Studies in Renal Physiology in Elective Major Surgery

Jevon Puckett

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery, The University of Auckland, 2018.

Abstract

INTRODUCTION: Acute kidney injury is a common cause of in-hospital morbidity and mortality. However, little is known concerning the non-cardiothoracic, non-vascular, non-urological and non-transplant patient undergoing elective surgery, and their risk of perioperative acute kidney injury.

METHODS: A systematic literature review was conducted to identify the incidence of and pertinent modifiable risk factors for the development of perioperative acute kidney injury in this population. A multi-centre case study was undertaken to ascertain the consequences of severe acute kidney injury as defined by the clinical outcome of renal replacement therapy. A retrospective cohort study was performed to ascertain the incidence of and clarify if anecdotal perioperative urine output was a risk factor for the development of acute kidney injury along with the quantity of intravenous fluid used to treat it. These studies will aid the design and implementation of a randomised non-inferiority trial testing the hypothesis that a lower urine output target is as safe as current practice and thus reducing the risk of perioperative fluid excess and its clinical consequences.

RESULTS: Acute kidney injury in this population is common at 5.07%. Increasing body mass index and use of perioperative angiotensin converting enzyme inhibitors are modifiable factors that potentially convey an increased risk for its development. Whilst rare, acute kidney injury in its severest form (requiring renal replacement therapy) has a mortality of 26% and amongst survivors, results in a significant reduction in long-term renal function. Whilst acute kidney injury appears to be uncommon, oliguria, as currently defined as ≥0.5ml/kg/h, is common in the general surgical population (84%), but does not appear to be correlated to a change in renal function and results in increased intravenous fluid administration. A lower perioperative urine output target of ≥0.2ml/kg/h is non-inferior to the traditional target of ≥0.5ml/kg/h using uNGAL as a surrogate biomarker of acute kidney injury, and reduces the risk of clinically significant administration of excess intravenous fluid.

CONCLUSION: Acute kidney injury is common, and whilst rare, its sequelae are clinically and financially significant. These studies have demonstrated that preoperative optimisation of patient factors can reduce these sequelae. Furthermore, they have shown that much of the intravenous fluid prescribed in the perioperative period is in response to perceived clinically significant low urine outputs. Employing a lower urine output target of ≥0.2ml/kg/h results in fewer patients receiving overhydration and its associated increase in mortality and morbidity without risking renal damage.

Dedication

To Emma—thank you for persevering with my endeavours throughout this and many other difficult times in our lives. Without your tenacious support this would not have been possible. No words are eloquent enough to describe my gratitude for your resolve when I was at my lowest; I am eternally grateful.

Acknowledgements

I wish to thank both Associate Professor **Mattias Soop** and Professor **Ian Bissett** for their counsel, wisdom and unequivocal support. The work in this thesis could not have been accomplished without their tireless efforts and I am forever indebted to them for not giving up on me. You are both a continued inspiration to me for your enthusiasm, dedication and patience—something I very much aspire to.

To the patients who participated in our trial, quite literally, the sentinel research that we have completed could not have been accomplished without their selfless acts.

To my parents, **John** and **Julie**, thank you for your love and support through this as with all things. I hope that you can be proud of the work that I have been able to achieve with the support of so many people.

Whilst I had the backing of the entire North Shore Hospital, from the laboratory to the wards, I would like to specifically mention **Anna Brown** (Clinical Nurse Specialist) and **Mark Wade** (Research Assistant). I am incredibly thankful for your time and effort with the trial. Without want for acknowledgement you went above and beyond to help deliver these important findings.

I am also grateful to my friends, Dr **Ryash Vather** and Dr **Lisa Brown,** who kept me on the straight and narrow and whose academic prowess with their own doctoral theses was inspirational.

I am fortunate that I was able to undertake this doctoral research in the Department of Surgery at the University of Auckland. Specifically, I know it has been challenging along my particular road and specifically without the help of **Scott Aitkin** (Research Network Manager), **Lois Blackwell** (PA) and **Parag Bhatnagar** (Database Manager), I suspect that there would have been many junctures when I would not have been able to continue my research.

And finally, I would like to thank the Health Research Council of New Zealand, The Awhina Health Campus, The Maurice and Phyllis Paykel Trust, The Department of Surgery, The Mercy Ascot Trust and the Sir John Logan Campbell Trust, who through their financial support made it possible to undertake this research to the standard that it deserves.

List of Publications

Puckett J, Pickering J, Palmer S, McCall J, Kluger M, De Zoysa J, Endre Z, Soop M. Low versus standard urine output targets in patients undergoing major elective abdominal surgery; A randomized noninferiority trial. Ann Surg. 2017: 265(5):874-881

List of Presentations

Puckett J. *High versus low urine output targets in surgical patients: A randomised controlled trial*. American Society of Colorectal Surgeons (ASCRS); Boston, USA; 02/06/2015

Puckett J. *Perioperative renal function and fluid therapy*. Auckland City Symposium (ASC); Auckland, New Zealand; 14/03/2015

Puckett J. *High versus low urine output targets in surgical patients: A randomised controlled trial*. Tripartite Colorectal Conference; Birmingham, UK; 01/07/2014

Puckett J. *High versus low urine output targets in surgical patients: A randomised controlled trial.* Surgery 2014: Cut With Care; Queenstown, New Zealand; 15/08/2014

Puckett J. *High versus low urine output targets in surgical patients: A randomised controlled trial.* Royal Australasian College of Surgeons Annual Scientific Congress (RACS ASC); Singapore; 04/05/2014

Puckett J. *The surgical stress response.* Enhanced Recovery After Surgery, Multi-Disciplinary Course; Auckland, New Zealand; 07/04/2014

Puckett J. *Perioperative fluid therapy*. Enhanced Recovery After Surgery, Multi-Disciplinary Course; Auckland, New Zealand; 07/04/2014

Puckett J. *High versus low urine output targets in surgical patients: An update.* Annual Baxter New Zealand Nephrology Conference; Auckland, New Zealand; 13/04/2013

Puckett J. *High versus low urine output targets in surgical patients.* Annual Baxter New Zealand Nephrology Conference; Auckland, New Zealand; 09/03/2012

Puckett J. *Peri-operative fluid boluses constitute an important source of fluid loading in elective colorectal surgery.* International Surgical Week (ISW); Yokohama, Japan; 30/08/2011

Puckett J. *Peri-operative fluid boluses for low urine output constitute a significant fluid load in elective colorectal surgery.* Surgical Research Network; Auckland, New Zealand; 09/09/2010

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACE	Angiotensin converting enzyme
ADH	Antidiuretic hormone
ADHB	Auckland District Health Board
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ANOVA	Analysis of variance
ANP	Atrial natriuretic peptide
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
ASA	American Society of Anaesthesiologists
AuSA	Australian Society of Anaesthetists
ASC	Annual Scientific Congress
ATN	Acute tubular necrosis
BMI	Body mass index
BNP	Brain natriuretic peptide
C&CDHB	Capital and Coast District Health Board
CCF	Congestive cardiac failure
CKD	Chronic kidney disease
CMDHB	Counties Manukau District Health Board
COPD	Chronic obstructive pulmonary disease
CVVD	Continuous veno-venous haemodialysis
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
ENT	Ear, nose and throat
ERAS	Enhanced Recovery After Surgery
ESRF	End-stage renal failure

GFR	Glomerular filtration rate
HD	Haemodiafiltration
ICU	Intensive care unit
IHD	Intermittent haemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
MAP	Mean arterial pressure
MDRD	Modification of diet in renal disease
NGAL	Neutrophil gelatinase-associated lipocalin
NHI	National Health Index
NSAIDs	Non-steroidal anti-inflammatory drugs
PAH	Para-aminohippurate
PIRRT	Prolonged intermittent renal replacement therapy
PL148	Plasma-Lyte 148® ™
POD	Postoperative day
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PVD	Peripheral vascular disease
RACS	Royal Australasian College of Surgeons
RCRI	Revised cardiac risk index
RIFLE	Risk, Injury, Failure, Loss, End-Stage Renal Failure
SEM	Standard error of the mean
SIRS	Systemic inflammatory response syndrome
UO	Urine output
WDHB	Waitemata District Health Board

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
The ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains published or unpublished co-authored work. **Please include one copy of this form for each co-authored work**. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements. Co-authored works may be included in a thesis if the candidate has written all or the majority of the text and had their contribution confirmed by all co-authors as not less than 65%.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 3	
Nature of contribution by PhD candidate	Study design and execution, data acquisition, analysis, manuscript write-up
Extent of contribution by PhD candidate (%)	95%

CO-AUTHORS

Name	Nature of Contribution
Ian Bissett	Supervision, manuscript write-up

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

Name	Signature	Date
Ian Bissett		14 September 2017

Last updated: 19 October 2015

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
The ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains published or unpublished co-authored work. **Please include one copy of this form for each co-authored work**. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements. Co-authored works may be included in a thesis if the candidate has written all or the majority of the text and had their contribution confirmed by all co-authors as not less than 65%.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 5	
Nature of contribution by PhD candidate	Study design and execution, data acquisition, analysis, manuscript write-up
Extent of contribution by PhD candidate (%)	95%

CO-AUTHORS

Name	Nature of Contribution
Mattias Soop	Supervision, study design and execution, analysis, manuscript write-up

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

Name	Signature	Date
Mattias Soop		14 September 2017

Last updated: 19 October 2015

THE UNIVERSITY OF AUCKLAND
SCHOOL OF GRADUATE STUDIES

Co-Authorship Form

Graduate Centre
The ClockTower – East Wing
22 Princes Street, Auckland
Phone: +64 9 373 7599 ext 81321
Fax: +64 9 373 7610
Email: postgraduate@auckland.ac.nz
www.postgrad.auckland.ac.nz

This form is to accompany the submission of any PhD that contains published or unpublished co-authored work. **Please include one copy of this form for each co-authored work**. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements. Co-authored works may be included in a thesis if the candidate has written all or the majority of the text and had their contribution confirmed by all co-authors as not less than 65%.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 6	
Nature of contribution by PhD candidate	Study design and execution, data acquisition, analysis, manuscript write-up
Extent of contribution by PhD candidate (%)	90%

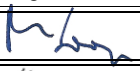
CO-AUTHORS

Name	Nature of Contribution
Mattias Soop	Study design, analysis, manuscript write-up
Ian Bissett	Supervision

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

Name	Signature	Date
Mattias Soop		14 September 2017
Ian Bissett		14 September 2017

Last updated: 19 October 2015

Chapter 1 – Introduction

"Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy."

Philippus Von Honenheim (1493–1541)

Major surgery is a cornerstone of modern medicine. With an estimated 45% of people living in the industrialised world undergoing some form of abdominal surgery within their lifetime, the reduction of perioperative mortality and morbidity is paramount(1).

Over recent decades, perioperative surgical care has undergone considerable advancement. With the advent of new surgical techniques(2), use of prophylactic antibiotics(3), development of intensive care therapies and the optimisation of perioperative care pathways(4), clinical outcomes after surgery have improved(5,6). Examples include the advent of laparoscopic surgery and Enhanced Recovery After Surgery (ERAS) protocols that have been developed with the specific aim of improving patient outcomes as part of a multimodal design. Whilst laparoscopy has been instrumental to the reduction of in-hospital length of stay, ERAS protocols take into consideration multiple facets of patient care to improve all outcomes throughout the entire surgical process. In spite of ERAS protocols, complications following elective surgery remain significant, specifically after abdominal surgery, ranging anywhere from 15–48%(7-9). Because of this and the complex nature and multimodal nature of ERAS protocols, the protocols are in constant need of updating as new developments and research becomes available regarding the attenuation of the surgical stress response.

1.1 Enhanced Recovery After Surgery Protocols

Since their instigation, ERAS protocols have worked to improve the quality of care of patients undergoing major elective surgery. Initially introduced in colorectal surgery with the subsequent adaption to other surgical specialties, the protocols were designed to challenge historical practices and their ad-hoc application to patients by individual clinician's personal preference, replacing them with evidence-based practices which as unimodal interventions have been shown to either attenuate or reduce the impact of the surgical stress response and thus improve clinical outcomes when compared to traditional approaches. For example, postoperative fasting used to be the standard for

patients undergoing bowel resection to reduce the risk of anastomotic leak, which was subsequently disproved in randomised controlled trials and meta-analyses in the early 2000s(10-12).

These evidence-based practices have been separated into three distinct time periods of patient care(13).

1.1.1 Preoperative

1.1.1.1 Education

Preoperative counselling is an often underestimated aspect of ERAS protocols. Designated clinic appointments utilising a specialist nurse have been shown to not only improve outcomes, but to also halve opiate analgesia in the postoperative period, a known instigator of prolonged gastrointestinal ileus(14).

1.1.1.2 Fasting and preoperative carbohydrates

Overnight fasting has been routine surgical practice, with the belief that an empty stomach reduces the risk of aspiration on induction of anaesthetic. A meta-analysis(15) and Cochrane review(16) of recent randomised controlled trials showed no difference in gastric content of patients fasted from midnight, when compared to those consuming a meal six hours and clear oral fluids up to two hours prior to anaesthesia. Such fasting also trends towards a dehydrated state prior to surgery, obviated by patients controlling their own volume status up to two hours prior to surgery.

Preoperative fasting is also associated with postoperative insulin resistance and a reduction in biochemical carbohydrate catabolism(17,18). It should be taken the evening prior to surgery in addition with a further 200ml two hours prior to surgery(19).

1.1.1.3 No bowel preparation

Mechanical bowel preparation was once a prerequisite for all colonic and rectal surgery, as it was thought to reduce faecal contamination of both anastomoses and wounds(20). Furthermore, mechanical bowel preparation significantly alters fluid homeostasis, leading to preoperative dehydration(21,22). The most recent Cochrane review of mechanical bowel preparation in elective colonic surgery, excluding rectal surgery, found no difference in either complications or mortality between patients receiving full mechanical bowel preparation, compared to rectal enemas or neither(19).

1.1.1.4 Medications

There is suggestion that restriction of sedating medications the night prior to surgery may help to maintain normal diurnal hormonal patterns and reduce complications(23).

1.1.2 Intraoperative

1.1.2.1 Epidural – mid-thoracic

Multimodal analgesia continues to be the gold standard for pain relief in the perioperative period. Specifically, the recent addition of a mid-thoracic epidural analgesia for open abdominal surgery has been shown to improve key outcome parameters, including postoperative pain(24), nausea and vomiting(14), as well as overall complications(25). These findings are thought to be due to a reduction in postoperative opiate use as well as chemical splanchnic sympathectomy, which may contribute to nausea and vomiting and propagation of ileus(26). Regarding laparoscopic approaches to colonic surgery, recent evidence suggests that transverse-abdominis plane blocks are equally effective at improving recovery of gut function compared to epidurals(27).

1.1.2.2 Avoidance of fluid and salt overload

Historically, surgical patients have received large volumes of intraoperative crystalloid fluid (0.9% saline). This was based on work by Shires in the 1960s showing a reduction in extracellular volume independent of blood loss but proportional to operative trauma following abdominal surgery(28). It was hypothesised that extracellular fluid was sequestered into additional compartments—"the non-anatomical third space".

More recently, this model has been questioned with the current aim of intraoperative fluid administration being the maintenance of normovolaemia(29) highlighting intravascular volume as being a key component of cardiac output and subsequent oxygen delivery to end-organs. Once normovolaemia has been achieved using physiological parameters ensuring correct end-diastolic volume, the preservation of mean arterial blood pressure is achieved via the use of vasopressors, negating the increased incidence of complications arising from fluid overload (30).

1.1.2.3 Surgical approach

Different surgical approaches to the abdominal cavity have risks and benefits. Contemporary abdominal surgery utilises a vertical midline as opposed to transverse

incision. Whilst postoperative pain is reduced in a transverse incision, the incidence of superficial wound infection and incisional hernia may be higher(31). With the advent of laparoscopic surgery, postoperative pain, infection and incisional hernia rates have further reduced. Laparoscopic approaches to colorectal surgery are advisable when appropriate, as it is also associated with a reduction in hospital length of stay, an increased time to return of gastrointestinal function and superficial wound infections(32).

1.1.2.4 Avoidance of drains

The use of drains, whether nasogastric or intra-abdominal, are to be minimised as they are associated with an increase in morbidity(33,34). A case can be made for short-term use of pelvic drains following low anterior resections, but not for routine colonic surgery above the pelvic brim. Likewise, the routine use of nasogastric tubes should only be used in the setting of a prolonged postoperative ileus resulting in vomiting(35,36).

1.1.2.5 Normothermia

Avoidance of hypothermia (or maintenance of normothermia) is essential in reducing postoperative complications(37). Excessive heat loss from anaesthetic vasodilation and excessive skin exposure to cold operating theatres is to be avoided(38).

1.1.3 Postoperative

1.1.3.1 Avoidance of fluid overload

A recent meta-analysis of randomised controlled trials comparing liberal and restrictive intravenous fluid regimes found that excess perioperative intravenous fluid administration resulted in a 2–3kg weight gain and increased the incidence of complications(39). Equally, the constitution of intravenous fluid given is important. Multiple randomised controlled trials have shown that crystalloids are superior to colloids for the resuscitation of the acutely shocked patient(40-42). However, heterogeneity amongst the type of crystalloids used did not identify which was superior(43-45). Following logistic regression modelling, a recent cohort study from the United States showed a direct correlation between the amount of chloride loading in more than 60,000 acutely shocked patients and mortality, thus favouring balanced crystalloids over 0.9% saline(46). Balanced crystalloids are therefore recommended for intraoperative fluid therapy. For postoperative maintenance requirements, 0.45% saline with 5% dextrose is recommended for those who are unable to tolerate oral fluid. This

contains 40mmol of both sodium and chloride in 1000ml and thus meets normal daily requirements of these electrolytes(47).

Despite acknowledging that the amount and type of intravenous fluid administration in the perioperative period is important, recent studies still highlight difficulties in avoiding such fluid overload within contemporary ERAS protocols(48,49). Specifically, low UO may play a role as a causative factor triggering the administration of intravenous fluid to treat this oliguria.

1.1.3.2 Urinary catheter

Urinary catheters are routinely placed for monitoring of renal function in the perioperative period. However, bedside interpretation of observations of urine output are dependent on a multitude of factors, including use of diuretics and vasoactive medications, as well as whether the fluctuations are a response to a pathophysiological insult resulting in acute kidney injury (AKI), or represent normal physiology. The exact transition from physiology to pathophysiology in specific populations remains unclear and consequently so does the threshold for instigation of treatment(50-53). Furthermore, UO monitoring via catheters is not benign with risks, including urinary tract infection and urethral strictures. Urinary catheters do have their place, specifically in patients who are at high-risk of urinary retention, i.e. patients who suffer from benign prostatic hyperplasia, or those undergoing rectal dissection who may develop postoperative bladder dysfunction.

1.1.3.3 Early postoperative oral nutrition

Despite traditional fears, early oral diet has been shown not to be associated with increased rates of anastomotic leak(11), although the risk of minor complications including vomiting may increase. Early feeding has also been shown to be beneficial with reduced hospital length of stay and complications such as wound infections(12).

1.1.3.4 Multimodal postoperative analgesia

Postoperative analgesia has changed significantly in recent years to incorporate a multimodal approach and reduce strong opiate use, known for their emetogenic effect. This approach incorporates mid-thoracic epidurals such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and tramadol. Whilst NSAIDs have been shown to be superior in effect to other analgesic, their association in the postoperative period with

anastomotic leak has been proposed(54). However, no conclusive data currently exists, and consequently they remain an integral part of the multimodal approach.

1.1.3.5 Prevention of nausea and vomiting

Nausea and vomiting is associated with numerous pre-morbid characteristics including female sex and smoking. However, it is more associated with opiate analgesia and specifically fluid overloading in the postoperative setting which delays early mobility and nutrition(55,56).

1.1.3.6 ERAS and urine output

Current surgical and anaesthetic teaching highlights the need for a perioperative UO of ≥0.5ml/kg/h(57,58) to pre-empt AKI. Despite this teaching, few published studies exist to support this target. In fact, the published literature suggests no association between perioperative UO and the subsequent development of AKI(52,53). However, these studies only provide low grade evidence so they neither support nor refute this target, hence urinary catheters remain to be protocol following major abdominal surgery.

Many components of contemporary ERAS protocols have potential influences on UO that may also compound perioperative UO targets. Avoidance of bowel preparation and overnight fasting avoid significant preoperative hypovolaemia. Conversely, use of epidural analgesia results in lower limb sympathectomy with venous pooling, and thus, relative hypovolaemia in the postoperative setting. This may result in hypotension with subsequent low UO either due to ANP or that a reduction in effective renal plasma below the limits of renal autoregulation, would result in a reduction in glomerular filtration rate and consequently UO. Patients with an epidural therefore often receive significant volumes of compensatory fluid infusion(59).

1.2 ERAS, audit and research

In spite of these interventions there remains room for improvement, with incidence of complications following contemporary colorectal surgery quoted between 35–55%(49,60). ERAS protocols are continually adapting to help reduce perioperative complications and improve patient outcomes, based on auditing contemporary practice(61) and incorporating robust research(13).

One area that current ERAS protocols have identified as requiring further investigation is the association between UO and perioperative renal function. Whilst there is a plethora of literature on perioperative renal function in the cardiothoracic population, very little has been published regarding patients undergoing major abdominal or even non-cardiothoracic population.

However, before we can understand perioperative renal physiology, we must first understand both normal renal physiology and the physiology of surgery itself.

1.3 Physiology

1.3.1 Normal renal physiology

1.3.1.1 Anatomy

The kidneys are extra-peritoneal organs positioned posteriorly and sub-diaphragmatically. They are made up of an outer cortex and an inner medulla. The medulla is encased by the cortex with its most medial aspect, the hilum, housing the insertion of the renal artery, vein and ureter. At the hilum, the medulla can further be divided into pyramids with multiple papillae at their tips. The papillae sit within the calyxes of the ureters, which collect urine. Both cortex and medulla predominantly consist of nephrons, collecting tubules and capillaries, responsible for the production of urine (Figure 1.1).

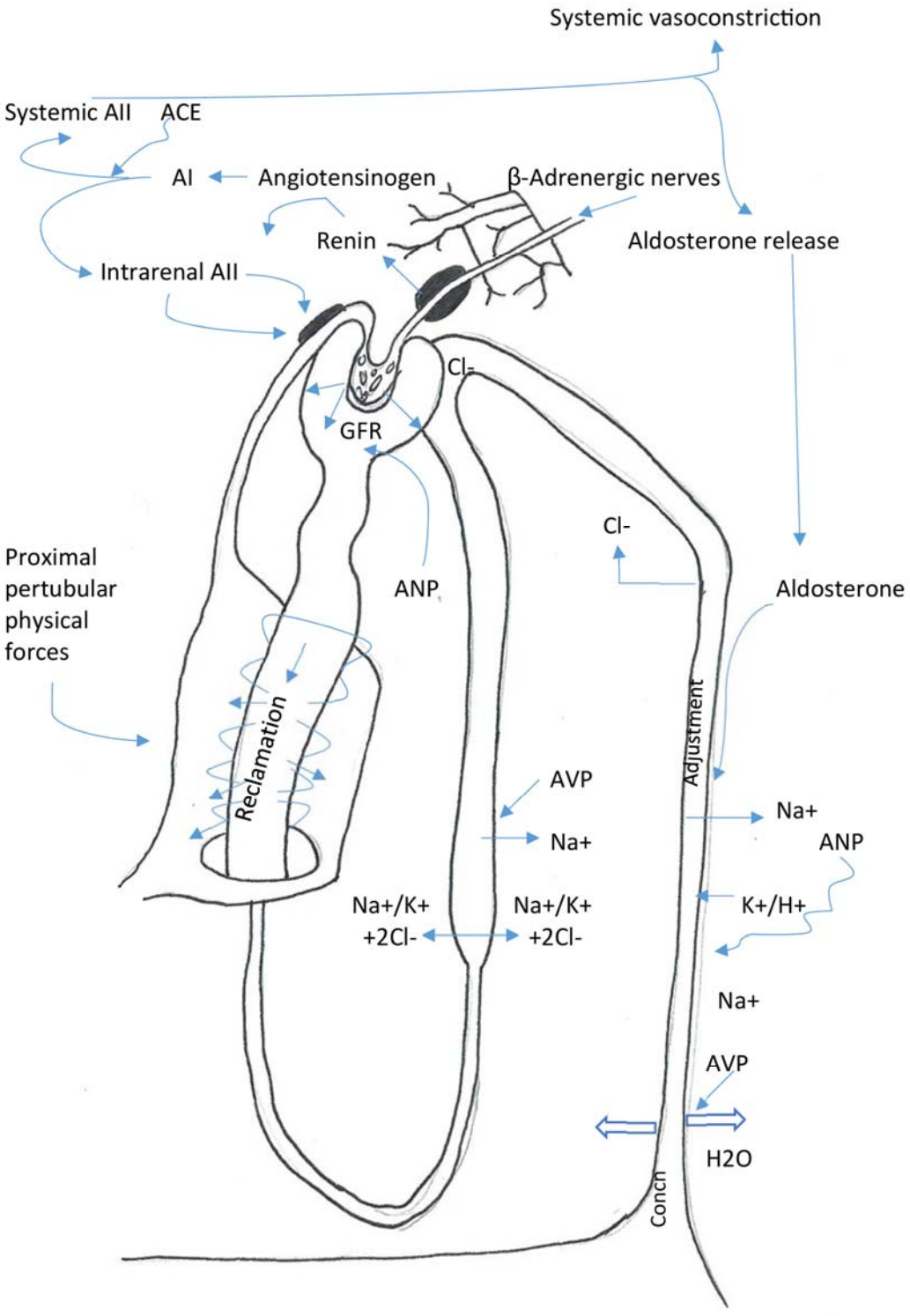


Figure 1.1. Effects on the renal tubule

1.3.1.2 Nephron

There are approximately 1,000,000 nephrons in each human kidney. The nephron comprises Bowman's capsule, proximal convoluted tubule, the loop of Henle (both descending and ascending limbs) and distal convoluted tubule. The separation of the ascending limb and distal convoluted tubule is marked by the macular densa, a set of

specialised cells in contact with both afferent and efferent arterioles at the level of Bowman's capsule. Bowman's capsule, or glomerulus, is designed to filter large volumes of plasma from the afferent arterioles, through the capillary endothelium and glomerular basement membrane, past the capillary podocytes and into Bowman's space, where it emerges into the proximal convoluted tubule. Running in parallel with the tubules are the peritubular capillaries in the cortex and the vasa densa in the medulla, formed from the efferent arterioles of the glomerulus. Their proximity to the renal tubule allows for the concentration of filtrate depending on changing physiological mechanisms throughout the body.

1.3.1.3 Physiology

The nephron is a complicated system that regulates the concentration of water and solutes in the filtrate. In basic terms, these concentrations are under the control of two mechanisms:

1.3.1.4 Neuronal innervation

The neural innervation of the kidneys is predominantly sympathetic, derived from the coeliac plexus. Its role in water and solute handling can be separated into two main mechanisms. The first mechanism is on smooth muscle in the afferent and efferent arterioles of the glomerulus. Contraction and relaxation of opposing smooth muscle in either sets of arterioles alters the blood flow through the glomerulus and thus the volume of plasma filtered. Using this myogenic mechanism, the body is able to regulate renal blood flow and glomerular filtration rate over mean arterial blood pressures between 50 and 200mmHg(62).

The second mechanism is on the cells of the macula densa, releasing vasoactive substance such as renin in response to decreased arterial pressure (baroreceptors), decrease in serum sodium concentration and innervation of the sympathetic nervous system (see below).

