts for patients at high risk for developing AKI; however, the precise methodology of e-alerting to optimize care processes and improve patient-centered outcomes is currently inconclusive.[64] Another potential measurable intervention would be the use of focused care bundles for the diagnosis and management of AKI, which may be associated with decreased rates of progression of AKI and hospital mortality.[63] When CRRT is initiated, evidence has suggested that specialized care teams can improve care processes and patient outcomes. Implementation of these inter-professional teams (consisting of nephrologists, intensivists, specialized trainees, CRRT specialized nurses and clinical pharmacists) recently was shown to improve the delivery of CRRT, including optimization of ultrafiltration rate, reducing unplanned downtime and decreasing ICU lengths of stay and mortality.[39] The integration of clinical pharmacists may facilitate appropriate medication adjustment or avoidance with recommendations for safe alternatives.[65]

Recent evidence confirms that CRRT is the most commonly applied form of renal support provided to critically ill unstable patients; and also confirmed many aspects of its routine care continue to vary widely and often fail to align with current best practice which has led to suboptimal quality of care and poor patient outcomes.[7,14,66,69] While these variations in practice stem, in part from knowledge and care gaps in the evidence base for AKI and CRRT

care, quality measures have not been proposed, developed or validated.[68] There is a strong need for a rigorous process to identify, validate, prioritize and evaluate quality measures in both AKI and CRRT care along with supporting their implementation into clinical practice to establish clear benchmark targets to ensure the appropriate and highest quality of management and delivery of AKI and CRRT care.[69]

2.6 Conclusions

The delivery of effective and safe healthcare are cornerstones of modern medicine. Since the publication of the IOM reports, there have been important advances in the quality and safety culture of health services delivery. Numerous quality and safety initiatives have improved care processes and outcomes for patients, such as the Health Quality Forum in the United States, the National Institute of Healthcare & Excellence in the UK and the Canadian Patient Safety Institute in Canada.[16,60,70] With a focus on AKI and CRRT in particular, initiatives have harmonized the definition of AKI, have created common nomenclature for CRRT, and have developed evidence-based guidelines for AKI prevention, early identification and management, including the provision of CRRT. However, recent data have shown considerable care gaps exist for patients with AKI or those treated with CRRT, implying the quality of care received by these patients is clearly suboptimal. To date, there has been little development of key quality measures of AKI or CRRT care that can be used to guide quality improvement initiatives, monitor and benchmark performance and the design of educational and/or accreditation programs.

Table 2-1 Models of CRRT care

Chronology of care	Responsibility	Single program model	Collaborative program model
CRRT set up	Prepare machine	CCN	NON-CCN
	Obtain supplies	CCN	NON-CCN
	Schedule initiation time	CCN	NON-CCN
	Order CRRT	CCMD	Nephrology MD
Initiate therapy	Prime machine	CCN	NON-CCN
	Obtain prelabs	CCN	NON-CCN
	Assess catheter function	CCN	NON-CCN
	Perform procedure	CCN	NON-CCN
	Monitor patient	CCN	CCN
Maintain therapy	Circuit monitoring	CCN	CCN
	Obtain ACG labs	CCN	CCN
	Prescribe fluid removal	CCMD	Nephrology MD w/CCMD
	Adjust ACG per protocol	CCN	CCN
	Bag changes	CCN	CCN
	Adjust rate per orders	CCN	NON-CCN
	Catheter care	CCN	CCN
Troubleshooting and other procedures	First responder to alarms	CCN	CCN
	Second respond to alarms	CCN	NON-CCN
	Recirculation procedure	CCN	NON-CCN
	Perform in OR	CCN	NON-CCN
	Reinitiate procedure	CCN	NON-CCN
Terminate therapy	Return blood (as necessary)	CCN	NON-CCN
	Discard filter set	CCN	NON-CCN

The single program model utilizes solely critical care team members while the collaborative Program model involves staff from both critical care and non-critical care staff. ACG – anticoagulation; CCMD – critical care medical doctor; CCN – critical care nurse; MD – medical doctor; NON-CCN – dialysis, extracorporeal, or perfusion nurse/team member; OR – operating room.

Table 2-2 National Institute for Health and Care Excellence clinical guidelines for acute kidney injury

Risk factors for development of AKI	Principles for prevention/detection of AKI	Management of AKI	Essential information and support for patients
Investigate for AKI in high risk adult patients*	Assess risk factors in high-risk adults having iodinated contrast***	Identify the causes of AKI	Give information about long-term treatment options, monitoring, self-management and support to patients with AKI in collaboration with a multidisciplinary team
Investigate for AKI in high-risk pediatric patients**	Assess risk factors in adults having surgery	Offer urgent ultrasonography when no identified cause of AKI is found	
	Ongoing assessment of patients in hospital	Discuss the management of AKI with a nephrology as soon as possible	
	Monitor serum creatinine regularly		

Summary of quality statements to be considered in all patients with AKI. AKI – acute kidney injury. Drugs with nephrotoxic potential – aminoglycosides, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, NSAIDs. Adapted from ref. 67.

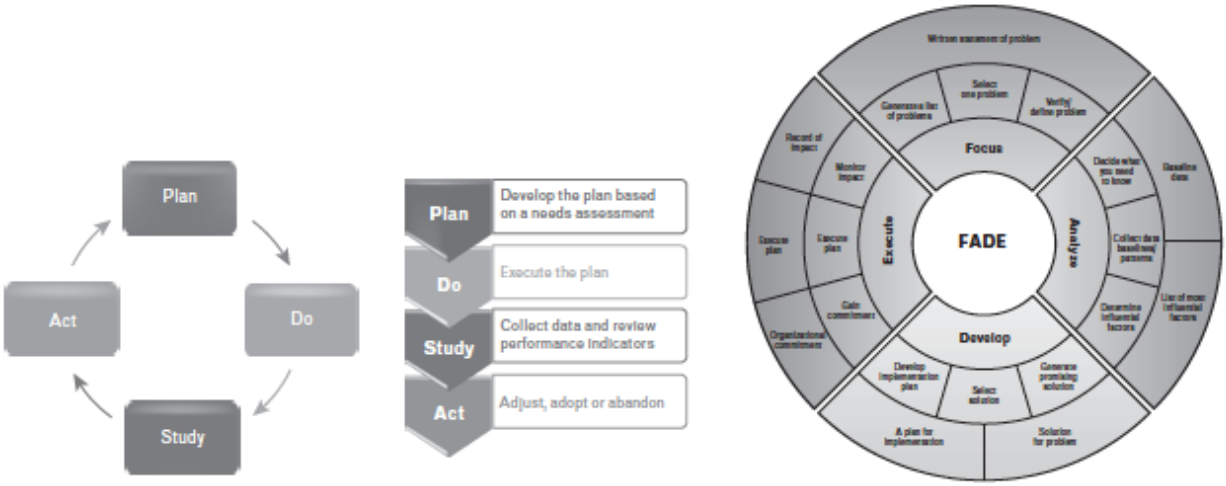
* CKD, CHF, DM, history of AKI, oliguria (urine output ≤0.5 ml/kg/h), neurological or cognitive impairment or disability, hypervolemia, use of drugs with nephrotoxic potential within the past week, use of iodinated contrast agents within the past week, symptoms or history of urological obstruction or conditions that might lead to obstruction, sepsis, deteriorating early warning scores, age ≥65 years.

** CKD, CHF, liver disease, history of AKI, oliguria (urine output ≤0.5 ml/kg/hour), young age or neurological or cognitive impairment or disability, hypervolemia, hypotension, severe diarrhea, use of drugs with nephrotoxic potential within the past week, symptoms or history of urological obstruction or conditions that might lead to obstruction, sepsis, deteriorating pediatric early warning score symptoms or signs of nephritis (i.e., edema or hematuria), hematological malignancy.

*** CKD, CHF, renal transplant, age ≥75 years, hypovolemia, increasing volume of contrast agent, intra-arterial administration of contrast agent.

CHF – congestive heart failure, CKD – Chronic kidney disease, DM – diabetes mellitus.

Figure 2-1 Comparison of continuous quality improvement models.



	PDSA Model	FADE Model
Step 1	**P**lan – Determine the intervention to improve the process or problem	**F**ocus - Define the problem, narrowing the focus of the problem or process to be improved
Step 2	**D**o – Implement the intervention (small scale/pilot)	**A**nalyze – Data collection to establish baselines and identify potential solutions
Step 3	**S**tudy – Analyze data and results	**D**evelop – Identify interventions and plan for implementation
Step 4	**A**ct – Refine processes based on data analysis	**E**xecute – Implement the intervention, with continuous data measuring and analysis

The plan-do-study-act focuses on implementing an intervention based on assumption of problems, evaluating small change interventions, making small adjustments to the intervention and then repeating the process. The focus-analyze-describe-execute centers on clearly identifying the problem with data analysis of the current situation prior to intervention planning, followed by the execution of the developed solution. Adapted with permission from ref. 62.

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CHAPTER 3: QUALITY INDICATORS OF CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) CARE IN CRITICALLY ILL PATIENTS: A SYSTEMATIC REVIEW

3.1 Introduction

Renal replacement therapy (RRT) is acutely applied in 4-8% of critically ill patients and the utilization has grown by greater than 10% per year over the past decade.[1-6] The AKI-EPI study found that continuous renal replacement therapy (CRRT) is the predominant form of RRT utilized, being the initial RRT modality in over 75% of critically ill patients.[7,8] There is considerable variation in the prescription and delivery of CRRT care, despite evidence to guide practice.[7,9] For example, while several high-quality randomized controlled trials (RCTs) have shown lower dose-intensity of CRRT is as effective as higher dose-intensity CRRT for patient outcomes, certain centers still routinely prescribe higher dose-intensity CRRT.[10,11] Yet, there remain large disparities in practice between prescribed and delivered dose of CRRT.[1,9] The mode of CRRT remains highly variable.[12] Despite recent evidence to suggest the superiority of regional citrate to maintain circuit patency, heparin use remains predominant in many ICUs.[13,14] Finally, the timing of when to initiate CRRT is uncertain and recent evidence from RCTs have shown conflicting results.[15,16] Such discrepancies likely contributes to wide practice variation. This likely represents a surrogate for suboptimal or poor quality of care.

While this variation may stem from important knowledge gaps in evidence to guide best practice, additional factors such as different providers (i.e., nephrology vs. intensive care), limited provider and/or institutional expertise, and a paucity of clearly defined quality indicators (QIs) to measure and monitor the quality of CRRT care likely contribute. The purpose of such QIs is to increase the reliability of care, homogenize complex interventions where risk is non-trivial and to enable benchmarking of performance. QIs can be further used as targets for continuous quality improvement initiatives aimed at evaluating new or revised

care processes, implementing new protocols or interventions and to stimulating innovative research.[17]

QIs can be defined using the Donabedian framework, and classified across three domains of healthcare: structure (i.e., settings, qualifications of providers, and organizational/ administrative systems), process (i.e., components of healthcare delivered), and outcomes (i.e., recovery, restoration of function and survival).[18] While QIs have been identified in other scopes of critical care (i.e., standardized mortality rate, rates of catheter-related bloodstream infection, compliance with venous thromboembolism/stress ulcer prophylaxis), I have found no study to date that has systematically mapped or evaluated the scope of QIs in CRRT care.[19-21]

Accordingly, I performed a systematic review to identify and define QIs of CRRT care. This is a vital initial step toward identifying, validating and implementing evidence-informed QIs to avoid or reduce low quality CRRT care, to guide best practice, optimize resource utilization and healthcare provider workload and improve patient outcomes. Moreover, QIs of CRRT care can be implemented to standardize and improve the reliability of CRRT practice, audit and benchmark CRRT performance over time.

3.2 Methods

I performed a systematic review using methodological approaches outlined in the Cochrane Handbook for Systematic Reviews of Interventions and described according to the PRISMA-P guideline.[22,23] Research ethics approval was not required. This systematic review was registered at PROSPERO (January 22, 2015 CRD42015015530).

Search Strategy for Identification of Studies

I developed a comprehensive search strategy in consultation with a Research Librarian that was peer-reviewed by a second research librarian.[24] I searched the following electronic databases: Ovid Medline in-Process & Other Non-Indexed Citations and Ovid Medline (1946 to present), Ovid Embase (1988 to 2015 Week 07), Cumulative Index to Nursing and Allied

Health Literature (CINAHL) via EBSCO host (1937 to present), Cochrane Library via Wiley (inception to present) including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed via NCBI Entrez limited to publications from 2014-2015. To locate reports of in-process research and other technology assessments not included in our main bibliographic databases, I searched the Health Services Research Projects in Progress (HSRProj), Health Services Research Resources (HSRR) and Health Services/Technology Assessment Texts (HSTAT) databases from the National Information Center of Health Services Research and Health Care Technology (NICHSR). My search strategy combined the following concepts: 1) continuous renal replacement therapy, hemofiltration, hemodialfiltration, dialysis, renal replacement therapy, renal support; and 2) intensive care, critical care, critical illness, multi-organ dysfunction, multi-organ failure. Grey literature sources were searched for technical reports, practice guidelines, and conference proceedings. Bibliographic records were exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database for screening. Studies were included if they mention *all* of the following themes: 1) *Quality indicator*, (i.e., intended to evaluate the care received by patients treated with CRRT), 2) *Intensive care*, (i.e., intended to refer to patients (adults, children and neonates) supported in an intensive care unit setting), and 3) *Continuous renal replacement therapy*, (i.e., the infrastructure, prescription, delivery or outcomes associated with CRRT). QIs were defined as any indicator intended to measure the structure, process or outcomes associated with the prescription and/or delivery of CRRT. Indicators could measure setting, machine and/or provider-related factors (i.e., structure QI), components of how CRRT delivery occurs (i.e., process QI) or morbidity and mortality associated with receipt of CRRT (i.e., outcome QI). I considered studies published in English, French, German, Italian and Spanish, as the majority of data have been published in these languages. I selected studies published after 1990, as this corresponded to when veno-venous CRRT circuits were established at standard of care. Finally, selected levels of evidence including all primary studies, secondary analyses or evidence syntheses, as well as targeted grey literature were reviewed. Studies were excluded if they did not fulfill all of the above criteria.

I used a two-stage process for study selection. First, two reviewers independently screened the titles and abstracts (when available) of search results to determine if a study met the general inclusion criteria. Each report was classified as either include or exclude. Disagreements were resolved by discussion. The full text of all citations classified as "include" by either reviewer were retrieved for in-depth review. The same two reviewers independently assessed the eligibility of each full text manuscript for final inclusion into the review. Again, disagreement was resolved by discussion.

Data Abstraction

Two independent reviewers extracted data using standardized, piloted, case report forms. All QIs were identified, abstracted and agreed upon by the two independent authors. The following data were abstracted from each citation: author identification, year of publication, title, journal of publication, language of publication, study design, identified quality indicator and the operational definition utilized.

Each QI was characterized based on its importance, scientific acceptability, usability and feasibility. Initially, 20% of citations (n=27) had their QIs characterized in duplicate. This was done to ensure consistent agreement and greater than 80% was achieved. Given high levels of redundancy, the remaining citations were extracted by a single reviewer. If there was uncertainty, QIs were again reviewed in duplicate and consensus on QI characteristics was achieved through discussion. Each QI was stratified (yes/no) according to whether study authors described it as being important to CRRT prescription, important to CRRT delivery, important to CRRT monitoring, important to patient-related outcomes, important to health resource utilization, or outlined its scientific basis, and described as being operationally feasible (i.e., easy to obtain or implement including integration into an electronic health record [EHR]).

Internal Validity and Risk of Bias Assessment

I assessed the internal validity of included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) for observational studies and the Cochrane Collaboration Risk of Bias tool was used to assess risk of bias in RCTs.[25] Observational studies were rated high

quality if they had a total score of 6 to 9, moderate quality with a score of 4 or 5 and poor quality if they had a score of 3 or fewer.[26]

Data Analysis

The primary analysis was descriptive and narrative. QIs were categorized according to the Donabedian framework by stratifying whether each QI measured a structure, process, or outcome related to CRRT care.[27] QIs were further evaluated using the four criteria proposed by the United States Strategic Framework Board for a National Quality Measurement and Reporting System (importance, scientific acceptability, usability and feasibility), as outlined above.[28]

3.3 Results

Search Results

My initial search strategy identified 8,374 citations, of which I included 133 articles (Figure 3-1). This consisted of 96 full text articles and 37 abstracts. These included 97 cohort studies, 24 RCTs, 10 case-control studies and 2 retrospective medical record audits (Table 3-1). All studies except one were published in English; a single study was published in Spanish.

Study Quality

Study quality was generally rated as high for observational studies and poor for RCTs. Study quality was assessed in 96 studies (72.2%). All of the RCTs (100%) were rated as having a high risk of bias (secondary to not being able to blind the treatment arms). The mean NOS score was 6 (range 4 – 9) and the majority of observational studies (n=73, 97.3%) were rated as high quality, and two studies (n=2, 2.7%) as moderate quality; no observational studies were rated as poor quality. Of the remaining studies identified (n=37, 27.8%), quality assessment was not possible due to insufficient data, due to being published in abstract form only.

Quality Indicators

A total of 18 QIs were identified in 238 separate instances and classified as structure (n=4, 22.2%), process (n=9, 50.0%) and outcome (n=5, 27.8%) indicators (Table 3-2). Filter life was the most commonly identified QI (n=98, 41.2%), followed by small solute clearance (n=46, 19.3%), bleeding (n=30, 12.6%), delivered dose (n=19, 8.0%) and downtime (n=14, 4.9%) (Table 3-2). There was significant heterogeneity in the definitions and criteria used to define each QI across studies (Table 3-3). The QIs were grouped across a six themes: complications (n=7, 38.8%), circuit (n=3, 16.7%), interruptions (n=2, 11.1%), education (n=2, 11.1%), clearance (n=1, 5.6%), and dose-delivery (n=1, 5.6%).

National Quality Measurement and Reporting Criteria

The characteristics of QIs discussed by study authors were mostly centered on the importance of QIs (n=144, 48.3%), followed by scientific acceptability (n=32, 10.7%) and then by usability and feasibility (n=17, 5.7%). Importance was further stratified across specific elements of CRRT care: importance to CRRT prescription (n=36, 25.0%), importance to CRRT delivery (n=33, 22.9%), importance to CRRT monitoring (n=11, 7.6%), importance to patient-related outcomes (n=40, 27.8%) and importance to health economics (n=24, 16.7%) (Table 3-2).

3.4 Discussion

I performed a comprehensive systematic literature search and evidence synthesis to catalogue the spectrum of quality indicators of CRRT care in critically ill patients.

Summary of key findings

First, I found 18 unique QIs across 6 themes within the Donabedian framework domains of structure, process and outcome. The majority of QIs focused primarily on processes of care for how CRRT was prescribed, monitored and delivered. Fewer QIs focused on structure, specifically related to the human, material and organizational factors involved in supporting a CRRT program, and outcomes relating to CRRT, including the health states of patients during and after treatment.

Second, the overall quality of identified studies describing QIs broadly ranged from poor to high quality. This was due to variability in study design, risk of bias and confounding and limited capacity for variable adjustment in analyses. Importantly, most studies were not specifically designed nor focused on the derivation, validation or evaluation of CRRT QIs.

Third, while clearly important as they relate to potential QIs, most authors did not comment on the vital characteristics based on the four criteria proposed by the National Quality Measurement and Reporting System Criteria. When they did, however, the importance of QIs as they related to patient-related outcomes was most commonly identified, followed by the importance for CRRT prescription and delivery, and finally by a discussion of the scientific basis of each QI. The usability, feasibility and operational parameters of how QIs may be integrated at the bedside, into an EHR and/or translated to providers was often not addressed.

Fourth, I was able to identify several QIs which consistently demonstrated high relevance as per the National Quality Measurement Reporting Criteria. These included filter life, small solute clearance and bleeding events. These QIs could readily be implemented for audit, performance and benchmarking purpose by CRRT programs. However, when attempting to standardize these parameters as QIs, one challenge is that there are multiple definitions on how to assess the need to change a filter or what is a significant and recordable bleeding event. I contend these will need refinement, consensus and validation. Furthermore, what specific solutes warrant measurement (and when), and what would constitute a meaningful change requires further rigorous evaluation and standardization.

Context with prior literature

Since the publication of the two Institute of Medicine reports, "To Err is Human: Building a Safer Health System," and "Crossing the Quality Chasm: A New Heath System for the 21st Century," there has been a greater emphasis on delivery of high quality and safe patient care.[29,30] There have been numerous initiatives to improve health and healthcare worldwide, including the Institute for Healthcare Improvement in the United States, the Canadian Patient Safety Institute in Canada and the European Commission on Public Health in Europe.[10,31] Other national initiatives have, in particular, addressed kidney-specific issues. The National

Confidential Enquiry into Patient Outcomes and Death report in the United Kingdom revealed that for patients with evidence of AKI [32], only 69% had received "good" care, highlighting that care in nearly a third of instances did not to meet minimum care standards. There have also been initiatives from kidney-specific groups, such as the National Kidney Foundation, which is dedicated to the awareness, prevention and treatment of kidney disease.[33] However, within any of these above initiatives, there have not been specific programs to address the quality of CRRT care. While it is true that the first ADQI conference sought to make evidence-based practice recommendations for CRRT care, the purpose of ADQI was not intended to generate new knowledge and establish QIs.[34] Accordingly, there currently exist no high quality, rigorous-validated and evidence-informed QIs focused on the prescription, delivery and monitoring of the quality of CRRT care across themes related to structure (e.g., educational programs), process (e.g., treatment interruptions) or outcome (e.g., adverse events).