1.3.1.5 Hormonal innervation

The kidneys are under the influence of multiple hormones:

Renin is released from the macula densa by multiple mechanisms, but principally following sympathetic innervation. Its role is in the conversion of angiotensinogen (an

alpha-2-globulin produced by the liver) into angiotensin I, that is subsequently converted into *angiotensin II* by angiotensin converting enzyme in the lungs. Angiotensin II is a potent vasoconstrictor via its action on the arterial smooth muscle, as well acting as an anti-natriuretic, via its action on reabsorption of sodium chloride in the tubule.

Antidiuretic hormone (ADH) or arginine vasopressor is a nonapeptide released by the pituitary gland in response to increases in plasma osmolality or by reductions in plasma volume (leading to an increase in plasma osmolality). Whilst being a potent vasoconstrictor, ADH primarily increases isolated water absorption in the distal convoluted tubule.

Aldosterone is a steroid hormone produced by the adrenal cortex, primarily in response to an increase in circulating angiotensin II. Its main function is long-term correction of plasma sodium levels by increasing reabsorption in the collecting tubules. This mechanism is enhanced by a similar action on the collecting tubules by ADH to water.

Natriuretic peptides act in opposition to the renal and adrenal hormones. Despite their names, both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are produced in the heart and are produced in response to baroreceptors in the atria responding to dilatation. They act on renal vasculature by way of relaxing the afferent arterioles to the glomerulus, thus increasing plasma volume filtered, and inhibit sodium reabsorption in the collecting tubules whilst also inhibiting the actions of the renin-angiotensin system.

By way of these processes (hormonal and neuronal), the body is able to regulate water and electrolyte balance as well as blood pressure (autoregulation). These mechanisms are excellent at retaining both water and sodium in situations of relative or absolute reduction of either. However, with the advent of intravenous fluid therapies, other states such as hypernatraemia or hyperchloraemia have become more common. In normal physiology, hypernatraemic states usually occur as a result of relative increase from dehydration and are thus easily corrected. Consequently, the body has not evolved an effective natural response to true hypernatraemia and can only correct this condition over several days(63).

1.3.2 Physiological response to surgery

Surgery has a profound effect on normal physiology with research over the last few decades spurring on the development of certain areas within ERAS protocols. Specifically, research has focused on reducing the surgical stress response by modulation of the immune and metabolic systems.

1.3.2.1 Immune

The surgical stress response of surgical trauma increases demand on various bodily systems(64). The systematic inflammatory response syndrome (SIRS) is a normal response to a range of stressors. However, with the advent of modern health care, SIRS has been well documented as a manifestation of an exaggerated and harmful immune response. This can present clinically as haemodynamic instability, immunosuppression and respiratory instability due to increased capillary permeability to water known as acute respiratory distress syndrome (ARDS)(65). In particular, increased levels of inflammatory mediators such as interleukin 6, have been shown to be linked to surgical morbidity(66,67), which can be blunted by the use of techniques employed by ERAS protocols(68,69). In cancer surgery, there is also an increased risk of tumour recurrence due to blunting of residual disease control(70).

1.3.2.2 Metabolic

The metabolic demands of surgery are equally well documented. Surgery results in increased energy demands(71). Compounding this, there is a decrease in nitrogen balance secondary to protein breakdown from muscles(72). Whilst there is good evidence supporting poorer surgical outcomes in malnourished states(73), there is minimal literature to support this net nitrogen loss and increased morbidity.

1.3.3 Renal pathophysiology

There are multiple mechanisms by which normal physiology can be adversely affected in the acute setting. These mechanisms are collectively termed AKI. Specifically when looking at the surgical population, a significant cause of AKI is acute tubular necrosis (ATN). ATN is a well described pathophysiological process characterised by three phases: initiation, maintenance and recovery.

1.3.3.1 Initiation of acute tubular necrosis

Initiation of ATN occurs as a consequence of the kidney's autoregulatory mechanisms becoming inundated and subsequently overwhelmed. The resulting reduction in glomerular filtration rate (GFR) causes hypoperfusion of the tubular cells, in particular the thick ascending and proximal tubule where it is located within the relative hypoxia of the renal medulla. Ischaemia of the cells leads to a reduction of adenosine triphosphate with a consequent build-up of intracellular free radicals and destruction of the phospholipid membranes. It also interferes with active ion transport across cell membranes, leading to swelling of the cell and further disruption to intracellular mechanisms. If ischaemia persists, cells die via necrosis. Whether damaged or dead, the breakdown products of these cells leak into the tubule lumen where they cause a relative obstruction and back pressure of filtrate through the glomerulus and already damaged cells, further perpetuating ATN.

Furthermore, ischaemia leads to a reduction in production of vasoactive substances, particularly those involved with vasodilation such as prostaglandins and nitric oxide, propagating vasoconstriction and hypoperfusion.

1.3.3.2 Maintenance of acute tubular necrosis

An increase in tubular salt load from cellular dysfunction results in continued afferent arteriole vasoconstriction as controlled by the macula densa. Combined with the above mechanisms, GFR is maintained at a pathophysiologically low level.

1.3.3.3 Recovery of acute tubular necrosis

Recovery from ATN is characterised by the restoration of the epithelial cells and re-establishment of normal intracellular function. Although this diuretic mechanism is not fully understood, it may be a consequence of the resulting intravenous fluid loading prescribed for critically unwell patients who develop AKI.

1.3.4 Perioperative renal physiology

1.3.4.1 Historical

A plethora of research has focused on blunting the surgical stress response via the optimisation of these perioperative systems, as well as the cardiovascular and

gastrointestinal systems. Comparatively, sparse literature exists examining perioperative effects on renal physiology.

The altered metabolism of water and electrolytes following surgery was first noted in 1905(74) by Harold Pringle, reporting his findings that ether anaesthetic resulted in oliguria within the first 30 minutes after induction, hypothesising that ether suppresses renal epithelial activity. His observations also showed that the oliguria persisted the longer the duration of anaesthesia, but could also be blunted, to some degree, by excessive intravenous fluid administration. Further studies followed, most notably by Frederick Coller in 1936(75), showing an obviation of this oliguria and avoidance of perioperative renal failure by the infusion of saline based intravenous fluids. His work and subsequent studies(76), sparked considerable interest in the field of perioperative renal physiology over the next decade, with major advances in its understanding. In 1949, Wilkinson et al showed a reduction in sodium excretion for up to six days following surgical trauma(77). Furthermore, their research revealed that the reduction was secondary to sodium reabsorption, as had been postulated by Coller's group, rather than the traditional view that it represented a depletion in total body sodium. His group also went on to describe renal potassium excretion following gastrectomy(78).

The culmination of this era of study was the landmark paper by Lewis and Le Quesne(79) in 1952, who amalgamated the research to date. Their study of 21 surgical patients proposed a three phase model explaining the findings of previous studies. The first phase (*primary water retention*) showed not only a reduction in UO within the first 24 hours after surgery, but an increase in urine osmolality secondary to chloride. These are the characteristic effects of ADH resulting in water retention. The overlapping second phase (*early sodium retention*), showed a high urine osmolality with a low concentration of sodium that was reversed by postoperative day 1. The third phases (*late sodium retention*), starting on postoperative days 1–2, comprised a prolonged retention of sodium, not attributable to water reabsorption, resulting in further weight gain. It was these studies that underpin our understanding of perioperative renal physiology regarding both salt and water retention.

Following their work, Francis Moore, cemented the idea that fluid balance, by expansion of the extracellular compartment, was primarily under the control of pituitary, cortical and renal hormones, in particular ADH(80,81). His work expanded on this oliguric phase

following induction of anaesthetic, secondary to an adrenergic and corticoid release, and further described a period of "brisk diuresis" at the cessation of this phase (although it would not be until 1964 when Moran junior's group were finally able to prove this phenomenon biochemically after the development of a highly sensitive method for detecting plasma ADH(82)). In summary of his work on perioperative renal physiology, and what could be considered the cornerstone of modern perioperative fluid physiology, Moore described that diminished excretory capacity for water should be borne in mind when prescribing postoperative fluids, as efforts to increase urine volumes by large infusions resulted only in the retention of a high proportion of the administered fluid(83).

Unfortunately in the 1950s, these works were abruptly overshadowed by America's foray into the Korean War, where large volumes of fluid resuscitation and the maintenance of high urine outputs were established as a clinical necessity for their battlefield trauma patients(84). His observation that the battlefield trauma patients with an adequate UO had a higher chance of survival, led him to suggest an arbitrary, but extremely influential recommendation that "urine output should be maintained at 30–40cc per hour".

This recommendation was soon adapted by his civilian colleagues in the emergency setting, but as the widely recommended 0.5ml/kg/h target. From here, it filtered through to the emergency surgical patient and further to the elective surgical patient. These findings were reinforced by similar clinical findings from the Vietnam War, in spite of published work identifying cases of pulmonary oedema secondary to administration of such volumes of intravenous fluids(85). These clinical data superseded the previous half century of research, imposing this new principle of liberal fluid in surgery to not only the trauma, but subsequently, the general surgical populations(86).

During this period, little research was conducted into the phenomenon of perioperative water and salt retention despite the physiology being at odds with clinical practice. Compounding this, surgeons were also becoming more aware of the danger of perioperative renal failure. In one of the first cohort studies to identify this concept, Sawyer studied 100 consecutive patients who had developed perioperative acute renal failure, wisely concluding that patients who undergo major surgery need particular renal evaluation(87). Unfortunately, he also concluded that: "early identification and vigorous treatment of pre-renal oliguria significantly reduces the incidence of renal parenchymal disorders". His observations were qualified by identifying that the patients consisted of a

heterogeneous group who developed severe postoperative complications including myocardial infarction and multi-organ dysfunction.

By the 1970s, this work had been taken further by Fidgor who attempted to differentiate "functional" versus "organic" renal failure in the same population(88). His conclusion was that the differentiation was irrelevant, as the treatment remained the same: "we invariably start with infusions in association with Mannitol therapy, with the aim of producing abundant diuresis without delay".

This literature dominated perioperative fluid therapy during these decades and perpetuated the need to maintain higher urine outputs in the surgical population with intravenous fluid therapy, blunting the postoperative decrease in diuresis to prophylactically treat AKI(89).

1.3.4.2 Contemporary

Specific understanding of contemporary perioperative renal physiology remains elusive. Firstly, little is known on how the kidneys respond to anaesthesia and the surgical insult, and specifically whether UO is truly a predictor of renal injury. Secondly, what are the important causes of AKI and do they include hypoperfusion and low UO? Thirdly, how common is AKI in elective surgery? Fourthly, what are the long-term outcomes of severe AKI? Certain treatment strategies known to influence the development of renal injury are noted below.

Preoperatively, suspected predispositions to renal injury should be addressed including the management of untreated hypertension, tight glycaemic control in diabetic patients and the temporary suspension of nephrotoxic medications where possible(90).

Intraoperatively, the maintenance of cardiac output in order to achieve adequate renal perfusion has been shown to reduce perioperative AKI(91). Periods of arterial hypotension reduce the net pressure driving the ultrafiltration process through the glomerulus(92). Whilst a reduction in ultrafiltration is rarely the sole cause of perioperative AKI, it is proposed as a contributing factor. Resulting tubular necrosis disrupts intracellular tight junctions leading to reduced membrane polarity, which alters the functionality of ion channels resulting in leakage of intracellular contents into the tubular lumen. This increased tubular volume leads to increased post-glomerular tubular pressure and consequently reduced GFR. This in turn activates feedback loops causing

vasoconstriction of the afferent glomerular arterioles, perpetuating a reduction in ultrafiltration. Unsurprisingly, intravenous volume therapy does not correct this negative feedback loop(92,93). However, there is no consensus on how strict one must be with the avoidance of hypotension. Some studies suggest that even brief episodes of mean arterial pressure (MAP) of <65mmHg are associated with the occurrence of AKI(94-96). Studies on the use of ionotropic medications and fluid volume preservation using individualised goal direction are contradictory in their results(91,97-99). Furthermore, the type of fluid used intraoperatively to support cardiac output remains controversial. Whilst some colloids, specifically synthetic starches have been associated with renal injury(100), no trial has yet to deliver a consensus as to whether one crystalloid is superior to another(101-103), although results from contemporary trials are awaited (PLUS trial)(104). It is known that 0.9% saline delivers hyperchloremic acidosis and reduced renal perfusion in healthy volunteers(105,106).

With the advent of intra-abdominal laparoscopic techniques, clinicians have postulated a link between intra-abdominal hypertension and compression of the retroperitoneum resulting in reduced effective renal plasma flow(107).

Anaesthetic medications have a profound effect on peripheral vascular resistance and cardiac output, and thus effective renal plasma flow. Propofol for example, leads to profound vasodilatation with a reduction in cardiac pre-load and hence hypotension, and may be nephrotoxic in itself.

1.4 Perioperative fluid management

1.4.1 Historical

With the knowledge obtained from his predecessors, Bernard Zimmerman (Professor and Chairman of the Department of Surgery of the West Virginia University School of Medicine 1960–1973), proposed a perioperative fluid regime that considered the impact of surgery on normal physiology(108). On the basis of normal fluid intake and insensible losses, he concluded that volumes of a salt-free solution, based on 1400–1500ml/square meter of body surface area would be sufficient to meet the maintenance needs of a patient denied the normal route of alimentation by disease or surgery. In addition to this, intravenous fluid would be required to replace the isotonic movement of fluids within the body, i.e. peripheral oedema. Specifically, a balanced crystalloid such as Ringer's lactate should be

used as it has a pH closer to that of plasma and a reduced chloride load compared to isotonic saline.

1.4.2 Contemporary

Since his published work, the principles of perioperative intravenous fluid management have not changed. However, surgical principles such as ERAS protocols have, for example, reduced the period of time for which patients are unable to use the normal alimentary tract for hydration, thus reducing the overall fluid load received by patients. Dr Gary Minto recently published in the British Journal of Anaesthesia summarising the perils of both fluid over and underload for the surgical patient(109).

Despite this, recent studies assessing fluid status in contemporary care have highlighted that patients are still receiving large volumes and inconsistent of fluid in the postoperative period(48,49,110). From the available data, it appears as though a large portion of this extra fluid is being prescribed to treat low urine outputs in the postoperative surgical patient. This is further backed up in contemporary surgical and anaesthetic medical text books that recommend the use of 0.5ml/kg/h(57,58) in order to prophylactically treat AKI.

1.5 Acute kidney injury

1.5.1 Definition and incidence of acute kidney injury

Acute kidney injury is a serious complication of any pathology effecting between 1–5% of all hospital patients(111-114). Within the intensive care population who develop the more severe end of the spectrum of AKI, non-cardiothoracic surgical patients constitute approximately one-third of total incidences(113). Given this proportion, our surgical population is relatively understudied as a group.

The term acute kidney injury has, in recent years, replaced acute renal failure in current medical terminology. Whilst the terminology may have changed, the definition relating to an acute fall in GFR has not. However, there are a multitude of different physiological and pathophysiological changes that can result in a reduced GFR.

1.5.2 Different aetiology and pathophysiology of acute kidney injury

To better understand the pathophysiology of kidney injury, many textbooks simplify aetiology into three basic categories(58,115).

1.5.2.1 Pre-renal

This encompasses all pathology leading to a reduction in effective renal plasma flow to the kidney below the kidney's ability to auto-regulate and consequently a reduction in GFR. These include hypovolaemic states secondary to haemorrhage or dehydration. Reduced blood flow can also result from reduced cardiac output states secondary to, but not inclusive of, congestive heart failure and liver cirrhosis resulting in a hyperdynamic circulation, increased pre-load which over time causes right sided cardiomyopathy.

1.5.2.2 Intrinsic

This group involves damage to the kidney itself, whether glomeruli, renal tubules or interstitium. Examples include glomerular nephritis, ATN as a consequence of a rapid deterioration in GFR, and nephrotoxicity secondary to contrast or medication induced nephritis.

1.5.2.3 Post-renal

Post-renal AKI is caused by blockage to the outflow of urine from the pyramids. Common causes include renal tract calculi, benign prostatic hyperplasia or extrinsic compression of the ureters (e.g. colonic malignancy). Increased pressure in the ureter propagates back through the proximal tubule and to the glomerular capsule, reducing GFR. A persistent decrease in GFR results in a thromboxane A and angiotensin II mediated drop in renal plasma flow with resultant ischaemia to the renal tubules. In complete obstruction, this can occur over days.

1.5.3 Problems with current acute kidney injury definitions

Whilst the aetiologies of AKI can be easily classified using this simplistic approach, the reality of defining exact causes of kidney injury are much more complex. Furthermore, our surrogate markers of renal function and health, for example reduced GFR, are also somewhat problematic. Precise measurement of GFR depends on the principle that a substance is freely excreted by the glomeruli and not secreted or absorbed(116):

$$GFR = \frac{\text{Urine Concentration} \times \text{Urine Flow}}{\text{Plasma Concentration}}$$

Figure 1.2. Glomerular filtration rate equation

Following detailed experiments investigating different substances that fulfilled these parameters, inulin was found to be the most reliable(117).

Inulin is a polysaccharide produced mainly by the rhizomes of plants. Its unique molecular structure makes it useful in the measurement of GFR as it is freely filtered by the glomerular apparatus and is not secreted nor reabsorbed by the renal tubules. Since the 1930s, varying methodologies have been trialled with the accepted gold standard measurement of GFR being described by Cole et al(118). Unfortunately, whilst the methodology is sound, the implications to clinical practice are somewhat more cumbersome, requiring the infusion of inulin intravenously to obtain steady state over three hours. This is not only a timely exercise but a costly one. Subsequently, various approximations were put forward to circumvent these problems, allowing an estimate of GFR in attempt to make the figures quicker, cheaper and thus more clinically practical.

1.5.3.1 Estimated glomerular filtration rates

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Figure 1.3. Cockcroft-Gault equation

The first formula to be published was by Cockcroft and Gault in 1976. It was based on the assumption that an estimate of creatinine clearance could be used as a surrogate for estimated glomerular filtration. However, whilst creatinine is freely filtered by the glomerular apparatus, it is also reabsorbed by the distal tubule in small amounts.

$$\text{eGFR} = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210\ if\ Black] \times [0.742\ if\ Female]$$

Figure 1.4. Modification of diet in renal disease equation

The MDRD (Modification of diet in renal disease) was the next formula to be submitted in 1999 and is now the most widely used calculator for GFR(119). The most widely version incorporates four variables: age, gender, ethnicity and serum creatinine. Other variations are available which in addition utilise serum urea and albumin. One notable drawback to the MDRD is that it was not developed or validated for normal renal function, that is to say eGFR > 60ml/min/1.73^2(120).

$$\text{eGFR} = 141 \times \min(\text{SCr/k},1)^{a} \times \max(\text{SCr/k},1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [1.159\ if\ Black]$$

Figure 1.5. Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)

Most recently (2009), the CKD-EPI formula was developed to improve upon the MDRD, in particular in the "normal" renal function group whose GFR is greater than 60ml/min(121). Whilst it outperforms the MDRD overall, it remains lacking in areas including calculation for elderly and Afro-Caribbean females.

All of the above formulae are however flawed, as they work on the assumption that creatinine is freely filtered, not absorbed or secreted. Creatinine is the breakdown product of phosphocreatine (found in skeletal muscle). Whilst creatinine is an excellent substitute for inulin in that it is produced by the body and is already at steady within the vasculature, it is however secreted in small amounts by the peritubular capillaries. This can change between 10–40% depending of physiological conditions that can mask significant changes in GFR leading to an overestimate of between 10–15%(119). Furthermore, creatinine based formulae do not take into account muscle mass, the main store of creatinine. Therefore, patients of a similar age but with differences in muscle mass as a result of cachexia for example, will have substantially variable estimates in their GFR.

In addition, the above estimates are only valid in steady state renal function. They are not valid in the event of rapidly deteriorating renal function such as in AKI and are only surrogates for renal function and not necessarily renal injury.

1.5.3.2 Acute kidney injury definitions

Since the turn of the millennium, physicians have become increasingly aware of the need for a standardised definition of AKI to reflect rapid changes in GFR. However, as previously discussed, estimates using these formulae are unreliable for this population. In recent years, a number of grading systems have been put forward in an attempt to better define and identify patients at risk of the sequelae of AKI (Tables 1.1, 1.2, Figure 1.6).

Stage	Serum creatinine criteria	Urine output criteria
1	Increase ≥26.4μmol/L (0.3mg/dl) OR to 150–200% of baseline	<0.5ml/kg/h for >6 hours
2	Increase of 200–300% of baseline	<0.5ml/kg/h for >12 hours
3	Increase of >300% of baseline OR ≥354μmol/L (4.0mg/dl) WITH an acute rise of ≥44μmol/L (0.5mg/dl)	<0.3ml/kg/h for 24 hours OR Anuria for 12 hours

Only one criterion (creatinine or UO) needs to be fulfilled to qualify for any stage. *Patients who receive renal replacement therapy (RRT) are considered to have met stage 3, irrespective of stage that they are in at the time of commencement of RRT.

Table 1.1. Acute Kidney Injury Network Criteria (AKIN)

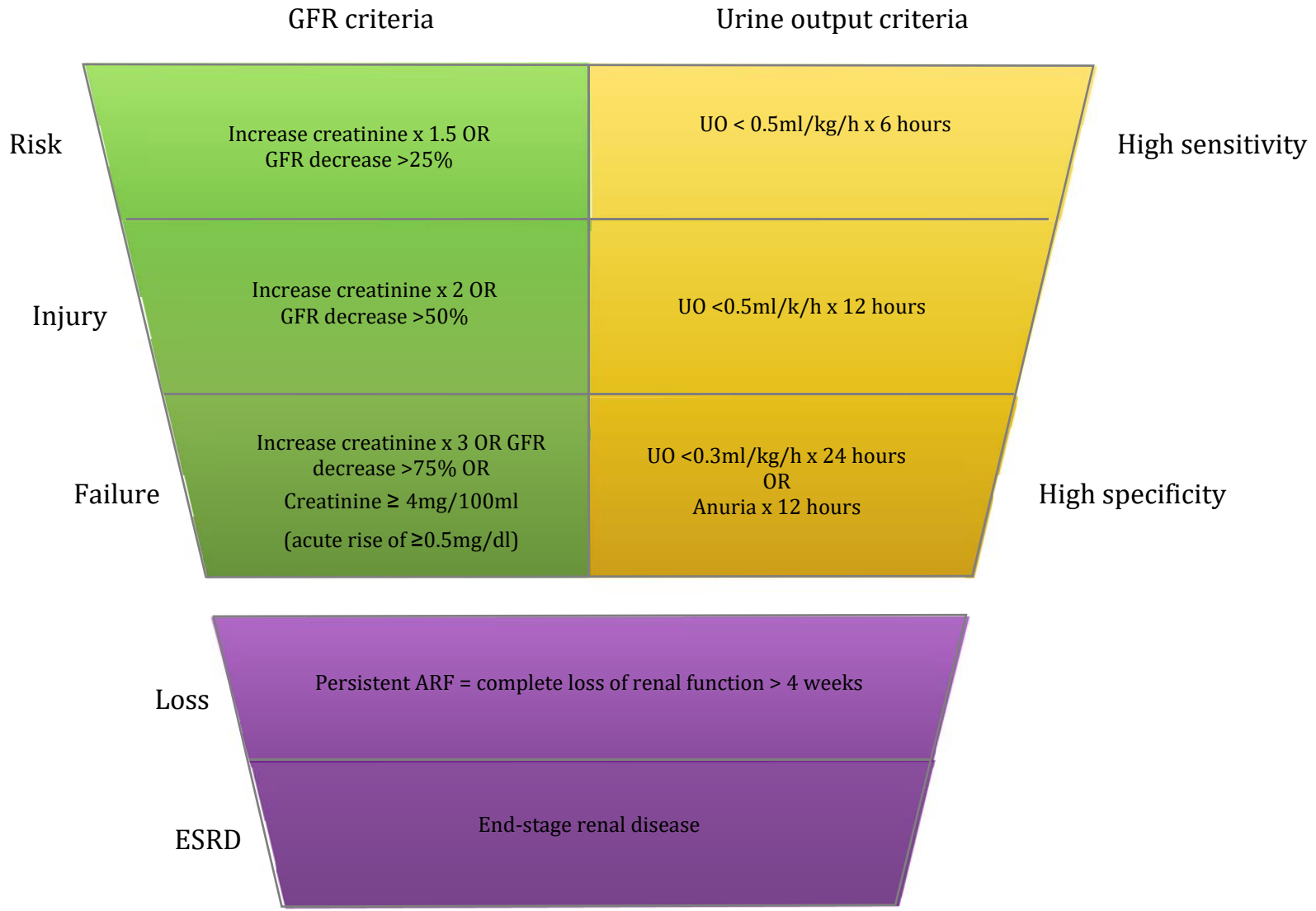


Figure 1.6. Risk, Injury, Failure, Loss, End-Stage (RIFLE)

Stage	Serum creatinine	Urine output criteria
1	1.5–1.9 times baseline OR ≥26μmol/L (≥3.0mg/dl) increase	<0.5ml/kg/h for 6–12 hours
2	2–2.9 times baseline	<0.5ml/kg/h for ≥12 hours
3	3.0 times baseline OR ≥354μmol/L (≥4.0mg/dl) increase OR Initiation of RRT OR Decrease in eGFR <35ml/min/1.73[2]	<0.3ml/kg/h for ≥ 12 hours OR Anuria for ≥ 12 hours

Table 1.2. Kidney, Disease: Improving Global Outcomes (KDIGO)

All three highlighted criteria are variations on the same theme—a rise in serum creatinine or decrease in UO indicates at-risk patients. However, falling UO is also a physiological response to correcting haemodynamic derangements(122), which includes patients undergoing intravenous fluid therapies—a vast proportion of the in-hospital population. Urine outputs are also not uniformly measured due to differing equipment and protocols within individual organisations, leading to potential bias. Furthermore, as highlighted earlier, changes in creatinine can be unreliable depending on patient demographics and are thus not validated in the setting of an acute reduction in glomerular filtration.

At present, these criteria are the gold standard for the diagnosis of AKI, because of the accessibility of laboratory testing for creatinine and the ease of UO measurements. However, newer biomarkers of AKI are being developed, in an attempt to identify specific types of AKI and at an earlier stage.

1.5.4 Different proposed novel biomarkers of acute kidney injury

1.5.4.1 Cystatin C

Serum cystatin C is a protein produced by nucleated cells. It is freely filtered by the glomerular capsule and is almost completely reabsorbed in the proximal tubule where it is completely catabolised(123) (Figure 1.7).