Prescribers and policy-makers for chronic maintenance dialysis programs have recognized this knowledge gap. A recent international panel of experts have selected standard QIs for chronic RRT. These also fall under the Donabedian domains of structure (e.g., access to medical services), process (e.g., Kt/V, serum albumin, hemoglobin, ferritin, phosphorus, calcium and parathyroid hormone) and outcomes (e.g., quality of life).[35] The National Quality Forum (NQF) has also recently endorsed 15 QIs focused on kidney care and an additional 4 QIs with reserve status (i.e., important QIs that have passed NQF criteria that are already operating at high levels of performance but might deteriorate if not being monitored).[36] However, none of these QIs relate to CRRT care in critical care settings.

My study begins to address this knowledge gap by having identified 18 potential QIs through a rigorous review of existing literature. These QIs were distributed across important themes of CRRT care, ranging from QIs related to the technological aspects of CRRT machinery (e.g., CRRT circuits), to CRRT prescription and delivery (e.g., blood clearance, dose-delivery and treatment interruptions), to training of CRRT providers (e.g., educational programs) and finally to outcomes (e.g., CRRT attributed complications). The identification of these QIs provides a basis for future work to prioritize, validate and evaluate these QIs

into a concise inventory of quality measures as a minimum standard for existing and new CRRT programs.

Limitations/strengths

While I believe that my review identifies and synthesizes an array of QIs in CRRT across many different themes and domains of quality measures, some of which can and should be implemented into routine CRRT care, there are notable limitations that warrant consideration. There was wide variability in study design and quality. As such, it was not feasible to perform a pooled analysis and only descriptive analysis was possible. In addition, there existed significant heterogeneity amongst the naming and defining of the 'same' QIs. I attempted to, when possible, to streamline QIs into a single operational indicator, but at this stage did not attempt to derive definitions of QIs. Future study should aim to refine and standardize the operational definitions for candidate QIs through rigorous evaluation and consensus. Furthermore, the characteristics of the QIs were often not addressed in the studies. While identifying QIs across a broad range of themes in CRRT care, certain 'obvious' QIs were not identified. Examples would include use of CRRT catheter insertion/maintenance bundles, use of protocols for the prescription and monitoring of CRRT, and program and provider-specific training and certifications. Finally, very few studies focused on primarily evaluating the identified QIs. Accordingly, study results could not be interpreted as they related to the QIs. However, the evaluation/validation of QIs was not the primary purpose of my study; rather, I sought to identify QIs in the existing literature. Future study should focus on the identification of additional QIs, evaluate how they relate to the quality of CRRT care and how they may be routinely integrated into CRRT programs.

Implications for health care providers, policy and future research

CRRT care should be monitored, reported and benchmarked. My systematic review identifies a complement of potential QIs for CRRT care that could be adopted by CRRT programs, but also importantly highlights existing knowledge-to-care gaps for how CRRT care is routinely evaluated and monitored. I contend selected QIs identified by my review could be readily integrated both clinically within ICUs which conduct CRRT to improve how CRRT care is measured and delivered, and as tools for continuous quality improvement initiatives and

research. Future steps require validation and consensus on the optimal definitions for each QI, identifying of additional QIs not captured by my search, and further rigorous evaluation to prioritize those showing the strongest association with important care processes and outcomes for targeted translation and implementation into practice. This will require inter-professional consensus across key CRRT stakeholders and users. Ideally, valid and evidence-informed QIs should be available to integrate into the next iteration of guidelines to inform minimum standards for CRRT care.

3.5 Conclusions

I identified 18 QIs across 6 domains of CRRT care. However, the definitions for these QI were heterogeneous and often poorly characterized. Future work should focus on the prospective evaluation of selected QIs to develop a concise inventory of QIs to measure, improve and benchmark CRRT care for critically ill patients.

Table 3-1 Baseline characteristics of included trials

Trial[a]	Source	Study Type	Patient population	Patients	Quality Indicator
DeVico (1)	Full text	Cohort	Adult cardiac surgery	15	Filter life Small solute clearance
Goonasekera (2)	Full text	Cohort	Pediatric acute liver failure	31	Filter life Downtime
Kee (3)	Full text	Cohort	Adult critically ill	551	Filter life SCT training Delivered dose Downtime
Schilder (4)	Full text	RCT	Adult critically ill	139	Filter life Downtime Complications
Claure-del Granado (5)	Full text	Cohort	Adult critically ill	244	Filter life Filter efficacy Delivered dose Bleeding
Treschan (6)	Full text	RCT	Adult surgical critically ill	66	Filter life Bleeding VTE events
Fernandez (7)	Full text	Case-control	Adult critically ill	36	Filter life
Lipcsey (8)	Full text	Cohort	Adult critically ill	380	VTE events
Chua (9)	Full text	Case-control	Adult critically ill	458	Catheter colonization CRBSIs
Dunn (10)	Full text	Cohort	Adult critically ill	355	Filter life
Ho (11)	Full text	RCT	Adult critically ill	94	Filter life
Crosswell (12)	Full text	Case-control	Adult critically ill	131	Filter life
Lee (13)	Full text	RCT	Adult critically ill	73	Filter life Bleeding
Prada Rico (14)	Abstract	Cohort	Pediatric critically ill	Unknown	Filter life
Fisher (15)	Abstract	Cohort	Adult critically ill	33	Delivered Dose Interruptions
Chenouard (16)	Abstract	Cohort	Pediatric critically ill	16	Filter Life Bleeding
Campbell (17)	Abstract	Case-control	Adult critically ill	188	Delivered Dose Downtime

					Bleeding
Han (18)	Abstract	Case-control	Adult critically ill	115	Filter Life
Mottes (19)	Full text	Cohort	Pediatric critically ill	80	SCT training
Goonasekera (20)	Full text	Cohort	Pediatric acute liver failure	31	Filter life Downtime
Leung (21)	Full text	Cohort	Adult critically ill	44	Filter life
Fealy (22)	Full text	Cohort	Adult critically ill	46	Filter life
Kalb (23)	Full text	Cohort	Adult critically ill	75	Filter life Delivered dose
Jacobs (24)	Abstract	Cohort	Adult critically ill	59	Filter life
Richardson (25)	Abstract	Cohort	Adult cardiac surgery	22	Delivered dose
Jacobs (26)	Abstract	Cohort	Adult critically ill	59	Filter life
Gojaseni (27)	Abstract	Cohort	Adult critically ill	40	Filter life
Ferraresi (28)	Abstract	Cohort	Adult critically ill	100	Filter life Catheter malfunction
Dalhulsen (29)	Abstract	Cohort	Adult critically ill	15	Filter life Small solute clearance
Avila (30)	Abstract	Cohort	Adult critically ill	21	Filter life
Cho (31)	Abstract	Cohort	Adult critically ill	37	Filter life Bleeding
Lyndon (32)	Full text	RCT	Adult critically ill	200	Small solute clearance Filter life Delivered Dose
Claure-del Granado (33)	Full text	Cohort	Adult critically ill	52	Small solute clearance Delivered dose Effluent volume
Chua (34)	Full text	Case-control	Adult acute liver failure	71	Filter life Bleeding
Zhang (35)	Full text	Cohort	Adult critically ill	54	Filter life
Lipcsey (36)	Abstract	Cohort	Adult critically ill	380	VTE events
Ezihe-Ejoifor (37)	Abstract	Audit	Adult critically ill	12	Small solute clearance Delivered dose Interruptions
Conception (38)	Abstract	Cohort	Adult critically ill	166	Small solute clearance Delivered dose
Claure-del Granado (39)	Full text	Cohort	Adult critically ill	52	Filter efficacy Small solute clearance
Kim (40)	Full text	Cohort	Adult critically ill	50	Filter life
Kim (41)	Full text	Cohort	Adult critically ill	50	Filter life

Tan (42)	Full text	Cohort	Adult critically ill	13	Filter life Effluent volume
Steen (43)	Abstract	Cohort	Adult critically ill	27	Fluid management Adherence to protocol
Saha (44)	Abstract	Case-control	Adult critically ill	121	Filter life Delivered dose
Kalb (45)	Abstract	Cohort	Adult critically ill	75	Filter life Delivered dose Downtime
Choi (46)	Abstract	RCT	Adult critically ill	24	Filter life
Baldwin (47)	Abstract	Cohort	Adult critically ill	38	Filter life
Parienti (48)	Full text	RCT	Adult critically ill	736	Filter life Downtime
Patienti (49)	Full text	Cohort	Adult critically ill	736	Catheter colonization CRBSIs
Garces (50)	Full text	RCT	Adult critically ill	40	Filter life Bleeding
Kim (51)	Full text	Cohort	Adult critically ill	30	Filter life
Fabbri (52)	Full text	RCT	Adult critically ill	110	Filter life Bleeding
Ooi (53)	Abstract	Cohort	Adult critically ill	43	Filter life Small solute clearance
Kleger (54)	Abstract	Cohort	Adult critically ill	Unknown	Filter life
Hackbarth (55)	Abstract	Cohort	Pediatric critically ill	20	Delivered dose Downtime
Guillermo (56)	Abstract	Cohort	Adult critically ill	18	Delivered dose
Casino (57)	Abstract	Cohort	Adult critically ill	18	Small solute clearance Delivered dose
Bentson (58)	Abstract	Case-control	Pediatric critically ill	67	Filter life
Kiser (59)	Full text	RCT	Adult critically ill	10	Filter life Bleeding VTE events
Vesconi (60)	Full text	Cohort	Adult critically ill	553	Delivered dose Interruptions
Burry (61)	Full text	Cohort	Adult critically ill	48	Filter life
Van Gemeren (62)	Abstract	Cohort	Adult critically ill	14	Filter life
Shidham (63)	Abstract	Cohort	Adult critically ill	16	Filter life
Sachdeva (64)	Abstract	Cohort	Adult critically ill	32	Filter life

Qiu (65)	Abstract	Cohort	Adult critically ill	77	Filter life Small solute clearance Bleeding
Chang (66)	Abstract	Cohort	Adult critically ill	65	Small solute clearance
Beitland (67)	Abstract	Case-control	Adult trauma	39	Filter life Downtime Catheter malfunction
Durao (68)	Full text	Cohort	Adult trauma	143	Filter life Delivered dose
Lanquetot (69)	Full text	Cohort	Adult cardiac surgery	48	Filter life
Olert (70)	Full text	Cohort	Adult critically ill	10	Filter life Bleeding
Davies (71)	Full text	RCT	Adult critically ill	45	Filter life
Elderkin (72)	Abstract	Audit	Adult sepsis	44	Filter life Bleeding
Boswell (73)	Abstract	Cohort	Adult critically ill	Unknown	Filter life
Nurmohamed (74)	Full text	Cohort	Adult critically ill	51	Filter life Small solute clearance Downtime Bleeding
Cubatolli (75)	Full text	Cohort	Adult critically ill	11	Filter life Interruptions
Joannidis (76)	Full text	RCT	Adult critically ill	44	Filter life Bleeding
Birnbaum (77)	Full text	RCT	Adult critically ill	20	Filter life
Nurmohamed (78)	Full text	Cohort	Adult critically ill	51	Filter life Small solute clearance Downtime Bleeding
Monti (79)	Full text	Cohort	Adult critically ill	431	Filter life Downtime Interruptions
Hackbarth (80)	Full text	Case-control	Pediatric critically ill	376	Filter life Bleeding
Betjes (81)	Abstract	RCT	Adult critically ill	48	Filter life Bleeding
De Pont (82)	Full text	Cohort	Adult critically ill	8	Filter life Small solute clearance
Bihorac (83)	Full text	Cohort	Adult critically ill	76	Filter life

					Small solute clearance Fluid management Bleeding
Bagshaw (84)	Full text	Cohort	Adult critically ill	87	Filter life
Kutsiogannis (85)	Full text	RCT	Adult critically ill	30	Filter life Small solute clearance Bleeding
Egi (86)	Abstract	Cohort	Adult critically ill	63	Filter life
Swartz (87)	Full text	Cohort	Adult critically ill	58	Filter life Small solute clearance
Nakada (88)	Full text	Cohort	Adult critically ill	54	Catheter colonization CRBSIs
Elhana (89)	Full text	Cohort	Pediatric critically ill	9	Filter life Small solute clearance
Monchi (90)	Full text	RCT	Adult critically ill	20	Filter life Bleeding
Cointault (91)	Full text	Cohort	Adult critically ill	17	Filter life Small solute clearance Bleeding
Baldwin (92)	Full text	Cohort	Adult critically ill	12	Blood flow
Uchino (93)	Full text	Cohort	Adult critically ill	48	Filter life Small solute clearance Downtime
Dorval (94)	Full text	Cohort	Adult critically ill	14	Filter life Small solute clearance
Mitchell (95)	Full text	Cohort	Adult critically ill	19	Filter life Small solute clearance
Tobe (96)	Full text	Cohort	Adult critically ill	15	Filter life
Biancofiore (97)	Full text	Cohort	Adult liver transplant	27	Filter life Bleeding
Venkataraman (98)	Full text	Cohort	Adult critically ill	115	Delivered dose
Fealy (99)	Full text	RCT	Adult critically ill	10	Filter life
Baldwin (100)	Full text	Cohort	Adult critically ill	40	Filter life
Fealy (101)	Full text	Cohort	Adult critically ill	10	Small solute clearance Downtime
Chadha (102)	Full text	Cohort	Adult critically ill	5	Filter life Small solute clearance
Morimatsu (103)	Full text	Cohort	Adult critically ill	99	Small solute clearance

Kozek-Langenecker (104)	Full text	RCT	Perioperative adult critically ill	49	Filter life Bleeding
Gabutti (105)	Full text	Cohort	Adult critically ill	12	Filter life Fluid management Bleeding
Chadha (106)	Full text	Cohort	Pediatric critically ill	5	Filter life Small solute clearance
Hoffman (107)	Full text	Cohort	Adult critically ill	24	Filter life Small solute clearance Delivered dose
Holt (108)	Full text	Cohort	Adult critically ill	14	Filter life
Baldwin (109)	Full text	RCT	Adult critically ill	33	Filter life
Vargas Hein (110)	Full text	RCT	Adult critically ill	17	Filter life Small solute clearance Bleeding
Tolwani (111)	Full text	Cohort	Adult critically ill	29	Filter life Bleeding
Gilbert (112)	Full text	Cohort	Adult critically ill	15	Small solute clearance
Kutsogiannis (113)	Full text	Cohort	Adult critically ill	9	Filter life Small solute clearance Bleeding
Baldwin (114)	Full text	Cohort	Adult critically ill	6	Filter life
Bellomo (115)	Full text	Cohort	Adult critically ill	47	Small solute clearance
Brunet (116)	Full text	Cohort	Adult critically ill	10	Small solute clearance
Reeves (117)	Full text	RCT	Adult critically ill	57	Filter life Bleeding Thrombocytopenia
Brockelhurst (118)	Full text	RTC	Adult critically ill	16	Filter life Small solute clearance
Holt (119)	Full text	Cohort	Adult critically ill	5	Filter life Blood flow Small solute clearance
Leslie (120)	Full text	RCT	Adult critically ill	26	Filter life
Bellomo (121)	Full text	Cohort	Adult critically ill	234	Small solute clearance
Bellomo (122)	Full text	Cohort	Adult critically ill	6	Small solute clearance
Bellomo (123)	Full text	Cohort	Adult critically ill	100	Filter life Small solute clearance
Freebairn (124)	Full text	Cohort	Adult critically ill	10	Small solute clearance
Alamartine (125)	Full text	RCT	Adult critically ill	6	Small solute clearance

Frankenfield (126)	Full text	Cohort	Adult trauma and septic	15	Small solute clearance
Bellomo (127)	Full text	Cohort	Adult critically ill	115	Small solute clearance
Bellomo (128)	Full text	Cohort	Adult critically ill	60	Small solute clearance
Bellomo (129)	Full text	Cohort	Adult critically ill	60	Filter life Small solute clearance
Bellomo (130)	Full text	RCT	Adult critically ill	64	Filter life Bleeding
Bellomo (131)	Full text	Cohort	Adult critically ill	12	Filter life Small solute clearance
Clark (132)	Full text	Cohort	Adult critically ill	11	Small solute clearance
Bellomo (133)	Full text	Cohort	Adult critically ill	50	Small solute clearance

A summary of baseline characteristics of included trials is included

RCT - randomized controlled trial; VTE - venous thromboembolic; SCT - specialized care team; CRBSIs - catheter-related bloodstream infection

[a] Bibliographic details of reference numbers (given in parentheses) are given belo

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Table 3-2 Categorization and relevance of identified quality indicators

Categorization of QIs as per the Donabedian Framework	Relevance of QIs							
	Importance (n=144)					Scientifically Acceptable (n=32)	Usability & Feasibility (n=17)	
	CRRT Prescription (n=36)	CRRT Delivery (n=33)	CRRT Monitoring (n=11)	Patient outcomes (n=40)	Health Economics (n=24)		Useable and/or feasible (n=15)	Ability to integrate into an EMR (n=2)
Structure (n=104)								
Filter life (n=98)	9	11	10	10	21	16	10	-
Blood Flow (n=2)	-	-	-	-	-	1	1	-
Filter Efficacy (n=2)	-	-	-	-	-	-	-	-
SCT Training (n=2)	-	-	-	-	-	-	-	-
Process (n=95)								
Small Solute Clearance (n=46)	16	12	1	19	-	11	-	2
Delivered dose (n=19)	6	5	-	1	1	1	1	-
Downtime (n=14)	-	-	-	-	1	-	2	-
Interruptions (n=5)	5	5	-	-	-	-	-	-
Fluid management (n=3)	-	-	-	-	-	-	-	-
Catheter colonization (n=3)	-	-	-	-	-	1	-	-
Catheter malfunction (n=2)	-	-	-	-	-	-	-	-
Effluent volume (n=2)	-	-	-	-	-	1	-	-
Adherence to protocol (1)	-	-	-	-	-	-	-	-
Outcome (n=39)								
Bleeding (n=30)	-	-	-	7	1	-	1	-
VTE events (n=4)	-	-	-	1	-	-	-	-
CRBSIs (n=3)	-	-	-	-	-	1	-	-
Thrombocytopenia (1)	-	-	-	1	-	-	-	-
Complications (1)	-	-	-	1	-	-	-	-

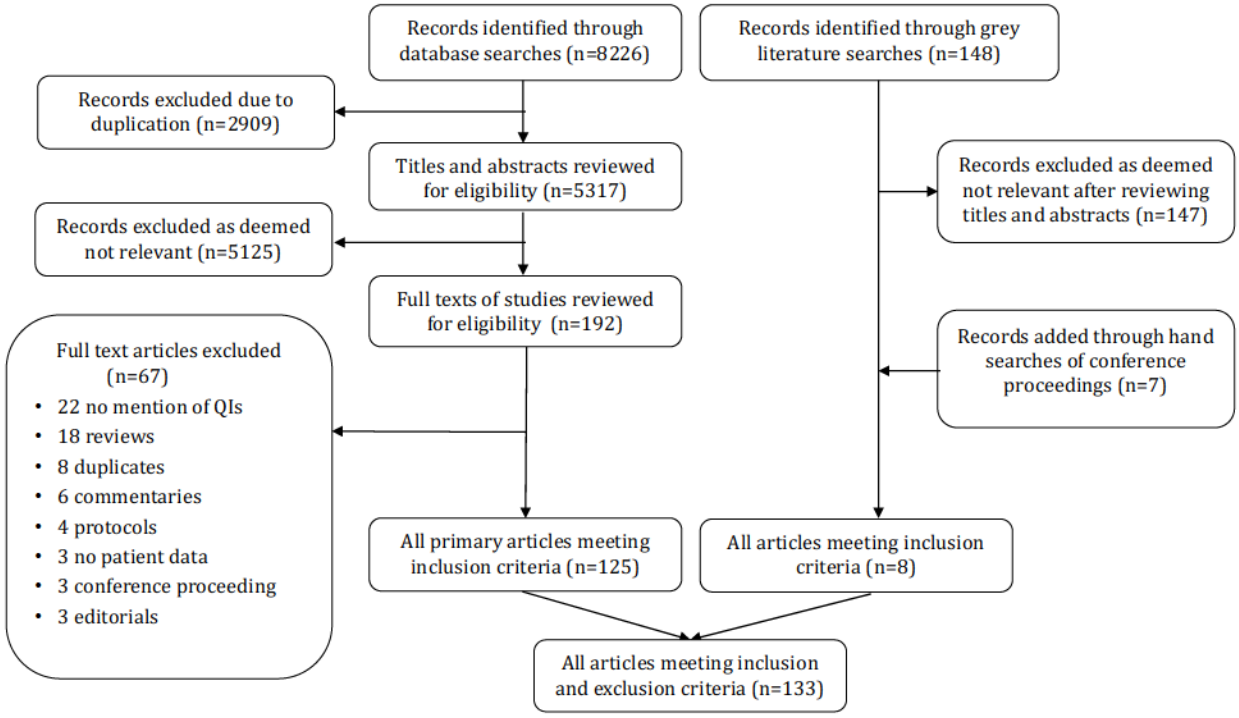
In the first column, the types of identified QIs are listed with the number of instances in parenthesis. In the subsequent columns, the breakdown of the characteristics of the identified QIs are given as per the four criteria proposed by the US Strategic Framework Board for a National Quality Measurement and Reporting System. Importantly, not all QIs had these characteristics described in the identified studies. A full list of individual components of the identified QIs are included in Supplementary material 3-4.
VTE - venous thromboembolic; CRBSIs - catheter-related bloodstream infection; SCT - specialized care team

Table 3-3 Examples of heterogeneity in QI definitions utilized across studies

Quality Indicator	Definitions			
Filter Life	Filter failed in more or less than 24 hours	Spontaneous clotting or TMP > 200mmHg	Spontaneous clotting or TMP > 250mmHg	Presence of clot in the filter or in the air-trap or elsewhere in the circuit
Small Solute Clearance	% delta creatinine or urea/24 hours	Comparison between 0 hour and 4 hours urea and creatinine clearance	Comparison between 0 hour and 24 hour urea and creatinine levels	K= E/P x QE where E is urea/creatinine concentration in effluent, P is urea/creatinine concentration in serum, QE is effluent flow rate)
Delivered Dose	Kt/V (urea)	Net ultrafiltration rate	Calculated from hourly effluent flow rate and duration of CRRT/day	Calculated using total effluent (the sum of the dialysate and ultrafiltrate) with correction for percentage predilution, and expressed as ml/kg/hour
Downtime	The amount of time CRRT was not running per 24 hour period	Time off pump in first 72 hours	period of time when CRRT was not applied from beginning to end of prescription	The period of time when CRRT was not applied between two consecutive morning biochemistry measurements
Bleeding	New onset bleeding requiring blood transfusion	Pulmonary hemorrhage	New onset bleeding requiring > 2 units PRBCs	Observation of gross bleeding plus one of: 1) drop is SBP or DBP by 20mmHg within 24 hours of bleeding, transfusion of 2 units PRBCs, not appropriate increase in in Hb, decrease in hematocrit % by 2%. Occult bleeding as absence of gross bleeding and decrease of hematocrit by 2% or failure of appropriate increase in Hb

This table shows examples of varying definitions across the retrieved studies of most common 'same' quality indicators. Definitions are listed from left to right as simplest to most complex. Only examples of the most common variations of definitions are given
TMP - transmembrane pressure; PRBCs - packed red blood cells; SBP - systolic blood pressure; DBP- diastolic blood pressure; Hb – hemoglobin

Figure 3-1 Flow diagram of study selection



PRISMA flow diagram of retrieved and included records. This flow diagram depicts the identified citations from the medical literature on the *left* and from the grey literature on the *right*. Of the 133 included citations, 96 were full-text articles and 37 were abstracts.