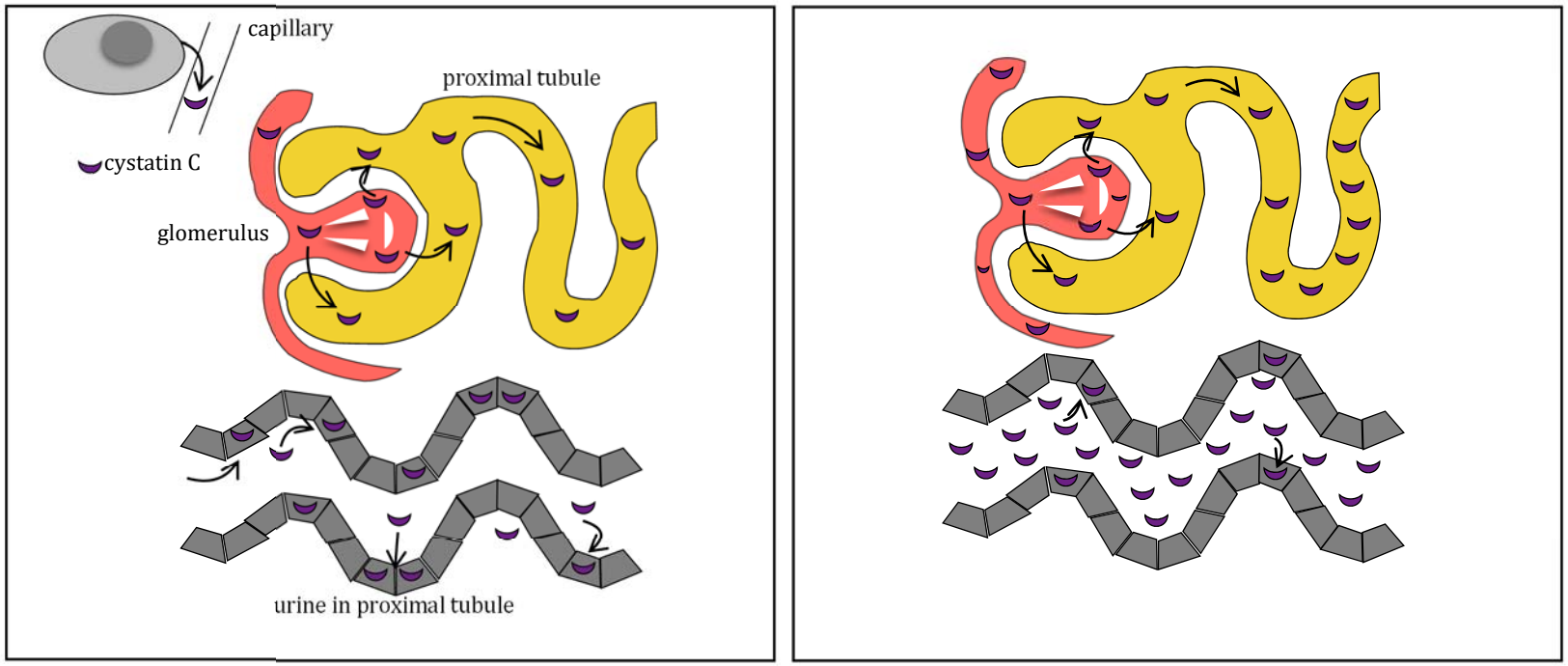


Figure 1.7. Cystatin C

In renal injury, less protein is filtered through the glomerulus but furthermore, less is reabsorbed by the proximal tubule leading to an increase in both plasma and urinary concentrations. Given these characteristics, cystatin C is therefore a more reliable marker of estimated GFR than creatinine as it is unaffected by the drawbacks previously described. It has also been validated in a number of clinical settings including cardiac surgery, transplant and contrast induced nephropathy, and a systematic review of 24 papers as far back as 2002(124) showed it to be statistically superior to creatinine as a marker of impaired GFR.

1.5.4.2 Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a lipocalin protein that was initially found in activated neutrophils, whose proposed action is that of a tubular iron scavenger and growth factor. It has subsequently been found to be excreted by various other cells in response to cell injury including those within the renal tubules.

It was discovered using functional genomics and is thought to play a part in the bacteriostatic mechanisms of the tubules and as an antioxidant(123) (Figure 1.8).

Of all of the novel biomarkers of renal injury, NGAL has been the most thoroughly investigated. It has been validated in multiple clinical settings including but not exclusively to cardiac surgery (both adult(125) and paediatric(126)), intensive care(127), transplant(128) and chronic renal impairment(129). Several cut-off levels have been prosed for different clinical scenarios: >273.6ng/ml for cardiac surgical patients, >155ng/ml for critically ill patients and >25ng/ml for trauma patients, although a recent meta-analysis of 65,000 pooled patients have suggested an general cut-off of >150ng/ml(130).

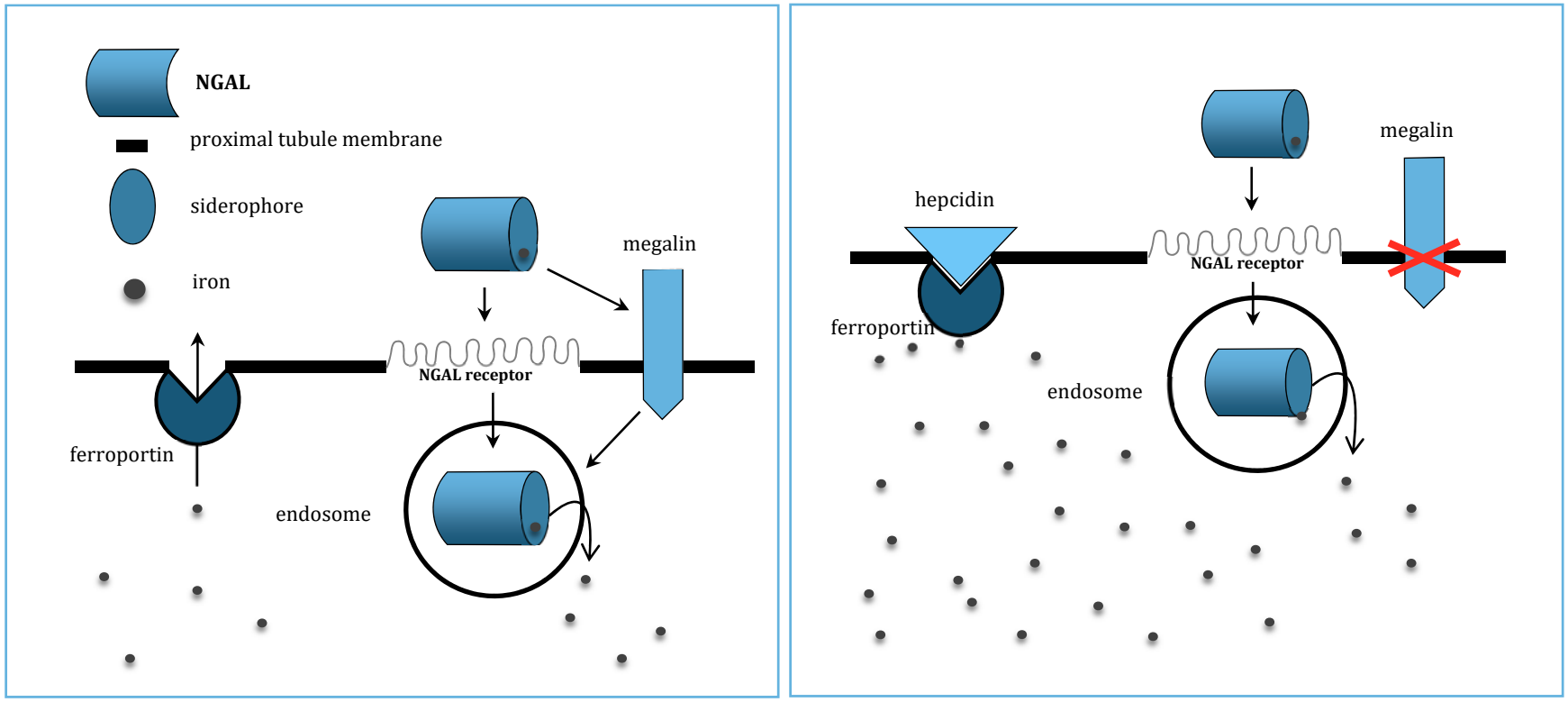


Figure 1.8. Neutrophil gelatinase-associated lipocalin

1.5.4.3 Kidney injury module 1

Kidney injury molecule 1 is a glycoprotein that is only up-regulated and expressed in the proximal tubules following ischaemic or nephrotoxic injury. In a number of cross-sectional studies, it was able to differentiate between pre and post-renal renal injury(131,132). The ectodomain of the molecule, the extent of the membrane proteins into the extracellular space, is shed following up-regulation and is therefore detectible in urine. As with the other biomarkers, it is not produced by the healthy kidney, therefore its use is only in the detection of established AKI and thus has no pre-injury predictive value.

1.5.4.4 Liver type fatty acid binding protein

Liver type fatty acid binding protein (L-FAMP) is produced by multiple organs; however its role is thought to be the same. The main roles include cellular uptake of free fatty acids from plasma as well as up-regulation of intracellular fatty acid metabolism. L-FABP helps to attenuate the build-up of free fatty acids, that are easily oxidised and can perpetuate cellular damage(133). Ergo, measurements of L-FABP may be useful in tissue injury secondary to oxidative stress. Furthermore, given its small size, it is freely filtered by the glomerulus and, like cystatin C, reabsorbed by the proximal tubule. This is useful for detecting tubular injury of any aetiology as there is a reduction in resorption by the proximal tubule and thus an increased urinary excretion(134). Whilst the majority of studies of L-FABP are laboratory or animal based, it has been tested in a number of clinical settings including diabetic nephropathy(135). However, this may limit its applicability in the setting of acute injury on a baseline of chronic diabetic induced nephropathy(136).

1.5.4.5 Interleukin 8

Interleukin 8 (IL8) is a pro-inflammatory cytokine which is a known mediator of acute tubular injury in experimental and animal models(137). It outperforms L-FABP in that it is induced and cleaved in the proximal tubule and is subsequently not raised in the setting of pre-renal, post-renal kidney injury or chronic renal impairment(138). Whilst it has also been validated in a number of clinical settings such as cardiac and transplant surgery(139), it showed low sensitivity in the paediatric population(140).

1.5.4.6 Tissue inhibitor of metalloproteinase-2/insulin-like growth factor binding protein 7

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) are both inducers of cell cycle arrest at the G1 phase of the cell cycle. In renal injury from ischaemia or inflammation, tubular cells arrest at the G1 phase in order to prevent cell division and subsequent apoptosis. Accumulation in the urine has been shown to be diagnostic of AKI whilst increasing amounts may be predictive of worsening grades of AKI(141). Specifically IGFBP7/TIMP2 have been investigated in the general surgical population, although only in one study comprising 107 patients(142).

1.6 Summary

Acute kidney injury is a common occurrence in the surgical population and a clinically and economically important problem for the surgical patient. Its occurrence is multifactorial and remains ill understood by this population.

Compounding this is the heterogeneity in its definition. Specifically, UO as a marker of AKI in specific populations may not be as relevant to the surgical patient compared to the critically ill patient, and as such, specific appraisal using novel biomarkers may be of benefit to further understand perioperative AKI. However, most novel biomarkers have only been used to demonstrate the occurrence of AKI at earlier time-points when compared to creatinine, and not been integrated into models with other surrogate markers of renal function to improve clinical outcomes. This has limited their use in clinical practice despite being widely available in a number of regions worldwide(143).

Chapter 2 – Thesis objectives

The introduction provided a brief overview of the historical basis for contemporary perioperative fluid management. It also highlighted the current flaws in the management of perioperative AKI, specifically relating to how it is currently defined using surrogate clinical and biochemical markers of renal function, and how this is treated with increasing volumes of intravenous fluid. As such, this thesis aims to answer the following specific questions to identify the scale and severity of the problem of perioperative AKI, the magnitude of intravenous treatments that are currently used to treat it and whether a different paradigm can be implemented to better manage this in the perioperative period:

1. Within the available literature, what is the actual incidence of perioperative AKI within the non-cardiothoracic, non-vascular, non-urological and non-transplant populations, and are there any associated risk factors that correlate with its development?
2. Given the unknown clinical consequences of mild biochemical AKI, using a clinical marker in its severest form, what is the incidence of AKI requiring RRT and what are its consequences regarding mortality and morbidity in this population?
3. We currently use UO as a surrogate marker of renal function and thus AKI in the perioperative period. However, how common is low UO in the perioperative period, what is its association with the development of AKI as defined by contemporary criteria and how much intravenous fluid is prescribed to treat it?
4. With the availability of newer biomarkers of AKI, can we ascertain whether perioperative UO is related to the occurrence of subsequent AKI? If it is not, what are its underlying mechanisms and can we redefine our UO targets to reduce the potential complications associated with fluid administration when treating it?

These questions will be answered using multiple methodologies to review, amalgamate, appraise and synthesise the current available literature.

Chapter 3 consists of a systematic literature review. The review will be undertaken to assess the incidence of AKI in the non-cardiothoracic, non-vascular, non-urological and non-transplant elective surgical population. Furthermore, risk factors for its development will be identified and analysed, and specifically whether UO has been identified as a predictor of perioperative AKI. To achieve this, the contemporary literature will be

searched to identify any patient centred or operative risk factors that have been demonstrated to have an impact on the incidence of perioperative AKI.

Chapter 4 consists of a national retrospective study of New Zealand intensive care units (ICUs) and aims to highlight the importance of avoiding severe AKI in the perioperative period. The specific study aims were to identify the incidence of patients within the thesis study population who developed severe AKI and who were clinically defined as requiring RRT, and to obtain data on their outcomes with respect to AKI. Furthermore, mortality rates, changes in long-term GFRs along with basic demographic data were collated to aid in the prediction of these complications.

Chapter 5 presents a retrospective review of prospectively collected data at the North Shore Hospital in Auckland. The study population included surgical patients undergoing elective colorectal surgery within an ERAS protocol with the aim of identifying the incidence of both perioperative oliguria and whether it had any association with the development of perioperative AKI. This highlighted the problem we faced with the traditional definition of oliguria as well as aiding in the design and power calculation of the planned randomised controlled trial.

Chapter 6 presents a randomised controlled non-inferiority study powered to test the hypothesis that perioperative UO is not correlated with the development of perioperative AKI. Patients were randomised to receive boluses of Plasma-Lyte 148® ™ (PL148) to bolster UO if it fell below the contemporary target of 0.5ml/kg/h or the trial target of 0.2ml/kg/h. Validated biomarkers of renal injury were used to define the occurrence of AKI. Furthermore, this study investigates a number of physiological mechanisms that may explain the occurrence of oliguria in the perioperative period and whether this is associated with the development of AKI.

The results from these studies will be collated and summarised in Chapters 7 and 8, with a view to recommendations concerning how current perioperative care can be modified to reduce the incidence of AKI and how modifications in the treatment of perioperative UO may result in the reduction of overall complications.

Hypotheses generated by the preceding chapters are explored in Chapter 9 as to potential future directions for research to clarify or progress the findings of this thesis.

Chapter 3 – Acute kidney injury in the elective non-cardiovascular patients: A systematic literature review

3.1 Introduction

Acute kidney injury is common, with a quoted incidence in the literature between 1–7% across all hospitalised patients(114,144,145). Furthermore, it has been well described that surgery is the leading cause of in-hospital AKI, representing 18–47% of all documented episodes(146).

However, until recently a lack of a unified definition of AKI has confounded these results. Groups such as the Acute Kidney Injury Network (AKIN)(112), Risk, Injury, and Failure; and Loss; and End-stage kidney disease (RIFLE)(112) and the Kidney Disease Improving Global Outcomes (KDIGO)(147) have sought to standardise our definition of AKI, allowing for more accurate assessments of AKI. Subsequently, a recent meta-analysis of global AKI found a pooled incidence of 21.6% in the adult in-patient population regardless of admission diagnosis(148). Given that AKI is independently associated with increases in hospital mortality(145,149), morbidity(113), length of hospital stay(150) and cost (£434million/year in the UK)(151), it is imperative to identify at-risk patients to reduce such adverse outcomes.

There is currently a plethora of research looking at the association of AKI in cardiovascular surgery(152,153). However, sparse literature exists examining the non-cardiovascular population. A recent review of the management of patients at-risk of AKI identified 22 papers of which only two were in the general surgical or orthopaedic populations(154). In 2012, general surgical and orthopaedic operations constituted approximately 50% of all operations performed in the UK, and improving outcomes in these non-cardiovascular specialties is paramount.

3.2 Study objectives

This study aimed to conduct a systematic review of the literature to determine the incidence of AKI in the elective, non-cardiovascular surgical population, along with important potential risk factors for the development of AKI in this population.

3.3 Methods

3.3.1 PRISMA

A systematic literature review was performed and reported in accordance with the Preferred Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines(155).

3.3.2 Eligibility criteria

All papers reporting renal outcomes in elective, adult (age > 16 years), non-cardiovascular surgery were eligible for this review. To reflect contemporary perioperative care, only papers from 1995 or later were included, and there were no language restrictions. Unpublished literature was eligible and to minimise bias, conference proceedings and dissertations were actively searched through.

Studies relating to cardiothoracic, vascular, transplant and urological surgeries were excluded due to known or perceived influences on renal function. Furthermore, studies incorporating all surgical specialties were only included if data could be subdivided to identify eligible procedures.

The minimum data set required for outcomes was: definition of AKI, overall incidence of AKI, and risk factor predictors.

3.3.3 Information sources, search terms and data extraction

Databases (MEDLINE, the Cochrane Library, Embase and CINHAL) were searched electronically. Furthermore, relevant articles were manually searched, using reference lists to identify relevant articles. Bibliographies of publications and electronically available abstracts from recent (five years or later) major conferences including the Royal Australasian College of Surgeons Annual Scientific Congress (RACS ASC), International Surgical Week (ISW), the American College of Surgeons Clinical Congress (ACS), the American Society of Anaesthesiologists (ASA) annual meetings and the Australasian Society of Anaesthetists (AuSA) National Scientific Congresses were hand searched. All sources were last searched in February 2017.

For the database searches, Boolean operators (AND/OR functions) were used to combine database specific indexed headings in conjunction with specific “keywords”. Various combinations of the following search terms were used: “acute renal failure” OR “acute kidney injury” OR “renal dysfunction” AND “perioperative period” “postoperative period”

AND “surgery”. The PubMed search engine was utilised with its ability to use automatic expansion of entered terms into relevant keywords, medical subject headings terms as well as related citation functions.

Electronic and manual screening of relevant abstracts was independently completed by two reviewers (Jevon Puckett [JP] and Rebecca Jaung [RJ]), with differences settled by consensus with a third author (Ian Bissett). Duplicates were removed with the remaining full-text reports of screened abstracts assessed for eligibility (JP) and data was independently extracted on a predetermined data sheet (JP and RJ). Exact data extraction included: 1) study publication details, 2) surgical specialty, 3) number of patients, 4) definition of AKI, 5) incidence of AKI, and 6) significant predictors, with levels of significance and odds ratios. Each study identified was assessed for quality using the Oxford Grading System(156).

3.3.4 Study analysis

Multiple risk factors were investigated via univariate analysis throughout all 20 studies identified in this review. Positive risk factors identified on univariate analysis were then subsequently put into a logistic regression model. Factors that were investigated fewer than three times were excluded from the analysis as interpretation of a minimal data set would lead to bias. Overall incidence of AKI was calculated on the basis of weighting by study size:

(Individual incidence of AKI x Study Population) / Total pooled population

3.3.5 Primary and secondary endpoints

Primary endpoints of this review were identified risk factors (along with odds ratios) for the development of AKI in the elective non-cardiovascular surgical patient. The secondary endpoint was the incidence of AKI following non-cardiovascular surgery.

3.4 Results

The initial search yielded 2,257 abstracts from database and manual searches, with no unpublished studies identified. After screening of titles and abstracts, duplicates from both reviewers were removed identifying 47 relevant studies for which the full-text was assessed (Figure 3.1). A further 27 studies were excluded on the basis of either containing emergent alongside elective populations, where the data could not be separated (n=10),

for including an excluded population (n=10), for being management reviews (n=3) or not relevant (n=4). Although authors of combined emergent and elective populations were contacted in an attempt to gain access to the raw data, none were obtained. There were no disagreements between authors at any stage requiring mediation from the senior author. Twenty relevant studies met the remaining and minimum data set and were subsequently included in this systematic review (Table 3.1)(157-176).

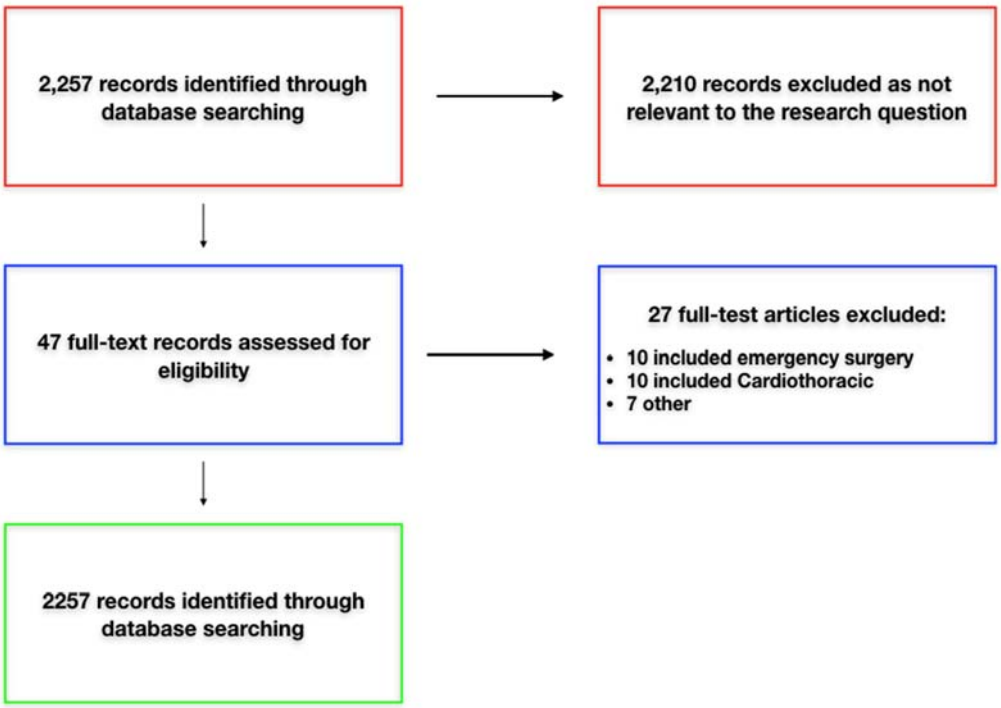


Figure 3.1. Eligibility of studies

3.4.1 Studies

Of the 20 studies, all had a retrospective analytical design, although in four, the data were collected prospectively. Nineteen were published in English language journals with one published in French which was translated. Nineteen papers were published in journals and one was a conference presentation. Three of the 20 studies analysed risk factors for the development of AKI using only a univariate methodology, while the remainder used both univariate and logistic regression. Eighteen studies were single-centre studies, with the remaining two having 450 patients split over two sites(167) and 1,170 over three sites(176) (Table 3.1).

Study	Population	Centres	Study design	AKI definition	AKI incidence (%)
Abdullah	1,230	1	Retrospective	KDIGO	2.9
Aveline	755	1	Prospective Observational	eGFR	32.7
Biteker	1,200	1	Prospective	RIFLE	6.7
Kim	4,718	1	Retrospective	KDIGO	14.8
Lee	595	1	Retrospective	AKIN	35.3
Naik	726	1	Retrospective	RIFLE	3.9
Sehgal	627	1	Retrospective	AKIN	21.9
Sharma	1,800	1	Retrospective	Creatinine – Absolute	2.8
Slankamenac	569	1	Prospective	RIFLE	15.1
Tateda	67	1	Retrospective	AKIN	13.4
Teixeira	450	2	Retrospective	KDIGO	22.4
Thakar	491	1	Retrospective	Creatinine – Relative	8.6
Weingarten	1,191	1	Retrospective Case Matched	Creatinine – Absolute	5.8
Weingarten	9,171	1	Retrospective	AKIN	1.8
Zhang	536	1	Retrospective	Creatinine – Relative	6.9
Long	6,287	1	Retrospective	KDIGO	4.2
Kim	1,309	1	Retrospective	KDIGO	4.4
Kambakamba	829	1	Retrospective	AKIN	8.2
Bekelis	19,894	1	Retrospective	–	1.5
Squires	1,170	3	Retrospective	Creatinine – Absolute	3

Table 3.1. Eligible studies

3.4.2 Assessment of methodology

Included studies were assessed using a quality assessment tool adapted from Taylor et al(177) aimed at evaluating confounding, selection bias, performance bias, detection bias, publication bias and applicability (Table 3.2). Each study was given a score out of a maximum of nine (Table 3.3).

Quality assessment criteria	Score		
	0	1	2
Was the study prospective?	No/NS	Yes	
Were the patients consecutive?	No/NS	Yes	
Was the study multi-centre in design?	No/NS	Yes	
Were appropriate inclusion/exclusion criteria stated?	No/NS	Yes	
Was appropriate modelling used to assess the data?	No/NS	Yes	
Was a validated definition of AKI used?	No/NS	Yes	
Were multiple surgical populations studied?	No/NS	Yes	
Were the number of patients studied sufficient?	<100	100–999	>1000

NS = Not stated(13)

Table 3.2. Quality assessment criteria

Author	Prospective	Consecutive	Multi-centre	Selection bias	Performance bias	Detection bias	Number of patients	Population	Score (9)
Biteker	1	1	0	1	1	1	2	1	**8**
Long	0	1	0	1	1	1	2	1	**7**
Kim	0	1	0	1	1	1	2	0	**6**
Slankemenac	1	1	0	1	1	1	1	0	**6**
Teixeira	0	1	0	1	1	1	1	1	**6**
Weingarten	0	1	0	1	1	1	2	0	**6**
Kim_HJ	0	1	0	1	1	1	2	0	**6**
Abdullah	0	1	0	0	1	1	2	0	**5**
Lee	0	1	0	1	1	1	1	0	**5**
Weingarten	1	0	0	1	1	0	2	0	**5**
Kambakamba	0	1	0	1	1	1	1	0	**5**
Aveline	1	1	0	1	0	0	1	0	**4**
Naik	0	1	0	0	1	1	1	0	**4**
Squires	0	1	1	0	1	0	1	0	**4**
Sehgal	0	1	0	0	0	1	1	0	**3**
Sharma	0	1	0	0	0	0	2	0	**3**
Thakar	0	1	0	0	1	0	1	0	**3**
Bekelis	0	1	0	0	0	0	2	0	**3**
Zhang	0	1	0	0	0	0	1	0	**2**
Tateda	0	0	0	0	0	1	0	0	**1**

Table 3.3. Quality assessment results

3.4.3 Incidence of acute kidney injury

The overall incidence of AKI was 5.07% ± 1.52 (SEM), however it varied considerably between different types of surgery: oesophageal (35.3%) and gastric surgery (14.0% ± 2.39 (SEM)) had the highest incidence of reported AKI, followed by liver (7.5% ± 2.74(SEM)) and abdominal surgery (5.4% ± 4.54 (SEM)). However, definitions for the development of postoperative AKI varied significantly between the papers and were divided into four main categories for ease of analysis:

1. Acute Kidney Injury Network criteria (AKIN)
2. Kidney Disease, Improving Global Outcome criteria (KDIGO)
3. Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE)
4. A decrease in estimated GFR (<60ml/min/1.73^2)

KDIGO was the most common definition used to identify AKI, being used in five of the twenty studies encompassing 13,944 (25%) of the pooled population. However, the actual incidence of AKI varied depending on the definition used and was calculated based on weighting by study size. When used, KDIGO diagnosed AKI in 8.26% ± 2.84(SEM) compared to RIFLE; 7.80% ± 2.93(SEM) and AKIN; 5.22% ± 4.29(SEM)(Figure 3.2).

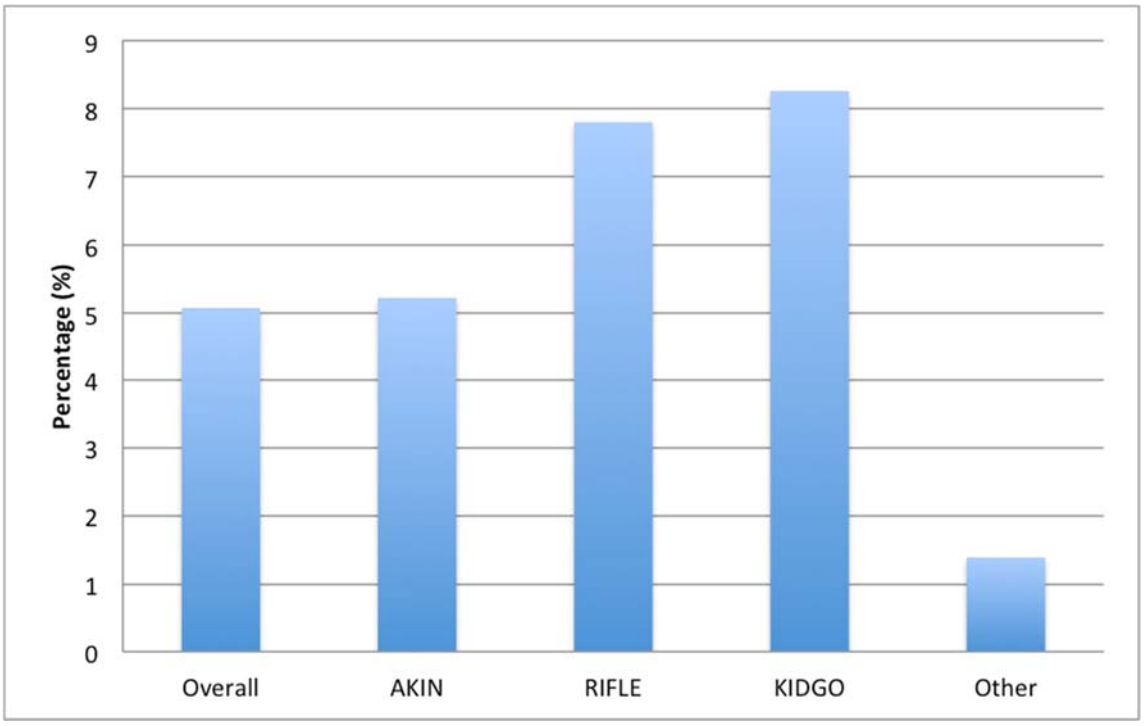


Figure 3.2. Incidence of acute kidney injury

3.4.4 Risk factor for acute kidney injury

The papers varied from small (67) to large numbers of participants (19,894) covering a range of specialties, with a total number of 53,615 pooled patients. Of these, neurosurgical, orthopaedic and abdominal surgeries constituted the majority of the overall population with 19,894, 11,862 and 6,737 patients studied respectively.

The mean pooled age of patients was 61.8 years with a male to female ratio of 54:46. The majority of studies (53%) excluded patients with severe or end-stage renal failure using various definitions, but most commonly because of patients requiring preoperative renal dialysis.

Three of the 20 studies included in this review used univariate analysis to identify risk factors(162,163,166). Using these risk factors in conjunction with the multivariate analyses, a table was created to identify how frequently each factor was identified, whether it was positively or negatively related to the incidence of AKI and the significance of the finding (Table 3.4).

Risk factor	Risk identified	Risk not identified	Total	% of studies where risk identified	Odds ratio
Revised coronary risk index	4	0	4	100	1.59–1.9
Increasing BMI	7	1	8	87.5	1.03–1.81
Angiotensin converting enzyme inhibitor	4	1	5	80	1.35–6.824
Albumin	3	1	4	75	0.52–1.9
Renal impairment	8	5	13	61.5	2.63–13.35*
Age (increased)	11	7	18	61.1	1.02–2.59*
ASA physical status	3	2	5	60	1.1–9.48*
Diabetes	7	6	13	53.8	1.5–3.12*
Transfusion	3	3	6	50	1.72–3.3*
Hyperlipidaemia	2	3	5	40	0.86–2.74*
Hypertension	4	7	11	36.4	0.83–2.37*
Gender (male)	4	8	12	33.3	0.68–1.75*
Diuretics	2	3	5	25	2.39–16.42
Vasopressors	1	4	5	20	1.1–1.87*
Duration of surgery/anaesthesia (increased)	1	5	6	16.7	0.9–1.14*
Chronic obstructive pulmonary disease	1	5	6	16.7	0.87–1.64*
Congestive cardiac failure	1	6	7	14.3	0.41–1.84*

Table 3.4. Summary of risk factors

3.4.5 Demographic

Demographic risk factors for the development of AKI were the most commonly investigated factors. Age was analysed as a possible risk factor in 18 studies with 11 (60%) finding increasing age to be a risk and seven finding no association with age. Gender was analysed in 12 of the studies with only four (33%) finding a positive correlation between male gender and the development of AKI.

3.4.6 Comorbidities

Of the comorbidities studied, hypertension (11), diabetes (13), pre-existing renal impairment (9) and BMI (Body mass index) (8) were the most commonly investigated factors. Presence of hypertension did not appear to be significantly correlated with the development of AKI, with only four (36%) of the 11 studies yielding a positive predictive result. In 54% of studies, the presence of diabetes came out as a positive predictor of AKI. Preoperative renal insufficiency would clinically appear to be a relevant risk factor, however only four (44%) of the nine studies that incorporated it into their multivariate analysis found that it was a predictive risk factor for AKI. BMI was investigated by eight studies with all bar one study finding increasing BMI to be a positive predictive risk factor for the development of AKI.

Neither congestive cardiac failure (CCF), hyperlipidaemia nor chronic obstructive pulmonary disease (COPD) fared well as positive predictors in this review. On balance, each factor was only studied in seven, five and six papers respectively out of 20.

Preoperative albumin was analysed as a risk factor in only four of the 20 studies, for which it was found to be a positive predictor in three out of four. However, the primary outcome of one paper(172) was to specifically assess the association of postoperative albumin on the development of AKI as opposed to the remaining three that studied preoperative albumin.

As a general marker of pre-morbid status, incorporating the most significant comorbidities, the revised coronary risk index (RCRI)(178) and the American Society of Anaesthetists (ASA)(179) were also evaluated by four and five of the 20 studies respectively. Increased RCRI score came out positive in all four compared to the increased ASA, which was only positive as a predictor in three out of the five studies.

3.4.7 Perioperative medication

Three specific categories of medications were identified for discussion from the collective 20 papers: use of angiotensin converting enzyme inhibitors (ACE), diuretics and perioperative vasopressors. Whilst each category was only identified in five of the 20 studies, the results were stark. Vasopressor use was only identified as a positive predictor of postoperative AKI in one of the five studies in which it was evaluated compared to ACE inhibitors, which were found to be a positive predictor in four out of five of the studies. Perioperative diuretic use lay in-between, being a predictor in only 40% of the five studies.

3.4.8 Perioperative factors

Only two intraoperative factors were evaluated within these 20 studies: Duration of surgery/anaesthesia and transfusion (six studies). Whilst duration of surgery was analysed in six of the 20 studies, only one study found increasing duration to be a positive predictor. Perioperative transfusions were also analysed in six of the 20 studies with 50% of studies finding an association with increasing number of transfusions and the development of AKI.

3.5 Discussion

In this systematic literature review of the elective, non-cardiovascular, non-transplant and non-urological surgical population, we found an overall incidence of AKI of 5.07% ± 1.52 (SEM). However, there was considerable heterogeneity between definitions of AKI leading to a large range between quoted incidences, thus making interpretation of the results challenging.

Studies were searched using a well-recognised search protocol (PRISMA) and appraised with a quality assessment tool. Risk factors were evaluated on the number of times they were studied and their percentage positivity in conjunction with the resulting odds ratios and confidence intervals. This study identified the following factors to be most likely to be associated with an increased risk of developing AKI in the perioperative period: RCRI/ASA, BMI, use of ACE inhibitor and pre-existing renal failure. Number of transfusions, perioperative serum albumin, diabetes and increasing age may afford an increased risk, whereas hypertension, CHF, COPD, hyperlipidaemia, gender, duration of surgery/anaesthesia and use of perioperative vasopressors or diuretics do not appear to

do so. Regarding the risk factors specifically identified in this review, a number require further discussion as being relevant as potentially modifiable factors.

3.5.1 Increased risk factors

Seven of the eight studies assessing BMI found it to be a significant risk factor for the development of perioperative AKI with odds ratios ranging from 1.03–1.81, however definitions for increased BMI varied considerably. This represented a large pooled population of 15,014, although was not examined by the two highest quality studies(159,173). It is clear that despite the heterogeneity in defining a cut-off for BMI, that increasing BMI is a positive risk factor and therefore even modest reductions in weight may help obviate this risk.

As with BMI, the use of ACE inhibitors was found to be a significant risk factor in four of the five studies in which it was investigated with odds ratios ranging from 1.35–6.824. These studies represented a pooled population of 5,421. Given that the use of ACE inhibitors is a binary variable and the quoted p values of ≤0.02, it follows that avoidance of perioperative use represents an easily modifiable and significant risk factor for the development of AKI. However, whilst a proportion of patients may be unable to withhold their ACE inhibitor for the duration of the perioperative period, no evidence exists to define the length of time required to stop these preoperatively in order to counteract this risk.

Pre-existing renal impairment was investigated in 13 of the studies with eight of the thirteen finding it to be a significant risk factor for the development of AKI with odds ratios ranging from 2.6–13.4. This variable also represented a large pooled population of 44,477. Despite the availability of a well-recognised staging system for chronic renal impairment, cut-offs for pre-existing renal impairment varied considerably from stages 2–5 (Table 3.5).

Stage	eGFR (ml/min/1.73²)	Description
1	≥90	Normal kidney function but urine, findings, structural abnormalities or genetic traits pointing to kidney disease
2	60–89	Mildly reduced kidney function and other findings (as for stage 1) that point to kidney disease
3a	45–59	Moderately reduced kidney function
3b	30–44	Moderately reduced kidney function
4	15–29	Severely reduced kidney function
5	<15 of dialysis	Very severe or end-stage kidney failure (sometimes called established renal failure)

Table 3.5. Chronic renal failure criteria

However, in the two largest study populations that investigated renal impairment(173,175), even stage 2 chronic kidney disease was identified as a risk factor for AKI (with p values ≤0.003). Whilst it is clearly a significant risk factor, pre-existing renal impairment is not easily modifiable and as such can only be noted in the preoperative assessment with a view to close perioperative monitoring for the development of AKI.

Preoperative functional status was assessed by both the RCRI and ASA scores and identified as a significant risk factor for the development of perioperative AKI in four of four studies and three of five studies respectively. The two studies of highest quality(159,173) were among those that analysed RCRI and ASA scores and found a significant relationship. The pooled population represented 8,692 and 9,702 respectively. Whilst a clear positive predictor of the development of perioperative AKI, both scores incorporate comorbidities including diabetes which have been studied in isolation in this review. Furthermore, the RCRI includes high-risk surgery defined as intra-thoracic and supra-inguinal vascular as well as intraperitoneal, two of which were excluded in the scope of this review. However, it follows that pre-morbid functional status is a significant predictor for development of AKI so efforts to optimise this in the preoperative period should be considered.

3.5.2 Potential risks factors

The presence of medically treated diabetes is likely to predict the development of AKI. Of the 13 studies that assessed this, seven showed a significant correlation with postoperative AKI and included those with a higher quality score including the three of the largest populations(159,169,170). The pooled population for diabetes was 45,621

with odds ratios for the development of AKI varying from 1.5–3.2 in these larger studies. Given the limited studies identified by this systematic literature review, the correlation between the development of AKI with increasing severity of diabetes (medically controlled versus insulin dependent) could not be elicited. With the clear links between diabetes and obesity(180), it follows that diabetes is a modifiable risk factor with preoperative diet and weight loss.

Eleven of the 18 studies that considered age found it to be a statistically significant predictor of AKI in the univariate analysis. When this was incorporated in logistic regression (or multivariate) regression, only two of these remained significant with a pooled population of 3,000 patients. Similar problems arose as with BMI and pre-existing renal insufficiency, in that no consensus on cut-off of age was proposed between the studies. This factor is also not amenable to improvement perioperatively, and could consequently only be highlighted in the perioperative assessment for increased perioperative monitoring.

Number of transfusions was a positive predictor in three of the six studies' odds ratios of 1.72–3.3. Although minimising transfusion may reduce the risk of AKI, transfusion may merely be a surrogate for other important risk factors such as intraoperative complications.

Of the four studies that considered plasma albumin levels, three found a significant correlation between low albumin and AKI, however, the best quality study did not find this(159). Where positive, the odds ratios were modest (1.4–1.92), but given albumin can also be used as a surrogate marker for multiple physiological and pathophysiological processes, including sepsis and nutritional, it is difficult to interpret its significance.

Gender was studied by 12 authors and found to be a positive predictor for the development of AKI in only four. Interestingly, all of the four positive studies found that male gender was associated with an increased risk of developing AKI, suggesting that this may represent a true correlation.

3.5.3 Unlikely risk factors

Hypertension was found to not correlate with the development of AKI in seven of the 11 studies that investigated it, with the best quality studies having conflicting results. The

criteria for diagnosis of hypertension differed in all 11 studies and this may confound the interpretation of these findings.

CCF and COPD were found to be positive predictors of the development of AKI in only one from six and seven studies respectively. The largest and best quality studies did not find a significant correlation; therefore, it appears these are unlikely to be important risk factors for AKI.

Hyperlipidaemia is unlikely to be a positive predictor for AKI as the two of the five studies assessing this that found a positive correlation were both of the poorest quality of assessment and included some of the smallest populations(168,171).

Only two perioperative factors were identified in this review: duration of surgery/anaesthesia and perioperative medication use. Duration of surgery was found to be a positive predictor in only one of the six studies that evaluated this, and was from the poorest performing study on qualitative assessment.

Perioperative medications including vasopressors and diuretics were investigated in five of the studies and only found to be associated with the development of AKI in one and two of these respectively. Kim et al(160) investigated 4,718 gastric cancer patients and found both vasopressors and perioperative diuretic use associated with AKI (odds ratios 2.39 and 1.87), however, the remaining studies contradicted this finding and were of similar quality. A more recent orthopaedic study found that intraoperative diuretics were statistically associated with AKI(172), however, the numbers requiring intervention were 11 from 1,309.

3.6 Limitations

AKI is a difficult outcome to study, as despite multiple international committees and copious research, no one unified method exists for its diagnosis. There was significant heterogeneity in the definitions used between all 20 studies, with the incidence of AKI varying between definitions: eGFR <60ml/min/1.73^2 (32.0%) to AKIN (4.62%). Furthermore, AKI was diagnosed by one of the three recognised contemporary criteria (albeit with minor alterations) in only 52% of the patients studied (27,778). However, Bekelis et al(175) whose cohort represents the largest of all the studies (19,894) did not define AKI. Therefore if excluded, the percentage of patients developing AKI using a recognised criterion increases to over 80%. In addition, different grades of AKI exist

depending on whether you use the RIFLE, AKIN or KDIGO classifications. Whilst all criteria define AKI based on the abrupt change in renal function (over 48 hours) from baseline, within each criteria there are also discrepancies in the definition of "baseline"(181); some assume any preoperative plasma creatinine to constitute baseline(182), whereas others define it as the lowest in-hospital recorded plasma creatinine(114), lowest of the first three in-hospital plasma creatinines(145), or, in the case of the perioperative population, the plasma creatinine immediately preceding surgery(183). Consequently, when studying risk factors for its development in reviews such as this, caution must be taken with the interpretation of the results.

Study sizes also varied considerably (67–19,894) and in a number of studies, too many independent variables were used for the size of their respective populations, risking over-fitting of the subsequent logistic regression models.

The study populations could also be considered to be significantly different, including spinal, oesophageal, gastric, abdominal, neurosurgical, general orthopaedic and bariatric surgery. However, an inadequate number of studies exists to specifically target each individual specialty with enough power for comparison of predictive risk factors. In other specialties, specific risk factors do exist which are known to risk the development of AKI, such as on-bypass surgeries, transplantation and surgery on the kidneys themselves. Therefore, this population can be considered to be homogenous regarding basic demographic and intraoperative risk factors. The difference in incidence of AKI between the specialties could therefore potentially be a reflection of the heterogeneity of AKI definitions, rather than different surgeries being a risk factor in themselves.

3.7 Conclusion

With only 20 papers published in the last 20 years, perioperative AKI remains an understudied area in our population of non-cardiothoracic, non-transplant, non-urological elective surgical patients. This is the most comprehensive systematic review to address perioperative AKI as a clinically important and common complication affecting one in twenty (5%) patients in our population. This review has highlighted two important risk factors for the development of AKI: increasing BMI and use of ACE inhibitors. These factors are easily assessed and modifiable in the preoperative setting and can reduce the incidence of perioperative AKI. We have further identified diabetes, pre-existing renal insufficiency (CRF), preoperative functional status and male gender to be potential risk

factors. Whilst not preoperatively modifiable, these allow for the identification of at-risk patients so that the severity of any ensuing AKI can be mitigated. This review has also reiterated the consensus of the literature that a unified definition of AKI is crucial for further research.

Chapter 4 – Long-term outcome of acute kidney injury requiring renal replacement therapy in patients undergoing major surgery: A longitudinal multi-centre case series

4.1 Background

The systematic literature review in Chapter 2 highlighted that not only is AKI a common problem in the hospital setting, but identifying patients who may be at-risk is fraught with difficulty due to a lack of a unified definition of AKI. Specifically, this heterogeneity confounds the interpretation of studies looking at the long-term sequelae of AKI in any given population. Whilst AKI definitions may differ, it is clear that patients requiring acute in-hospital RRT have developed the worst grade of AKI. For example, irrespective of which definition is used, there is evidence linking renal sequelae of AKI to the severity of the injury(184-188), with a recent meta-analysis of 13 retrospective studies revealing an incidence for the development of chronic kidney disease (CKD) or end-stage renal failure (ESRF) as 25.8% and 8.6% respectively in the intensive care population(189). One study from America(190) specifically investigated patients with pre-existing CKD (eGFR<45ml/min) who developed in-hospital AKI requiring RRT in the intensive care unit, revealing a mortality of 4.6% and requirement for ongoing RRT of 49%. A recent retrospective study in cardiothoracic surgery evaluated 11,899 patients who developed perioperative AKI requiring RRT(191). The results showed a 52% age dependent 30-day mortality with 13% becoming dialysis dependent. Furthermore, renal sequelae may not be the only consideration, with retrospective studies from Taiwan linking the severity of AKI with coronary(192) and thrombo-embolic(193) complications.

Although multiple other studies have looked at the association between AKI and CRF, these data remain difficult to interpret because they encompass either the whole intensive care population(194-196), or just the cardiothoracic surgical population(183,191). No specific data exist that study the elective non-cardiothoracic, non-transplant, non-vascular and non-urological surgical population. It is therefore logical to investigate this population as the majority of surgical patients who are represented in the literature at present are from the transplant or cardiothoracic population.

4.2 Study objectives

The primary aim of this study was therefore to identify the incidence of the most severe AKI (i.e. requiring RRT as a definite clinical endpoint) in the elective non-cardiothoracic,

non-vascular, non-transplant, non-urological surgical patient. Secondary aims were to investigate its mortality and morbidity (specifically the renal sequelae), and to assess risk factors for the development of such severe AKI, correlating this with the available evidence in the contemporary literature.

4.3 Methods

4.3.1 Ethics approval

This retrospective study was conducted in accordance with the guidelines published by the National Ethics Advisory Committee of New Zealand(197).

Ethics approval was sought and gained from the University of Auckland Human Participation Ethics Committee (Ref: 010771) prior to data collection. Locality assessment and approval was then sought and gained from each district health board (DHB) approached for this study.

4.3.2 Data extraction

4.3.2.1 Study population

We aimed to study adult patients within New Zealand, undergoing major elective surgery. Patients were excluded from the following groups due to specific or perceived effects on perioperative renal function: cardiothoracic, vascular, transplantation or renal/urological surgery. The resulting population included patients within the specialties of general surgery, gynaecology, orthopaedic, plastics and ear nose and throat (ENT). Patients who underwent their surgery prior to August 2013 were included in this retrospective review to allow a minimum of a 12-month follow-up of renal function. Patients were included if they developed a complication that required acute RRT during the primary hospital stay. However, patients were excluded if they were on RRT preoperatively or were admitted for emergency surgery. Furthermore, to ascertain any reduction in renal function, patients were excluded if no plasma creatinine was documented within 6–18 months following discharge (this time period was chosen as a prerequisite of stable renal function requires a minimum of three months(198)).

4.3.2.2 Localities

Throughout New Zealand, all acute RRT is conducted in ICUs. The six largest ICUs within New Zealand were invited to participate in this study. Four accepted and were able to

provide data: Waitemata District Health Board (WDHB), Auckland City Hospital (ADHB), Capital and Coast District Health Board (C&CDHB) and Counties Manukau District Health Board (CMDHB). Together, these four units serve 41.6% of the New Zealand population (WDHB 12.7%, ADHB 10.9%, C&CDHB 6.5%, CMDHB 11.5%)(199).

Each of the four included units maintains a prospectively collected database run by either a clinical nurse specialist or database manager. Because each intensive care unit had unique prospective databases set up at different times, each database had to be searched individually and by necessity, the time period of inclusion differed between each site:

ADHB – Set up in February 1993, the database was coded to allow searches for dialysis. This included haemodiafiltration (HD), continuous veno-venous dialysis (CVVD), intermittent haemodialysis (IHD) and prolonged intermittent renal replacement therapy (PIRRT).

WDHB – Set up in January 2007, the database was coded to be able to search terms for HD, CVVD, and IHD, with the ability to search for dialysis as an "other" search term.

C&CDHB – Set up in May 2012, the database did not code for dialysis per se, but did code for invasive venous access. This allowed the database to be searched for "dialysis catheter" as a surrogate, revealing 147 potential patients.

CMDHB – Set up in December 2009, the database was coded to be able to search terms for HD, CVVD, and sustained low efficiency dialysis.

To ensure complete data capture for their respective time periods, clinical coding departments at each site were also asked to provide a list of NHIs coded as having emergency RRT during their hospital stay. These codes were linked to the electronic discharges allowing a simple database search. Data, prior to the instigation of electronic discharge summaries, were therefore not captured. However, at one site, electronic discharge summaries were only instigated 10 years following the commencement of the ICU database. Consequently, data for this review that was extracted from the ICU databases superseded that of the electronic discharge summaries, as the capture rate was significantly higher than that from the clinical coding.

Each clinical coding department was also asked to provide a denominator for the study in the form of number of major elective surgeries within general surgery, gynaecology,

orthopaedic, plastics and ENT, performed at their respective institutions. The respective Royal Colleges were contacted to formulate a list of what was considered to be a major operation for each specialty with these being submitted to each DHB. The incidence of AKI requiring RRT could thus be more accurately identified.

4.3.2.3 Demographic data

Basic demographic data were retrieved from the electronic patient information system portal (Concerto©) at all four sites. Demographic data collected included age, gender weight, height, ethnicity and comorbidities. Known risk factors for the development of AKI were identified from electronically available clinic letters or anaesthetic assessment forms and recorded on the basis of the systematic literature review (Chapter 3) as well as empirical observations. These included: medically treated hypertension (with an ACE inhibitor), diabetes, COPD, peripheral vascular disease (PVD) and hepatic impairment (as graded by the Childs-Pugh score)(200).

Perioperative data were collected in the same fashion. Preoperative renal function was estimated using the MDRD formula from the latest available preoperative plasma creatinine on Concerto©. ASA, along with use of epidural, specialty of surgery and duration of surgery were recorded after examining the anaesthetic record for each patient. In the postoperative period, information deemed clinically relevant or associated with chronic renal failure from the literature(196), including type of complication resulting in AKI, duration and type of RRT (hours) and length of ICU and hospital stay (hours and days) were included in the study database. These data were gleaned from both written and electronic records.

4.3.2.4 Specific plasma creatinine data

Because of the retrospective nature of the study, preoperative renal function was based on the closest plasma creatinine prior to the elective operation. All creatinine concentrations were checked up to one year prior to this point to ensure stability for greater than three months. Postoperatively, creatinine concentrations were recorded as peak pre-dialysis, upon discharge from hospital and at three, six, nine and 12 months following discharge where available. The most recent creatinine and its date were also noted.

4.3.2.5 Statistical analysis

Data are reported as proportions, means ± standard deviation or medians (interquartile ranges) where appropriate. Using statistical software JMP™(JMP Version 10, SAS Institute Inc., Cary, NC, USA), Kaplan-Meier curves were constructed for both overall survival and dialysis free survival. Wilcoxon signed-rank tests were used to assess repeated measures of GFR.

Univariate analysis was performed on predictors of renal function as measured by change in eGFR from baseline to between 6 and 18 months following hospital discharge. All independent variables were assessed for normality using the Shapiro-Wilk test and transformed to either log or into quartiles as appropriate. Because neither the baseline eGFR of its log transformation were normally distributed, baseline eGFR was incorporated into the logistic regression model as a covariate. Positive predictors on univariate analysis ($p<0.20$) as well as suggested predictors from the literature were also subsequently evaluated using a logistic regression model. Because eGFR was not normally distributed, the data were transformed into quartiles. Accordingly, the multivariable analyses were performed both on quartiles of GFR (logistic regression) and on percentage change in GFR at 6–18 months (which was normally distributed, linear regression).

4.4 Results

Following identification of all appropriate patients utilising the individualised methodologies aforementioned, a total of 1,273 patients who required RRT while in ICU were identified. Study data were then extracted from electronic and physical patient records. 1,215 patients met exclusion criteria (Table 4.1) leaving 58 for analysis.

Variable	ADHB (412)	WDHB (267)	CMDHB (468)	C&CDHB (126)	Total
No surgery	152	129	240	79	601
Acute surgery	91	122	155	191	387
Preoperative dialysis	126	1	44	8	179
Cardiothoracic surgery	0	0	2	14	16
Urological surgery	9	0	15	1	25
Transplant surgery	3	0	1	2	6
Vascular surgery	0	0	0	1	1
Total	382	252	457	124	1,215

Table 4.1. Exclusion criteria

During the study period, 39,808 elective major operations of the included types were undertaken at three of the four institutions where data was available (ADHB – 23,648, WDHB – 12,749, and C&CDHB – 3,411). Accordingly, the incidence of AKI requiring RRT following major elective non-cardiothoracic, non-transplant, non-vascular and non-urological surgery was 0.11%.

Of the population who developed AKI requiring RRT, 15 patients died during their in-hospital admission with the remainder having follow-up plasma creatinines available. The demographic data of all patients (n=58) as well as patients who survived (n=43), are described in Table 4.2.

Variable	Total (n=58)	Survivors (n=43)
Age	60.7 ± 15.0	58.9 ± 16.1
Gender		
Male	37 (64)	23 (53)
Female	21 (36)	20 (47)
ASA class		
1	8 (14)	6 (13.9)
2	19 (33)	16 (37.2)
3	21 (36)	14 (32.6)
4	10 (17)	7 (16.3)
Weight (kg)	87.5 ± 24.9	85.6 ± 24.7
BMI (kg/m^2)	28.8 ± 10.5	28.8 ± 7.0
Preoperative eGFR (ml/min/1.73m^2)	70.0 ± 30.5	68.8 ± 33.8
CKD stage		
>90ml/min/1.73m^2	15 (26)	11 (25.6)
60–90ml/min/1.73m^2	22 (38)	15 (34.9)
30–60ml/min/1.73m^2	14 (24)	10 (23.3)
15–30ml/min/1.73m^2	5 (9)	5 (11.6)
<15ml/min/1.73m^2	2 (3)	2 (4.7)
Ethnicity		
Caucasian (European)	43 (74)	31 (72.1)
Caucasian (Indian)	3 (5)	2 (4.7)
North East Asian	2 (3)	1 (2.3)
South East Asia	1 (2)	1 (2.3)
Pacific Islander	9 (16)	8 (18.6)
Comorbidities		
Diabetes	23 (49)	20 (46.5)
Hypertension	35 (60)	24 (55.8)
PVD	4 (7)	2 (4.7)
Childs-Pugh B liver disease	4 (7)	2 (4.7)
COPD	5 (9)	3 (7.0)
Congestive heart failure	3 (5)	3 (7.0)

Data are n (%), means ± SD or median (25–75th quartiles) for non-parametric data.

Table 4.2. Patient demographics

Most patients were male with a mean age of 61. Patients were on average, Caucasian, overweight and had mild renal impairment (eGFR 70ml/min/1.73^2). Almost 75% of patients who developed severe AKI had undergone a general surgical operation, with orthopaedic operations being the next most common (10%). The majority of patients

required RRT as a consequence of a major complication: septic (31), cardiac (7), haemorrhagic (7), respiratory (3), ischaemic bowel (2) and isolated renal failure (1). The isolated renal failure complication was diagnosed as ATN of unknown aetiology.