3.6 References

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CHAPTER 4: A MODIFIED DELPHI PROCESS TO IDENTIFY, RANK AND PRIORITIZE QUALITY INDICATORS FOR CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) CARE IN CRITICALLY ILL PATIENTS

4.1 Introduction

Continuous renal replacement therapy (CRRT) is the most common renal replacement therapy (RRT) modality for critically ill patients supported in ICU settings worldwide.[1] While evidence-based clinical practice guidelines (CPGs) have been published to direct the prescription and delivery of CRRT, it remains highly susceptible to institutional and individual practice variations.[1-4] This contributes to suboptimal CRRT care and quality. While quality and safety have always been central tenants in medicine, there has been recent increased emphasis on the application of formalized mechanisms to implement measures to monitor and evaluate the delivery of healthcare to patients. The Institute of Medicine has stressed the need for quality improvement and patient safety.[5,6] However, these initiatives have largely did not include acute kidney injury (AKI) and CRRT.[7-10] While a few notable initiatives have led to the development of a consensus classification scheme for the diagnosis for AKI, CPGs for AKI, and initiatives for the effective and safe application of CRRT in critically ill patients.[11-13] Accumulating literature has suggested that the quality of care received by patients with AKI is poor, suffers from numerous deficiencies and has significant institutional and provider practice variation.[14] A Healthcare Quality Improvement Partnership report in the United Kingdom has noted that for patients with AKI, less than half received "good" care, and fewer than a third who developed AKI in hospital received adequate care.[15] To better monitor the quality of care, quality indicators (QIs) are necessary. QIs can facilitate greater reliability of care, homogenize complex interventions, and provide a platform for benchmarking of performance. QIs can be further used as targets for continuous quality improvement initiatives aimed at evaluating new or revised care processes, implementing new protocols or interventions, reducing variability in the delivery of healthcare and stimulating innovative research.[16]

This observed variation in practice and suboptimal quality of care in CRRT may stem, in part, from a lack of validated QIs. In order to address this important knowledge gap, I have undertaken a research program to identify, define and prioritize QIs of CRRT care. I have previously conducted a systematic review which identified 18 potential QIs.[17] However, the QIs were not rigorously evaluated and their appropriateness to contemporary clinical practice was uncertain.

To further inform the development of a prioritized list of key QIs for CRRT care, I undertook a 3-stage, modified Delphi process with an international multidisciplinary panel of leaders in critical care nephrology. My aim was to achieve consensus among experts among the most important QIs to measure and monitor performance that may be utilized by *any* CRRT program.

4.2 Methods

This modified Delphi process was performed according to a pre-specified protocol and adhered to published recommendations for reporting.[18] Approval of the study was obtained from the Health Research Ethics Board of the University of Alberta (Pro00064315) prior to commencement.

Panel Selection

An inter-professional panel of participants was selected based on clinical expertise, academic and scholarly contributions in the areas of critical care nephrology. The panel consisted of knowledge users and inter-disciplinary stakeholders included intensivists, nurses, nephrologists, educators, pharmacists, decision-makers and industry representatives from North and South America, Europe, Australasia (Table 4-1).

Participants were approached with an introductory email including a letter of invitation out-lining the study rationale and methodology.

Overview of the modified Delphi process

An initial list of potential QIs was obtained from my systematic review.[17] Two rounds of questions were distributed via internet-based questionnaires to all participants between September 2016 and February 2017. Panelists provided consent to participate in the entire modified Delphi process by participating in the first round of the survey. Reminder emails were sent at two and four weeks after distribution of each round. If panelists failed to respond to the first round of the survey, they were excluded from participation in the second round. A third Delphi round was conducted in person during an international critical care nephrology meeting in San Diego, USA (Figure 4-1).

Round 1

Panelists were emailed a user-unique link to a questionnaire developed using the internet-based platform Survey Monkey (https://www.surveymonkey.com). The list of CRRT QIs was presented to panelists, grouped according to the Donabedian framework of *structure, process* and *outcomes* domains for quality measures. Panelists were asked to respond to the appropriateness of each potential QIs for CRRT care as "yes," "no," or "unsure." Open-ended questions were also provided so that panelists could provide comments for each potential QI, and could also list other potential QIs that they believed were important, and not otherwise listed. A QI from Round 1 was included in Round 2 if at least 50% of panelist deemed it appropriate to include; otherwise it was excluded from Round 2. Panelists were informed of exclusions at the introduction of Round 2.

Round 2

The second round of the process was based on a refined list of QIs. The refined list was developed from responses for each QI posed in Round 1, as well as from responses to the open-ended questions. Panelists were again asked to respond to the appropriateness of each potential QI with "yes," "no," or "unsure." Sample descriptions of each QI were provided, and panelists were asked to respond to the validity of elements from a proposed definition of each potential QI using a 7-point Likert scale that ranged from "strongly disagree," to "strongly agree." Panelists evaluated each QI based on proposed type of indicator, elements of its definition, the precision of its definition, its reliability and validity, the proposed

benchmark for the QI, any (if applicable) risk adjustment to be considered for the QI, and finally how well the QI has the potential for targeting quality improvement. Panelists were also provided with the opportunity to contribute open-ended comments and to propose additional potential QIs for evaluation in future rounds. Consensus for inclusion of a QI was deemed important for CRRT care if greater than 75% respondents answered "yes" to include the QI. Consensus was achieved to exclude the QI if greater than 75% of respondents answered "no" to include the QI. QIs that had responses not falling into either of these 2 categories were included in Round 3 for further discussion.

Round 3

Following completion of the first two online Rounds, an in-person panelist meeting was conducted to discuss QIs for which consensus was not achieved. An information letter was sent to the participants prior to this meeting, outlining the meeting format and goals of the meeting. A list of QIs to be discussed along with results from Round 2 were also included in this letter.[19]

The format of the meeting was a 1-hour round table session chaired by members of the study steering committee (O.G.R. and R.T.N.G.). Each "uncertain" QI was discussed, and panelists were provided a paper survey to vote "yes," or "no," to determine if each QI was important to include as a measure of CRRT monitoring and performance. QIs with greater than 50% of panelists responding as "yes" were included in our final list of potential QIs for CRRT care; those with greater than 50% of panelists responding as "no" were excluded from the final list of QIs.

Analysis

Results were tabulated at the completion of each round and entered into an Excel (Microsoft Corp, Redmond, Washington, USA) spreadsheet. Following the completion of Round 2, mean (95% confidence interval) responses on the 7-point Likert scale were calculated for each question. QIs with mean scores of 0-3 were categorized as of low agreement, 4-5 as moderate agreement, and 6-7 as representing high degree of agreement (13). Only those QIs

either included at the conclusion of Round 2 or Round 3 were selected as a prioritized rank list of QIs of CRRT care.

4.3 Results

A total of 48 inter-professional stakeholders were invited as panelists, and 41 (85.4%) agreed to participate in my modified Delphi process. The characteristics of the panelists are shown in Table 4-1. There were 31 men and 10 women. These included 11 intensivists, 18 nephrologists, 7 nurses/educators, 1 pharmacist, 2 decision-makers and 2 industry representatives. Twenty-seven panelists were from North America, 9 from Europe, 4 from Australasia and 1 from South America.

In total, 33 (82.5%) of invited panelists participated in Round 1. Panelists provided responses that eliminated 5 previously identified QIs (blood flow rate, effluent volume, catheter colonization, thrombocytopenia and venous thromboembolism events) and proposed 5 additional QIs (fluid overload at time of CRRT initiation, medication prescription and adjustment, reassessment of CRRT prescription, time from prescription to initiation and CRRT-related hypotension) (Table 4-2).

In Round 2, 28 (84.9%) panelists who participated in Round 1 responded in Round 2. The panelists were again asked to provide responses to the revised list of 18 QIs from Round 1 (Table 4-2). No new QIs were proposed in this Round. There was consensus to include 7 (38.9%) of the QIs, and uncertainty on whether to include 11 (61.1%) of the QIs. No QIs were eliminated in Round 2. I also asked panelists to evaluate proposed definitions for the 18 QIs according to a 7-point Likert. These included elements on how important and useful each QI was to quality improvement, the reliability, and validity of each QI. There was high agreement for the 11 QIs as they applied to CRRT care (filter lifespan, delivered dose, downtime, fluid management, bleeding, CLABSIs, time from prescription to initiation, daily CRRT prescription, medication prescription and adjustment, hypotension and catheter dysfunction), and moderate agreement for the remaining 7 QIs (filter efficacy, specialized

team training, small solute clearance, treatment interruptions, protocol adherence, adverse events and percentage fluid overload at initiation).

In Round 3 16 inter-professional panelist were included. No new QIs were proposed. After discussion, 7 (63.6%) of QIs were deemed important to include, 4 (36.4%) were excluded, and 2 QIs (downtime and treatment interruption) were combined as a single QI (downtime), to generate a final prioritized list of CRRT QIs. This generated a final consensus list of 13 prioritized QIs for CRRT monitoring and performance (Table 4-3). These included 2 structure QIs (filter life and specialized care team training), 7 process QIs (delivered dose, downtime, fluid management, medication adjustment, small solute clearance, time from prescription to therapy, therapy prescription) and 4 outcome QIs (adverse events, bleeding, catheter dysfunction, catheter-line associated bloodstream infections) (Figure 4-2). The QIs encompassed five health care quality domains: safe (n=4, 30.8%), effective (n=3, 23.1%), efficient (n=3, 23.1%), patient-centered (n=2, 15.4%) and timely (n=1, 7.7%).[20] Amongst panelists, the mean agreement to include the QIs was high (mean 6.17, 95% CI 5.938 to 6.396). The majority of the QIs (n=10, 76.9%) had high agreement while a minority of QIs (n=3, 23.1%) had moderate agreement (Figure 4-3).

4.4 Discussion

I performed a rigorous modified Delphi process involving a spectrum of inter-professional stakeholders and CRRT knowledge users to identify, rank and prioritize key quality indicators for CRRT care that may be utilized to measure quality and performance in any CRRT program.

Summary of key findings

First, my modified Delphi process generated a consensus inventory of 13 key quality indicators for CRRT care across the Donabedian domains of structure, process and outcome. The majority of QIs focused primarily on *processes* of care for how CRRT was prescribed, monitored and delivered. Fewer QIs focused on *outcomes* involving to CRRT-related

complications and only two QIs focused on *structure*, specifically in terms of human, material and organizational factors involved in supporting a CRRT program.

Second, the identified QIs spanned across five health care quality domains. Most commonly QIs were focused on *safe*, *efficient* and *effective* health care delivery, but were also related to *patient-centered* and *timely* delivery of care. No CRRT QI was specifically related to *equitable* delivery of health care. However, my focus was on monitoring the prescription, delivery and outcomes associated with CRRT care and had minimal relevance to the *equitability* of health care delivery

Third, among the panelists, there was agreement on the importance, usefulness, reliability and validity of each QI for ensuring high quality delivery of CRRT to critically ill patients. This was evident as there was at least moderate agreement for all QIs included in the final list by the panelists. Furthermore, 11 QIs achieved high agreement amongst the panelists. Fourth, the final list of 13 QIs encompassed a prioritized list of the most important QIs as they related to broad CRRT care. This was ensured by having an international inter-professional panel of experts. Furthermore, while in Round 1 five new QIs were proposed by panelists, in Round 2, no new QIs were proposed; hence I believe that saturation of potential QIs was acheived. While further QIs may be proposed regarding specific CRRT modalities (i.e., calcium concentrations in citrate anticoagulation) as per specific institutional CRRT programs, our proposed list of QIs for CRRT care is broadly generalizable and may be utilized across any program. I believe this prioritized list of QIs could represent a minimum set to be used for monitoring CRRT performance and establishing benchmarks for high quality CRRT care.

Context with prior literature

My modified Delphi process builds on my previous work which identified 18 potential QIs of CRRT care.[17] While my systematic review did identify a number of potential indicators, they were not rigorously evaluated, and their suitability into clinical practice was not assessed. My modified Delphi process eliminated 9 QIs that were determined to be not sufficiently relevant. Based on feedback from our panelists, potential QIs were excluded

from the list most commonly due to being perceived as not sufficiently important to CRRT monitoring and performance to be included (i.e., blood flow rate, effluent volume) or not being associated with clinically relevant outcomes (i.e., dialysis catheter colonization). Other QIs were not included due to perceived high likelihood of variability in use between centers (i.e., urea and/or creatinine clearance to determine filter efficacy). This was especially true for 'adherence to protocol,' where the content and form of protocols will differ. Additionally, as protocols are center specific, it would be conceivable that centers may alter their protocols in response to their reporting results, thus greatly decreasing the importance and validity of this QI.

Several potential QIs, while clinically important, lacked standards for measurement (i.e., how to best measure fluid overload), lacked consensus for clinically important values (i.e., definition for hypotension episodes and over what time period is to be considered clinically significant) or posed challenges for capacity to be adjudicated as being primarily related to CRRT (i.e., thrombocytopenia and venous thromboembolism events). Finally, two of the QIs were combined as a single measure (downtime and treatment interruption) after discussion amongst the panelists to limit duplication of QIs and to achieve a concise list of the most important QIs.

Agreement by panelists regarding quality indicators

My list of QIs was appraised as measures of quality for CRRT care by the panelists. They were evaluated based on their proposed definition, the precision of this definition, their reliability and validity, the proposed benchmark for the QI, any (if applicable) risk adjustment to be considered for the QI, and finally how well the QI may facilitate quality improvement. All of the QIs had at least moderate agreement on the perceived validity of theirs parameters by the panelists (mean agreement range 5.26 to 6.74) and several QIs (filter life, catheter dysfunction, delivered dose, downtime, fluid management, medication adjustment, time from prescription to initiation, therapy prescription, bleeding, catheter dysfunction, CLABSIs and hypotension) had high agreement. However, not all of these QIs were deemed to be important measures of CRRT quality. Additionally, several of the QIs which were deemed to only have moderate consensus agreement by the panelists were

included in the final list of QIs for CRRT care (SCT Training, small solute clearance and adverse events). SCT training was believed to be poorly defined and was perceived to have potential for high variability between centers. Small solute clearance was believed to not have established benchmarks both in which solute should be used for measurement and what would constitute an appropriate benchmark. Adverse events were believed to be poorly defined, too broad, and inconsistently reported between centers. After discussion in Round 3 there was consensus that these QIs have importance in assessing CRRT care and should be included; however, should be tailored to institutional practices. Further evaluation will be required to determine which specific parameters may be most generally acceptable applied to all CRRT programs.

Strengths/Limitations

My study had a number of strengths. First, the first two rounds of this modified Delphi procedure allowed for anonymity of responses from panelists, which may provide a more accurate account of their beliefs the most important aspects of quality monitoring and local practices by reducing social desirability bias.[21] This approach minimized the risk of a dominant panelist unduly influencing the panel that can be observed in a less structured setting, such as a focus group, and allowed each panelist to present their opinions with equal weighting, regardless of seniority.[22, 23] This was most important as these first two rounds encompassed providers from many different streams within critical care nephrology, while the third round only featured academic leaders from this field. Second, this modified Delphi process was conducted online and at an in-person meeting. This allowed the inclusion of panelists from across the world and from a broad inter-professional background. Third, the process allowed panelists to re-evaluate their opinions after receiving feedback on responses from other participants, ensuring convergence towards to most "correct" answer as the Delphi progressed. Finally, as potential QIs were based on both published and unpublished literature as well as on the opinions of panelists, our final list of QIs for CRRT care incorporated different forms of evidence to inform a range of quality indicators.

There are also notable limitations that warrant consideration. First, panelists were selected by my study team, thus selection bias may have existed. However, I specifically invited

panelists across disciplines as they relate to CRRT care and throughout all geographical areas. This ensured that all CRRT stakeholders were represented on my panel, and that any regional differences in CRRT prescription and delivery were addressed. Unfortunately, my panel did not include any patients or patient-family members, and it was possible that this may have resulted in less focus and/or recognition of patient-centeredness in the selection and consensus on proposed QIs. Second, I focused on QIs that may relate to any CRRT program. Hence certain protocol specific QIs (i.e., serum calcium concentrations with citrate anticoagulation protocols) may have been omitted. However, my focus was to establish a minimal core list of evidence-informed and consensus-driven QIs for CRRT care to which programs may be able to add additional QIs as appropriate. Finally, my modified Delphi process focused on obtaining input on elements of their definitions, but not the actual feasibility of measuring these QIs. Future work is required to determine the practicality and accuracy in measuring these variables in clinical settings.

Implications for health care providers, policy and future research

CRRT care should be monitored, reported and benchmarked to ensure the delivery of the highest quality of care. My modified Delphi process has identified 13 QIs that may be used across any CRRT program. Future steps require the implementation and evaluation of these QIs into CRRT programs to ensure that they are operational and feasible, and that benchmarks may be established. The optimal measurement and reporting mechanism of these QIs will need to be determined as they relate to documentation and the uptake of electronic health records (EHRs) in healthcare institutions. Ideally, as these benchmarks are determined, these valid and evidence-based QIs should be incorporated into the next iteration of guidelines to inform minimum standards for CRRT care.

4.5 Conclusions

I have established an inventory of 13 quality indicators for CRRT care across the Donabedian framework and five heath care quality domains. Future work should focus on integration and further evaluation of these QIs into a prioritized list of CRRT QIs that may be

utilized to monitor performance and ensure high quality delivery of CRRT across both programs.

Table 4-1 Characteristics of panelists

Primary Specialty	Number (%)	Geographical Location			
		North America	South America	Europe	Australasia
Intensive Care	11 (27)	7	-	4	-
Nephrology	18 (44)	11	1	4	2
Educator	7 (17)	5	-	-	2
Pharmacy	1 (2)	1	-	-	-
Decision-Maker	2 (5)	1	-	1	-
Industry	2 (5)	2	-	-	-

Educators are those related to CRRT clinical nursing educators. Decision-makers are individuals involved in medical leadership such as hospital directors and medical administrators. Finally, representatives from industry include any individual providing CRRT support or expertise.

Table 4-2 The modified Delphi process

	Quality Indicator	Decision to Include in List			Final Decision
		Yes (%)	No (%)	Uncertain (%)	
Round 1	Blood Flow	27.3	51.5	21.2	Exclude
	Filter Efficacy	54.5	12.1	33.3	**Include in Round 2**
	Filter Life	81.8	12.1	6.1	**Include in Round 2**
	Specialized Care Team Training	69.7	12.1	18.2	**Include in Round 2**
	Adherence to Protocol	72.7	12.1	15.2	**Include in Round 2**
	Catheter Colonization	30.3	45.5	24.2	Exclude
	Catheter Dysfunction	81.8	9.1	9.1	**Include in Round 2**
	Delivered Dose	93.9	6.1	0	**Include in Round 2**
	Downtime	78.7	6.1	15.2	**Include in Round 2**
	Effluent Volume	48.5	30.3	21.2	Exclude
	Fluid Management	75.8	12.1	12.1	**Include in Round 2**
	Interruptions	69.7	15.2	12.1	**Include in Round 2**
	Small Solute Clearance	81.8	15.2	3	**Include in Round 2**
	Bleeding	69.6	15.2	15.2	**Include in Round 2**
	Adverse Events	97.0	0	3	**Include in Round 2**
	CLABSIs	78.8	9.1	12.1	**Include in Round 2**
	Thrombocytopenia	30.3	42.4	27.3	Exclude
	VTEs	33.3	51.5	15.2	Exclude
Round 2	Filter Efficacy	52.0	24.0	24.0	Discuss
	Filter Life	78.5	3.6	17.9	**Include**
	Specialized Care Team Training	80.8	11.5	7.5	**Include**
	Adherence to Protocol	59.3	22.2	18.5	Discuss
	Catheter Dysfunction	69.2	11.6	19.2	Discuss
	Delivered Dose	92.3	0	7.7	**Include**
	Downtime	69.2	15.4	15.4	Discuss
	Fluid Management	63.0	18.5	18.5	Discuss
	*Fluid Overload at Initiation	48.1	22.2	29.6	Discuss
	Interruptions	48.0	28.0	24.0	Discuss
	*Medication Prescription & Adjustment	74.1	7.4	18.5	Discuss
	*Reassessment of CRRT Prescription	80.0	8.0	12.0	**Include**
	Small Solute Clearance	48.1	33.3	18.5	Discuss
	*Time from Prescription to Initiation	77.8	7.4	14.8	**Include**
	Adverse Events	33.3	40.7	25.9	Discuss
	Bleeding	80.8	7.7	11.5	**Include**
	CLABSIs	80.0	0	20.0	**Include**
	*Hypotension	59.3	14.8	25.9	Discuss
Round 3	Filter Efficacy	6.2	93.8	n/a	Exclude
	Adherence to Protocol	40.0	60.0	n/a	Exclude
	Catheter Dysfunction	100.0	0	n/a	**Include**
	Downtime	60.0	40.0	n/a	**Include – combine**
	Fluid Management	80.0	20.0	n/a	**Include**
	Fluid Overload at Initiation	0.0	100.0	n/a	Exclude
	Interruptions	60.0	40.0	n/a	**Include – combine**
	Medication Prescription and Adjustment	100.0	0	n/a	**Include**
	Small Solute Clearance	66.7	33.3	n/a	**Include**

	Adverse Events	60.0	40.0	n/a	**Include**
	Hypotension	37.5	62.5	n/a	Exclude

Quality Indicators discussed in each of the 3 Delphi rounds are presented above, stratified across the three Donabedian domains of *Structure, Process* and *Outcomes* in light, medium and dark grey, respectively. In Round 1, QIs with less than 50% decision to include were excluded from Round 2. In Round 2, starred QIs are ones suggested by panelists in Round 1. In this Round QIs with greater than 75% agreement to include were automatically included into the prioritized list. The remaining were QIs where consensus was not achieved were discussed in Round 3 and a final decision was made on whether to include or exclude the QIs in question from the list of prioritized CRRT QIs. CLABSI – catheter line-associated bloodstream infection; CRRT – continuous renal replacement.