4.4.1 Survival

Fifteen patients died during their in-hospital stay. Kaplan-Meier curves were constructed including all 58 patients for both overall survival as well as the RRT free survival (43 patients) and are presented below (Figures 4.2 and 4.3).

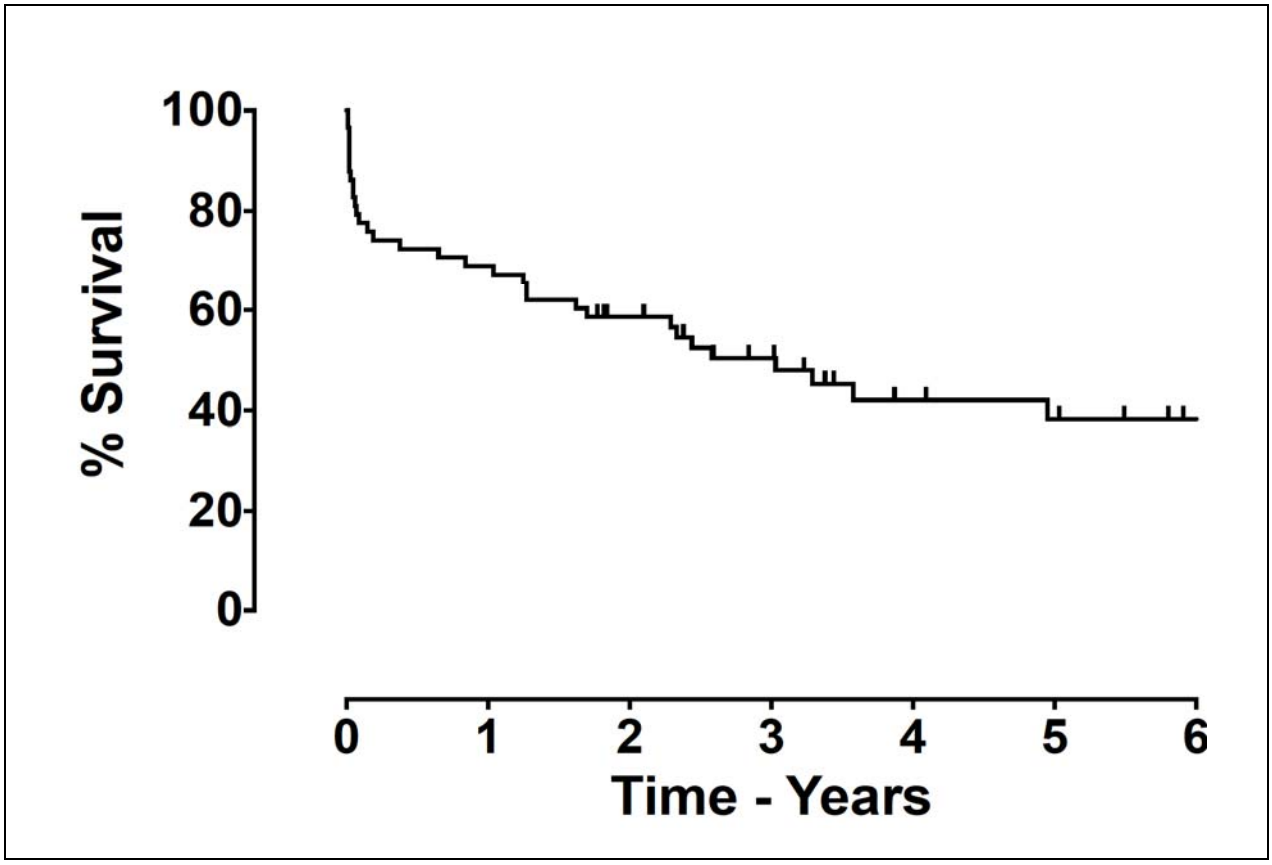


Figure 4.1. Kaplan-Meier survival

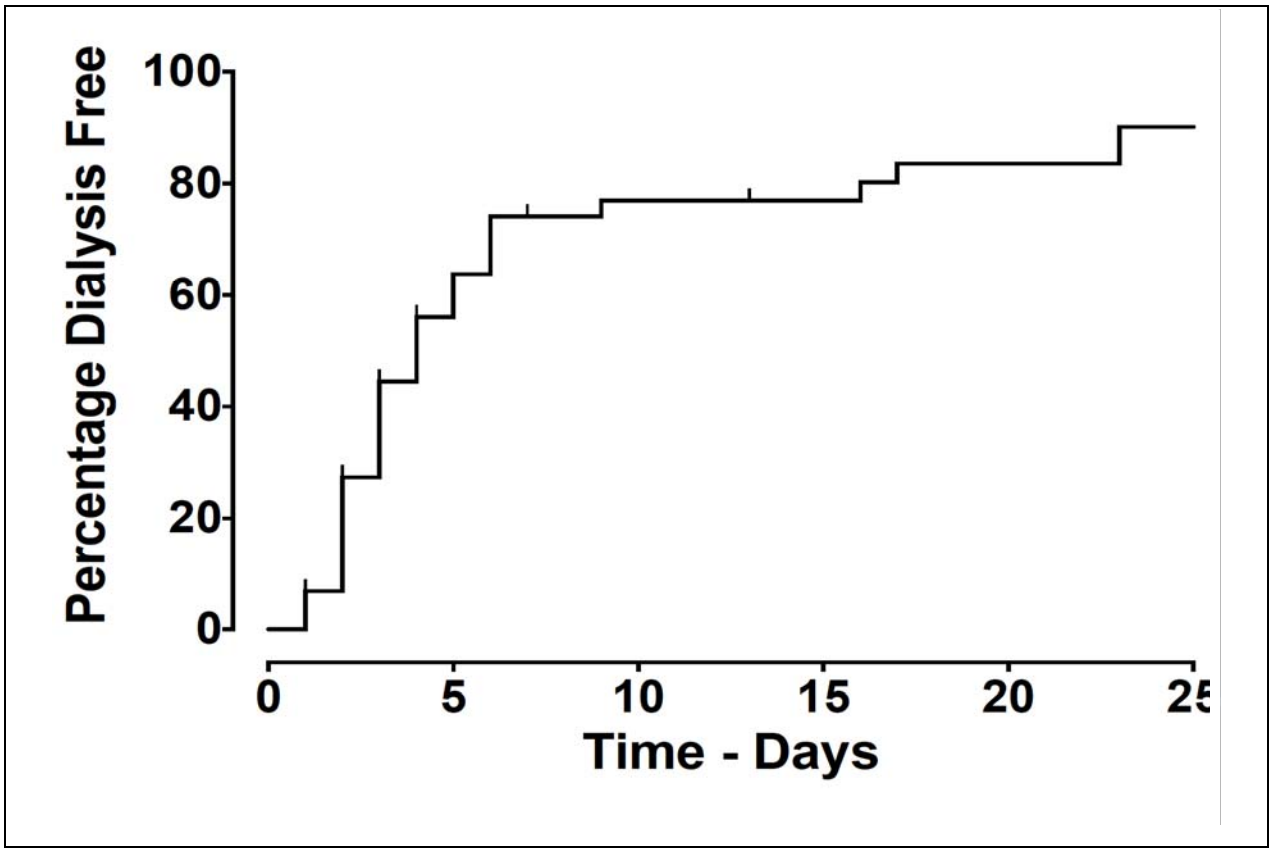


Figure 4.2. Percentage of patients dialysis free

The sharpest gradient of the Kaplan-Meier curve for survival comes within the in-hospital admission. Within the first three weeks after commencement of RRT, 20% of patients had died (Figure 4.2). By five years post insult, overall survival was poor at ≤40% (Figure 4.3).

Regarding dialysis free survival, of the 43 patients who survived their acute complication, only three (7.5%) became dialysis dependent. The majority of patients (~80%) required fewer than seven days of RRT and by day 24, the AKI of all patients who did not require ongoing RRT had resolved (Figure 4.3).

For renal sequelae, Wilcoxon signed-rank test was applied to GFRs at various time periods as trough GFRs and follow-up GFRs were not normally distributed. In the short-term, renal function appeared to normalise with no significant difference between baseline and three months. However, when renal function was assessed in the medium term (between 6–18 months) for those who were not dialysis dependent, there was a statistically significant reduction in eGFR ($p=0.0024$) from a mean of 70.0ml/min/1.73^2 at baseline to 56.2ml/min/1.73^2 (Figure 4.3)—a reduction from mild to moderate CKD.

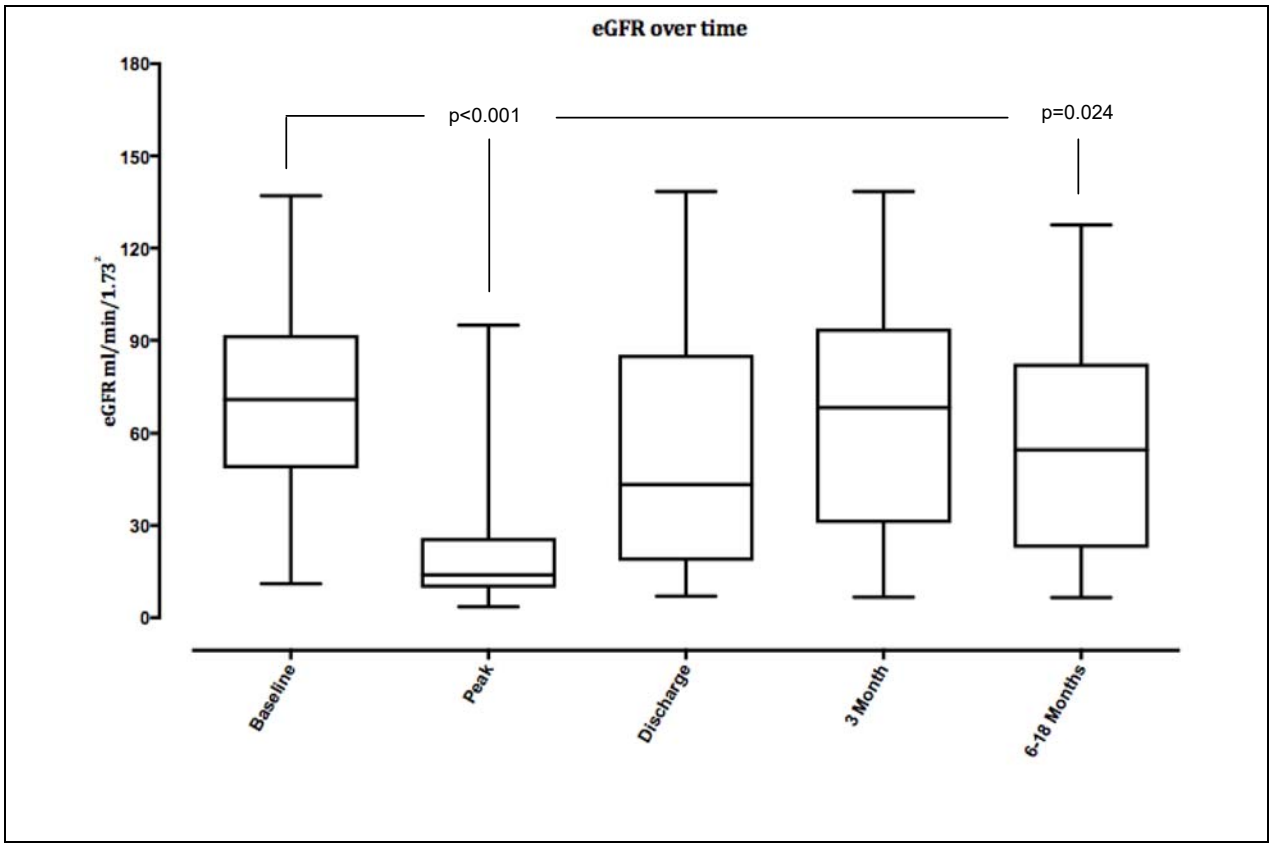


Figure 4.3. Change in eGFR over time

4.4.2 Univariate analysis

On univariate analysis, baseline GFR was used as a covariate. The results revealed that the only factor that appeared to potentially influence long-term renal function was duration of ICU therapy (p=0.087, factor estimate 5.534) (Table 4.3). Given the factor estimate of 5.534, increased length of ICU stay appears to convey a positive predictive influence on renal function.

Variable	p value	Factor estimate
Age	0.869	Quartile 2 vs 1: 1.088 Quartile 3 vs 2: -6.460 Quartile 4 vs 3: 7.727
Gender	0.345	0.873
BMI	0.378	0.646
NIDDM	0.248	3.874
HTN	0.623	1.995
PVD	0.649	4.523
COPD	0.787	-2.262
CHF	0.806	-7.545
Liver (CP)	0.568	4.205
ASA	0.401	ASA 2 vs 1: 0.728 ASA 3 vs 2: -0.072 ASA 4 vs 3: -0.172
Operation type	0.664	General: -1.873 Gynaecological: 43.819 Neurological: -34.294
Operation length (h)	0.960	-0.671
Epidural	0.770	3.231
RRT duration (d)	0.440	Quartile 2 vs 1: 12.363 Quartile 3 vs 2: 13.017 Quartile 4 vs 3: 3.678
RRT duration (h)	0.494	Quartile 2 vs 1: -9.662 Quartile 3 vs 2: 7.931 Quartile 4 vs 3: -8.058
ICU duration (log)	0.087	5.534
Peak GFR	0.738	0.087
RRT prescription	0.435	HD: 0.534 CCRT: 6.736
Complication type	0.705	Cardiac: -2.472 Haemorrhagic: -6.598 Respiratory: -1.397 Other: 5.497

Table 4.3. Univariate analysis of risk factors of long-term eGFR

If the analysis was re-run for percentage change in GFR at 6–18 months post discharge (which was normally distributed), the result also approached, but did not quite meet statistical significance (p=0.0512).

4.4.3 Multivariable analysis

Given the small sample size after exclusion of the 15 deaths (n=43), only three variables could be included in the multivariable analysis.

From the systematic literature review, BMI and grade of chronic failure were included in the final model as predictors of negative renal outcomes.

From the univariate analysis, increasing duration of intensive care stay was included as it approached statistical significance as a positive predictor of renal function, and therefore was deemed to be clinically relevant to this analysis. Unfortunately, a regression model could not be identified despite using baseline GFR as a covariate factor.

4.5 Discussion

This was the first study to attempt to quantify the incidence of severe AKI in the routine elective non-cardiothoracic, non-vascular, non-transplant surgical population. The overall incidence of AKI requiring RRT in this population was rare at 0.11%. However, the occurrence of such severe AKI was associated with significant mortality, with an in-hospital mortality of 26% and a five year all-cause mortality of 55%. Morbidity was also clinically affected. Whilst the majority of patients had recovery of their renal function within two weeks, 7% (3) of the survivors developed ESRF requiring permanent RRT. When compared to the current literature regarding all course AKI in ICU patients, these results compare favourably, with Wald et al who reported rates of 21.7% and 26.6% for persisting requirement for RRT in continuous RRT and intermittent haemodialysis respectively(201) from 2,315 patients over a 10 year period. No significant difference was identified between differing types of RRT in the current study.

When comparing our population to the cardiothoracic population, our population had a lower incidence of RRT. A study of 22,589 patients(183) undergoing cardiothoracic surgery reported an incidence of 1.8% requiring renal dialysis therapy postoperatively, however, this study did not report data concerning recovery of renal function. A more recent retrospective study of 16,1000 patients in the United States(202) also confirmed a

2% incidence of AKI requiring RRT, but also found a statistically significant increase in the development of ESRF with increasing severity of AKI.

In our study in patients that survived their acute episode of AKI, there was a statistically significant reduction in renal function with a mean drop of ~14ml/min/1.73^2, equating to a worse grade of chronic renal failure from CKD 2 to CKD 3. This finding is also supported by the ICU literature with two large studies of 79,000(203) and 233,803(204) confirming increased risk for the development of worsening CRF with severity of AKI. This becomes clinically relevant as patients with CKD stage 2 are mostly managed in the community with lifestyle changes, compared with CKD stage 3 when renal physician input is required and medication for the control of hypertension is normally instigated. Given the added association of CRF with overall mortality and morbidity in the literature(205,206), the subsequent decline in GFR and thus progression in renal damage in these patients would appear clinically important.

Despite the very large number of intensive care patients initially identified, the power of this study remains an issue. Only 43 patients had plasma creatinine values available at the 6–18 month period, allowing for the evaluation of any reduction in GRF. The lack of power of the study may have meant that independent predictive factors that are clinically important may not have been identified. This also prevented the construction of a logistic regression model. Consequently, only duration of ICU stay came close to statistical significance on analysis, and furthermore, was actually correlated with a better long-term renal outcome. Intuitively, one might infer that a longer duration of ICU treatment should be associated with a worse outcome as a surrogate for more severe disease(207,208). However, there is evidence from other studies that support our finding; Lipsett's study demonstrate that whilst mortality and overall cost is increased with prolonged duration of ICU admission, functional and quality of life outcomes were similar to patients who did not require an ICU stay(209). It could therefore be hypothesised that a prolonged period in an ICU results in more frequent observations, earlier interventions, and thus, a reduced severity of complications.

Although this was a case controlled retrospective study with associated shortcomings, this study included a large number of ICU patients from across New Zealand to identify those suffering from this rare complication. Whilst only four of the six ICU units across New Zealand that were approached responded to invitations to participate, these four

centres are the four largest in New Zealand, representing 41.6% of the national population. There was however, significant variation between the prospective databases kept at each institution studied. Some units specifically recorded and coded dialysis, whereas others simply recorded the requirement for a dialysis catheter. Nonetheless, a comparison of hospital clinical coding did not yield any further events of acute dialysis. Notwithstanding the flaws highlighted in the methodology, AKI requiring acute dialysis was rare (0.11%) in this group of patients undergoing elective, major abdominal surgery.

4.6 Conclusion

The incidence of severe AKI requiring RRT in the elective non-cardiothoracic, non-vascular and non-transplant population is rare. However, the sequelae of this are of clinical importance in relation to both in-hospital mortality (26%) and five year all-cause mortality (55%). Long-term renal morbidity was also significantly affected with a mean drop of 14ml/min/1.73m^2 in eGFR resulting in a clinically significant drop from CKD stage 2 to 3. Within the limitations of this study, increased duration of ICU admission appeared to offer long-term protection of renal function. However, given the rarity of severe AKI, what is the clinical relevance for the routine postoperative patient?

Chapter 5 – Perioperative oliguria: Incidence and clinical significance in elective major colorectal surgery

5.1 Background

From the previous chapters, a conclusion can be reached that the occurrence of perioperative AKI in the non-cardiothoracic, non-vascular, non-urological and non-transplant population is uncommon (5.07%). However, in its severest form as defined as the need for RRT, whilst rare (0.11%), has significant risk of mortality and morbidity. Current perioperative fluid management strategies still highlight the potential uses for goal directed therapies based on haemodynamic parameters that still include UO(210,211). However, three recent meta-analyses of these regimes have analysed 15–36 studies looking at the association between correcting UO as a surrogate marker for perioperative renal dysfunction and overall perioperative outcomes(212-214). All three meta-analyses concluded that there was insufficient evidence to target urine outputs in order to prevent AKI. In particular, one meta-analysis found an overall increase in 30 day mortality when correction of low UO was achieved within a goal directed fluid regime(214). However, these studies suffer from significant heterogeneity with regard to patient populations, including cardiothoracic, vascular, ICU, high-risk, paediatric, abdominal and orthopaedic patients. Additionally, each of the studies included in the meta-analyses only identified urine outputs as a secondary measure and thus were not powered to show a difference in outcomes. This paucity of direct data illustrates the need for further research into whether perioperative fluid strategies targeting UO are valid, specifically in the elective surgical population as defined in this thesis.

The mainstay of this thesis therefore relates to the prospective randomised controlled trial challenging contemporary perioperative fluid management, specifically relating to the treatment of UO (Chapter 6). Aspects that are critical to the design of the trial include ascertaining the incidence of perioperative oliguria (as currently defined as <0.5ml/kg/h) in order to correctly power the main trial. Furthermore, with recent literature trending fluid prescriptions towards both operative and postoperative euvolaemia(55,56,215,216), it is imperative to identify current fluid trends and prescriptions at our institution to ensure that there will be sufficient variability to allow the instigation of the randomised controlled trial. Looking at maintenance fluid prescription as well as bolus fluid prescription with indication will give valuable information as to the adherence of

institutional protocols (North Shore Hospital Early Warning Score) regarding the treatment of oliguria.

Basic demographic data and number of patients studied during the retrospective study will also aid the assessment of feasibility and planning of logistics for the main trial. Specifically, this study will identify whether enough elective colon and small bowel surgery is conducted at our institution, in the required population, to allow sufficient time for recruitment or whether a multi-centre trial would be necessary. Logistic regression analysis of the demographic data may also highlight important factors associated with perioperative AKI that would need to be recorded in the formal trial database.

5.2 Objectives

The primary aim of this study was to identify the incidence of perioperative oliguria and AKI, and the fluid prescribed to obviate this. Secondary aims included a logistic regression analysis to identify demographic and operative predictors of the development of AKI.

5.3 Methods

This retrospective study was conducted in accordance with the guidelines published by the National Ethics Advisory Committee of New Zealand(197). Approval was sought from the Awhina Health Campus at WDHB, New Zealand, as formal ethics approval and patient consent was not required for the purposes of audit.

5.3.1 Data extraction

All consecutive adult patients undergoing elective colon, rectal or small bowel surgery under three colorectal surgeons at the North Shore Hospital, Auckland, between January 2009 and July 2010 were retrospectively identified from a prospectively designed and run ERAS database.

5.3.1.1 Demographic data

Basic demographic, operation and complication data was collated and entered into the database by an ERAS clinical nurse specialist in accordance with ERAS collaborative guidelines(217). These data included: age, gender, ASA grade of anaesthesia(218), length of operation (defined as time from skin incision to final closure), weight, height, BMI, type of surgery, approach to surgery defined as laparoscopic (complete or assisted) or open (including conversion to open), and in-hospital plus 30 day complications as diagnosed by

the clinical nurse specialist and clinical teams using the Veteran's Administration Total Parenteral Nutrition Trial criteria(219) and graded as per the Clavien-Dindo classification(220).

5.3.1.2 Specific fluid and haemodynamic data

National Health Index (NHI) numbers were then correlated to electronic and paper-based records and further detailed data were collected on perioperative fluid balance. Intravenous fluid volumes were recorded, both maintenance and bolus fluid administrations defined as a prescription of 250ml a colloid run within a 60 minute period, either 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride (Voluven®, Fresenius Kabi New Zealand Ltd, Auckland, New Zealand) or 4% succinylated gelatin, sodium hydroxide and water (Gelofusine®, Biomed Ltd, Auckland, New Zealand). Indications for fluid blousing were recorded via correlation with patient clinical notes along with concurrent haemodynamic data from the observations charts. Indications were recorded as "isolated oliguria" (without concomitant hypotension of blood loss) or "other" (hypotension or blood loss regardless of association with oliguria). Oliguria was defined as a UO of <0.5ml/kg/h as per current clinical practice(57,58). After 08:00 on postoperative day (POD) 1, UO measurements were reduced to standard ward observations. Consequently oliguria was redefined as <2ml/kg/4hour.

These data were separated into two distinct periods; intraoperatively (being defined as the time of arrival in the preoperative area) and postoperatively (defined as the time of transfer to the postoperative care unit). Intraoperative maintenance fluid therapy consisted of a balanced crystalloid fluid solution of Plasma-Lyte 148® (Baxter Healthcare Ltd, Auckland, New Zealand), while postoperative maintenance fluid therapy was provided by 4% glucose with 0.18% saline solution (Dextrose Saline®, Baxter Healthcare Ltd, Auckland, New Zealand).

If complete fluid balance data was not recorded, patients were excluded from the study.

5.3.1.3 Specific plasma data

Preoperative plasma creatinine data was recorded from the hospital online biochemical portal Concerto. Recent values within four weeks of the planned operation were taken to represent an accurate reflection of the patient's renal function in a normally hydrated state. Plasma creatinine levels were also recorded at 08:00 on POD2 to represent early

postoperative renal function. Furthermore, the highest plasma creatinine level up to POD30 was recorded to capture late "perioperative" renal dysfunction. Any renal dysfunction was then categorised into groups as set out by the AKIN(150). All estimations of GFRs were made according to the Modified Diet in Renal Disease equation(221).

5.3.2 Surgical principals

At the time of this study, whilst ERAS principles were generally adhered to, no formalised ERAS protocol had been instigated at our institution. Therefore, choices of surgical approach, modality of analgesia, bowel preparation and postoperative diet were not standardised, but rather left to surgeon preference. However, all patients were allowed free access to clear oral fluids from POD1.

For data entry, surgical approach consisted of either laparoscopic or open as previously discussed. Perioperative analgesic regimes were left to the assessment of the anaesthetist including epidural or spinal anaesthetic, or a combination of oral and intravenous analgesics including opiate based patient controlled analgesia systems. Epidural anaesthetic was administered via a mid-thoracic approach and consisted of a combination of bupivacaine 0.125% and fentanyl 2mcg/ml(Biomed Ltd, Auckland, New Zealand). Successful epidural analgesia was recorded as successful based on patient self-reporting scores of ≤4 on a numerical scale of 0–10 at 48 hours following operation.

5.3.3 Statistical analysis

Data are reported as proportions, means ± standard deviation or medians (interquartile ranges) where appropriate. For the purposes of the logistic regression analysis of the development of AKI by AKIN criteria (excluding UO as this was a predictive variable), both empirical observations and a detailed literature search were used to identify putative predictors of perioperative renal injury. These included: increasing age (159,167), male gender (160,222), increased ASA class (159,223), increased BMI(161,171), diabetes mellitus treated by oral medication or insulin(159,170), increased duration of surgery(224), intraoperative NSAID therapy(158,225), epidural analgesia, increased number of episodes of perioperative oliguria, increased perioperative UO and decreased perioperative fluid administration.

Using statistical software JMP™(JMP Version 10, SAS Institute Inc., Cary, NC, USA), predictors were individually analysed, adjusting for baseline plasma creatinine levels as

the current definition of AKI. Predictors alongside baseline creatinine were subsequently analysed using backwards linear stepwise regression and basing the optimum model on the Akaike information criterion. Specifically, postoperative plasma creatinine was not normally distributed and the significant skew did not allow for accurate analysis. Accordingly, postoperative plasma creatinine levels were divided into quartiles, allowing for putative predictors of this outcome to be evaluated by multivariate logistic regression. The same 13 factors with the addition of all 30-day complications (Clavien-Dindo grade) were evaluated as predictors of late postoperative creatinine as a surrogate marker for the development of AKI.

5.4 Results

Following identification of all appropriate patients, a total of 176 patients were included in this study. Seven patients were excluded as at the time of surgery, a bowel resection was either not appropriate or contraindicated. A further 29 patients were excluded as the fluid balance data recorded in the clinical notes was incomplete. A total of 140 patients were therefore included in the analyses (Table 5.1).

Variable	(n=140)
Age (years)	66 ± 18
Gender	
Female	76 (54)
Male	64 (46)
ASA class	
1	16 (11)
2	83 (59)
3	40 (29)
4	1 (1)
Weight (kg)	74.7 ± 17.8
BMI (kg/m)	26.7 ± 5.6
Duration of surgery (h)	3.35 ± 1.17
Operation completed laparoscopically	57 (41)
Epidural analgesia working ≥24 hours after surgery (%)	74 (53) *
Type of surgery	
Right sided segmental colectomy	60 (43)
Left-sided segmental colectomy	24 (17)
Subtotal colectomy	5 (4)
Proctectomy (low anterior resection or abdominoperineal resection)	43 (31)
Proctocolectomy	3 (2)
Other #	5 (4)

Table 5.1. Basic demographics

Preoperative eGFR was 93 **±** 42ml·min^{-1}·1.73m^{-2} and 49 (35%), 27 (19%) and 1 (1%) of patients had mild, moderate and severe CKD (eGFR of 60–90, 30–60 and 15–30ml·min^{-1}·1.73m^{-2}), respectively.

Clinical outcomes are presented in Table 5.2. Half of the patients in this cohort had a complication within 30 days of surgery (perioperative period), the majority having complications graded I or II as defined by the Clavien-Dindo complication score(220). Nine patients (6%) required re-operation within the perioperative period; four for an

anastomotic dehiscence, two for a small bowel obstruction, two for an iatrogenic bowel injury and one for fascial dehiscence. Three patients (2%) required intensive care admission following any complication. There were no deaths. Nineteen patients (14%) were readmitted to hospital within the first perioperative period as previously defined.

Variable	(n=140)
Postoperative length of stay (days)	7 (5–10) days
Patients with complications within 30 days	70 (50)
Most severe complication graded I	23 (16)
Most severe complication graded II	32 (23)
Most severe complication graded IIIa	5 (4)
Most severe complication graded IIIb	7 (5)
Most severe complication graded IVa	1 (1)
Most severe complication graded IVb	2 (1)

Table 5.2. Clinical outcomes

Because the data extracted covered two distinct time periods within the patient journey, their analyses have subsequently been divided accordingly. The intraoperative period concerns itself with the time period during which the patient was under general anaesthesia. The postoperative period constitutes the time from the postoperative admission unit, extending out to 48 hours.

5.4.1 Intraoperative fluid balance

The intraoperative fluid balance is presented in Table 5.3. During surgery, patients received 2387 ± 1007ml fluid as continuous infusions and had a UO of 545 ± 458ml. Ten patients had one or more episodes of oliguria during surgery as defined by contemporary practice. Sixty-one patients received fluid boluses; nearly all boluses were given for intraoperative hypotension or bleeding rather than isolated oliguria (Table 5.3). Of the 61 patients who received intraoperative boluses, patients received a mean 2.9 ± 1.4 boluses each. This equated to a clinically relevant additional fluid load of 725 ± 340ml (29%) above and beyond their continuously infused volumes. Estimated blood loss was available for 28 of the 170 patients only, and hence is not expressed in this review.

	Intraoperative period	Postoperative period
Continuous infusions (ml/kg/h)	10.8 ± 6.2	1.1 ± 0.6
Mean UO (ml/kg/h)	2.5 ± 2.7	1.1 ± 0.4
Number of patients with oliguria	10 (7)	117 (84)
Total number of episodes of oliguria	23	765
Number of patients who received fluid boluses	61 (44)	87 (62)
Total number of fluid boluses administered	174	322
For isolated oliguria	4 (2)	185 (57)
For other indications	170 (98)	137 (43)

Table 5.3. Perioperative fluid balance

5.4.2 Postoperative fluid balance

During the first 48 hours after surgery, 3687 ± 1727ml of fluids were given as continuous infusions and patients passed 3761 ± 1231ml of urine (Table 5.3). The vast majority of patients (117 or 84%) had a minimum of one or more episode of oliguria during this period. However, the mean number of episodes among the 117 patients was 6.5 ± 4.5 over the 48 hour postoperative period. Eighty-seven patients received fluid boluses during this period. However, in contrast to the intraoperative period, the majority (57%) of boluses were given for isolated oliguria, i.e. UO <0.5ml/kg/h in the absence of derangements in other vital observations such as blood pressure, pulse or respiratory rates. These 87 patients received 3.7 ± 3.8 boluses each, which to put into clinical context, was equivalent to an additional infused volume of 925 ± 942ml or 22% above the continuous infusions.

5.4.3 Plasma creatinine concentration changes: POD2

In a similar vein to the analyses of fluid administration and urine outputs, changes in postoperative plasma creatinine concentrations were analysed over two distinct time periods. Because not all complications related to surgery become evident within the hospital admission, creatinine concentrations were used as a surrogate marker of AKI within the first 48 hours (hospital admission) and their peak within the perioperative period (when related to complications was defined as within the first 30 days(220)).

Within the whole study population, plasma concentrations of creatinine did not change significantly from preoperative (82 ± 24 $\mu mol \cdot l^{-1}$) to POD2 (80 ± 27 $\mu mol \cdot l^{-1}$). The range of changes was large however, varying from -60 to +45 $\mu mol \cdot l^{-1}$, or percentage change of -51 to +63 %.

Using plasma creatinine concentrations alone as a surrogate to define AKI(226), only four patients (3%) had increases of 50–100%, fulfilling the criteria for AKI stage 1. The creatinine rise was however transient and had normalised by POD30 in all four patients. At no point within the first two days following surgery did the increase in plasma creatinine concentration of any of the patients studied exceed 100%, i.e. no patients developed an AKI stage 2 or greater on creatinine criteria.

5.4.4 Predictors of plasma creatinine concentrations: POD 2

Because only four patients developed AKI based on creatinine criteria, isolated analysis to determine predictors would be inappropriate. Therefore, analyses were performed on the basis of change in plasma creatinine concentrations:

Univariate evaluation (adjusting for preoperative plasma creatinine) of 17 categories of data was undertaken. These analyses identified male gender and epidural analgesia as significantly associated with a higher plasma creatinine on POD2, while the other 11 factors were not (Table 5.4).

Variable	p value	Factor estimate
Age (years)	0.924	-0.056
Male gender	0.050	-21
ASA class	0.624	ASA 1 vs 2: -12 ASA 2 vs 3: -26 ASA 3 vs 4: 54
BMI (kg/m^2)	0.229	2.3
Preoperative eGFR	0.945	0.019
Duration of surgery (hours)	0.002	26
Epidural analgesia used	0.060	19
NSAID used	0.948	1.0
Number of intraoperative and postoperative episodes of oliguria	0.286	2.2
Intraoperative UO (ml/kg/h)	0.777	-1.1
Postoperative UO (ml/kg/h)	0.593	-14
Intraoperative intravenous fluid volume (ml/kg/h)	0.991	0.018
Postoperative intravenous fluid volume (ml/kg/h)	0.713	6.0
0 vs I	0.914	-2.9
I vs II	0.054	-60
II vs III	0.328	38
III vs IV	0.001	240

Table 5.4. POD2 univariate analysis

On multivariate analysis (as described previously), the final regression model ($p<0.0001$, $R^2=0.67$) retained four putative predictors (in addition to preoperative plasma creatinine), of which three were independent predictors: male gender, epidural analgesia and number of perioperative episodes of oliguria (Table 5.5). Thus, 10 factors, including UO and fluid administration were not found to be significant predictors of early postoperative plasma creatinine changes.

Although statistically significant, the parameter estimates were small for the variables identified on both univariate and multivariate analyses (Tables 5.4 and 5.5).

	p value	Factor estimate
Male gender	0.014	3.94
Epidural analgesia used	0.020	3.53
Number of perioperative episodes of oliguria	0.040	0.66
Intraoperative intravenous fluid volume (ml/kg/h)	0.116	0.35

Table 5.5. POD2 multivariate analysis

5.4.5 Peak plasma creatinine concentrations: POD3–30

The distribution of this dependent variable was heavily skewed towards the lower range. At group level, the plasma concentration of creatinine rose significantly from baseline [78 (68–90)] to peak levels [88 (71–112) $\mu mol \cdot l^{-1}$, $p<0.0001$, Wilcoxon signed-rank test].

In addition to the patients with significant increases in plasma creatinine by POD2 discussed previously, by POD30, a further six (4%), one (1%) and five (4%) patients had creatinine increases of 50–100%, >100% and >200%, respectively. Whilst one patient fulfilled the criteria for AKI stage 3, no patients received RRT. Plasma creatinine had normalised by POD30 in all 12 patients.

5.4.6 Predictors of peak plasma creatinine concentrations: POD3–30

Univariate evaluation (correcting for preoperative creatinine) indicated that male gender and increasing complications grades were associated with increasing peak plasma creatinine on POD3–30 (Table 5.6). Multivariate logistic regression analysis yielded a model with an explanatory power of 28% ($p<0.0001$, $R^2=0.285$), retaining three putative predictors (in addition to baseline plasma creatinine). Male gender and increased complications grades were independent predictors in this model. The factor estimates were substantial, in particular for increasing complication grades (Table 5.7). The other factors evaluated, including oliguria, UO and fluid administration were not predictors on univariate or multivariate analyses.

Variable	p value	Factor estimate
Age (years)	0.924	-0.056
Male gender	0.050	-21
ASA class	0.624	ASA 1 vs 2: -12 ASA 2 vs 3: -26 ASA 3 vs 4: 54
BMI (kg/m^2)	0.229	2.3
Preoperative eGFR	0.945	0.019
Duration of surgery (hours)	0.002	26
Epidural analgesia used	0.060	19
NSAID used	0.948	1.0
Number of intraoperative and postoperative episodes of oliguria	0.286	2.2
Intraoperative UO (ml/kg/h)	0.777	-1.1
Postoperative UO (ml/kg/h)	0.593	-14
Intraoperative intravenous fluid volume (ml/kg/h)	0.991	0.018
Postoperative intravenous fluid volume (ml/kg/h)	0.713	6.0
0 vs I	0.914	-2.9
I vs II	0.054	-60
II vs III	0.328	38
III vs IV	0.001	240

Table 5.6. POD3–30 univariate analysis

Variable	p value	Factor estimate
Male gender	0.006	-28
Duration of surgery (hours)	0.007	25
Intraoperative intravenous fluid volume (ml/kg/h)	0.088	2.6
0, I, II and III vs IV	0.002	110
0 and I vs II and III	0.073	18

Table 5.7. POD3–30 multivariate analysis

5.5 Conclusion and discussion

In the present study, the incidence of perioperative oliguria (as traditionally defined) in elective major surgery, and effects on postoperative renal function, have for the first time been quantified. Such oliguria occurred frequently and in the vast majority of patients during the first 48 hours after surgery. It was associated with frequent administration of intravenous fluid boluses, resulting in significant additional fluid volume administration. Despite the importance attributed to urinary output in perioperative care, there was no clinically relevant association between subsequent renal function and perioperative

oliguria, UO, or intravenous fluids volumes. These findings challenge the current practice of maintaining a perioperative UO of ≥0.5ml/kg/h.

However, several independent predictors of renal dysfunction were identified. Renal dysfunction in the late postoperative period, measured as peak concentration of plasma creatinine within the first 30 postoperative days, was independently associated with female gender, duration of surgery and critical illness.

While previous studies have highlighted that substantial fluid overloading occurs in the majority of patients in contemporary surgical care(48,49), the causes of such fluid overloading have not been identified. Fluid overloading results in increased morbidity(39,223,227-231), and balanced fluid therapy is therefore considered a key component in contemporary perioperative care(64). However, attempts at implementing balanced fluid regimens to avoid fluid overloading have been difficult to achieve in practice(48). Despite a relatively high maintenance fluid therapy in this patient cohort, an additional fluid load of some 29% was given as fluid boluses, mostly in response to isolated and uncomplicated oliguria. This research is the first study to identify that episodes of oliguria (as traditionally defined), are a major cause of additional fluid administration. Furthermore, this additional fluid administration may be avoidable, as oliguria was not found to be associated with subsequent renal dysfunction.

The lack of association between perioperative UO and subsequent renal dysfunction in the present study is not surprising. It has long been known that oliguria is a physiological response to injury, preserving sodium and water in the recovering organism(232). This response is primarily mediated by antidiuretic hormone(233), renin-angiotensin II-aldosterone activation(234) as well as an increased sympathetic nerve action(233) on tubular cells. It is a strong physiological response that cannot easily be blunted by excess fluid administration(89,235), an observation that is supported by the present finding of large volumes administered to accomplish a relatively small increase in diuresis.

Although plasma creatinine was an endpoint in this study, rather than AKI, comparisons with previous attempts at linking perioperative UO and the development of AKI can be made. The present study is consistent with such studies, which all refute such a relationship. The largest such study is a multivariate regression analysis of a database of 65,043 patients undergoing general surgical procedures across the United States from 2003–2006(222). This analysis failed to identify perioperative UO as a predictor of

subsequent AKI. Interestingly, recent randomised trials comparing traditional perioperative care with enhanced-recovery care have accepted perioperative UO down to 0.17ml/kg/h(236) or nil(237) as part of protocols, and not reported any cases of AKI.

Certain factors were shown to be associated with plasma creatinine at early (48 hours after surgery) and late postoperative time-points (peak concentrations within the first 30 days after surgery). For early plasma creatinine, three factors were shown to be independent predictors of higher values: male gender, epidural analgesia and number of episodes of perioperative oliguria. However, all predictors had very small factor estimates limiting the clinical relevance of these findings. For example, adjusting for other factors, each episode of oliguria was associated with an increase in plasma creatinine of only 0.66 μmol/L.

During the late postoperative time-point, female gender, duration of surgery and the occurrence of postoperative grade IV complications were identified, with each factor having clinically significant factor estimates. Interestingly, female gender was identified as an important factor in the present study, contrary to findings by Kheterpal et al(222) and a recent review of the literature(238) that identified male gender as a predictor of AKI within the first 30 days of surgery. We cannot explain this finding, but on univariate analysis, baseline plasma creatinine was significantly lower in female than in males.

Duration of surgery was an independent predictor with every extra hour in theatre associated with a peak plasma creatinine rise of 25μmol/L, as were grade IV complications with a factor estimate of 110μmol/L. Importantly, the majority of grade IV complications were septic, and none were isolated AKI. These findings are novel. No recent retrospective(222,223,225) or current literature reviews(224,238) have identified duration of surgery or specifically studied complication grade as positive predictors. These studies included both emergency and elective surgery. Durations of emergency surgeries are often shorter and carry higher risks of complications, which may explain the discrepancy with the present findings.

In contrast to the present study, some previous studies have identified age(53,158,222,224,238), ASA grade(223) and BMI(53,238) as significant predictors of postoperative AKI. Additional factors previously identified include pre-morbid cardiovascular disease(53,222-224,238), hepatic dysfunction(53,222,238), non-insulin dependent diabetes mellitus(222,224,225,238), and nephrotoxic medication

administration (in particular NSAIDs)(158,239), but they were not analysed in the present study as this data was not available.

There are weaknesses with this study. Whilst this is a single-centre study based on prospectively collected audit data and very detailed perioperative fluid balance data, it is significantly smaller than studies employing large multi-centre databases. Secondly, this study was completed prior to the instigation of an enhanced-recovery care pathway, and thus there was considerable variation in intravenous fluids regimens and diet. Consequently, oral fluid intake was poorly recorded and could not be included in analyses. Thirdly, whilst current literature has proposed a link between intraoperative and postoperative nephrotoxic substance administration and renal dysfunction, only intraoperative NSAID use was recorded in the present study. Data on administration of diuretics and postoperative NSAIDs would have been valuable additions to this study.

In conclusion, this is the first study to quantify the clinical problem of perioperative oliguria as it is currently defined. Some 84% of patients had episodes of oliguria in the first 48 hours after surgery. Significant additional intravenous fluid volumes were administered to treat episodes of oliguria in otherwise stable patients. There was no clinically significant association between oliguria, UO, or fluid administration and subsequent renal dysfunction. The rationale behind the current practice of liberal fluid administration to achieve urine outputs of ≥0.5ml/kg/h in the perioperative period can therefore be questioned. Moreover, on the basis of the present and previous studies, the definition of perioperative oliguria as UO of <0.5ml/kg/h can be challenged.

Chapter 6 – High versus low urine output targets in patients undergoing major abdominal surgery: a randomised non-inferiority trial

6.1 Introduction

Along with recent observational data(52,53), the conclusions from the previous study (Chapter 4) suggest that UO was not associated with the development of AKI, as defined by the RIFLE, KIDGO or AKIN criteria. Specifically, UO did not correlate to a change in plasma creatinine levels in the perioperative period. However, perioperative UO remains a measure upon which great importance is placed as a marker of renal hypoperfusion and thus renal injury. Since an association between fluid resuscitation to achieve a UO target of 0.5ml/kg/h and increased survival was demonstrated by two American wartime surgeons (Curtis Artz and John Howard) during the Korean War (1950–1953)(84), the practice of treating both emergency surgical patients in such a manner has persisted and pervaded into the elective surgical population. Current literature continues to dictate that the maintenance of perioperative UO at 0.5ml/kg/h is prophylactic against the development of AKI(57,58,240). The question of whether the observational studies more than 60 years ago in a different population of patients are applicable to the contemporary care of the elective surgical patient is therefore questionable.

This practice also seems at odds with what is currently known about renal physiology in the general population. Based on the kidney's ability to concentrate and excrete the ~500mOsm of solutes produced in the smallest volume of urine possible (400ml), a UO of 0.2ml/kg/h in the community population is physiologically considered to be the definition of oliguria. Below this limit, solutes cannot be further concentrated and reduction in excretion is linearly correlated with a continued reduction in UO(241). The elective surgical patient, who present from this community population, further undergoes a stressful stimulus in the form of surgery. From the early 20th century, the hormonal and neuronal response to such stimuli has been well documented(75,77,242) and is integral to the surgical stress response. The resulting reabsorption of water and electrolytes manifests as an acute reduction in UO(89).

Therefore, the tradition of intravenous fluid administration to overcome a physiological response appears ill founded and unnecessary. Not only may this practice be unnecessary, there is good evidence to suggest that it may in fact be harmful. In a series of randomised

controlled trials from the early 2000s(56,216), liberal intravenous fluid therapy in the perioperative period was shown to increase complication rates in the landmark study by Bridgette Brandstrup in 2003(215). A more recent meta-analysis of these trials by Dileep Lobo's group(39), found that as little as 2–3kg of weight gain from such fluid administration doubles the risk of a complication. Consequently, perioperative euvolaemia has been incorporated into many ERAS protocols in an attempt to obviate this risk. In spite of ERAS protocols reducing intravenous maintenance fluid administration, fluid overload (2–3kg of perioperative weight gain) remains a significant problem. Recent observational studies from some centres have reported an average of >8000ml of fluid administration within the first 48 hours after surgery(49), whilst others have report >50% of patients becoming "overloaded"(48). In keeping with the findings from Chapter 4, these observational studies have highlighted the treatment of perceived oliguria, as traditionally defined as ≤0.5ml/kg/h, as a potential causative factor in perioperative fluid overload. If this contemporary oliguria target in the elective surgical patient was shown to be unnecessary, then this fluid administration could be negated and theoretically the risk of perioperative complications could be reduced.

6.2 Study objectives

We therefore hypothesise that the lower UO target of 0.2ml/kg/h in the elective surgical patient is non-inferior regarding the occurrence of AKI as the traditionally defined target of 0.5ml/kg/h, and results in a lower intravenous fluid administration.

Secondary outcomes were aimed at elucidating perioperative renal physiology, specifically changes in effective renal plasma flow and GFR, renal hormonal variation and the biochemical plasma and urine sequelae.

6.3 Methods

6.3.1 Ethical approval

This prospective, randomised controlled, non-inferiority, open labelled trial was conducted in accordance with the guidelines published by the National Ethics Advisory Committee of New Zealand(197). It was undertaken at the North Shore Hospital, Takapuna, Auckland, New Zealand and was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611001157965).

6.3.2 Study population

All adult patients scheduled for elective colon or small bowel resection at a single-centre (North Shore Hospital, Takapuna, Auckland, New Zealand) were considered eligible for inclusion into the trial. Potential participants were screened from all colorectal clinics in advance. Patients were then approached by the surgical team and invited to discuss the trial with the research fellow, where they were given verbal and written information regarding the trial (Appendix B). Approximately one week following their clinic appointment, patients were then telephoned to confirm their participation. Written consent was obtained from all participants (Appendix A).

Patients were excluded from recruitment if they met certain criteria based on the current literature analysed in previous chapters:

1. Moderate renal impairment as defined by eGFR <60ml/min/1.73^2 given the experimental nature of the study.
2. Previous AKI stage 2 or higher of any aetiology(150).
3. Proteinuria of any aetiology based on an albumin creatinine ratio of ≥30mg/mmol(243), or ≥100mg/dL or protein on morning urine dipstick analysis(244).
4. Previous renal surgery, specifically nephrectomy/single functioning kidney or renal transplantation.
5. Administration of nephrotoxic substances ≤48 hours prior to surgery, including angiotensin converting enzyme inhibitors (ACE), angiotensin II inhibitors, non-steroidal anti-inflammatory drugs (NSAIDS excluding aspirin), aminoglycosides, glycopeptides, diuretics and intravenous radio-opaque dyes.
6. Inability to withhold use of ACE inhibitor, angiotensin II inhibitor, diuretic or NSAID therapy during the perioperative period.
7. ASA ≥ grade IV.
8. Childs-Pugh B liver disease.
9. BMI ≥35 kg/m^2.
10. Pregnancy or breastfeeding.
11. Rectal surgery due to perceived confounding of urinary function from per-sacral neuropraxia.

Intraoperatively, participants were excluded from treatment on the basis of either massive haemorrhage (defined as ≥50% of total blood volume) or ureteric injury. Any participant who met these criteria was nonetheless included in the intention to treat analysis.

6.3.3 Randomisation and blinding

At induction of anaesthesia, participants were allocated to either the control or intervention arm using off site computer generated random sequencing. Participants were assigned in a 1:1 ratio without stratification, to either receive blousing intravenous fluid to maintain ≥0.5ml/kg/h (control) or ≥0.2ml.kg/h (intervention). Due to the nature of the trial, participants were not blinded to their allocation. The intervention was commenced at the time of induction of anaesthesia and continued until 08:00 on POD2.

6.3.4 Outcomes

6.3.4.1 Primary endpoints

As previously discussed in Chapters 1 and 3, the definition of AKI is dependent on the criteria used. Moreover, current clinical and biochemical markers of AKI (plasma creatinine and UO) have significant challenges regarding interpretation, especially in the perioperative period, as they are surrogate markers of renal function and not renal injury per se. Following discussion with international experts in the field, the primary outcome for this trial was chosen to be able to specifically identify renal injury. Biomarkers for the detection of renal injury have been investigated in recent years with NGAL being the most validated to date(125,245-252). NGAL fulfils the majority of important characteristics that are necessary for its use as a surrogate biomarker. It encompasses a significant component to the overall pathogenesis of AKI and at an earlier stage than contemporary surrogate biomarkers, at a point when the injury remains reversible(253). It can delineate between differing types of acute tubular injury, such as pre-renal or intrinsic and it furthermore, has a dose dependent rise in proportion with the degree of injury(254).

A recent meta-analysis of a pooled population of 16,500 surgical and critically ill patients identified a cut-off value of 150ng/mL for the detection of AKI, with an overall (ROC) receiver operator curve of 0.83(130). Whilst the majority of the 58 papers identified in this meta-analysis were in the ICU, cardiothoracic and paediatric populations, one paper (Nickolas) evaluated acute adult surgical trauma patients(255). Their cut-off was well below the 150ng/mL defined in the most recent meta-analysis of 25ng/mL. Given this was

both the lowest cut-off and in a population most similar to our elective general surgical population, this limit was chosen as the non-inferiority limit margin. Urine was collected for analysis between 08:00 and 20:00 on POD1 as the primary endpoint, and analysed as a continuous measure as per Nickolas. Non-inferiority methodology was used as it would have been unethical to use a placebo arm as it would have caused harm. Whilst bias can be introduced via the use of an inappropriate non-inferiority margin, this was taken into account by using a considerably smaller margin than quoted in the meta-analysis(256).

6.3.4.2 Secondary endpoints

Secondary endpoints to further assess for renal injury included serum cystatin C, an alternative but equally well validated marker of renal function (a surrogate of glomerular filtration(257)). Serum creatinines were also recorded at the same time periods as the contemporary marker of renal health to compare these novel biomarkers against contemporary criteria of AKI. Effective renal plasma flow and direct measurements of GFR were also measured pre and postoperatively to investigate the effect of surgery on renal function. Renal hormones renin, aldosterone, angiotensin II and ADH were monitored during the study period alongside all fluid balance data including daily weights where possible. Whilst the trial was not powered to investigate clinical outcomes, these were recorded as a matter of interest.

6.3.5 Trial protocol

The trial period began approximately one week prior to surgery and finished 30 days postoperatively.

6.3.5.1 Preoperative period

Following verbal confirmation of patient enrolment, participants were asked to attend the outpatient department of the North Shore Hospital at 07:30 approximately one week prior to their operation. Baseline blood and urine samples for haemoglobin, creatinine, plasma and urine electrolytes and osmolalities, renal hormones and NGAL were taken using ethylenediaminetetraacetic acid (EDTA) or heparin based collection tubes as appropriate.

Infusion studies for ERPF (effective renal plasma flow) and GFR were commenced at 09:00 and measured by para-aminohippurate (PAH) (10%, Merck; Whitestation, NJ, USA) and sinistrin (25% Inutest, Fresenius Kabi Austria; Linz, Austria) clearance studies

respectively (Appendix D). A five minute bolus of PAH and sinistrin was infused based on calculations to achieve intravascular concentrations of 20mg and 2mg/100ml respectively(118) using an Alaris pump (GH Guardrails, Alaris Medical Systems, San Diego, USA). Continuous infusions were then continued for 180 minutes to obtain steady state within the plasma. Steady state calculations were achieved by multiplying the estimated GFR (ml/min) by 0.2 (estimated as normal extracellular total body water being 20%). PAH clearance was assumed to be approximately five times greater than that of sinistrin(118). Venous blood samples were taken at 160 and 180 minutes to allow an average value to be calculated. Samples were placed in an EDTA tube, chilled and processed immediately. Urine samples, including urine volumes, were also recorded and processed in the same manner. These were stored in a -100°C freezer as backups in case of discrepancies with the serum samples. Serum PAH and sinistrin samples were batch processed at the Canterbury Health Laboratories in Christchurch using a colorimetric method (Shimadzu LC10AD system equipped with an SP20 UV detector and Gilson 203 autosampler).

6.3.5.2 Intraoperative period

This trial was undertaken within an established perioperative enhanced-recovery protocol(6). Preoperatively, participants received 400ml of a 12.5% carbohydrate solution approximately three hours prior to induction of anaesthesia. Oral bowel preparation was not used in accordance with current guidelines(258).

Following randomisation at induction, a urinary catheter was placed using aseptic technique. Urine volume was recorded, a sample taken for urinary electrolytes, osmolality and NGAL with the remainder being discarded. The trial protocol was then commenced. In the control arm, participants were assessed for haemodynamic instability if hourly UO fell below 0.5ml/kg/h. Participants were deemed to be clinically unstable if they exhibited ≥2 or more surrogate markers or end-organ hypoperfusion; MAP <65 mm Hg, heart rate >100/min, respiratory rate >20/min, symptomatic hypotension, and were resuscitated as per clinical indication with a balanced crystalloid, Plasma-Lyte 148® (Baxter Healthcare Ltd, Auckland, New Zealand) or blood if appropriate. In the absence of instability, participants received a bolus of 250ml of PL148® over 15 minutes to bolster their UO. In the intervention arm, participants were clinically assessed if their UO fell below 0.5ml/kg/h (Appendix C) and treated accordingly if they were found to be unstable. If no

instability was present, UO was simply monitored and only intervened upon with a bolus of 250ml of Plasma-Lyte 148® over 15 minutes if it fell below 0.2ml/kg/h (Appendix C). All intravenous fluid was administrated using Alaris pumps (GH Guardrails, Alaris Medical Systems, San Diego, USA).