Table 4-3 Proposed CRRT quality indicators

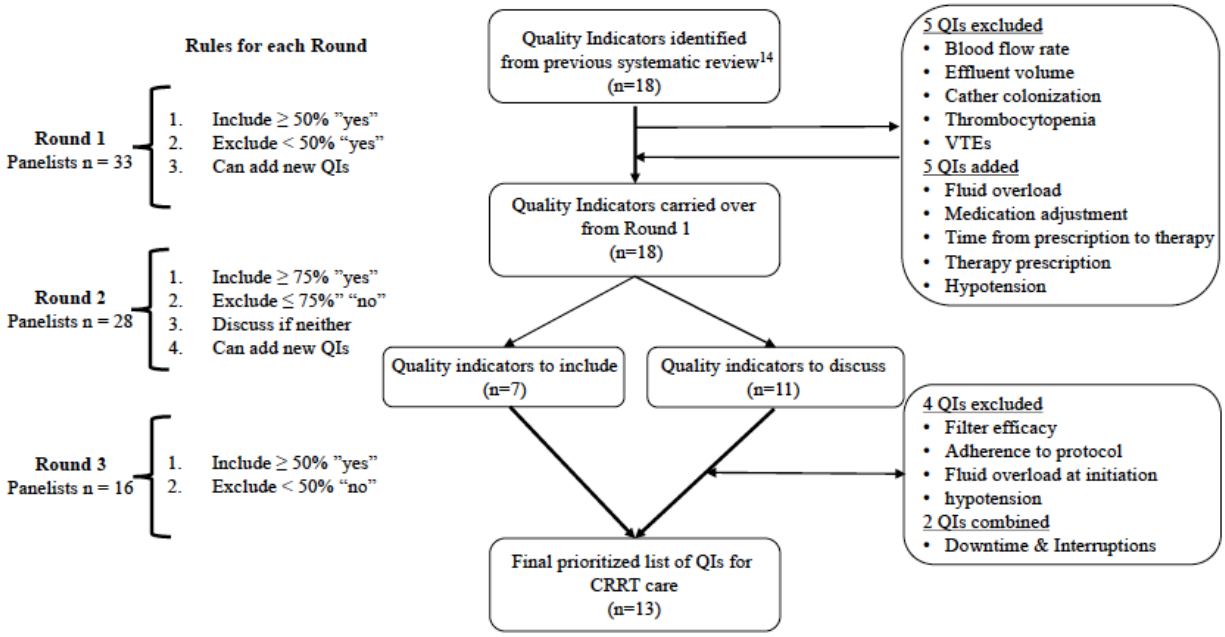
Quality Indicator	Relationship to Quality	Definition	Operational Definition	Proposed Benchmark	Risk Adjustment	Sampling Frame
SCT Training	Effective	Specialized inter-professional team of nurses, physicians and allied health providers (e.g., dietician, pharmacists, biomedical engineer, medical informatics) specifically trained to prescribe, deliver and monitor CRRT[24]	Number of CRRT providers with training/ Total number of CRRT providers	100% of providers	none	Quarterly
Filter Life	Efficient	The duration of patency of each CRRT filter. Filter change is dictated by consistently elevated transmembrane pressures of over 250 mmHg for greater than 5 minutes[25]	Number of filter lasting 72hrs/ Total number of filters used	> 50% filters	1. Pre-existing hypercoagulable states 2. Planned circuit disruptions	Monthly
Time from Prescription to Therapy	Timely	The time gap from when CRRT orders are written and when the CRRT circuit is running	# of times the time gap is > 4h/ # of CRRT initiations[26]	> 75% of CRRT initiations	1. Acuity of illness	Monthly

Therapy Prescription	Patient-centered	Daily orders written for CRRT	Patient orders for CRRT/ Patient days of CRRT	100% of CRRT-days	none	Monthly
Medication Adjustment	Patient-centered	Medications adjusted for CRRT (by pharmacist or physician)	# of medications with dose adjustment/ # of medications requiring dose adjustment	100% of medications	none	Monthly
Delivered Dose	Effective	The dose of CRRT that is actually delivered to the patients[27]	(Actual delivered dose / 24hrs)/ (Prescribed dose /24hrs)	> 80% of dose	none	Monthly
Fluid Management	Effective	The UF that is removed from patients	(UF removed / 24hrs)/ (Prescribed UF /24hrs)	> 80% of ultrafiltrate	none	Monthly
Small Solute Clearance	Efficient	Change or relative stability in small solutes over time[28]	[sCr (d1) – sCr (d2)]/ [sCr (d2)]	No increases (i.e., change ≤0)[29]	1. Type of filter used 2. CRRT modality	Monthly
Downtime	Efficient	The time CRRT was not operating[30]	Time CRRT off per day	< 10% of the time	1. Planned stoppage times	Monthly
Adverse Events	Safe	Any event that occurs during CRRT requiring an incident report to be completed	# of adverse events number of patients on CRRT	0 events	none	Monthly
Bleeding	Safe	Any bleeding complications that occurs while on CRRT requires the transfusion of ≥ 1 unit of PRBCs during CRRT treatment	Bleeding events requiring ≥ 1 unit of PRBCs/ # of patients on CRRT[31]	0 events/ patient	1. Coagulopathy 2. Thrombocytopenia 3. Active bleeding otherwise explained	Quarterly

Catheter Dysfunction	Safe	Any alterations to conventional catheter protocol or requiring catheter replacement[27]	# of catheters, dysfunction-free/ # of catheters with dysfunction	≥ 80% of catheters	1. Catheter location 2. Hypercoagulable state	Quarterly
CLABSIs	Safe	A primary bloodstream infection in a patient that had a dialysis line within the 48 hour period before the development of the bloodstream infection and is not a bloodstream infection related to an infection at another site AND the dialysis line was in place on the date of the event or day prior[32]	CLBSIs/ # Catheter-line days *100	0 events	1. Catheter location 2. Type of patient (i.e., medical, surgical, immuno-compromised, burn)	Quarterly

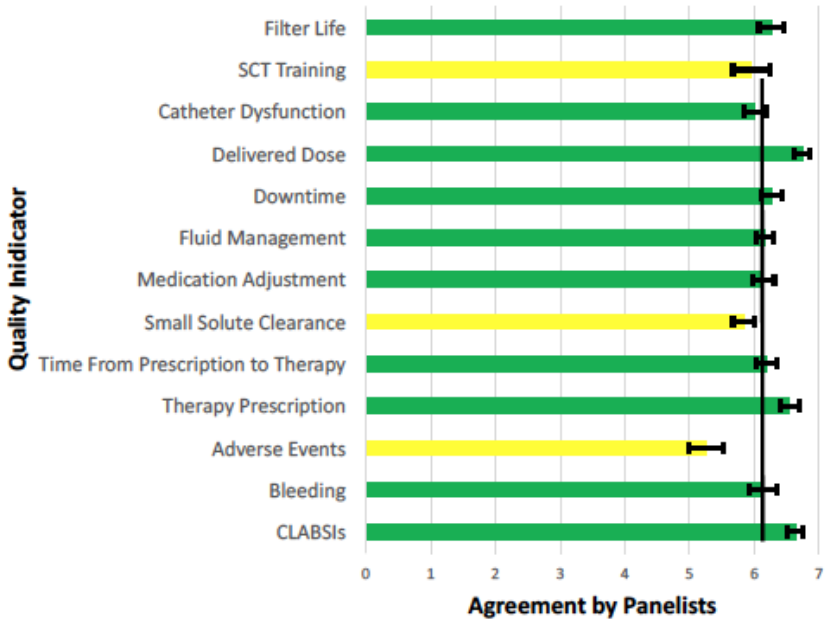
Table 4-3. Quality Indicators are presented above, stratified across the three Donabedian domains of *Structure, Process* and *Outcome* as highlighted by the light, medium and dark grey, respectively. We have proposed definitions and benchmarks for each QI, which may be adapted to individual units as per institutional practices. These QIs should be reviewed either monthly or quarterly based on the expected frequency of events and CRRT program practices. CLABSI – catheter line-associated bloodstream infections; CRRT – continuous renal replacement therapy; SCT – specialized care team.

Figure 4-1 Modified Delphi process



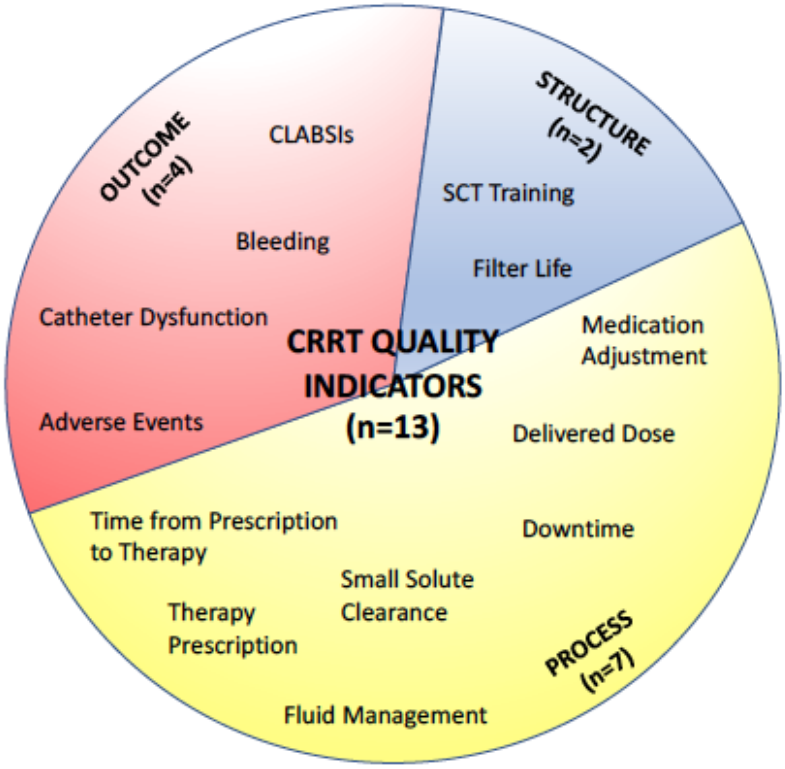
On the left, are shown the 3 rounds of the Delphi along with the number of panelists in each round. In the middle is the progression of QIs through each round, with the right panel illustrating QIs that were eliminated and excluded in each round. Note that no QIs were added or excluded in Round 2. QI – quality indicator; VTE – venous thromboembolic.

Figure 4-2 Agreement for final list of QIs



The bars represent the mean scores with 95% confidence intervals. The horizontal line represents the median score for all indicators. Quality Indicators with a high agreement are indicated in green, and those with a moderate agreement indicated in yellow. CLABSI – catheter line-associated bloodstream infections; SCT – specialized care team.

Figure 4-3 Final list of QIs



This pie chart indicates the final list of 13 QIs for CRRT care. As evident, most identified QIs for CRRT care were process QIs and evaluated how CRRT was performed. Fewer QIs focused on patient-related CRRT outcomes, while the fewest on the physical and organizational structure relating to CRRT. CLABSI – catheter line-associated bloodstream infections; SCT – specialized care team.

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CHAPTER 5: SUMMARY

5.1 Overview of the Research

Quality and safety have always been important in medicine. However, it was not until the turn of the millennium that deficiencies in our delivery of safe healthcare and mechanisms to address these issues were formally addressed and publicized.[1,2] Since the time of these publications, there has been greater emphasis on ensuring the delivery of high quality care to our patients. There has been a move to develop organizations to ensure the success of these programs. The Canadian Institute for Health Information provides data and reports to ensure optimal health to Canadians; the Agency for Healthcare Research and Quality and the National Quality Forum focus on improving the quality and value of healthcare, and in establishing benchmarks for healthcare delivery in the United States; and the National Institute of Healthcare and Excellence provides guidance, advice, information services for health and quality standards in the United Kingdom.[3-6] Furthermore, organizations such as the Canadian Patient Safety Institute and the Health Quality Council of Alberta have been created with a focus on quality and safety in medicine, and to ensure that there is continual quality improvement initiatives being conducted to guarantee the delivery of the best possible healthcare.[7,8] The development of specific quality improvement development methodologies such as the PDSA (*plan, do, study, act*) and FADE (*focus, analyze, develop, evaluate*) have continued this process of quality development, and ultimately to the establishment of specific quality indicators (QIs) for benchmarking of the delivery of healthcare. These quality initiatives have also progressed to include the field of critical care nephrology, of which acute kidney injury (AKI) and continuous renal replacement therapy (CRRT) are key components. Organizations such as the Acute Dialysis Quality Initiative (ADQI), the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) have been developed to streamline definitions for AKI, and to develop consensus guidelines to reduce the variability in the delivery of CRRT. [9-11] These organizations have developed consensus definitions and evidence-based guidelines to assist with the diagnosis and management of AKI. However, while certain CRRT QIs have been proposed by individual programs, these organizations as a whole recognize that there is very little data to support and establish well validated QIs for CRRT care, and there is no current consensus on which of these

QIs may be most important, or on which benchmarks to use to evaluate the delivery of CRRT.[12] This has been recognized as a significant knowledge gap, and one that has been identified as the next avenue of research in critical care nephrology.[11]

Thus, to overcome this knowledge gap, I developed this current research program focused on the development of quality indicators for CRRT care.

5.2 Objectives

The objectives were accomplished through three different fashions. First, a review of the literature on quality and safety in critical care was performed.[14] This review served as a literature synthesis, as well as to establish a knowledge base of quality development methodology and the current state of quality and safety in critical care nephrology.

Using my work for this review to establish and build a knowledge base, I developed the next phases of my work on QIs for CRRT care. This consisted of a systematic review of the existing literature to determine what QIs for CRRT care currently exist.[15] The findings of this review were used to inform my second project, a modified-Delphi process to continue to identify and now define and rank the most important of these QIs.

A Delphi process is a multi-phase structured communication process where results from each phase are fed back to respondents with the goal to eventually converge on the 'correct' results.[13] I conducted modified-Delphi process where the first two rounds occurred via a web-based platform, while the third round consisted of a round table in person meeting. The purpose of this modified-Delphi process was to develop a prioritized list of the most important potential QIs for CRRT care.

5.3 Summary of the Findings

The review of safety and quality for AKI and CRRT highlighted that while there was ongoing work to establish consensus definitions and guidelines for the management of AKI, there was a quality of care for patient developing AKI in hospital and undergoing RRT remained poor. It also underscored the lack of rigorously defined QIs for CRRT care.[14] Furthermore, it highlighted that there were very few studies that have examined the quality of care provided to patients with AKI and who receive CRRT. It provided insight into avenues in which to approach this shortcoming, including developing improving identification of risk factors for the development of AKI, the fashion and timeliness in which AKI is diagnosed, monitored, investigated and suggested a more streamlined and cohesive approach to its management.[6] Additionally, this review identified even fewer studies evaluating the quality of care delivered to patients undergoing CRRT, and highlighted that while this has been repeatedly identified as a knowledge gap, there has been no systematic program to address this shortcoming and that this remains a priority for critical care nephrology organizations.

Using the findings from this review, I conducted a comprehensive systematic review in five citation databases (Medline, Embase, CINAHL, Cohcrane Library and PubMed) and select grey literature sources.[15] This review was broad in scope, yielding 8374 citations. Ultimately, 133 studies fulfilled eligibility. These included 97 cohort studies, 24 randomized controlled trials, 10 case-controlled studies, and 2 retrospective medical audits. In total, 18 potential QIs for CRRT care were identified. However, QIs were characterized by heterogeneous definitions, varying quality of derivation, and had limited evaluation. Furthermore, several 'obvious' QIs were not identified in my systematic review. This did lay the groundwork for my next phase of work which was the modified-Delphi process.

To ensure the identification of all possible QIs for CRRT care, better define the QIs in a consensus fashion and arrive at a prioritize list of QIs for CRRT care, I undertook a modified-Delphi process. This process occurred over two rounds of web-based surveys followed by a third round which consisted of an in-person meeting of our panelists. Ultimately, I established an

inventory of 13 prioritized QIs for CRRT care across the Donabedian framework for quality measures of structure, process and outcome that may be used in any CRRT program.

5.4 Implications for Future Research

The current research work was directed at firstly identifying, and then defining and ranking the most important QIs for CRRT care. In my review, I found that there existed a lack of specified QIs for CRRT care. My systematic review identified existing QIs for CRRT care, and my modified-Delphi process defined and ranked the most important of these QIs. The next steps of this research program will require the evaluation and integration of these prioritized QIs into CRRT programs. Currently, an outline for this research program is in place. To evaluate the priority list of QIs in their application to clinical practice and establishment of robust operational benchmarks for CRRT programs, firstly a pilot integration project will be undertaken. This will begin with local evaluation of the identified QIs, and will then serve to evaluate which of the identified QIs are operational, and which QI is feasible to integrate into clinical practice. As each QI is piloted and operationalized, they will inform the broader implementation of QIs in CRRT care and will support the safe and effective CRRT care for critically ill patients. Ultimately, a CRRT Quality Dashboard will be developed that will be applicable to any CRRT program to ensure ongoing high quality monitoring and performance in CRRT care.

This research program also established a novel method for the evaluation of studies from large-scale systematic reviews. In chapter 2, we described our systematic review of QIs for CRRT care.[15] We identified 133 studies from which data was extracted. The primary objective was to identify QIs. This was extracted in duplicate. However, to abstract data for the secondary objective, to characterize the relevance of these QIs as per the individual studies, duplicate abstraction was not feasible due to the volume of data to be abstracted. To overcome this, data was abstracted in duplicate for the first 20% of studies. Abstracted data was then compared, and as there was greater than 80% agreement between reviewers, the remaining citations were abstracted by a single reviewer. This methodology ensured appropriate data abstraction, and also permitted the feasibility of such a broad systematic review. With the publication and

establishment of this methodology, it will allow for future studies to follow this protocol and the ongoing achievability of broad and large scale systematic reviews.

Finally, the modified-Delphi process established a mechanism to engage panelists worldwide and from multiple disciplines through its web-based platform. It also incorporated aspects of a traditional Delphi process by having an in-person meeting. The methodology behind this novel modified-Delphi process will serve as framework for future Delphi process so as to ensure most broad stakeholder and expert engagement.

5.5 Implications for Clinical Practice

CRRT is a complex and costly life-sustaining technology used in our sickest, most critically ill patients. However, there currently exist no reliable and rigorously evaluated means to measures its ongoing quality of delivery. This research program has identified, defined and prioritized QIs for CRRT care. They will serve as targets to benchmark so as to ensure optimal delivery of this therapy. The next steps, as outlined above, will be to pilot these QIs into local programs.

Ultimately, as these QIs become operationalized and benchmarks firmly established, a dashboard of QIs will be created and reports generated that will be reviewed by local CRRT committees. The ultimate goal is that these QIs will be systematically adopted with so that these evidence-based QIs may be used in clinical and educational programs in order to achieve greater efficacy and efficiency in CRRT use, which in turn may result in significant cost savings in CRRT prescription and delivery, and ultimately in improved patient-related outcomes.

5.6 Limitations

Despite the many strengths of my research, including the rigor of the systematic review protocol, the broad scope of literature search, and the wide group of multidisciplinary stakeholders and experts for the modified-Delphi process, this program was not without limitations. A challenge for both projects was the lack of pre-existing studied and validated QIs. As a consequence of

this, most of QIs identified in the systematic review did not serve as the primary endpoints of the included studies. As such, there were not rigorously evaluated, and heterogeneously defined. However, they did serve to inform the modified-Delphi process which addressed these shortcomings.

The modified-Delphi process consisted of a broad inter-professional panel of CRRT stakeholders and experts. However, one weakness of this panel was that it did not include any patients or patient-families. Accordingly, QIs relating to patient centered outcomes may not have been fully identified or prioritized. That being the case, there were still four QIs identified that tied into patient-centered outcomes. The purpose of the modified-Delphi process was to establish a minimal list of QIs for CRRT to which programs may be able to add additional QIs as appropriate, and this may be done in future work. Finally, the current program of work did not evaluate the QIs in terms of feasibility but rather on face validity. Operationalizing the QIs will be the focus of next phase of work stemming from this research.