During surgery, participants received 5mL/kg/h of Plasma-Lyte 148® and 5mL/kg/h of 4% succinylated gelatin, sodium hydroxide and water (Gelofusine®, Biomed Ltd, Auckland, New Zealand). A further 500ml of Plasma-Lyte 148® and 500ml of Gelofusine® were infused if the event of a prolonged operation time greater than three hours. After individualised induction, anaesthesia was maintained using desflurane. In the event of open surgery, analgesia was provided by mid-thoracic epidural analgesia (bupivacaine 0.125% and fentanyl 2mcg/mL) during and 48 hours after surgery. For laparoscopic surgery, epidural or intrathecal (morphine) analgesia was used. Hypotension during surgery was treated with vasopressor infusion or boluses of packed red blood cells if appropriate.

Venous blood and urine sampling was undertaken at 2 hours, 6 hours and 10 hours following induction of anaesthesia and at 08:00 and 20:00 thereafter until 08:00 on POD3. Venous samples were taken from a dedicated sampling 16guage Venflon™withdrawing 5ml and discarding prior to serum sampling. The cannula was then locked with 5ml of heparinised saline 10units/ml.

6.3.5.3 Postoperative period

After completion of surgery, participants were maintained with 500ml of glucose with 0.18% saline (Dextrose Saline®, Baxter Healthcare Ltd, Auckland, New Zealand) until 08:00 on POD1 when all maintenance intravenous fluid administration was discontinued. Participants were encouraged to commence an oral diet from four hours from extubation.

At 09:00 on POD1, the ERPF and GFR studies were repeated using the same methodologies described for the preoperative measurements.

The fluid bolus protocol was continued at 08:00 on POD2. Urine output was measured using an hourly urometer catheter. To ensure human error was avoided, total UO was also measured at each sampling time-point using a graded measuring cylinder.

Participants were follow-up at POD30 and any perioperative complications were recorded as per the Clavien-Dindo classification(220).

6.3.6 Statistical analysis

All statistical analyses for this trial were performed using JMP 11.2 for Mac OS X (SAS Institute, Cary, NJ) with oversight from the WDHB appointed statistician Lifeng Zhoo.

6.3.6.1 Power

Power calculations for this non-inferiority trial were based on a recent study on the development of AKI in trauma patients(259). Their study compared uNGAL values of 10µg/L compared to 25µg/L as a limit for AKI and found a sensitivity and specificity of 91% and 95% respectively. Based on these results, an absolute increase of 15µg/L or a relative increase of 2.5 times the value of uNGAL compared to the 0.5ml/kg/h was used.

In order to demonstrate non-inferiority based on the above data, at a power of 90% and using a one-sided unpaired t-test with the standard medical significance criterion of 0.05, 18 participants would be required in each group. Given that the required recruitment was relatively small, a dropout rate of 10% was included for safety, leaving 20 participants per group required.

An independent safety monitoring committee was set up given the nature of the study. Trial data and clinical outcomes were analysed following completion of participant 4 and 20 to ensure trial safety. Specific patient data was analysed as required in the event of a serious complication.

6.3.6.2 Specific biochemical assays

Urine NGAL was analysed at the Canterbury Health Laboratories using chemiluminescent microparticle immunoassay (Architect ci8200 analyser, Abbott Diagnostics, Chicago, Illinois, USA). Samples were analysed in duplicate to reduce error. Normality testing for uNGAL showed non-normal distribution and was subsequently transformed to log-normal with a non-inferiority margin of 0.92 (ln2.5) being used.

Serum cystatin C was determined by particle-enhanced immunonephelometry (Dade Behring Marburg GmbH). Cystatin C was normally distributed with a non-inferiority increase of 0.4mg/L being used(260).

Serum creatinine was used with an absolute increase of 26.4 μmol/L being used as a definition of AKI stage 1(261).

ERPF and GFR had limits set at 100ml/min and 30ml/min/1.73^2 respectively(118).

6.3.6.3 Other biochemical assays and clinical outcomes

For secondary biochemical endpoints for repeated measurements such as osmolalities and renal hormones, differences within and between the groups were evaluated by two-way mixed-effects analysis of variance (ANOVA) with post-hoc testing by Tukey's honestly significant difference test.

Concerning clinical outcomes and other non-repeated measures, Mann-Whitney's test, Fisher's exact test, and multivariable linear regression were used as required.

6.4 Results

Potential participants were screened through the colorectal clinics at the North Shore Hospital between November 2011 and July 2013. Of the 212 patients screened, 134 were eligible of whom 75 declined to participate (Figure 6.1). The main reasons for exclusion participation was moderate chronic renal impairment as defined as an eGFR of <60ml/min/1.73^2 (Table 6.1).

Exclusion criteria	Potential participants
eGFR <60ml/min/1.73^2	26
Cognitive/emotional inappropriateness	16
Age > 85 years	11
BMI > 35	10
Previous renal injury	5
ASA ≥ IV	4
Ongoing requirement for nephrotoxic medication	3
Previous AKI > stage 2	1
Other	14
Total	90

Table 6.1. Exclusions

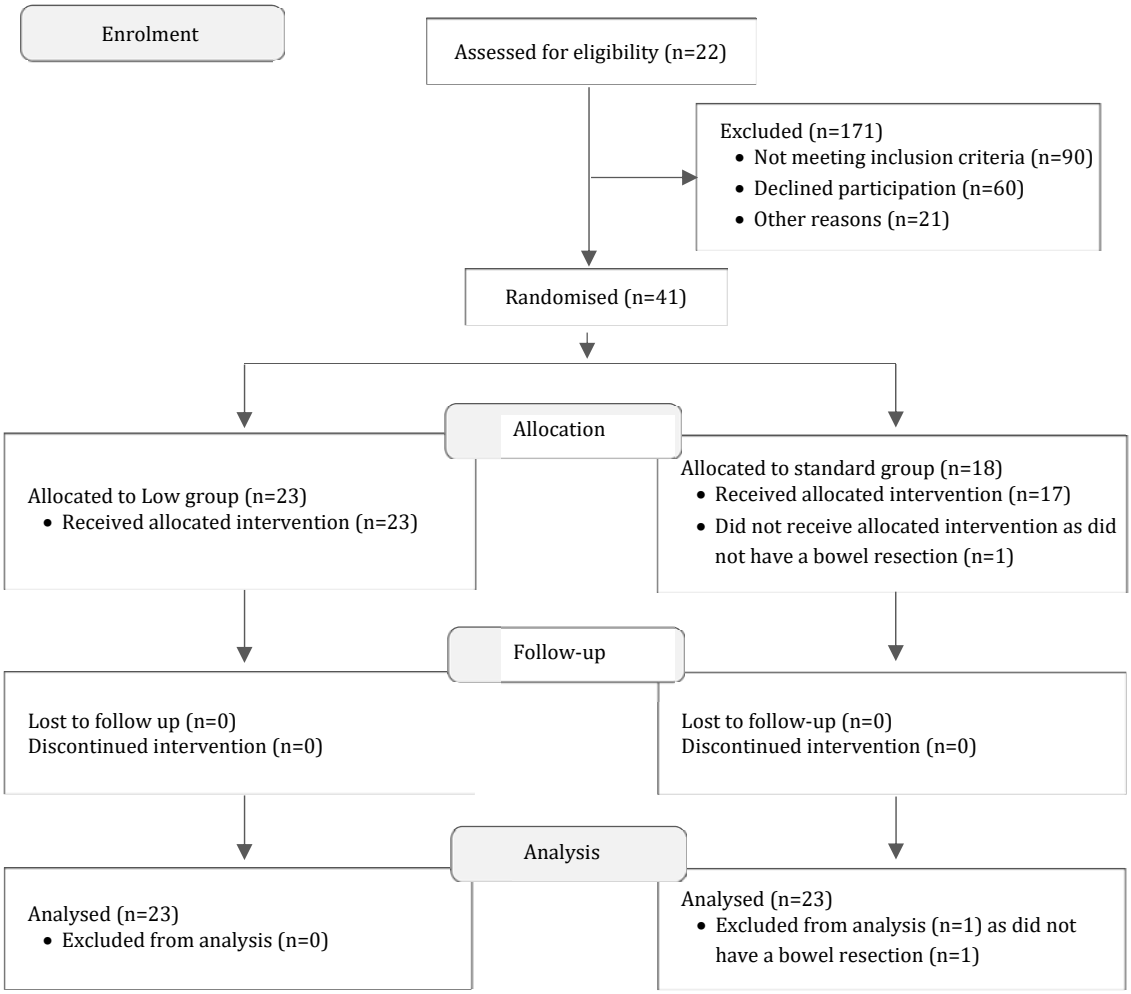


Figure 6.1. Enrolment flow chart

After exclusion and participant declination, 44 patients were enrolled in the study. At induction of anaesthesia, 41 patients were randomised to either the intervention of 0.2ml/kg/h group (n=23) or the standard of 0.5ml.kg/h group (n=18). One patient was excluded from the overall analysis as they did not undergo a bowel resection at the time of laparotomy secondary to unresectable disease (Figure 6.1).

6.4.1 Demographics

Basic demographic data is described in Table 6.2. The two groups were matched for their baseline and intraoperative demographics with the exception of working epidural anaesthesia, which was statistically higher in the 0.5ml/kg/h control group (p=0.006).

	0.5ml/kg/h (Control group) n=17	0.2ml/kg/h (Intervention group) n=23
Age (years)	66 (12.6)	67 (8.6)
Sex		
Male	5 (29%)	8 (35%)
Female	12 (71%)	15 (65%)
Weight (kg)	80.1(8.9)	82.8 (14.0)
BMI (kg/m^2)	27.4 (3.26)	27.8 (3.63)
Duration of surgery (minutes)	240 (75)	180 (59)
Laparoscopic surgery	11(65%)	13 (57%)
Working epidural ≥ 24 hours	15 (88%)	14 (61%)
Surgical resection		
Right hemicolectomy	3 (18%)	15 (65%)
Left hemicolectomy	13 (76%)	8 (35%)
Total colectomy	1 (6%))	0 (0%)

Table 6.2. Basic demographics

6.4.2 Fluid balance

During the interventional portion of the trial, total fluid volumes between the two groups were significantly different (p=0.0004) with the 0.5ml/kg/h control group receiving 2320ml extra fluid. On more in depth analysis of the fluid prescriptions, the difference was found to be secondary to bolus administration for isolated oliguria (p<0.0001) as per the design of the trial, compared to maintenance intravenous fluid therapy being statistically similar (p=0.856) (Table 6.3). Oral fluid intake was similar in both groups (p=0.344).

UO was lower in the 0.2ml/kg/h intervention group as expected from the trial design (p=0.03) (Table 6.3). A physiological recovery diuresis was noted on POD1 but approximately 6 hours earlier in the 0.2ml/kg/h group as compared to the 0.5ml/kg/h group (Figure 6.2).

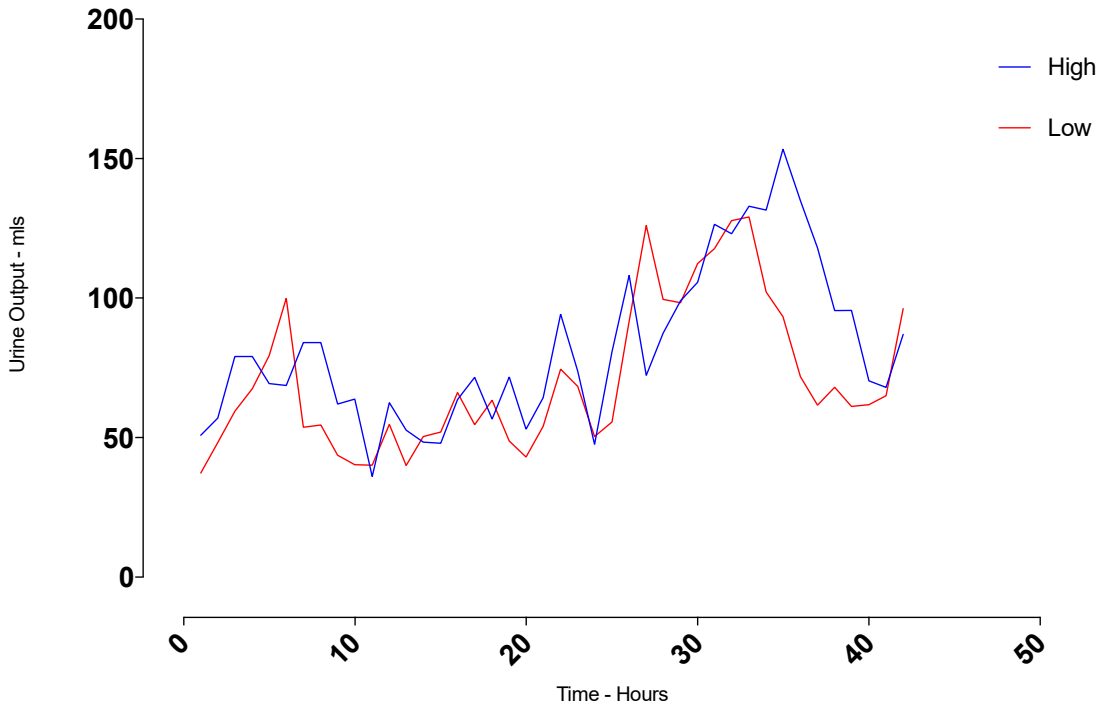


Figure 6.2. Mean urine output

Whilst every participant in the study had a least one episode of oliguria as defined by the traditional <0.5ml/kg/h target, participants in the 0.2ml/kg/h intervention group had more episodes: 21.5(18.4–24.5) versus 8.6(5.0–12.2, p<0.0001). Four participants in the 0.2ml/kg/h intervention group received boluses (n=8) for clinical end-organ hypoperfusion compared to only two participants (n=3) in the 0.5ml/kg/h control group. Of note, one of these participants in the 0.2ml/kg/h returned to theatre on POD1 secondary to intra-abdominal haemorrhage, requiring four of the eight boluses in this group.

Regarding total fluid balance, there was no statistically significant difference between the two groups (p=0.11). However, taking into consideration resection specimen weight, overall change in body weight approached statistical significance between the groups: 0.28kg(-1.03–0.47) in the 0.2/kg/h intervention group compared to 0.85kg(-0.02–1.73) in the 0.5ml/kg/h control group (p=0.053).

	0.5ml/kg/h (Control group)	0.2ml/kg/h (Intervention group)	p
Total IV fluids, ml	5490 (4570–6410)	3170 (2380–3960)	0.0004
IV fluid boluses, ml	3010 (2230–3700)	645 (56–1230)	<0.0001
IV maintenance fluid, ml	2470 (2060–2890)	2520 (2160–2880)	0.856
Oral fluids, ml	2980 (2260–3700)	3430 (2810–4050)	0.344
UO, ml	4470 (3710–5230)	3360 (2700–4010)	0.030
Total fluid balance, ml	3840 (2600–5090)	3034 (1970–4100)	0.323

Table 6.3. Fluid balance

6.4.3 Markers of acute kidney injury

6.4.3.1 uNGAL

uNGAL was collected a various different time points during the trial: 0, 2, 6 and 10 hours after induction, then at 08:00 and 20:00 on POD1, 2 and 3, with a follow-up measurement at POD30.

For the purposes of the primary endpoint, uNGAL was collected during from 08:00–20:00 on POD1. The 0.2ml/kg/h intervention group was non-inferior to the 0.5ml/kg/h control group whether analysed as concentration, excretion or uNGAL/urinary creatinine concentrations (Table 6.4).

	0.5ml/kg/h (Control group)	0.2ml/kg/h (Intervention group)	p
uNGAL concentration 08:00–20:00, µg/L	18.4 (8.3–21.2)	14.7 (7.6–28.9)	0.0011
uNGAL excretion 08:00–20:00, mg	13.9 (8.19–22.0)	12.7 (7.05–16.0)	<0.0001
uNGAL / creatinine concentration 08:00–20:00, µg/g	17.0 (11.9–22.1)	13.6 (9.05–21.3)	<0.0001

Table 6.4. Urinary neutrophil gelatinase-associated lipocalin

Furthermore, both mean uNGAL concentrations and total excretion of uNGAL ($P_{\text{non-inferiority}}$ <0.0001) throughout the duration of intervention (up to 08:00 on POD2) were non-inferior between the groups (Figure 6.3).

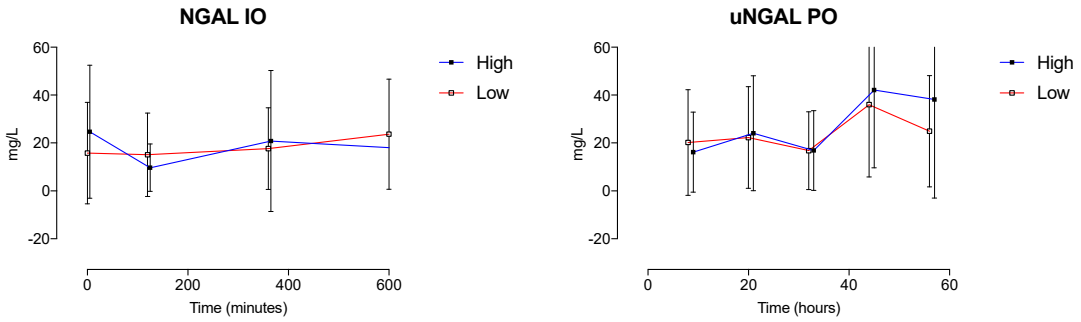


Figure 6.3. Perioperative uNGAL

6.4.3.2 Cystatin C

Likewise, cystatin C (as an estimate of GFR) was similar between the groups at both the primary endpoint (08:00 on POD1) and throughout the intervention ($P_{non\text{-}inferiority}$ <0.0001; Figure 6.4).

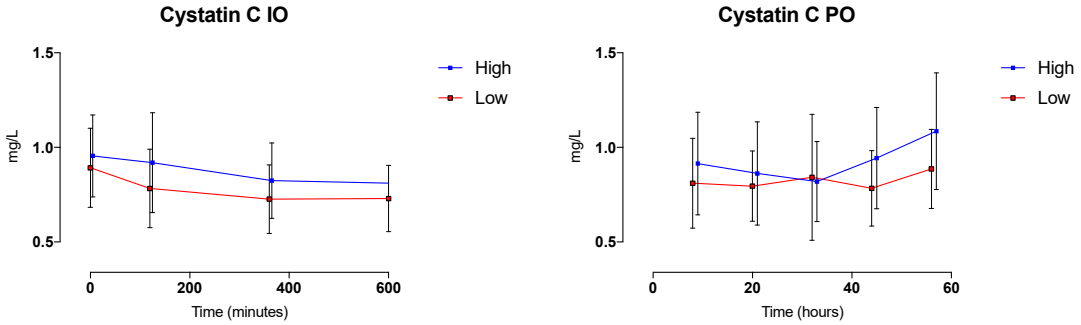


Figure 6.4. Perioperative cystatin C

6.4.3.3 Creatinine

Using contemporary clinically available markers of renal health, serum creatinine remained similar between the groups at 08:00 on POD1 and throughout the intervention period ($P_{non\text{-}inferiority}$ <0.0001; Figure 6.5). The analysis remained non-inferior if baseline creatinine was accounted for.

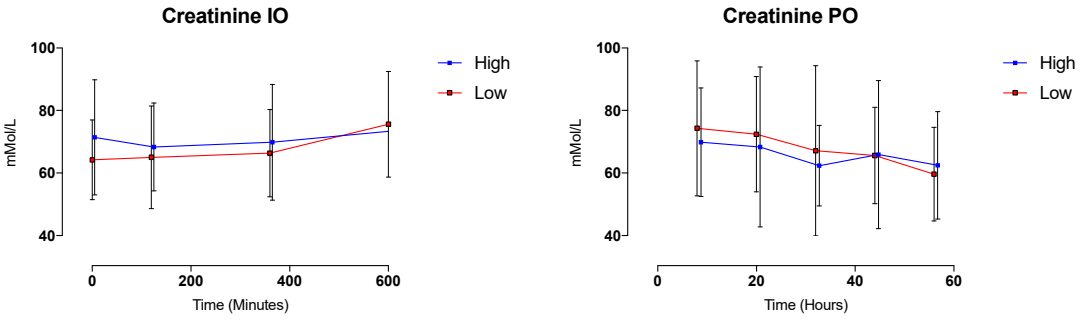


Figure 6.5. Perioperative creatinine

On creatinine criteria, AKIN stage 1 occurred in 2/17 (12%) and 4/23 (17%) in the 0.5ml/kg/h and 0.2ml/kg/h groups respectively. AKIN 2 occurred in 0/17and 1/23 respectively.

6.4.4 Renal hormones

Using a repeated measures ANOVA, there were no significant differences between groups during the study period (Table 6.5).

Renal hormone	p value
Renin	0.207
Aldosterone	0.120
ADH	0.433
Angiotensin II	0.322

Table 6.5. Renal hormones

However, there were significant statistical differences between baseline and two hours post induction of anaesthesia in all hormones (Figure 6.6). This would be consistent with the stress response to surgery observed by Lewis in 1952(79).

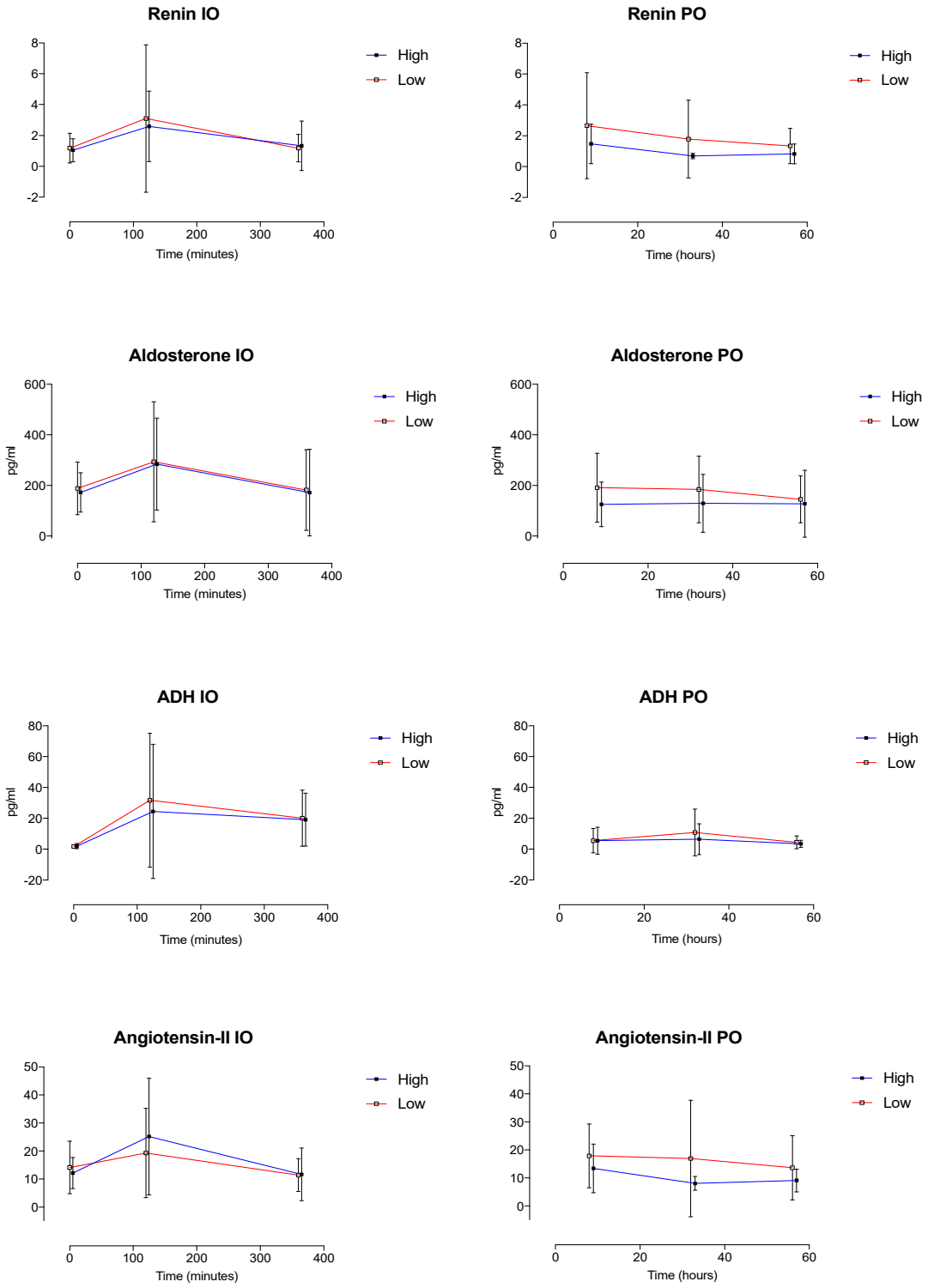


Figure 6.6. Renal hormones

6.4.5 Urinary electrolytes

Likewise, there was no significant difference between groups regarding urinary electrolytes and creatinine throughout the study intervention. However, there were significant differences between baseline and 08:00 in urinary potassium and urinary

osmolality (p=0.049, p=0.024; Figure 6.7). This again reflects previous work on renal physiology where sodium is retained in times of stress at the expense of potassium(79).

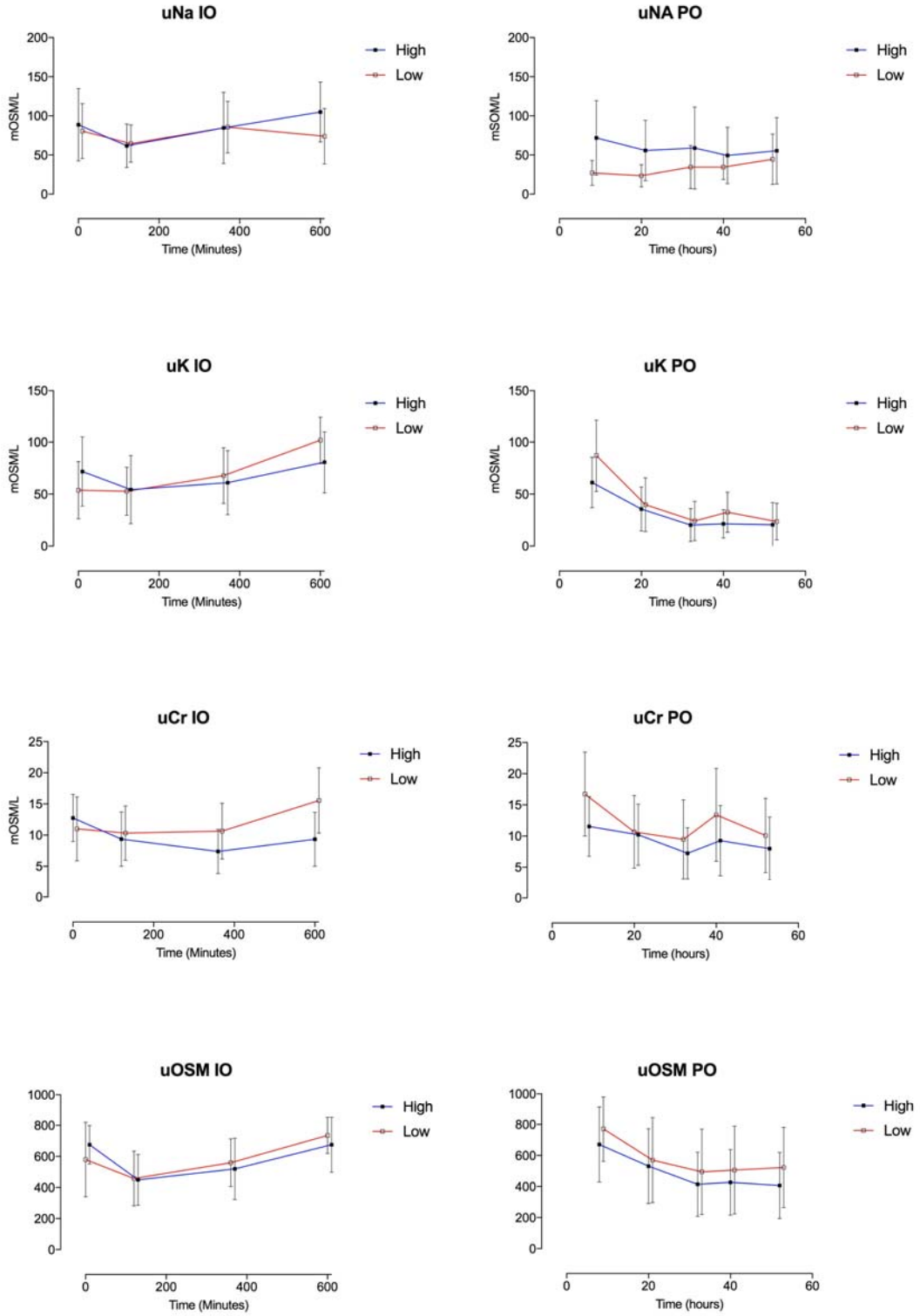


Figure 6.7. Urinary electrolytes

6.4.6 Renal function studies

A statistically significant difference was found between groups when comparing the response to surgery on ERPF (p=0.0339). Participants in the 0.5ml/kg/h group had a greater absolute increase in their ERPF in the postoperative period than compared to those in the 0.2ml/kg/h group (Figure 6.8). However, there was not a statistically significant change between pre and postoperative values if analysed as a whole group.