5.7 Conclusions

In the first part of this research, the literature surrounding quality and safety in AKI and CRRT was reviewed. Although work has been conducted to streamline definitions for AKI and to establish consensus criteria for the management of patients with AKI, there has been a paucity of studies to evaluate these issues for CRRT. This has led to a significant knowledge gap which this program sought to address.

The second phase of this research evaluated the literature for current QIs for CRRT care. The systematic review was broad in context, reviewing the literature from five medical databases as well as from the grey literature. From 133 eligible studies, we identified 18 potential QIs across the three Donabedian domains of structure, process and quality. However, the evaluation of these QIs as limited and not precisely defined.

The third phase of this work built upon the systematic review to further identify potential QIs not previously found, and to better characterized those identified and to determine a prioritized list of

QIs to be implemented into clinical practice. Ultimately, after three rounds of a modified-Delphi process, saturation of potential QIs was achieved, and a prioritized list of the 13 most important QIs was developed (Table 5-1). This list of QIs for CRRT will be used in future work to pilot the implementation of these QIs into clinical practice to determine which ones may be most easily operational, and to develop validated benchmarks to measure and improve CRRT care for critically ill patients.

Table 5-1 Prioritize List of Quality Indicators for CRRT Care

Domain	Quality Indicator
Structure	Filter Life
	SCT Training
Process	Delivered Dose
	Downtime
	Fluid Management
	Medication Adjustment
	Time from Prescription to Therapy
	Therapy Prescription
	Small Solute Clearance
Outcome	Adverse Events
	Bleeding
	Catheter Dysfunction
	CLABSIs

The prioritized list of the 13 identified quality indicators for CRRT care, stratified as per the Donabedian framework for quality measures. SCT – specialized care team; CLABSIs – catheter line-associated bloodstream infections.

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Quality measures for acute kidney injury and continuous renal replacement therapy

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Purpose of review
Quality and safety are important priorities in the care of critically ill patients. For patients with acute kidney injury (AKI) or for those receiving continuous renal replacement therapy (CRRT), measures and outcomes associated with quality of care have been suboptimally developed and evaluated. The review is timely as it summarizes current quality practices in AKI and CRRT, and presents ongoing and future developments.

Recent findings
The review begins with the history of quality and safety in healthcare. We then discuss the current quality of care offered in AKI and CRRT. Quality measure development methodology, such as plan-do-study-act and the focus-analyze-describe-execute models and lean thinking are then presented and discussed. Finally, recent evidence for quality in AKI and CRRT care, including proposed quality measures, are discussed.

Summary
Few studies have examined the quality of care provided to patients with AKI and CRRT. Evidence suggests opportunities to improve the quality of care received by patients at risk of or who have developed AKI. Priorities for improving quality of care exist across several important themes including risk identification, diagnosis, monitoring, investigation, and strategies for management. Similarly, evidence-informed quality measures of CRRT care have not been rigorously evaluated. These are important knowledge-to-care gaps that require further investigation.

Keywords
acute kidney injury, continuous renal replacement therapy, quality, safety

INTRODUCTION

Quality and safety have long been important ideals to achieve in medicine. However, recently there has been emphasis on the application of formalized mechanisms to implement and monitor measures to assess the quality and safety of care delivered to patients. This was first publicized in 1999 by the Institute of Medicine (IOM) and then further characterized by their 2001 report, 'Crossing the Quality Chasm: A New Health System for the 21st Century' [1,2]. Since the publication of these reports, there have been a few notable quality improvement initiatives focused on acute kidney injury (AKI) and continuous renal replacement therapy (CRRT) [3,4▪▪,5,6]. These have contributed to the development of a consensus classification scheme for the diagnosis for AKI, clinical practice guidelines for AKI, and initiatives for the effective and safe application of CRRT in critically ill patients. However, recent literature suggests that the quality of care received by patients with AKI has numerous deficiencies, generally remains poor, and that there may be an attributable morbidity and mortality associated with iatrogenic complications and suboptimal quality of care [7▪▪]. Numerous challenges still remain, especially in CRRT care.

CRRT is generally delivered to the most severely ill patients, often with multiorgan dysfunction and receiving complex multimodality support. These patients are often the most susceptible to medical errors and adverse events and have a high observed mortality (exceeding 35–40%) [8▪,9]. Accordingly, the delivery of care that is considered high quality

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KEY POINTS

- Quality and safety have become driving initiatives in the delivery of healthcare.
- Ensuring higher quality of care in AKI centers around risk identification, recognition, diagnosis, investigation, monitoring, and management.
- There is significant practice variation in the prescription of CRRT and this is an important measure of poor quality CRRT care.
- Future avenues of research will involve identifying and studying metrics on the prescription and delivery of high quality and safe CRRT care as well as incorporating simulation in CRRT educational programs.

and safe is particularly essential for these patients, where small lapses in care or adverse events may have more significant consequences. In this review we provide a high-level overview of the history of the development of the quality and safety culture in medicine. Next we will discuss the current quality of care and quality initiatives offered in AKI and CRRT. We then present quality and safety development methodologies used in healthcare before finally presenting the evidence for quality and safety in AKI and CRRT and future avenues for improving these important patient-centered measures.

SUMMARY OF QUALITY AND SAFETY CULTURE IN MEDICINE

Healthcare is not as safe as it should be. The 1999 IOM 'To Err is Human' revealed that between 44 000 and 98 000 die each year in the United States from preventable medical errors [1]. A subsequent Canadian study exposed that adverse events occur frequently – an estimated 185 000 occur yearly, and nearly 70 000 of these are potentially preventable [10]. The 1999 IOM report advocated for a comprehensive approach to improve patient safety [11]. A follow-up IOM publication, 'Crossing the Quality Chasm' identified six specific aims of improvement of care: safety, effectiveness, patient-centered, timely, efficient, and equitable care [1]. Since the publication of that report, there has been an increase in patient safety initiatives, patient safety publications, and a significant growth in the funding for patient safety and quality initiatives and research [11]. Healthcare systems are investing considerable resources to improve workplace and patient safety, are promoting and cultivating a culture of safety to help anticipate and prevent such errors and also to document and investigate these events if they should occur [12▪]. These initiatives have led to continuous quality improvement initiatives to enhance the process of quality in hospitals, and in the patient safety climate to improve patient safety outcomes, including in AKI and CRRT [13▪].

DISCUSS CURRENT QUALITY OF CARE OFFERED TO ACUTE KIDNEY INJURY/ CONTINUOUS RENAL REPLACEMENT THERAPY

The quality of care in AKI and CRRT has been recognized as a priority issue [14▪]. There currently exist several organizations that strive to deliver high-quality evidence-based therapy in AKI and CRRT care. These include the Acute Dialysis Quality Initiative (ADQI), the Acute Kidney Injury Network (AKIN), the Kidney Disease: Improving Global Outcomes Initiative (KDIGO), and the National Institute for Health and Care Excellence (NICE) [15▪▪–17▪▪]. These groups aim to comprehensively evaluate the scientific literature focused on AKI and acute renal replacement therapy (RRT), so as to inform best practice standards and existing knowledge gaps for the risk identification, diagnosis, monitoring, investigation, and management of AKI and related therapies (including CRRT). KDIGO has published comprehensive evidence-based clinical practice guidelines for AKI that include a harmonized consensus definition and classification scheme for AKI. The long desired intent of a consensus definition has been to facilitate more rigorous and applicable scientific inquiry for how to prevent, diagnose, and manage AKI [18,19]. Yet, AKI remains exceedingly common among hospitalized patients, is often predictable and avoidable and is frequently mismanaged. This may be especially true during off-peak (i.e., weekend and night-time) admissions. This was demonstrated in a recent large American cohort study that found increased in-hospital mortality (7.3 vs. 6.7%, $P < 0.05$) for patients admitted with AKI during the weekend [20]. The mortality difference may be multifactorial stemming from delayed recognition of AKI, delayed nephrology consultation, and delayed initiation of RRT. Nevertheless, it is an important finding and one that merits further study.

Ideally, strategies to improve the quality of care received by patients with AKI or receiving CRRT should be aligned with the core six aims identified in the 2001 IOM report. Examples for CRRT would include the delivery of CRRT aimed at minimizing iatrogenic complications (i.e., bleeding, hypotension, electrolyte and acid–base abnormalities, and catheter-related infections) [21▪]. Prescription of CRRT dose and selection of anticoagulation should be evidence based, and routinely measured and

benchmarked [22▪]. Conceivably, CRRT should not be offered to all patients, in particular not in those who are unlikely to derive clinically significant benefit [23]. When indicated, CRRT should be available in a timely manner and initiated efficiently [24]. The provision of CRRT generally increases the cost and complexity of support for critically ill patients with AKI; however, support should be managed in a cost-effective manner [25▪▪,26]. Finally, mechanisms should ensure that, if indicated, access to CRRT is universal, understanding that depending on the specific health settings there are wide variations in its availability. Although these are examples of noble targets for improved quality of care, there has been limited rigorous evaluation of how best to measure and around strategies for implementation. We believe there are wide variations in AKI and CRRT care that may be further classified as center-specific, provider-specific, and machine-specific variations.

Center-specific education standards

When evaluating quality of care, there are many different aspects of care that need to be considered. Regional districts and centers often independently establish unique CRRT protocols and/or preferentially utilize variable operating parameters and technologies to suit local practice (i.e., specific CRRT mode, such as continuous veno-venous hemofiltration, continuous veno-venous hemodialysis or continuous veno-venous hemodiafiltration, anticoagulation strategy, or CRRT dose) [27–29]. Whether this contributes to observed site-specific variation in the utilization of CRRT and associated patient outcome remains uncertain [30]. Centers may also have a particular practice with referral patterns to nephrology for assistance in managing AKI. When nonspecialists manage AKI, key assessments for the management of AKI may not be performed [31]. Delayed nephrologist consultation ($\geq$48 h after development of AKI) may also lead to increased in-hospital mortality in ICU patients as demonstrated in an American study of four academic ICUs (67 vs. 40%, $P = 0.003$) [32]. Hence early and appropriate specialist consultation and a team management approach are pivotal elements to high-quality management of AKI.

Improved quality of care for AKI and CRRT may also follow a volume-outcome relationship. Theoretically, high performing CRRT centers, where large numbers of patients are routinely treated, may have more developed infrastructure (i.e., educational/training/certification programs or more experienced and knowledgeable providers). Similarly, low-volume centers may have limited opportunity for the staff to perform and refine the technical and nontechnical skill necessary to develop sustainable expertise [33]. Volume-outcome relationships have been shown with other technologies applied to critically ill patients, such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in acute respiratory distress syndrome, where high-volumes centers (and transfer to centers of excellence) are associated with improved outcomes [34]. The care model, along with the infrastructure and process demands for CRRT programs, may also be variably impacted in institutions that provide additional complex extracorporeal support therapies (i.e., therapeutic plasma exchange and ECMO) or perform complex cardiothoracic and solid organ transplantation. In these settings, CRRT is often run in parallel with one or more other complex life-support therapies. Here greater infrastructure and staffing support for these technologies may exist, eliminating therapy disruptions therefore enabling opportunity for improved delivery and quality of the prescribed therapies [35,36▪].

Provider-specific factors

The choice to initiate CRRT is influenced by institutional standards as well as the provider's experience and training. The provider's training and background, intensivist versus nephrologist, likely contributes, in part, to the variation in CRRT prescription and delivery. Numerous aspects of CRRT care lack standardization and risk practice variations. When to start and stop therapy, when to safely transition to IHD, the optimal methods and techniques for monitoring fluid removal and temperature management during CRRT delivery are among these variables and exist as important knowledge gaps that still need to be addressed [37,38▪,39]. However, in the absence of a clear evidence base and well developed educational standards, institutions develop their own practices, with the potential to systematically introduce institutional and provider-specific preferences and biases in how best to provide care for patients with AKI and those receiving CRRT [33]. Novel guidelines from the ADQI, AKIN, and KDIGO as well as national associations are required to better guide optimal CRRT care.

The model of nursing care is a potentially important determinant of quality of CRRT care, but also susceptible to practice variation. These are dependent on the available resources within the institution. There are two basic nursing models, single versus collaborative models (Table 1). There is no consensus on the merit of either model, and each has distinct benefits; however, these need to be further evaluated [40–42]. With the single program model, one group assumes full responsibility for all aspects of care

Table 1. Roles and responsibilities of single and collaborative program continuous renal replacement therapy models[a]

Chronology of care	Responsibility	Single program model	Collaborative program model
CRRT set up	Prepare machine	CCN	NON-CCN
	Obtain supplies	CCN	NON-CCN
	Schedule initiation time	CCN	NON-CCN
	Order CRRT	CCMD	Nephrology MD
Initiate therapy	Prime machine	CCN	NON-CCN
	Obtain prelabs	CCN	NON-CCN
	Assess catheter function	CCN	NON-CCN
	Perform procedure	CCN	NON-CCN
	Monitor patient during procedure	CCN	CCN
Maintain therapy	Circuit monitoring	CCN	CCN
	Obtain ACG labs	CCN	CCN
	Prescribe fluid removal	CCMD	Nephrology MD w/CCMD
	Adjust ACG per protocol	CCN	CCN
	Bag changes	CCN	CCN
	Adjust rates per orders	CCN	NON-CCN
	Catheter care	CCN	CCN
Troubleshooting and other procedures	First responder to alarms	CCN	CCN
	Second responder to alarms	CCN	NON-CCN
	Recirculation procedure	CCN	NON-CCN
	Perform in OR	CCN	NON-CCN
	Reinitiation procedure	CCN	NON-CCN
Terminate therapy	Return blood (as necessary)	CCN	NON-CCN
	Discard filter set	CCN	NON-CCN

ACG, anticoagulation; CCMD, critical care medical doctor; CCN, critical care nurse; MD, medical doctor; NON-CCN, dialysis, extracorporeal, or perfusion nurse/team member; OR, operating room.
[a]The single program model utilizes solely critical care team members, whereas the collaborative program model involves staff from both critical care and noncritical care staff.

delivery [40,42]. This theoretically minimizes the potential for miscommunication between provider teams (i.e., necessity for additional sign-over). In contrast, the collaborative program model shares the responsibilities between different provider groups based on their area of expertise [42]. The most example of a collaborative care model is a partnership between the dialysis program and the critical care program. Duties are shared and determined by discipline expertise, often with the dialysis nurse performing set-up and initiation, whereas the critical care nurse assumes the hour-to-hour bedside care [41]. The complexity of providing care to CRRT patients necessitates a multidisciplinary team. Appropriately, CRRT teams are more inclusive, consisting of physicians, nurses, pharmacists, respiratory therapists, and other vital services [43▪,44▪].

Machine-specific factors

There are machine-specific factors that may be used to gauge the quality of CRRT delivery. Examples of common measures of CRRT quality in the literature have included number of filters utilized or filter life span, hours of CRRT provided per day (i.e., unplanned downtime) and prescribed versus delivered CRRT dose [45]. However, other factors remain unknown and require further study. These include the optimal time to replace CRRT filters and the optimal type and composition of the replacement and dialysate solutions [39]. Machine complexity combined with the level of nursing knowledge can impact the quality of CRRT care. Navigating machine alarms and recognizing and responding to the changing patient condition will be more challenging for the inexperienced user resulting in interruptions in therapy. These all have the potential to interrupt therapy and create discrepancies between the prescribed and delivered dose [46]. However, the potential to incorporate simulator devices into CRRT training may help mitigate these factors and may be topics for future research [47▪].

Patient-specific factors

Along with center and provider-specific factors, patient-specific factors may also lead to potentially

avoidable variation in the quality of CRRT delivery. The location and type of catheters and forms of anticoagulation are the most important of these. The recent KDIGO clinical guidelines recommend right internal jugular access preferentially over femoral access. This was because of a theoretical increased infectious risk, but this evidence is ungraded and may be more applicable for patients considered obese [48,49]. Femoral access may be associated with increased filter life span, decreased mechanical complications, and sparing of upper extremity vascular access for long-term RRT access. Accordingly, as per current best practices and utilizing an evidence-based approach, CRRT should be ideally initially delivered via uncuffed and nontunneled femoral dialysis catheters to minimize infectious complications and to prolong filter life span [49,50▪].

Selecting the most appropriate type of anticoagulation based on evidence and patient-specific factors is also a key quality consideration. In CRRT, systemic heparin has long been the standard form of anticoagulation. However, regional citrate anticoagulation (RCA) has recently gained significant evidence in terms of increased filter life span, decreased bleeding, and reduced costs [51▪,52,53,54▪,55▪]. There is a theoretical risk of citrate toxicity in liver diseased patients and infants, but RCA has been demonstrated to be a safe form of anticoagulation even for these patients [56,57]. A systematic review of evidence supports the safe and efficacious role of RCA in CRRT over systemic heparin [58]. RCA has also been recently compared with regional heparin and protamine. A recently published large multicenter study involving 212 patients and 857 CRRT circuits evaluated the efficacy and safety of these two forms of regional anticoagulation. Ultimately, RCA provided improved filter life span (39.2 vs. 22.8 h, $P = 0.0037$) and less adverse events (2 vs. 11, $P = 0.011$) when compared with heparin and protamine [59▪▪]. Although the benefits of RCA are clear, many of its nuanced issues are yet to be resolved. There are many different RCA protocols involving variable solutions, differing calcium replacement protocols along with inconsistent monitoring techniques for efficacy that remain important knowledge gaps that require further study.

DISCUSS QUALITY/SAFETY MEASURE DEVELOPMENT METHODOLOGY

As safety and quality in medicine have become priorities, quality and safety measure development methodologies have also become important. These strategies provide a data decision driven structure for improving patient outcomes [60▪]. Two of the most important of these strategies include the plan-do-study-act (PDSA) and focus-analyze-describe-execute (FADE) models (Fig. 1). The PDSA is a four-step ('plan, do, study, act') model for recognizing, implementing, and evaluating change. It has been used for developing interventions as well as evaluating and reporting progress to improving the delivery of AKI services [61▪]. The FADE model is characterized by four broad steps: 'focus' to define and verify the process to be improved, 'analyze' the data to establish baselines, identify root causes and point towards possible solution, 'develop' action plans for improvement, and 'execute' and 'evaluate' the implementation of the action plan and to monitor the system to ensure success [62▪▪]. The FADE model has been used to develop educational programs in healthcare and identify areas that require further improvement [63]. The highest of these quality measures may be endorsed by the National Quality Forum, which is the gold standard for healthcare quality and means to ensure widespread adoption [64▪]. Lean thinking has also been used to reduce CRRT-related costs, improve the efficiency of CRRT workflow, and improve satisfaction among staff [65▪]. This is a form of quality improvement that has been adopted from the car manufacturing industry. It utilizes value stream mapping to identify nonvalue added wastes and inefficiencies in a system and to create permanent solutions to eliminate these wastes [66]. Other methods such as checklists, Six Sigma methodology, and Kaizen methods have been used in the prescription and delivery of CRRT [60▪,65▪]. These have led to the development of protocols and documentation for CRRT that have decreased practice variation among different providers and have reduced errors in its prescriptions and delivery. Regardless of the method, the goal for any CRRT safety and quality improvement strategy is to mitigate risk, minimize adverse events, and improve the efficacious delivery and quality of care.

DISCUSS POTENTIAL/CURRENT EVIDENCE FOR QUALITY/SAFETY MEASURES IN ACUTE KIDNEY INJURY/RENAL REPLACEMENT THERAPY

NICE has recently published guidelines for quality and safety in AKI. They were developed using rigorous methodology. Specific questions were developed in a PICO ('population, intervention, comparison, outcome') framework. Following this, a systematic review of the literature was performed. For included studies, the risk of bias was evaluated. The results were then analyzed and assessed by meta-analysis where appropriate before assessing the evidence quality by outcome (Grading of Recommendations Assessment,

	PDSA Model	FADE Model
Step 1	**P**lan – Determine the intervention to improve the process or problem	**F**ocus - Define the problem, narrowing the focus of the problem or process to be improved
Step 2	**D**o – Implement the intervention (small scale/pilot)	**A**nalyze – Data collection to establish baselines and identify potential solutions
Step 3	**S**tudy – Analyze data and results	**D**evelop – Identify interventions and plan for implementation
Step 4	**A**ct – Refine processes based on data analysis	**E**xecute – Implement the intervention, with continuous data measuring and analysis

FIGURE 1. Comparison of continuous quality improvement models. The plan-do-study-act focuses on implementing an intervention based on assumption of problems, evaluating small change interventions, making small adjustments to the intervention and then repeating the process. The focus-analyze-describe-execute centers on clearly identifying the problem with data analysis of the current situation prior to intervention planning, followed with executing the developed solution. Adapted with permission from [62▪▪].

Table 2. National Institute for Health and Care Excellence clinical guidelines for acute kidney injury

Risk factors for development of AKI	Principles for prevention/ detection of AKI	Management of AKI	Essential information and support for patients
Investigate for AKI in high-risk adult patients[a]	Assess risk factors in high-risk adults having iodinated contrast[c]	Identify the causes of AKI	Give information about long-term treatment options, monitoring, self-management and support to patient with AKI in collaboration with a multidisciplinary team as appropriate
Investigate for AKI in high-risk pediatric patients[b]	Assess risk factors in adults having surgery	Offer urgent ultrasonography when no identified cause of AKI is found	
	Ongoing assessment of patients in hospital	Discuss the management of AKI with a nephrologist as soon as possible	
	Monitor serum creatinine regularly		

Summary of quality statements to be considered in all patients with AKI. AKI, acute kidney injury. Drugs with nephrotoxic potential – NSAIDs, aminoglycosides, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or diuretics. Modified from [67▪▪].
[a]CKD, CHF, DM, history of AKI, oliguria (urine output ≤0.5 ml/kg/h), neurological, or cognitive impairment or disability, hypervolemia, use of drugs with nephrotoxic potential within the past week, use of iodinated contrast agents within the past week, symptoms or history of urological obstruction or conditions that might lead to obstruction, sepsis, deteriorating early warning scores, age ≥65 years.
[b]CKD, CHF, liver disease, history of AKI, oliguria (urine output ≤0.5 ml/kg/h), young age or neurological or cognitive impairment or disability, hypervolemia, hypotension, severe diarrhea, use of drugs with nephrotoxic potential within the past week, symptoms or history of urological obstruction or conditions that might lead to obstruction, sepsis, deteriorating pediatric early warning score symptoms or signs of nephritis (egoedema or hematuria), hematological malignancy.
[c]CKD, CHF, renal transplant, age ≥75 years, hypovolemia, increasing volume of contrast agent, intra-arterial administration of contrast agent. CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus.

Development and Evaluation; GRADE) and finally interpreting the evidence. This produced a total of 51 recommendations in the management of AKI [67▪▪]. These guidelines were created as it was recognized that a large proportion of AKI is preventable, and that the risk identification, prevention, early recognition are key factors in the initiatives to decrease the incidence of AKI, prevalence of chronic kidney disease and attributable death [67▪▪]. A list of quality statements based on the National Health Service outcomes framework that is to be considered in all patients with AKI has also been proposed (Table 2). These statements outline the population at risk of AKI, how to monitor this at risk population and how to proceed with best care and required therapy for these people. This includes specialist referral and initiation of RRT/CRRT when appropriate [67▪▪]. At times, significant delays in the recognition of AKI may occur, and an electronic system may be used to ensure its timely identification [68▪]. Incorporating care bundles for the diagnosis and management of AKI may be associated with decreased rates of progression of AKI and decreased hospital mortality [68▪]. When CRRT is initiated, most recent evidence has suggested that because of the complexity of the patients and CRRT-related factors, specialized care teams (SCTs) should be put into place. Implementation of these teams (consisting of nephrologists, intensivists, specialized trainees, CRRT specialized nurses, and clinical pharmacists) was shown to improve the optimal delivery of RRT, including the rate of ultrafiltration, reduced downtime per day, and decreased patient length of ICU stay and mortality [43▪]. In particular, clinical pharmacists may assist with medication adjustment to prevent medication accumulation and to ensure appropriate antibiotic dosing [69▪]. Finally, a previously published worldwide practice survey suggested that while CRRT was the most commonly prescribed form of RRT to critically ill patients, many aspects of its care varied, and often do not align with best practices [70,71▪]. These practice variations may stem from important knowledge gaps in evidence for CRRT care and delivery, and are themselves considered a measure of poor quality [72]. There is a clear need for rigorous evaluation to identify, validate, prioritize, and evaluate various quality indicators in CRRT care and how they may be implemented into clinical practice to support safe and effective CRRT delivery for critically ill patients [73▪].

CONCLUSION

Quality and safety have become cornerstones in medicine, especially in the management of critically ill patients. Since the publication of the IOM reports,

there have been important advances in the quality and safe delivery of health services. Quality and evidence-based initiatives have been created to seek consensus and evidence-based recommendations. In AKI, the definition has been streamlined, and guidelines have been created for its prevention, early identification, and appropriate management. However, important gaps in the quality of care in AKI still remain. Research in the delivery of CRRT has revealed the importance of specialized teams and a group-based approach and has led to improved processes of care and patient outcomes. Simulation is becoming more important in CRRT training programs but still requires further validation. However, many unknowns still remain, in particular on how to best measure the quality of CRRT delivery. These are challenges that will need to be addressed in the future and most importantly, when identified, will need to be integrated into training programs and protocols in CRRT management to ensure the utmost in the quality of delivered CRRT care.

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A recent systematic review of 19 studies that examined studies using CRRT in parallel with ECMO. CRRT along with ECMO was determined to be safe and improved fluid balance.

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The review by the ADQI group examined the role of mechanical fluid removal in critically ill patients. It was determined that in fluid overloaded patients unresponsive to pharmacological therapy mechanical removal should be considered as an adjunctive therapy.

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The prospective study evaluated 556 patients treated with CRRT and the effects of management by a specialized CRRT team. Using a SCT decreased the number of filters used, down-time per day, ICU length of stay, and 28-day mortality.

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In this prospective cohort study of 334 patients who started CRRT for severe AKI, patients were divided into groups based on SCT application. The down-time per day, lost time per filter-exchange, 28, and 90-day mortality were significantly decreased in the SCT group.

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The study evaluated the use of high-fidelity patient-simulation scenarios to analyze the performance and usefulness of the device to realistically generate clinical conditions and problems in simulated patients. The device was found to be very useful for training healthcare professionals in CRRT management with good student and teacher satisfaction and quick, accurate and real-time monitoring of pressure changes concordant with the usual clinical problems to be simulated.

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This was a retrospective study of 131 patients evaluating the mean filter run times based on catheter access site. The study determined that vascular access for CRRT plays a significant role in determining filter life and that temporary dialysis catheters should be preferentially placed in the femoral site.

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The retrospective comparative cohort study compared RCA versus systemic heparin for CRRT anticoagulation in children. It determined that RCA provided significantly longer circuit survival versus heparin and that it was a safe and effective anticoagulation method for CRRT in children.

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54. ■ Schilder L, Nurmohamed SA, Bosch FH, *et al.* Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multicenter randomized clinical trial. Crit Care 2014; 18:472–481.

This was a multicenter RCT of 139 that compared RCA to systemic heparin. Mortality rates did not differ between groups but filter survival time was superior for RCA versus systemic heparin (46 vs. 32 h, $P = 0.02$), as were the numbers of filters used, off time within 72 h and costs during the first 72 h of CRRT.

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The article reviewed the literature on pediatric and adult literature comparing RCA versus systemic heparin for CRRT anticoagulation. It found that CRRT is the most common modality of RRT in the ICU and that RCA is commonly employed.

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This was one of the first studies comparing RCA with regional heparin anticoagulation and protamine reversal. It was a large 212 patient study from seven ICUs in Australia and New Zealand. It detemined that RCA was associated with prolonged filter life and less adverse events when compared with regional heparin anticoagulation.

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The article reviewed various quality improvement strategies and metrics in healthcare. It specifically detailed four quality-improvement tools – checklists, Six Sigma methodology, lean thinking, and Kaizen.

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The authors used the PDSA service improvement approach to develop an intervention to evaluate current delivery of AKI management and to test and generate new ideas relating to the patients' needs. Here they highlight the PDSA methodology and cycle.

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This is an online patient safety and quality improvement module that describes various methods of quality improvement such as the FADE model, PDSA, and Six Sigma models.

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64. National Quality Forum. http://www.qualityforum.org/Home.aspx. ■

This is the website of the National Quality Forum. It is a not-for-profit organization that works to catalyze improvements in healthcare. Endorsement by the National Quality Forum is the gold standard for any quality measure in healthcare.

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The study evaluated the implementation of the lean principles to examine the workflow for CRRT preparation, and develop an educational program to limit CRRT product waste. The implementation of this program led to reduced CRRT solution waste, improved efficiency of CRRT workflow, and increased satisfaction among the staff.

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This is the NICE guidelines for the prevention, detection, and management up to the point of renal replacement therapy in acute kidney injury. It is an evidence-based graded summary of the current literature surrounding AKI.

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The single center study conducted at a tertiary care center evaluated the before and after effects of implementation of care bundles for AKI. Ultimately, when completed within 24 h, there was a significant reduction in hospital mortality (18.0 vs. 23.1%, $P = 0.46$).

69. Cox ZL, McCoy AB, Matheny ME, *et al.* Adverse drug events during AKI and its ■ recovery. Clin J Am Soc Nephrol 2013; 8:1070–1078.

This is the first study to characterize drug events related to worsening and improving renal function. Nine hundred and thirty-eight patients with changing renal function were followed and it was determined that 52 patients had adverse drug-related events and 29 patients had therapeutic failures, mostly relating to antibiotic underdosing. These results highlight the importance of appropriate renally-adjusted medication dosing.

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71. Hoste EA, Bagshaw SM, Bollomo R, *et al.* Epidemiology of acute kidney injury ■ in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41:1411–1423.

This was an international cross-sectional study of critically ill patients performed in 97 centers in 33 countries. They determined that AKI occurred in 57.3% of patients, and that increasing AKI severity was associated with increased mortality. Finally, 13.5% of patients were treated with RRT and the majority of RRT procedures were with CRRT (75.2%).

72. Tolwani A. Continuous renal-replacement therapy for acute kidney injury. N Engl J Med 2012; 367:2505–2514.

73. Rewa O, Eurich E, Stelfox H, *et al.* Quality indicators in continuous renal ■ replacement therapy (CRRT) care in critically ill patients: protocol for a systematic review. Syst Rev 2015; 4:102.

This is a protocol for an ongoing systematic review to identify quality indicators in CRRT care. It is the first step of a larger program that will later prioritize and evaluate these quality indicators as they apply to clinical practice.

Rewa et al. Systematic Reviews (2015) 4:102
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SYSTEMATIC REVIEWS

PROTOCOL Open Access

Quality indicators in continuous renal replacement therapy (CRRT) care in critically ill patients: protocol for a systematic review

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Abstract

Background: Renal replacement therapy is increasingly utilized in the intensive care unit (ICU), of which continuous renal replacement therapy (CRRT) is most common. Despite CRRT being a relatively resource-intensive and expensive technology, there remains wide practice variation in its application. This systematic review will appraise the evidence for quality indicators (QIs) of CRRT care in critically ill patients.

Methods: Ovid MEDLINE, Ovid EMBASE, CINAHL, and the Cochrane Library including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), and databases from the National Information Center of Health Services Research and Health Care Technology will be searched for original studies involving QIs in CRRT. Gray literature sources will be searched for technical reports, practice guidelines, and conference proceedings. Websites of relevant organizations will be identified, and industry leaders in the development and marketing of CRRT technology and non-profit organizations that represent key opinion leads in the use of CRRT will be contacted. We will search the Agency of Healthcare Research and Quality National Quality Measures Clearinghouse for CRRT-related QIs. Studies will be included if they contain quality measures, occur in critically ill patients, and are associated with CRRT. Analysis will be primarily descriptive. Each QI will be evaluated for importance, scientific acceptability, usability, and feasibility using the four criteria proposed by the United States Strategic Framework Board for a National Quality Measurement and Reporting System. Finally, QIs will be appraised for their potential operational characteristics, for their potential to be integrated into electronic medical records, and on their affordability, if applicable.

Discussion: This systematic review will comprehensively identify and synthesize QIs in CRRT. The results of this study will fuel the development of an inventory of essential QIs to support the appropriate, safe, and efficient delivery of CRRT in critically ill patients.

Systematic review registration: PROSPERO CRD42015015530.

Keywords: Quality indicator, Effectiveness, Continuous renal replacement therapy, Dialysis, Critical care, Intensive care

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Background

Acute renal replacement therapy (RRT) is used in 8–10 % of critically ill patients, to support injured or overtly failing kidneys in the context of multiple organ dysfunction syndrome [1–4]. RRT utilization is increasing steadily [2–5]. Population-based estimates have suggested the incidence of acute RRT has increased by greater than 10 % per year over the past decade and continuous renal replacement therapy (CRRT) remains the most common form of RRT used in intensive care unit (ICU) settings [6–8]. While CRRT has not shown a clear survival benefit over conventional intermittent forms of RRT in critically ill patients, [9–11] recent data have shown initial therapy with CRRT may be associated with improved long-term recovery of kidney function [12, 13]. These observations imply the utilization of CRRT will continue to increase.

CRRT is a continuous method of blood purification that theoretically provides slow uninterrupted clearance of retained endogenous and exogenous toxins, along with providing acid-base, electrolyte, and volume homeostasis. While CRRT is intended to function 24 h a day (analogous to a native kidney), it is often interrupted [14, 15]. Unplanned treatment interruption can negatively impact its efficiency and safety [14]. Recent trials have shown lower dose-intensive CRRT (25 ml/Kg/h) is as effective as higher dose-intensive (40 ml/Kg/h) CRRT on outcomes, [1] a view supported by the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury [5]. However, there remains important disparity in practice between the prescribed and delivered dose in CRRT [6]. Many additional aspects of CRRT in critically ill patients remain uncertain, in particular the ideal circumstances and optimal timing for when to initiate CRRT [9, 11]. This again contributes to heterogeneity in the practice and delivery of suboptimal quality CRRT care [7, 8, 16, 17]. These issues can be broadly classified into potential quality domains related to the prescription and delivery of CRRT (Table 1).

While CRRT is generally a resource-intensive and expensive technology [3, 10, 18], it remains the default modality of support most frequently used for severely ill patients at high risk for death [1, 8, 12, 13]. Practice variation in utilization of CRRT has been shown to independently contribute to higher risk for less favorable outcomes and itself is considered a measure of poor quality care [14, 15, 19]. While this variation may stem from important knowledge gaps in evidence to guide best practice, different providers (e.g., nephrology vs. intensive care) and limited provider and institutional expertise in CRRT, coupled with a paucity of clearly defined quality measures of CRRT care, are likely also important contributors. To date, no study has systematically mapped or evaluated the scope of quality measures in CRRT care.

Table 1 Summary of potential quality indicator themes and measures

Themes	Measures
Dose prescription	High vs. low dose
Dose delivery	Percentage of prescribed dose delivered
Anticoagulation selection	Heparin vs. citrate vs. none
Anticoagulation monitoring	PTT monitoring, citrate monitoring
Anticoagulation complications	Bleeding, hypocalcaemia, incidence of HIT
Treatment interruption	Number of interruptions and duration of interruptions; time to establish new circuit
Catheter-related issues	Infections, bleeding, obstruction/thrombosis
Circuit-related issues	Filter clotting, pressure alarming

HIT heparin-induced thrombocytopenia

Accordingly, we will perform a systematic review of quality indicators (QIs) of CRRT care. This is a critical initial step to reduce low-quality CRRT care, optimize resource utilization, and improve outcomes. We believe our review will map important themes in CRRT care to identify and close "evidence care gaps" through better monitoring, reporting, benchmarking, and process reassessment.

Methods

Study design

We will perform a systematic review to identify and evaluate QIs for the prescription, delivery, and monitoring and their association with patient-centered and health economic outcomes (if available) for critically ill patients receiving CRRT using the guidelines from Cochrane and Center for Reviews and Dissemination and described according to the PRISMA-P guideline (Additional file 1) [20–22].

Study registration

This systematic review is registered with PROSPERO (CRD42015015530).

Criteria for considering studies for this review

Inclusion criteria

Studies will be included if they mention *all* of the following themes: (1) *quality measure*, i.e., intended to evaluate the care received by patients treated with CRRT; (2) *intensive care*, i.e., intended to refer to patients (adults, children, and neonates) supported in an intensive care unit setting; (3) *continuous renal replacement therapy*, i.e., the prescription, delivery, or outcome associated with CRRT; (4) language of study being English, French, German, Italian, or Spanish; (5) publication after

1990; and (6) levels of evidence, all primary studies (i.e., randomized control trials, cohort studies, case-control studies, case series, and qualitative or mixed methods studies), secondary analyses, or evidence syntheses (i.e., systematic reviews, meta-analyses, and Cochrane reviews), as well as targeted gray literature including technical reports from industry or to governments or health care agencies. These studies will not be limited to comparative studies and will include any literature with mention of QIs. An initial screening of retrieved literature considered drug monitoring and drug levels as a potential QI; however, given the extensive number of citations related to this theme, we believed this would be ideally suited to a separate dedicated study and omitted is from this systematic review.

Exclusion criteria

Studies will be excluded that do not fulfill all of the above criteria.

Search methods for identification of studies

The search strategy will be developed in consultation with an information specialist at the Alberta Research Centre for Health Evidence (ARCHE) at the University of Alberta and will be peer-reviewed by another librarian [23]. The information specialist will search electronic databases: Ovid MEDLINE, Ovid EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host, and the Cochrane Library including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, databases from the National Information Center of Health Services Research and Health Care Technology will be searched. A combination of the following search themes will be used: (1) continuous renal replacement therapy, hemofiltration, hemodialfiltration, dialysis, renal replacement therapy, and renal support and (2) intensive care, critical care, critical illness, multi-organ dysfunction, and multi-organ failure (see Table 2). Results will be limited to human studies, published in English, French, German, Italian, or Spanish since 1990. Bibliographic records will be exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database for screening.

Additional sources will be included in the search strategy. The cited and citing references of selected key studies will be searched for relevant articles. Gray literature sources will be searched for technical reports, practice guidelines, and conference proceedings. We will identify and search the websites of relevant organizations (i.e., Canadian Society of Nephrology, European Societies of Nephrology [ERA-EDTA], National Kidney Foundation, American Society of Nephrology, American Society for Artificial Internal Organs, European Society for Artificial Organs). Industry leaders in the development and marketing of CRRT technology (i.e., Baxter-Gambro Renal Inc., NxStage Inc., Fresenius Medical Care Inc., Bellco Inc., Medica Inc.) will be contacted. Non-profit organizations that represent key opinion leads in critical care nephrology and the use of CRRT (i.e., Acute Dialysis Quality Initiative) will also be contacted. We will search the Agency of Healthcare Research and Quality National Quality Measures Clearinghouse (www.qualitymeasures.ahrq.gov) for CRRT-related quality measures. Finally, we will survey an inter-disciplinary group of knowledge users, clinical experts, and decision-makers (i.e., physicians, nurses, engineers) experienced with the provision of CRRT in critically ill patients to elicit additional potential quality measures.

Data extraction and analysis

Eligible articles will be identified through two phases. In the first phase, two authors will independently review the titles and abstracts of all retrieved articles and documents using EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) for potential inclusion into the systematic review. Disagreements will be resolved through discussion. In the case of unresolved matters, a third party will be involved. In the second phase, full texts of the selected articles will be retrieved and information abstracted using standardized forms. The same two authors will conduct this independently. Abstracted data will be then compared amongst the two authors, and disagreements will also be resolved through discussion. In the case of unresolved matters, a third party will be involved. The authors of the retrieved studies and/or documents will be contacted for further information if necessary. Methodological quality will be rated using the Newcastle-Ottawa Quality Assessment Scale (NOS) for observational studies and a modified version of BOAS for before-after studies, as applicable [24]. Qualitative studies will be evaluated using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN checklist) with four-point scale [25].

QIs will be identified from included articles and documents and from the survey of experts and key stakeholders. Two independent authors will collect data on the properties of measurement and characteristics of each of the identified QIs. The relevance of each QI will then be evaluated using the four criteria proposed by the United States Strategic Framework Board for a National Quality Measurement and Reporting System (importance, scientific acceptability, usability, and feasibility) [26]. Importance will be based on how each QI may inform about CRRT prescription, delivery, and monitoring and association with patient-centered and health economic outcomes. Scientific acceptability will assess how plausible each QI measures attributes of CRRT and

Table 2 The strategy will be adapted and executed in the above databases for the full search: Ovid MEDLINE, CINAHL@ VIA EBSCOHOST, EMBASE@ VIA OBID, AND Cochrane Library

1.	Acute Kidney Injury/th
2.	Hemodiafiltration/
3.	Renal Dialysis/
4.	Renal Replacement Therapy/
5.	(dialys* or hemodialys* or haemodialys*).tw,kf.
6.	(haemodiafiltrat* or haemo diafiltrat* or haemofiltrat* or haemo filtrat* or hemodiafiltrat* or hemo diafiltrat* or hemofiltrat* or hemo filtrat*).tw,kf.
7.	(renal replacement adj2 (therap* or treatm* or support*)).tw,kf.
8.	RRT.tw,kf.
9.	or/1-8
10.	(24h or 24hr* or 24 hour* or 24 hr* or continual* or continuous* or twenty four hour* or twenty four hr* or twentyfour hour* or twentyfour hr*).mp.
11.	and/9-10
12.	CRRT.tw,kf.
13.	or/11-12
14.	Critical Care/
15.	Critical Illness/
16.	exp Intensive Care/
17.	Intensive Care Units/
18.	exp Intensive Care Units, Pediatric/
19.	Multiple Organ Failure/
20.	critical care.tw,kf.
21.	critical* ill*.tw,kf.
22.	(ICU* or NICU* or PICU*).tw,kf.
23.	intensive care.tw,kf.
24.	intensivist*.tw,kf.
25.	(multi* organ adj (disfunction* or dis function* or dysfunction* or dys function* or failure*)).tw,kf.
26.	(multi* system adj (disfunction* or dis function* or dysfunction* or dys function* or failure*)).tw,kf.
27.	or/14-26
28.	and/13,27
29.	animals/ not (animals/ and humans/)
30.	28 not 29
31.	limit 30 to (english or french or german or italian or spanish)
32.	limit 31 to yr="1990-Current"
33.	remove duplicates from 32

outcomes. Usability and feasibility will characterize the logistics and process of implementation of each QI into clinical practice. These outcomes will be further evaluated in the second phase of this project when the evidence base for each QI will be evaluated and ranked by key knowledge users, stakeholders, and experts. Candidate QIs will be each evaluated for their operational characteristics such as association with circuit lifespan, resource intensity (i.e., nursing workload), and health care costs, as well as for their potential to be integrated into electronic medical records, if applicable.

Analysis

Descriptive analyses will be performed on all articles and QIs. Each QI will be categorized first according to the structure, process, and outcome framework and then by agreed upon domains of evaluation. The Donabedian framework for examining health services and evaluating

quality of care, along with the identified relevant domains of evaluation, will be used and modified as the models and frameworks are identified. Due to the anticipated heterogeneity of QIs and methods of ascertainment, a comprehensive inventory of QIs will be developed and summarized as counts and proportions. These summary counts and proportions will be further stratified based on relevant features such as study design, domains of health care quality, rank, and domains of evidence and evaluated using chi-square tests. When possible, articles and QIs will be pooled and further analysis will be performed; however, due to the heterogeneity as well as broad scope of material, it is expected that it will not be possible to pool all QIs for analysis. All analyses will be performed using STATA statistical software, version 13 (StataCorp, College Station, Texas).

Discussion

CRRT is the predominant form of acute RRT provided to critically ill patients, and its utilization is increasing. CRRT is a complex technology that is resource intensive, costly, and requires specialized training by health providers and is susceptible to treatment error.

There is considerable practice variation in CRRT care. CRRT can be prescribed and delivered by either or both nephrology and/or intensive care [27]. To date, we are unaware of any prior comprehensive and rigorous evaluation of QIs in CRRT care. In our view, given the complexity, cost, and resource intensiveness of CRRT implementation, this is a critical knowledge gap in the delivery of one of the core life support technologies that define intensive care. This systematic review will establish an inventory of potential CRRT-specific QIs that will provide knowledge users, clinicians, administrators, and researchers with robust measures to continuously appraise the quality, safety, and effectiveness of CRRT care. Moreover, these QIs may present opportunities for further innovation in CRRT care, contribute to improve patients' outcomes, and better utilization of health resources. We believe that this systemic review is timely and will make a valuable contribution by helping to identify and address current existing evidence care gaps. Moreover, our systematic review will lead to future opportunities to establish a research agenda that will continue to address deficiencies in our knowledge surrounding QIs in the delivery of CRRT.

From our systematic review, the next steps in our program will involve an evaluation of each identified CRRT QI by key knowledge users, stakeholders, and experts. QIs will be ranked using a Delphi process to develop a prioritized consensus inventory of relevant CRRT QIs across the spectrum of CRRT care for implementation into clinical practice. We anticipate the findings from our review and this consensus process will inform broader implementation of quality measures in CRRT care and be integrated into educational and/or training programs to support safe and effective CRRT care for critically ill patients.

Expected limitations

It is anticipated that due to the paucity of focused literature on QIs in CRRT care, the scope of QIs will show considerable heterogeneity across a spectrum of scientific rigor and relevance. The comparisons across strata of QIs are likely to be underpowered in chi-squared analysis owing to the anticipated heterogeneity across measures; however, such analysis is not the primary objective of the review. It is also anticipated that some of the QIs will be significant and high quality while others will be poorer quality. In addition, we have limited our search strategy to include only studies published in selected languages (English, French, German, Italian, or Spanish). We recognize this may result in omission of studies describing potential QIs; however, we believe these languages will capture the majority of high-quality published research in CRRT. We will utilize the NOS or COSMIN checklist to quantify and evaluate the risk of bias across studies, and these measures will be included in our analysis. Finally, it is expected that there will be limited evidence of impact of adoption of individual or combinations of QIs in CRRT programs.

Additional file

Additional file 1: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist: recommended items to address in a systematic review protocol.

Abbreviations

CRRT: continuous renal replacement therapy; ICU: intensive care unit; QI: quality indicator; RRT: renal replacement therapy.

Competing interests

SMB and RTNG have consulted and received honoraria from Baxter Inc. OR is supported by an unrestricted educational grant from Baxter Inc. Baxter Inc. has had no role in the development or preparation of this protocol.

Authors' contributions

OR was responsible for the preparation of the protocol and manuscript preparation. DE, SMB, and OR were responsible for finalizing the protocol, statistical methods, and completion of the final manuscript. HS and RTNG provided expert content expertise and assisted with preparation of the protocol and manuscript. LH informed the methods for conducting the review. RF developed the search strategy in consultation with OR, PMV and SMB and conducted the search. SMB conceived the project and developed the protocol, and all authors provided critical revision of the protocol and final manuscript. SMB will guarantee the content of the review. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW

Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review

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Abstract

Objectives: Renal replacement therapy is increasingly utilized in the intensive care unit (ICU), of which continuous renal replacement therapy (CRRT) is most common. Despite CRRT being a relatively invasive and resource intensive technology, there remains wide practice variation in its application. This systematic review appraised the evidence for quality indicators (QIs) of CRRT care in critically ill patients.

Design: A comprehensive search strategy was developed and performed in five citation databases (Medline, Embase, CINAHL, Cochrane Library, and PubMed) and select grey literature sources. Two reviewers independently screened, selected, and extracted data using standardized forms. Each retrieved citation was appraised for quality using the Newcastle–Ottawa Scale (NOS) and Cochrane risk of bias tool. Data were summarized narratively.

Measurements and main results: Our search yielded 8374 citations, of which 133 fulfilled eligibility. This included 97 cohort studies, 24 randomized controlled trials, 10 case-control studies, and 2 retrospective medical audits. The quality of retrieved studies was generally good. In total, 18 QIs were identified that were mentioned in 238 instances. Identified QIs were classified as related to structure ($n = 4$, 22.2 %), care processes ($n = 9$, 50.0 %), and outcomes ($n = 5$, 27.8 %). The most commonly mentioned QIs focused on filter lifespan ($n = 98$), small solute clearance ($n = 46$), bleeding ($n = 30$), delivered dose ($n = 19$), and treatment interruption ($n = 5$). Across studies, the definitions used for QIs evaluating similar constructs varied considerably. When identified, QIs were most commonly described as important ($n = 144$, 48.3 %), scientifically acceptable ($n = 32$, 10.7 %), and useable and/or feasible ($n = 17$, 5.7 %) by their primary study authors.

Conclusions: We identified numerous potential QIs of CRRT care, characterized by heterogeneous definitions, varying quality of derivation, and limited evaluation. Further study is needed to prioritize a concise inventory of QIs to measure, improve, and benchmark CRRT care for critically ill patients.

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Work performed at the University of Alberta.

Take-home message: We identified 18 potential quality indicators (QIs) of continuous renal replacement therapy (CRRT) care in the current literature. However, as a result of significant definition heterogeneity and limited evaluation, further study is needed to better prioritize these QIs to measure, improve, and benchmark CRRT care for critically ill patients.

Systematic review registration: PROSPERO CRD42015015530.

Keywords: Quality indicator, Effectiveness, Continuous renal replacement therapy, Dialysis, Critical care, Intensive care

Introduction

Renal replacement therapy (RRT) is acutely applied in 8–10 % of critically ill patients and the utilization has grown by greater than 10 % per year over the past decade [1–6]. The AKI-EPI study found that continuous renal replacement therapy (CRRT) is the predominant form of RRT utilized, being the initial RRT modality in over 75 % of critically ill patients [7, 8].

There is considerable variation in the prescription and delivery of CRRT care, despite evidence to guide practice [7, 9]. High-quality randomized controlled trials (RCTs) have shown that lower dose-intensity CRRT is as effective as higher dose-intensity CRRT for patient outcomes [10, 11]. Yet, there remain large disparities in practice between prescribed and delivered dose of CRRT [5, 9]. The mode of CRRT remains highly variable [12]. Despite recent evidence to suggest the superiority of regional citrate to maintain circuit patency, heparin use remains predominant in many ICUs [13, 14]. Finally, the timing of when to initiate CRRT is uncertain and recent evidence from RCTs has shown conflicting results [15, 16]. Such discrepancies likely contribute to wide practice variation. This likely represents a surrogate for suboptimal or poor quality of care.

While this variation may stem from important knowledge gaps in evidence to guide best practice, additional factors such as different providers (i.e., nephrology vs. intensive care), limited provider and/or institutional expertise, and a paucity of clearly defined quality indicators (QIs) to measure and monitor the quality of CRRT care likely contribute. The purpose of such QIs is to increase the reliability of care, homogenize complex interventions where risk is non-trivial, and to enable benchmarking of performance. QIs can be further used as targets for continuous quality improvement initiatives aimed at evaluating new or revised care processes, implementing new protocols or interventions, and stimulating innovative research [17].

QIs can be defined using the Donabedian framework, and classified across three domains of healthcare: structure (i.e., settings, qualifications of providers, and organizational/administrative systems), process (i.e., components of healthcare delivered), and outcomes (i.e., recovery, restoration of function, and survival) [18]. While QIs have been identified in other scopes of critical care (i.e., standardized mortality rate, rates of catheter-related bloodstream infection, compliance with venous thromboembolism/stress ulcer prophylaxis), we have found no study to date that has systematically mapped or evaluated the scope of QIs in CRRT care [19–21].

Accordingly, we performed a systematic review to identify and define QIs of CRRT care. This is a vital initial step toward identifying, validating, and implementing evidence-informed QIs to avoid or reduce low-quality CRRT care, to guide best practice, optimize resource utilization and healthcare provider workload, and improve patient outcomes. Moreover, QIs of CRRT care can be implemented to standardize and improve the reliability of CRRT practice, audit and benchmark CRRT performance over time.

Methods

We performed a systematic review using methodological approaches outlined in the Cochrane Handbook for Systematic Reviews of Interventions and described according to the PRISMA-P guideline (Supplementary material 1) [22, 23]. Research ethics approval was not required. This systematic review was registered at PROSPERO (January 22, 2015 CRD42015015530).

Search strategy for identification of studies

We developed a comprehensive search strategy in consultation with a research librarian (R.F.) that was peer-reviewed by a second research librarian [24]. We searched the following electronic databases: Ovid Medline In-Process & Other Non-Indexed Citations and Ovid Medline (1946 to present), Ovid Embase (1988–2015 week 07), Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host (1937 to present), Cochrane Library via Wiley (inception to present) including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed via NCBI Entrez limited to publications from 2014 to 2015. To locate reports of in-process research and other technology assessments not included in our main bibliographic databases, we searched the Health Services Research Projects in Progress (HSRProj), Health Services Research Resources (HSRR), and Health Services/Technology Assessment Texts (HSTAT) databases from the National Information Center of Health Services Research and Health Care Technology (NICHSR). Our search strategy combined the following concepts: (1) continuous renal replacement therapy, hemofiltration, hemodialfiltration, dialysis,

renal replacement therapy, renal support; and (2) intensive care, critical care, critical illness, multi-organ dysfunction, multi-organ failure (Supplementary material 2). Grey literature sources were searched for technical reports, practice guidelines, and conference proceedings (Supplementary material 3). Bibliographic records were exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database for screening.

Studies were included if they mention all of the following themes: (1) quality indicator (i.e., intended to evaluate the care received by patients treated with CRRT), (2) intensive care (i.e., intended to refer to patients (adults, children, and neonates) supported in an intensive care unit setting), and (3) continuous renal replacement therapy (i.e., the infrastructure, prescription, delivery, or outcomes associated with CRRT). QIs were defined as any indicator intended to measure the structure, process, or outcomes association with the prescription and/or delivery of CRRT. Indicators could measure setting, machine, and/or provider-related factors (i.e., structure QI), components of how CRRT delivery occurs (i.e., process QI), or morbidity and mortality associated with receipt of CRRT (i.e., outcome QI). We considered studies published in English, French, German, Italian, and Spanish, as the majority of data have been published in these languages. We selected studies published after 1990, as this corresponded to when veno-venous CRRT circuits were established. Finally, selected levels of evidence including all primary studies, secondary analyses or evidence syntheses, as well as targeted grey literature were reviewed. Studies were excluded if they did not fulfill all of the above criteria.

We used a two-stage process for study selection. First, two reviewers (O.G.R. and P.M.V.) independently screened the titles and abstracts (when available) of search results to determine if a study met the general inclusion criteria. Each report was classified as either include or exclude. Disagreements were resolved by discussion. The full-text versions of all citations classified as "include" by either reviewer were retrieved for in-depth review. The same two reviewers (O.G.R. and P.M.V.) independently assessed the eligibility of each full-text manuscript for final inclusion into the review. Again, disagreement was resolved by discussion.

Data abstraction

Two independent reviewers (O.G.R. and P.M.V.) extracted data using standardized, piloted, case report forms. All QIs were identified, abstracted, and agreed upon by the two independent authors (O.G.R. and P.M.V.). The following data were abstracted from each citation: author identification, year of publication, title, journal of publication, language of publication, study design, identified quality indicator, and the operational definition utilized.

Each QI was characterized on the basis of its importance, scientific acceptability, usability, and feasibility. Initially, 20 % of citations ($n = 27$) had their QIs characterized in duplicate (O.G.R. and P.M.V.). This was done to ensure consistent agreement and greater than 80 % was achieved. Given high levels of redundancy, the remaining citations were extracted by a single reviewer (O.G.R.). If there was uncertainty, QIs were again reviewed in duplicate and consensus on QI characteristics was achieved through discussion. Each QI was stratified (yes/no) according to whether study authors described it as being important to CRRT prescription, important to CRRT delivery, important to CRRT monitoring, important to patient-related outcomes, important to health resource utilization, or outlined its scientific basis, and described as being operationally feasible [i.e., easy to obtain or implement including integration into an electronic medical record (EMR)].

Internal validity and risk of bias assessment

We assessed the internal validity of included studies using the Newcastle–Ottawa Quality Assessment Scale (NOS) for observational studies and the Cochrane Collaboration Risk of Bias tool was used to assess risk of bias in RCTs [25]. Observational studies were rated high quality if they had a total score of 6–9, moderate quality with a score of 4 or 5, and poor quality if they had a score of 3 or fewer [26].

Data analysis

The primary analysis was descriptive and narrative. QIs were categorized according to the Donabedian framework by stratifying whether each QI measured a structure, process, or outcome related to CRRT care [27]. QIs were further evaluated by O.G.R. and P.M.V. using the four criteria proposed by the US Strategic Framework Board for a National Quality Measurement and Reporting System (importance, scientific acceptability, usability and feasibility), as outlined above [28].

Results

Search results

Our initial search strategy identified 8374 citations, of which we included 133 articles (Fig. 1). This consisted of 96 full-text articles and 37 abstracts. These included 97 cohort studies, 24 RCTs, 10 case-control studies, and 2 retrospective medical record audits (Table 1). All studies except one were published in English; a single study was published in Spanish.

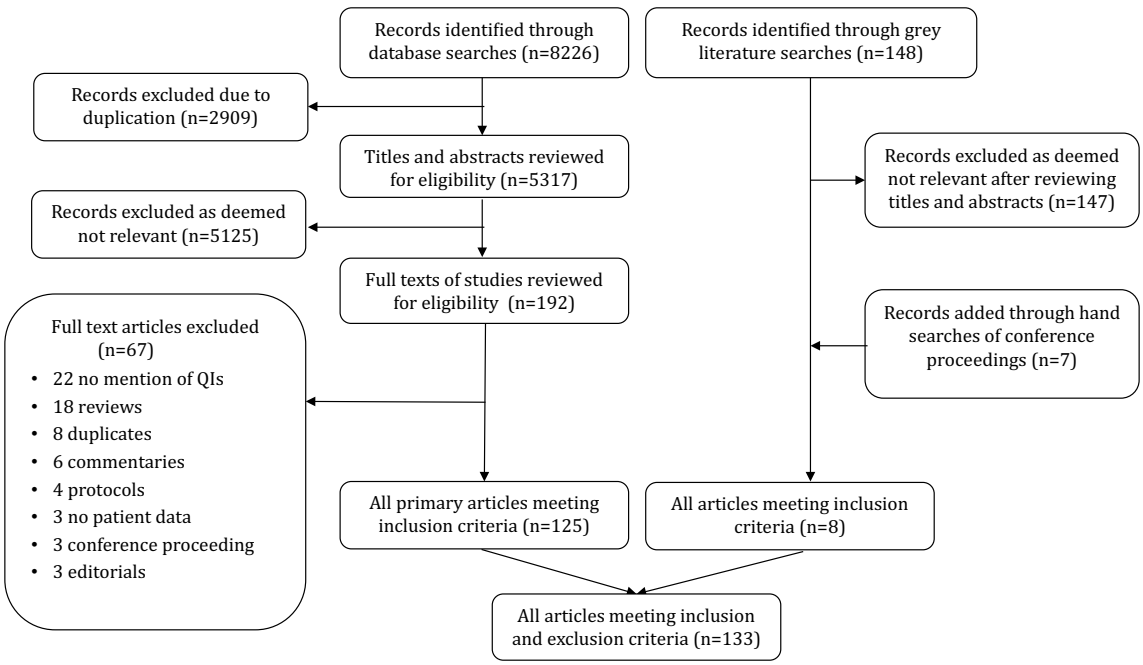

Fig. 1 PRISMA flow diagram of retrieved and included records. This flow diagram depicts the identified citations from the medical literature on the *left* and from the grey literature on the *right*. Of the 133 included citations, 96 were full-text articles and 37 were abstracts

Study quality

Study quality was generally rated as high for observational studies and poor for RCTs. Study quality was assessed in 96 studies (72.2 %). All of the RCTs (100 %) were rated as having a high risk of bias (secondary to not being able to blind the treatment arms). The mean NOS score was 6 (range 4–9) and the majority of observational studies ($n = 73$, 97.3 %) were rated as high quality, and two studies ($n = 2$, 2.7 %) as moderate quality; no observational studies were rated as poor quality. Of the remaining studies identified ($n = 37$, 27.8 %), quality assessment was not possible because of insufficient data due to being published in abstract form only.

Quality indicators

A total of 18 QIs were identified in 238 separate instances and classified as structure ($n = 4$, 22.2 %), process ($n = 9$, 50.0 %), and outcome ($n = 5$, 27.8 %) indicators (Table 2). Filter life was the most commonly identified QI ($n = 98$, 41.2 %), followed by small solute clearance ($n = 46$, 19.3 %), bleeding ($n = 30$, 12.6 %), delivered dose ($n = 19$, 8.0 %), and downtime ($n = 14$, 4.9 %) (Table 2). There was significant heterogeneity in the definitions and criteria used to define each QI across studies (Table 3). The QIs were grouped across a six themes: complications ($n = 7$, 38.8 %), circuit ($n = 3$, 16.7 %), interruptions ($n = 2$, 11.1 %), education ($n = 2$, 11.1 %), clearance ($n = 1$, 5.6 %), and dose delivery ($n = 1$, 5.6 %).

National quality measurement and reporting criteria

The characteristics of QIs discussed by study authors were mostly centered on the importance of QIs ($n = 144$, 48.3 %), followed by scientific acceptability ($n = 32$, 10.7 %), and then by usability and feasibility ($n = 17$, 5.7 %). Importance was further stratified across specific elements of CRRT care: importance to CRRT prescription ($n = 36$, 25.0 %), importance to CRRT delivery ($n = 33$, 22.9 %), importance to CRRT monitoring ($n = 11$, 7.6 %), importance to patient-related outcomes ($n = 40$, 27.8 %), and importance to health economics ($n = 24$, 16.7 %) (Table 2).

Discussion

We performed a comprehensive systematic literature search and evidence synthesis to catalogue the spectrum of quality indicators of CRRT care in critically ill patients.

Summary of key findings

First, we found 18 unique QIs across six themes within the Donabedian framework domains of structure, process, and outcome. The majority of QIs focused primarily on processes of care for how CRRT was prescribed,

Table 1 Baseline characteristics of included trials

Trial[a]	Source	Study type	Patient population	Patients	Quality indicator
DeVico (1)	Full text	Cohort	Adult cardiac surgery	15	Filter life
					Small solute clearance
Goonasekera (2)	Full text	Cohort	Pediatric acute liver failure	31	Filter life
					Downtime
Kee (3)	Full text	Cohort	Adult critically ill	551	Filter life
					SCT training
					Delivered dose
					Downtime
Schilder (4)	Full text	RCT	Adult critically ill	139	Filter life
					Downtime
					Complications
Claure-del Granado (5)	Full text	Cohort	Adult critically ill	244	Filter life
					Filter efficacy
					Delivered dose
					Bleeding
Treschan (6)	Full text	RCT	Adult surgical critically ill	66	Filter life
					Bleeding
					VTE events
Fernandez (7)	Full text	Case control	Adult critically ill	36	Filter life
Lipcsey (8)	Full text	Cohort	Adult critically ill	380	VTE events
Chua (9)	Full text	Case control	Adult critically ill	458	Catheter colonization CRBSIs
Dunn (10)	Full text	Cohort	Adult critically ill	355	Filter life
Ho (11)	Full text	RCT	Adult critically ill	94	Filter life
Crosswell (12)	Full text	Case control	Adult critically ill	131	Filter life
Lee (13)	Full text	RCT	Adult critically ill	73	Filter life
					Bleeding
Prada Rico (14)	Abstract	Cohort	Pediatric critically ill	Unknown	Filter life
Fisher (15)	Abstract	Cohort	Adult critically ill	33	Delivered dose
					Interruptions
Chenouard (16)	Abstract	Cohort	Pediatric critically ill	16	Filter life
					Bleeding
Campbell (17)	Abstract	Case control	Adult critically ill	188	Delivered dose
					Downtime
					Bleeding
Han (18)	Abstract	Case control	Adult critically ill	115	Filter life
Mottes (19)	Full text	Cohort	Pediatric critically ill	80	SCT training
Goonasekera (20)	Full text	Cohort	Pediatric acute liver failure	31	Filter life
					Downtime
Leung (21)	Full text	Cohort	Adult critically ill	44	Filter life
Fealy (22)	Full text	Cohort	Adult critically ill	46	Filter life
Kalb (23)	Full text	Cohort	Adult critically ill	75	Filter life
					Delivered dose
Jacobs (24)	Abstract	Cohort	Adult critically ill	59	Filter life
Richardson (25)	Abstract	Cohort	Adult cardiac surgery	22	Delivered dose
Jacobs (26)	Abstract	Cohort	Adult critically ill	59	Filter life
Gojaseni (27)	Abstract	Cohort	Adult critically ill	40	Filter life
Ferraresi (28)	Abstract	Cohort	Adult critically ill	100	Filter life
					Catheter malfunction

Table 1 continued

Trial[a]	Source	Study type	Patient population	Patients	Quality indicator
Dalhulsen (29)	Abstract	Cohort	Adult critically ill	15	Filter life
					Small solute clearance
Avila (30)	Abstract	Cohort	Adult critically ill	21	Filter life
Cho (31)	Abstract	Cohort	Adult critically ill	37	Filter life
					Bleeding
Lyndon (32)	Full text	RCT	Adult critically ill	200	Small solute clearance
					Filter life
					Delivered dose
Claure-del Granado (33)	Full text	Cohort	Adult critically ill	52	Small solute clearance
					Delivered dose
					Effluent volume
Chua (34)	Full text	Case control	Adult acute liver failure	71	Filter life
					Bleeding
Zhang (35)	Full text	Cohort	Adult critically ill	54	Filter life
Lipcsey (36)	Abstract	Cohort	Adult critically ill	380	VTE events
Ezihe-Ejoifor (37)	Abstract	Audit	Adult critically ill	12	Small solute clearance
					Delivered dose
					Interruptions
Conception (38)	Abstract	Cohort	Adult critically ill	166	Small solute clearance
					Delivered dose
Claure-Del Granado (39)	Full text	Cohort	Adult critically ill	52	Filter efficacy
					Small solute clearance
Kim (40)	Full text	Cohort	Adult critically ill	50	Filter life
Kim (41)	Full text	Cohort	Adult critically ill	50	Filter life
Tan (42)	Full text	Cohort	Adult critically ill	13	Filter life
					Effluent volume
Steen (43)	Abstract	Cohort	Adult critically ill	27	Fluid management
					Adherence to protocol
Saha (44)	Abstract	Case control	Adult critically ill	121	Filter life
					Delivered dose
Kalb (45)	Abstract	Cohort	Adult critically ill	75	Filter life
					Delivered dose
					Downtime
Choi (46)	Abstract	RCT	Adult critically ill	24	Filter life
Baldwin (47)	Abstract	Cohort	Adult critically ill	38	Filter life
Parienti (48)	Full text	RCT	Adult critically ill	736	Filter life
					Downtime
Patienti (49)	Full text	Cohort	Adult critically ill	736	Catheter colonization
					CRBSIs
Garces (50)	Full text	RCT	Adult critically ill	40	Filter life
					Bleeding
Kim (51)	Full text	Cohort	Adult critically ill	30	Filter life
Fabbri (52)	Full text	RCT	Adult critically ill	110	Filter life
					Bleeding
Ooi (53)	Abstract	Cohort	Adult critically ill	43	Filter life
					Small solute clearance
Kleger (54)	Abstract	Cohort	Adult critically ill	Unknown	Filter life
Hackbarth (55)	Abstract	Cohort	Pediatric critically ill	20	Delivered dose
					Downtime
Guillermo (56)	Abstract	Cohort	Adult critically ill	18	Delivered dose

Table 1 continued

Trial[a]	Source	Study type	Patient population	Patients	Quality indicator
Casino (57)	Abstract	Cohort	Adult critically ill	18	Small solute clearance
					Delivered dose
Bentson (58)	Abstract	Case control	Pediatric critically ill	67	Filter life
Kiser (59)	Full text	RCT	Adult critically ill	10	Filter life
					Bleeding
					VTE events
Vesconi (60)	Full text	Cohort	Adult critically ill	553	Delivered dose
					Interruptions
Burry (61)	Full text	Cohort	Adult critically ill	48	Filter life
Van Gemeren (62)	Abstract	Cohort	Adult critically ill	14	Filter life
Shidham (63)	Abstract	Cohort	Adult critically ill	16	Filter life
Sachdeva (64)	Abstract	Cohort	Adult critically ill	32	Filter life
Qiu (65)	Abstract	Cohort	Adult critically ill	77	Filter life
					Small solute clearance
					Bleeding
Chang (66)	Abstract	Cohort	Adult critically ill	65	Small solute clearance
Beitland (67)	Abstract	Case control	Adult trauma	39	Filter life
					Downtime
					Catheter malfunction
Durao (68)	Full text	Cohort	Adult trauma	143	Filter life
					Delivered dose
Lanquetot (69)	Full text	Cohort	Adult cardiac surgery	48	Filter life
Olert (70)	Full text	Cohort	Adult critically ill	10	Filter life
					Bleeding
Davies (71)	Full text	RCT	Adult critically ill	45	Filter life
Elderkin (72)	Abstract	Audit	Adult sepsis	44	Filter life
					Bleeding
Boswell (73)	Abstract	Cohort	Adult critically ill	Unknown	Filter life
Nurmohamed (74)	Full text	Cohort	Adult critically ill	51	Filter life
					Small solute clearance
					Downtime
					Bleeding
Cubatolli (75)	Full text	Cohort	Adult critically ill	11	Filter life
					Interruptions
Joannidis (76)	Full text	RCT	Adult critically ill	44	Filter life
					Bleeding
Birnbaum (77)	Full text	RCT	Adult critically ill	20	Filter life
Nurmohamed (78)	Full text	Cohort	Adult critically ill	51	Filter life
					Small solute clearance
					Downtime
					Bleeding
Monti (79)	Full text	Cohort	Adult critically ill	431	Filter life
					Downtime
					Interruptions
Hackbarth (80)	Full text	Case control	Pediatric critically ill	376	Filter life
					Bleeding
Betjes (81)	Abstract	RCT	Adult critically ill	48	Filter life
					Bleeding
De Pont (82)	Full text	Cohort	Adult critically ill	8	Filter life
					Small solute clearance

Table 1 continued

Trial[a]	Source	Study type	Patient population	Patients	Quality indicator
Bihorac (83)	Full text	Cohort	Adult critically ill	76	Filter life
					Small solute clearance
					Fluid management
					Bleeding
Bagshaw (84)	Full text	Cohort	Adult critically ill	87	Filter life
Kutsiogannis (85)	Full text	RCT	Adult critically ill	30	Filter life
					Small solute clearance
					Bleeding
Egi (86)	Abstract	Cohort	Adult critically ill	63	Filter life
Swartz (87)	Full text	Cohort	Adult critically ill	58	Filter life
					Small solute clearance
Nakada (88)	Full text	Cohort	Adult critically ill	54	Catheter colonization
					CRBSIs
Elhana (89)	Full text	Cohort	Pediatric critically ill	9	Filter life
					Small solute clearance
Monchi (90)	Full text	RCT	Adult critically ill	20	Filter life
					Bleeding
Cointault (91)	Full text	Cohort	Adult critically ill	17	Filter life
					Small solute clearance
					Bleeding
Baldwin (92)	Full text	Cohort	Adult critically ill	12	Blood flow
Uchino (93)	Full text	Cohort	Adult critically ill	48	Filter life
					Small solute clearance
					Downtime
Dorval (94)	Full text	Cohort	Adult critically ill	14	Filter life
					Small solute clearance
Mitchell (95)	Full text	Cohort	Adult critically ill	19	Filter life
					Small solute clearance
Tobe (96)	Full text	Cohort	Adult critically ill	15	Filter life
Biancofiore (97)	Full text	Cohort	Adult liver transplant	27	Filter life
					Bleeding
Venkataraman (98)	Full text	Cohort	Adult critically ill	115	Delivered dose
Fealy (99)	Full text	RCT	Adult critically ill	10	Filter life
Baldwin (100)	Full text	Cohort	Adult critically ill	40	Filter life
Fealy (101)	Full text	Cohort	Adult critically ill	10	Small solute clearance
					Downtime
Chadha (102)	Full text	Cohort	Adult critically ill	5	Filter life
					Small solute clearance
Morimatsu (103)	Full text	Cohort	Adult critically ill	99	Small solute clearance
Kozek-Langenecker (104)	Full text	RCT	Perioperative adult critically ill	49	Filter life
					Bleeding
Gabutti (105)	Full text	Cohort	Adult critically ill	12	Filter life
					Fluid management
					Bleeding
Chadha (106)	Full text	Cohort	Pediatric critically ill	5	Filter life
					Small solute clearance
Hoffman (107)	Full text	Cohort	Adult critically ill	24	Filter life
					Small solute clearance
					Delivered dose
Holt (108)	Full text	Cohort	Adult critically ill	14	Filter life

Table 1 continued

Trial[a]	Source	Study type	Patient population	Patients	Quality indicator
Baldwin (109)	Full text	RCT	Adult critically ill	33	Filter life
Vargas Hein (110)	Full text	RCT	Adult critically ill	17	Filter life
					Small solute clearance
					Bleeding
Tolwani (111)	Full text	Cohort	Adult critically ill	29	Filter life
					Bleeding
Gilbert (112)	Full text	Cohort	Adult critically ill	15	Small solute clearance
Kutsogiannis (113)	Full text	Cohort	Adult critically ill	9	Filter life
					Small solute clearance
					Bleeding
Baldwin (114)	Full text	Cohort	Adult critically ill	6	Filter life
Bellomo (115)	Full text	Cohort	Adult critically ill	47	Small solute clearance
Brunet (116)	Full text	Cohort	Adult critically ill	10	Small solute clearance
Reeves (117)	Full text	RCT	Adult critically ill	57	Filter life
					Bleeding
					Thrombocytopenia
Brockelhurst (118)	Full text	RTC	Adult critically ill	16	Filter life
					Small solute clearance
Holt (119)	Full text	Cohort	Adult critically ill	5	Filter life
					Blood flow
					Small solute clearance
Leslie (120)	Full text	RCT	Adult critically ill	26	Filter life
Bellomo (121)	Full text	Cohort	Adult critically ill	234	Small solute clearance
Bellomo (122)	Full text	Cohort	Adult critically ill	6	Small solute clearance
Bellomo (123)	Full text	Cohort	Adult critically ill	100	Filter life
					Small solute clearance
Freebairn (124)	Full text	Cohort	Adult critically ill	10	Small solute clearance
Alamartine (125)	Full text	RCT	Adult critically ill	6	Small solute clearance
Frankenfield (126)	Full text	Cohort	Adult trauma and septic	15	Small solute clearance
Bellomo (127)	Full text	Cohort	Adult critically ill	115	Small solute clearance
Bellomo (128)	Full text	Cohort	Adult critically ill	60	Small solute clearance
Bellomo (129)	Full text	Cohort	Adult critically ill	60	Filter life
					Small solute clearance
Bellomo (130)	Full text	RCT	Adult critically ill	64	Filter life
					Bleeding
Bellomo (131)	Full text	Cohort	Adult critically ill	12	Filter life
					Small solute clearance
Clark (132)	Full text	Cohort	Adult critically ill	11	Small solute clearance
Bellomo (133)	Full text	Cohort	Adult critically ill	50	Small solute clearance

A summary of baseline characteristics of included trials is included

RCT randomized controlled trial, *VTE* venous thromboembolic, *SCT* specialized care team, *CRBSIs* catheter-related bloodstream infections

[a] Bibliographic details of reference numbers (give in parentheses) are included in Supplementary material 5

monitored, and delivered. Fewer QIs focused on structure, specifically related to the human, material, and organizational factors involved in supporting a CRRT program, and outcomes relating to CRRT, including the health states of patients during and after treatment.

Second, the overall quality of identified studies describing QIs broadly ranged from poor to high quality. This was due to variability in study design, risk of bias and confounding, and limited capacity for variable adjustment in analyses. Importantly, most studies were not

Table 2 Categorization and relevance of identified QIs

Categorization of QIs as per the Donabedian framework	Relevance of QIs							
	Importance ($n = 144$)					Scientifically acceptable ($n = 32$)	Usability and feasibility ($n = 17$)	
	CRRT prescription ($n = 36$)	CRRT delivery ($n = 33$)	CRRT monitoring ($n = 11$)	Patient outcomes ($n = 40$)	Health economics ($n = 24$)		Useable and/or feasible ($n = 15$)	Ability to integrate into an EMR ($n = 2$)
Structure ($n = 104$)								
Filter life ($n = 98$)	9	11	10	10	21	16	10	–
Blood flow ($n = 2$)	–	–	–	–	–	1	1	–
Filter efficacy ($n = 2$)	–	–	–	–	–	–	–	–
SCT training ($n = 2$)	–	–	–	–	–	–	–	–
Process ($n = 95$)								
Small solute clearance ($n = 46$)	16	12	1	19	–	11	–	2
Delivered dose ($n = 19$)	6	5	–	1	1	1	1	–
Downtime ($n = 14$)	–	–	–	–	1	–	2	–
Interruptions ($n = 5$)	5	5	–	–	–	–	–	–
Fluid management ($n = 3$)	–	–	–	–	–	–	–	–
Catheter colonization ($n = 3$)	–	–	–	–	–	1	–	–
Catheter malfunction (n = 2)	–	–	–	–	–	–	–	–
Effluent volume ($n = 2$)	–	–	–	–	–	1	–	–
Adherence to protocol (1)	–	–	–	–	–	–	–	–
Outcome ($n = 39$)								
Bleeding ($n = 30$)	–	–	–	7	1	–	1	–
VTE events ($n = 4$)	–	–	–	1	–	–	–	–
CRBSIs ($n = 3$)	–	–	–	–	–	1	–	–
Thrombocytopenia (1)	–	–	–	1	–	–	–	–
Complications (1)	–	–	–	1	–	–	–	–

In the first column, the types of identified QIs are listed with the number of instances in parenthesis. In the subsequent columns the breakdown of the characteristics of the identified QIs are given as per the four criteria proposed by the US Strategic Framework Board for a National Quality Measurement and Reporting System. Importantly, not all QIs had these characteristics described in the identified studies. A full list of individual components of the identified QIs are included in Supplementary material 4

VTE venous thromboembolic, *CRBSIs* catheter-related bloodstream infections, *SCT* specialized care team

Table 3 Examples of heterogeneity in QI definitions utilized across studies

Quality indicator	Definitions			
Filter life	Filter failed in more or less than 24 h	Spontaneous clotting or TMP >200 mmHg	Spontaneous clotting or TMP >250 mmHg	Presence of clot in the filter or in the air-trap or elsewhere in the circuit
Small solute clearance	% delta creatinine or urea/24 h	Comparison between 0 and 4 h urea and creatinine clearance	Comparison between 0 and 24 h urea and creatinine levels	$K = E/P \times QE$ where E is urea/creatinine concentration in effluent, P is urea/creatinine concentration in serum, QE is effluent flow rate
Delivered dose	Kt/V (urea)	Net ultrafiltration rate	Calculated from hourly effluent flow rate and duration of CRRT/day	Calculated using total effluent (the sum of the dialysate and ultrafiltrate) with correction for percentage predilution, and expressed as ml/kg/h
Downtime	The amount of time CRRT was not running per 24 h period	Time off pump in first 72 h	Period of time when CRRT was not applied from beginning to end of prescription	The period of time when CRRT was not applied between two consecutive morning biochemistry measurements
Bleeding	New onset bleeding requiring blood transfusion	Pulmonary hemorrhage	New onset bleeding requiring > 2 units PRBCs	Observation of gross bleeding plus one of: 1 drop in SBP or DBP by 20 mmHg within 24 h of bleeding, transfusion of 2 units PRBCs, inappropriate increase in Hb, decrease in hematocrit % by 2 %. Occult bleeding as absence of gross bleeding and decrease of hematocrit by 2 % or failure of appropriate increase in Hb

This table shows examples of varying definitions across the retrieved studies of most common 'same' quality indicators. Definitions are listed from left to right as simplest to most complex. Only examples of the most common variations of definitions are given

TMP transmembrane pressure, *PRBCs* packed red blood cells, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Hb* hemoglobin

specifically designed nor focused on the derivation, validation, or evaluation of CRRT QIs.

Third, while clearly important as they relate to potential QIs, most authors did not comment on the vital characteristics based on the four criteria proposed by the National Quality Measurement and Reporting System Criteria. When they did, however, the importance of QIs as they related to patient-related outcomes was most commonly identified, followed by the importance for CRRT prescription and delivery, and finally by a discussion of the scientific basis of each QI. The usability, feasibility, and operational parameters of how QIs may be integrated at the bedside, into an EMR and/or translated to providers were often not addressed.

Fourth, we were able to identify several QIs which consistently demonstrated high relevance as per the National Quality Measurement Reporting Criteria. These included filter life, small solute clearance, and bleeding events. These QIs could readily be implemented for audit, performance, and benchmarking purposes by CRRT programs. However, when attempting to standardize these parameters as QIs, one challenge is that there are multiple definitions of how to assess the need to change a filter or what is a significant and recordable bleeding event exist. We contend that these will need refinement, consensus, and validation. Furthermore, what specific solutes warrant measurement (and when) and what would constitute a meaningful change require further rigorous evaluation and standardization.

Context with respect to prior literature

Since the publication of the two Institute of Medicine reports, "To Err is Human: Building a Safer Health System," and "Crossing the Quality Chasm: A New Heath System for the 21st Century," there has been a greater emphasis on delivery of high quality and safe patient care [29, 30]. There have been numerous initiatives to improve health and healthcare worldwide, including the Institute for Healthcare Improvement in the USA, the Canadian Patient Safety Institute in Canada, and the European Commission on Public Health in Europe [31–33]. Other national initiatives have, in particular, addressed kidney-specific issues. The National Confidential Enquiry into Patient Outcomes and Death report in the UK revealed that for patients with evidence of AKI [34], only 69 % had received "good" care, highlighting that care in nearly a third of instances did not to meet minimum care standards. There have also been initiatives from kidney-specific groups, such as the National Kidney Foundation, which is dedicated to the awareness, prevention, and treatment of kidney disease [35]. However, within any of these above initiatives, there have not been specific programs to address the quality of CRRT care. While it is true that the first ADQI conference sought to make evidence-based practice recommendations for CRRT care, the purpose of ADQI was not intended to generate new knowledge and establish QIs [36]. Accordingly, there currently exist no high-quality, rigorously validated, and evidence-informed QIs focused on the prescription, delivery, and monitoring of the quality of CRRT care across themes related to structure (e.g., educational programs), process (e.g., treatment interruptions), or outcome (e.g., adverse events).

Prescribers and policy-makers for chronic maintenance dialysis programs have recognized this knowledge gap. A recent international panel of experts has selected standard QIs for chronic RRT. These also fall under the Donabedian domains of structure (e.g., access to medical services), process (e.g., Kt/V, serum albumin, hemoglobin, ferritin, phosphorus, calcium, and parathyroid hormone), and outcomes (e.g., quality of life) [37]. The National Quality Forum (NQF) has also recently endorsed 15 QIs focused on kidney care and an additional four QIs with reserve status (i.e., important QIs that have passed NQF criteria that are already operating at high levels of performance but might deteriorate if not being monitored) [38]. However, none of these QIs relate to CRRT care in critical care settings.

Our study begins to address this knowledge gap by having identified 18 potential unique QIs through a rigorous review of existing literature. These QIs were distributed across important themes of CRRT care, ranging from QIs related to the technological aspects of CRRT machinery (e.g., CRRT circuits), to CRRT prescription and delivery (e.g., blood clearance, dose-delivery, and treatment interruptions), to training of CRRT providers (e.g., educational programs), and finally to outcomes (e.g., CRRT attributed complications). The identification of these QIs provides a basis for future work to prioritize, validate, and evaluate these QIs into a concise inventory of quality measures as a minimum standard for existing and new CRRT programs.

Limitations/strengths

While we believe that our review identifies and synthesizes an array of QIs in CRRT across many different themes and domains of quality measures, some of which can and should be implemented into routine CRRT care, there are notable limitations that warrant consideration. There was wide variability in study design and quality. As such, it was not feasible to perform a pooled analysis and only descriptive analysis was possible. In addition, there existed significant heterogeneity amongst the naming and defining of the "same" QIs. We attempted, when possible, to streamline QIs into a single operational indicator, but at this stage did not attempt to derive definitions

of QIs. Future study should aim to refine and standardize the operational definitions for candidate QIs through rigorous evaluation and consensus. Furthermore, the characteristics of the QIs were often not addressed in the studies. Furthermore, while identifying QIs across a broad range of themes in CRRT care, certain "obvious" QIs were not identified. Examples would include use of CRRT catheter insertion/maintenance bundles, use of protocols for the prescription and monitoring of CRRT, and program and provider-specific training and certifications. Finally, very few studies focused on primarily evaluating the identified QIs. Accordingly, study results could not be interpreted as they related to the QIs. However, the evaluation/validation of QIs was not the primary purpose of our study; rather, we sought to identify QIs in the existing literature. Future study should focus on the identification of additional QIs and evaluate how they relate to the quality of CRRT care and how they may be routinely integrated into CRRT programs.

Implications for healthcare providers, policy, and future research

CRRT care should be monitored, reported, and benchmarked. Our systematic review identifies a complement of potential QIs for CRRT care that could be adopted by CRRT programs, but also importantly highlights existing knowledge-to-care gaps for how CRRT care is routinely evaluated and monitored. We contend that selected QIs identified by our review could be readily integrated both clinically within ICUs which conduct CRRT to improve how CRRT care is measured and delivered, and as tools for continuous quality improvement initiatives and research. Future steps require validation and consensus on the optimal definitions for each QI, identification of additional QIs not captured by our search, and further rigorous evaluation to prioritize those showing the strongest association with important care processes and outcomes for targeted translation and implementation into practice. This will require interprofessional consensus across key CRRT stakeholders and users. Ideally, valid and evidence-informed QIs should be available to integrate into the next iteration of guidelines to inform minimum standards for CRRT care.

Conclusions

We identified 18 potential QIs across six domains of CRRT care. However, the definitions for these QI were heterogeneous and often poorly characterized. Future work should focus on the prospective evaluation of selected QIs to develop a concise inventory of QIs to measure, improve, and benchmark CRRT care for critically ill patients.

Electronic supplementary material
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Abbreviations
CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; RRT: Renal replacement therapy; QI: Quality indicator.

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Compliance with ethical standards

Conflicts of interest
SM.B. and R.T.N.G. have consulted and received honoraria from Baxter Inc. O.G.R. is supported by an unrestricted educational grant from Baxter Inc. Baxter Inc. has had no role in the study conception, protocol development, article selection, analysis, or preparation of this manuscript.

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