Conversely, GFR remained similar in both groups, however, there was a statistically significant difference between pre and postoperative values (p=0.0334; Figure 6.8), with participants seeing an increase in filtration rates in the postoperative period.

Given the percentage of working epidural anaesthesia was significantly different between the two groups, a multivariate linear regression model was run to elucidate any association with the primary and secondary outcomes. Only postoperative GFR was significantly associated with epidural anaesthesia (p=0.034, R^2=0.17). Those with working epidural anaesthesia had a smaller increase in GFR (15.9ml/min/1.73^2) compared to those that did not (33.9ml/min/1.73^2).

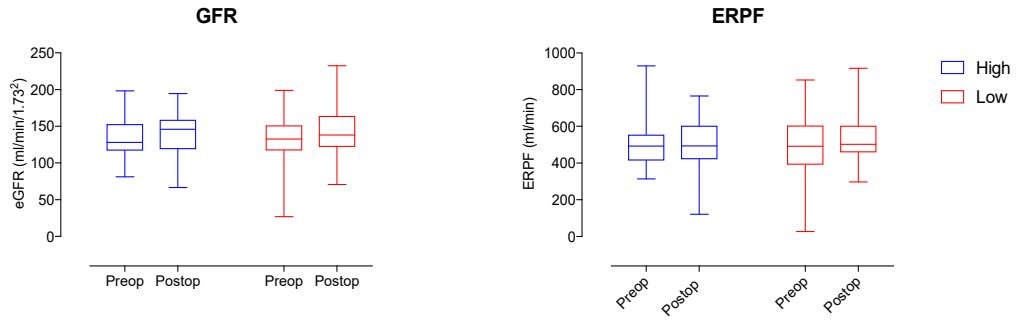


Figure 6.8. GFR and ERPF studies

6.5 Discussion

The findings from this trial show that in the perioperative period, a reduction in the UO target from 0.5ml/kg/h to 0.2ml/kg/h is non-inferior when comparing multiple contemporary and novel markers of renal health. Consequently, we have managed to show a reduction in perioperative intravenous fluid administration of approximately 2300ml. These findings challenge the principles of surgical perioperative fluid management that have been doctrine since the 1950s.

Since the landmark study by Bridgette Brandstrup(215), a reduction in perioperative fluid administration has shown to reduce the relative risk of associated morbidity. In these trials, a reduction in intravenous fluid prescription was achieved through maintenance fluids alone. However, with the advent of ERAS protocols, maintenance fluid administration in the perioperative period was standardised and subsequently had less of an impact on overall fluid overload. The results of this trial show that a further 2300ml of unnecessary fluid, in the form of intravenous blousing, can be obviated. These volumes of fluid are clinically important, with recent literature has demonstrating that volumes of excess intravenous fluid of between 2300–3800ml in the perioperative period are associated with a relative increase in complications of 36–45%(56,216) and a reduction in return to normal gastrointestinal physiology(30). These results are further backed up by a recent international multi-centre retrospective study of >1900 patients treated within an ERAS protocol that found fluid overload was an independent predictor of complications (Odds ratio 0.35)(262).

Whilst the sample size for this trial was small, multiple measures of renal health were used to evaluate any potential harm. Specifically, a subtle change in uNGAL was used to power the trial (15µg/L), based on only one small study of trauma patients. However, Hasse and Lobo(125) recently conducted a meta-analysis of uNGAL values to establish a cut-off for the detection of renal injury. They concluded that a value of 150µg/L was sensitive enough to detect early renal damage. Therefore, the findings from the present study can be considered valid to prove non-inferiority with the addition that no participants in the intervention group had uNGAL values that exceeded the 150µg/L cut-off. Furthermore, the above trial was of a size that, whilst adequately powered, also allowed for detailed recordings of clinically relevant fluid balances on an hourly basis, as well as frequent and multiple assessments of renal health and physiology. The trial was complete within an ERAS protocol that allowed for more accurate analysis of the data, given that the groups remained standardised with regards to all other ancillary postoperative care.

Non-inferiority was demonstrated with not only the primary endpoint, but also with all secondary endpoints of renal health. However, non-inferiority was not demonstrated in postoperative GFR, with the intervention group having a smaller increase than the control. Whilst the difference was statistically significant, both groups had an increase that would be contrary to expected pathophysiology of renal injury. This is perhaps

explained by the increase in cardiac pre-load from intravenous therapy (hence a smaller rise in the intervention group) in combination with the surgical stress response as demonstrated by an increase in the renin-aldosterone, angiotensin axis and subsequent increase in urinary osmolality. There is sparse data on ERPF and GFR in the non-cardiothoracic surgical patient, with only one study in the orthopaedic population finding no difference between pre and postoperative values(263). However, the study only looked at changes in the immediate postoperative period.

6.5.1 Limitations

Given the small sample size, interpretations concerning clinical outcomes cannot be made. Having said this, there were no significant differences found between hospital lengths of stay or complication grade. Specifically, two patients in both the trial and control group had grade 3 or greater complications as per the Clavien-Dindo classification. One patient in each group developed an anastomotic leak requiring radiological percutaneous drainage, however they were discharged within 10 days of their operation. One patient in the control group developed a drug interaction with Tramadol and Felodpine leading to a significant natriuresis, resulting in an acute drop in serum sodium to 117 and seizure. The patient was admitted to the North Shore ICU where the medications were stopped and the sodium corrected. There were no clinical sequalae and the patient was discharged on POD7. After review of the data by the independent monitoring committee, no association was found between the fluid therapies prescribed in the trial protocol. One patient in the intervention arm unfortunately died as a result of a postoperative myocardial infarction. In the early hours of the morning of POD1, the patient became unstable with tachycardia, hypotension and oliguria. As per the trial protocol (Appendix C), the patient was immediately resuscitated and investigated with a CT scan, finding an anastomotic haemorrhage. The patient returned to theatre for control of the haemorrhage by 08:00 on POD1. Following this, the trial protocol was continued and completed on POD3. The patient recovered well and was ready for discharge. Unfortunately on the evening of POD5, the patient was found in cardiac arrest in his chair and was unable to be resuscitated. He had a strong family history of significant cardiovascular disease with every male member of the family dying of myocardial infarction in their 50s. After review by the independent monitoring committee, no association between fluid administration and the myocardial infarction was identified, given the event occurring 48 hours post completion of the trial when intravenous fluid administration had ceased.

In both cases of grade 4 complication or above, the trial protocol and biochemical analysis identified the respective complications at an earlier stage than would have been otherwise clinically identified, thus potentially introducing bias into the interpretation of any difference in complications rates.

Of the minor complications (grade 1 or 2), there were 10 and 7 respectively in the intervention and control group. The majority of the complications were superficial wound infections with three patients developing a postoperative ileus of whom one in each group required temporary intravenous nutrition to POD10. One patient in each group developed a cardiovascular complication, with the patient in the intervention arm developing atrial fibrillation which resolved with oral metoprolol, and the patient in the control group developing congestive heart failure secondary to intravenous fluid therapy. From the available literature, fluid balance is clearly important in relation to complications, however, the numbers in this trial are not sufficient to identify any statistically significant difference in clinical outcomes.

Secondly, lack of clinical blinding could be considered to contribute to a type 2 error in a small trial. However, this is unlikely to be a confounder in this case as the assessments were numerical biochemical endpoints reported by laboratory staff who were blinded to participant intervention.

Finally, the findings are limited in their generalisability, as patients with moderate or severe chronic renal impairment were excluded from this trial. Thirty-five (15%) of all patients screened were excluded on this basis. Whilst there was also no difference between groups with mild renal impairment or normal renal function, stratification and block randomisation could have been used to ensure equal numbers of each sub-group.

6.6 Conclusion

This study has demonstrated that adopting a lower UO target of 0.2ml/kg/h in the patient undergoing elective bowel resection without significant risk factors for the development of renal injury as non-inferior to chasing the current target of 0.5ml/kg/h using uNGAL as a surrogate biomarker of renal tubular injury. Crucially, by adopting this simple intervention, the volume of perioperative intravenous fluid therapy can be reduced, helping to avoid excess fluid administration which may be associated with increased complications.

Chapter 7 – Summary of results

This thesis aimed to answer the following questions regarding perioperative renal physiology:

1. Within the available literature, what perioperative factors correlate with the development of perioperative AKI?
2. Severe AKI is associated with both mortality and morbidity in the general population. Specifically, how important is it to avoid in our study population i.e. the elective non-cardiothoracic surgical patient?
3. If perioperative oliguria is not associated with AKI, then using current definitions, how common is it and what are its sequelae?
4. With the availability of newer biomarkers of AKI, can we ascertain whether perioperative UO is related to the occurrence of subsequent AKI? If it is not, what are its underlying mechanisms?

The first study described a systematic review of potential risk factors for the development of perioperative AKI. The literature was searched using the PRISMA guidelines(155) between 1995 and 2016. The search identified 2,257 results of which 20 were deemed relevant to the major elective non-cardiothoracic, non-vascular, non-urological and non-transplant population. Quality assessment of each study and analysis of the combined data was performed on the extracted data and identified that increasing BMI and perioperative use of angiotensin II converting enzyme inhibitors are risk factors in the development of perioperative AKI. The presence of diabetes, CRF, pre-morbid functional status and male gender were also identified as potential risk factors that should alert clinicians to the need for a higher degree of vigilance to prevent AKI in the perioperative period.

The second study described a multi-centre cohort of patients undergoing major elective non-cardiothoracic, non-vascular, non-urological and non-transplant population. Data extracted from four ICUs, representing 42% of the national population revealed an incidence of 0.11% for patients who developed complications resulting in AKI that required acute RRT. Whilst the incidence is clearly rare, the consequences are significant with an in-hospital mortality rate of 26% and a five year all-cause mortality rate of 55%. Morbidity was significantly affected with survivals having a reduction in eGFR of

14ml/min/1.73^2, clinically correlating with an increase from mild to moderate renal impairment (Figure 4.3).

The third study described a retrospective study of prospectively collected data at North Shore Hospital, Auckland, New Zealand. Anecdotally, UO is used to assess renal function in the perioperative period, but neither of the previous studies highlighted this as a risk factor for the development of perioperative AKI. Of the 140 patients assessed between January 2009 and July 2010, 84% developed AKI as defined by a UO of <0.5ml/kg/h, with an average number of episodes per patient of 6.5 ± 4.5. These episodes resulted in a mean fluid challenge of 925 ± 942ml per patient aimed at treating isolated periods of oliguria. Given the meta-analysis by Lobo(30), which showed that even modest salt and water retention resulting in 2–3 kilograms of weight gain in the perioperative period doubles the risk of complications, these findings are important. Specifically, in both univariate and multivariate analysis, this study refutes the dogma that decreased UO directly correlates with a deterioration in postoperative renal function. This finding indicates that there is a need for a change to the current accepted UO requirement in the perioperative period.

The fourth and final study described a randomised controlled, non-inferiority trial aimed at challenging the contemporary perioperative UO target of 0.5ml/kg/h. Following power calculations, 41 patients undergoing elective small bowel and colonic resections at North Shore Hospital between November 2011 and July 2013 were randomised to one of two arms. They received fluid boluses to bolster UO above either the conventionally accepted limit of 0.5ml/kg/h or a limit of 0.2ml/kg/h (defined by renal physiology). Patients in both groups were otherwise treated as per local ERAS protocol. The primary outcome was occurrence of AKI as defined by an increase in uNGAL between 08:00 and 20:00 on POD1. uNGAL concentrations were non-inferior between the two groups ($P_{\text{non-inferiority}}$ <0.0001). Other more contemporary markers of renal health, creatinine and more robust estimates of GFR cystatin C also showed non-inferiority between the two groups ($P_{\text{non-inferiority}}$ <0.0001).

Secondary outcomes looking at perioperative renal physiology revealed the activation of the renin-aldosterone-angiotensin II system, and more importantly, the release of ADH within hours of induction of anaesthetic. This resulted in a lower physiological UO, confirmed on analysis of urinary osmolalities as an increase in salt and water retention as opposed to a reflection of pathology i.e. AKI. Furthermore, these physiological

mechanisms were not reduced by the presence of epidural or spinal anaesthesia, with a paradoxical increase in both ERPF and actual GFR ($p=0.0339$ and $p=0.0334$).

Chapter 8 – Discussion and conclusions

As highlighted in this thesis, AKI is an important consideration for the safety of the perioperative patient, with an increased relative risk of morbidity and mortality(264). In particular, major surgery in isolation was found to be the second commonest predisposing factor for the development of AKI(265). This is also an important public health consideration with a significantly increased financial outlay compared to patients who have an uncomplicated recovery(266). Furthermore, with an increasingly aged and comorbid population, the incidence of perioperative AKI is likely to increase dramatically. Specifically concerning comorbidities, a recent analysis from Europe(267) identified 20% of its perioperative non-cardiac surgical patients to have a degree of chronic renal impairment, a probable risk factor for the development of perioperative AKI as outlined in Chapter 3. Perioperative AKI, particularly its incidence, is however difficult to study as types of surgery vary considerably as do patient populations undergoing each type of surgery(268). Compounding this issue further is the heterogeneity in definitions of AKI that can lead to statistically significantly differences in incidence, depending on which criterion is used and whether each criterion uses only biochemical endpoints (decrease in GFR) or UO(269).

Additionally, the majority of research appears to target the cardiovascular surgical population and depending on definition, perioperative AKI can be as common as 30%(270-272). However, studies investigating the non-cardiac surgical population reveal that a substantial number incorporate vascular surgery(273,274) or acute admission(275-278) into this major non-cardio population—a significant population bias.

Chapter 3 explored these issues with regard to the most commonly performed major surgeries: the major elective non-cardiothoracic, non-vascular, non-urological and non-transplant population. To our knowledge, this is the first study to investigate suspected and potentially modifiable risk factors in this specific and common population. In concordance with individual literature, CKD, established and medically treated diabetes, male gender and poor pre-morbid functional status places patients at an increased risk for the development of perioperative AKI(279). Use of ACE inhibitors and increased BMI were found to be potential risk factors for the development of AKI in this subset of patients, which can be addressed in the preoperative period.

However, with the lack of a unified definition(147,149,280), perioperative AKI is a difficult topic to investigate as underlined by the systematic literature review. Chapter 4 attempted to address this issue by using the need for RRT in the perioperative period as a predetermined endpoint. Whilst making selection criteria more definitive, this endpoint also allowed the investigation of those who were affected the most severely. This is of particular importance given that approximately 30% of patients admitted to ICUs have, or will develop, AKI(281,282), of whom between 3–8% will require RRT(251,283). Given surgical patients contribute almost 50% of the workload to ICUs(284), defining the incidence and severity of AKI in this population is of importance.

With a representative sample of the national population, Chapter 4 found that AKI requiring RRT is rare, with an incidence of 0.11% in the elective major non-cardiothoracic, non-vascular, non-urological and non-transplant population. Whilst rare, the sequelae of such severe AKI are stark with five year survival only at 45% in keeping with the current literature of all-cause mortality in the intensive care population as a whole(285), but with an increased rate of in-hospital mortality (26%). In addition, amongst the survivors there was a statistically significant and clinically relevant drop in stage of CKD on average from CKD 2 to 3, along with a reduced need for continued RRT of 7% compared to ~25% in the combined intensive care population(201). This is the first research that specifically assessed the impact of severe perioperative AKI in the elective major non-cardiothoracic, non-vascular, non-urological and non-transplant population, with the vast majority of patients (75%) coming from the general surgical population who developed a septic complication resulting in AKI. In itself, this is an important finding emphasising the rarity of AKI as an isolated complication, but also that it appears to predominantly affect the general surgical population. Consequently, it can be argued that following identification of patients potentially at risk in the preoperative period, monitoring for the development of general complications postoperatively may be of more value than exclusively trying to identify AKI in isolation.

Chapter 5 documents contemporary monitoring for AKI of postoperative surgical patients. In the acutely unwell patient, UO increases the sensitivity of the contemporary AKI criteria (RIFLE, AKIN and KDIGO) in diagnosing AKI(147,286-288), however, there is sparse literature to suggest that this translates into the elective surgical population. Anecdotally, a UO target of 0.5ml/kg/h is required for renal protection, which is typically attained by the administration of intravenous fluid. However, significant postoperative

fluid overload, as shown in a meta-analysis by Lobo et al(39), to be 2400ml in the first 48 hours after surgery, doubles risk of complication. Therefore, the retrospective study described in Chapter 5 looked at how common isolated oliguria, as defined by <0.5ml/kg/h in the elective colorectal resection population, and the magnitude of intravenous fluid therapy administered to counter this phenomenon. At North Shore Hospital in Auckland, patients from a prospectively collated database were analysed and the incidence of isolated oliguria was found in 84%, resulting in a mean intravenous fluid administration of 925ml. Interestingly, there was no correlation between urine outputs and change in plasma creatinine in these patients. Whilst not at the 2000ml described by Lobo's group, it does constitute a clinically significant amount of fluid used to treat a theory proven in the critically unwell patient, but has not been shown to translate into the elective surgical population.

Consequently, Chapter 6 set out a randomised controlled trial, which tested the hypothesis that elective surgical patients are similar to the community population. Therefore a UO target of 0.2ml/kg/h in the perioperative period could be accepted, as derived from the kidney's ability to concentrate and excrete the maximum amount of solute.

From the research presented in this thesis, the following conclusion can be drawn:

Perioperative AKI requiring acute RRT is rare, but its sequelae regarding both mortality and morbidity are significant.

Literature is sparse regarding AKI in the elective major non-cardiothoracic, non-vascular, non-urological and non-transplant population. However, to reduce the risk of developing AKI, the available literature suggests that patients should be advised to lose weight prior to surgery and if clinically appropriate, any angiotensin converting enzyme inhibitor therapy should be withheld during the perioperative period.

Clinicians should also be aware that male patients, those with poor preoperative functional status, those who suffer from CRF or diabetes represent increased risk groups and should be closely monitored for the development of AKI.

Low UO is common after elective bowel resection and results in clinically significant fluid administration. It is currently used as a surrogate for the development of AKI, however,

perioperative UO is not associated with a change in plasma creatinine and thus the development of AKI.

Low perioperative UO in isolation is a physiological response to surgery and not indicative of the development of AKI. Regarding AKI, accepting a lower perioperative UO target of 0.2ml/kg/h is as safe compared to the conventional target of 0.5ml/kg/h and results in a clinically significant decrease in perioperative fluid administration. This may reduce complications from unnecessary fluid administration.

Chapter 9 – Future directions for research

This thesis has attempted to highlight the current pitfalls in our recognition and treatment of perioperative AKI. Specifically, this research emphasised the heterogeneity in definitions of AKI and the need for a unified definition. It is impossible to draw conclusions from studies measuring an outcome that has as of yet, not been clearly defined. This thesis also identified a lack of published literature with regards to AKI in the elective non-cardiothoracic, non-vascular, non-urological and non-transplant population. In particular, intraperitoneal surgery i.e. bowel resections, have a profound effect on fluid physiology and homeostasis, more so than other non-bypass related surgery.

Therefore, it is proposed:

1. Further studies aimed at the validation of novel biomarkers for the detection of AKI (e.g. NGAL or KIM1) in the elective non-cardiothoracic, non-vascular, non-urological and non-transplant population are conducted.
2. Large prospective studies are conducted using these biomarkers as a robust definition of AKI to identify patient and procedural factors that may increase the risk of perioperative AKI for hypothesis generation.
3. Findings from these hypothesis-generated steps could then be extrapolated into interventions that could be explored using randomised controlled trials, such as the trial described in Chapter 6.
4. And regarding Chapter 6, given the approximately 2300ml of extra intravenous fluid that can be obviated by using the 0.2ml/kg/h UO target, a further randomised controlled trial is warranted, powered to detect a reduction in perioperative complications as theorised by Dileep Lobo's group(30).

Appendix A – Randomised controlled trial: Participant consent form

Waitemata District Health Board
Te Wai Awhina

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES
The University of Auckland
Private Bag 92019
Auckland
New Zealand.

Consent Form for Participants

A Safety Study of High vs. Low Urine Output Targets in Surgical Patients: a clinical trial

Principal researcher: Name **Mattias Soop**
Position **Senior Lecturer and Consultant Surgeon**

University of Auckland
Contact **021 924 919**

Request for interpreter

English	I wish to have an interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai
Chinese		---	---
Deaf	I wish to have a NZ sign language interpreter	Yes	No

I have read and I understand the information sheet dated **13th June, 2011** for volunteers taking part in the study designed to evaluate if a lower urine output after surgery results in less complications without harming the kidneys.

I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.

Study title: ***High vs. Low Urine Output Targets in Surgical Patients***
Version #3: *Dated 13th of June 2011*
Principal Investigator: Mr Mattias Soop
Site: Waitemata DHB

I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my continuing health care.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.

I understand the compensation provisions for this study (explained on your study information sheet).

I have had time to consider whether to take part in the study.

I know who to contact if I have any health problems during the study.

I know who to contact if I have any questions about the study in general.

- I agree to my GP or other current health provider being informed of my participation in this study *(this decision will not affect your ability to enter the study)*.

  ☐ **Yes** ☐ **No**

- I agree to some of my blood samples being stored for possible future analysis. I understand that if I do not consent to this, it will not exclude me from participating in the study.

  ☐ **Yes** ☐ **No**

- I would like a copy of the results at the end of the trial. (The results of this study may not be available for several years). Please let us know if you change address so that we are able to keep in touch.

  ☐ **Yes** ☐ **No**

By signing this form, I ……*(full name)* freely give my consent to take part in this research.

Signature:	
Date:	
Person obtaining consent:	
Signature:	
Date:	
Researcher's contact number:	

One copy to be given to participant, one copy filed in participant's medical record

Appendix B – Randomised controlled trial: Participant information sheet

Waitemata District Health Board
Te Wai Awhina

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

The University of Auckland
Private Bag 92019
Auckland
New Zealand,

Participant Information Sheet

High vs. Low Urine Output Targets in Surgical Patients: a randomised assessor-blinded safety study.

Principal researcher: Mr Mattias Soop
Consultant Surgeon, Waitemata District Health Board
Senior Lecturer, University of Auckland

Introduction

You are invited to participate in a research study at North Shore Hospital. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve for you.

Taking part is completely voluntary (your choice) and if you decide you do not wish to take part in the study, it will not affect any future care or treatment, or the timing of your surgery. If you decide to take part in the study, you can opt out (withdraw your consent to participate) at any time without giving a reason, and this will in no way affect your continuing health care.

Participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue. The nature of the study, the benefits, risks, discomforts and other information about the study are discussed in further detail below. This information sheet may contain words that you do not fully understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take this information sheet and consent form home to think about, or discuss with family or friends, before making your decision.

We encourage you to read this information sheet carefully, and if you wish to discuss it with your family and whanau.

If you need an interpreter to help you understand the study, one can be provided for you.

About the study

What are the study aims?

In this study we aim to better understand how the kidneys work after surgery. Our goal is to further reduce the risks of major surgery. Current standard practice is to give a generous amount of intravenous fluids (drip) to people undergoing surgery. The amount of fluids given is mainly guided by the urine output. It is adjusted so that a high urine output is maintained during and after surgery. In a 75-kg person, urine output is traditionally maintained at about 0.9 litre per day.

However, recent studies show that giving less fluid (thereby avoiding fluid overloading) greatly reduces the risk of complications after surgery. One consequence on giving less fluid is that urine output falls to a lower rate. Only a small number of studies exist on such lower rates of urine output, and these studies indicate that a lower urine output by itself has no harmful effects. In this study, we are observing how kidney function is regulated after surgery and what the effects are of a high and a low urine output.

Where will the study be held?

The research will be carried out at North Shore Hospital by Dr Jevon Puckett, Research Fellow in the Department of Surgery, University of Auckland. Study supervisors are Mr Mattias Soop (Consultant Surgeon), Dr Michal Kluger (Consultant Anaesthetist) and Dr Janak De Zoysa (Consultant Renal Physician). Researchers from Christchurch Hospital also work with us on this study. They will analyse some of the tests taken during the study.

How many participants will be involved?

We intend to study 40 participants in this study. You have been invited to participate because you will be undergoing bowel surgery at North Shore Hospital.

What will happen during the study?

In 3-5 days, our research Fellow or Research Nurse will telephone you to answer any questions you may have about the study. If you wish to participate, we will ask some additional questions about your health to make sure this study is safe for you.

Before surgery:

You will then be given an appointment for the preoperative kidney test to be done. This test is done in the hospital about one week before your surgery. You will be asked to have nothing to eat or drink overnight, except for water. The test takes about 4 hours during which you rest in a armchair or a bed. It involves having one intravenous (IV) line (cannula) inserted in each arm. Two compounds called sinistrin and para-aminohippurate (PAH) will be then infused over 3 hours:

Sinistrin: This is a starch derived from a plant (red squill). This allows us to measure your kidney function directly.

PAH: This is a sodium salt that is allows us to estimate the blood flow to your kidneys.

During this time you will have 3 blood samples taken from the other cannula to test the levels of these compounds. During this test you can drink water, and once the infusion is finished you will be provided with a sandwich lunch.

During surgery:

.

Urine output determines how much extra fluid patients are given after surgery. When urine output falls below a certain level, extra fluid is prescribed. All fluid will be given through an intravenous drip as per normal care. In order to find out what level is best, participants will be randomised to one of two groups: Group A or Group B (randomisation means that you are put into a group by chance, as in the flip of a coin):

Group A: Participants in this group will be given fluid in order to maintain the standard urine output target: 0.5ml/kg/hour or about 0.9 litre per day in a 75-kg person.

Group B: These participants will be given fluid in order to maintain a lower urine output target: 0.2ml/kg/hr or 0.36 litre per day in a 75-kg person.

After surgery:

These fluid targets are used from the start of surgery until 48 hours after surgery. In the morning of the first day after your surgery, the 4-hour sinistrin-PAH test will be repeated. You will only drink water from midnight in preparation for this test. Blood and urine samples will also be taken each morning and evening for 48 hours after your surgery to monitor kidney function. The urine samples will be collected from the urinary catheter that you will have as part of normal surgical care. The blood samples will be collected from a vein in your arm (or from a central line if this is available).

Approximately 4 weeks after your surgery you will have a check-up with your surgeon's team in the outpatients clinic as per normal care. At this visit you will have one final extra blood and urine test to check your kidney function.

How long will the study last?

Your time in the study will be from one week prior to your surgery to 30 days after. This will require one extra visit to the hospital (the sinistrin-PAH test a week before surgery).

What will happen to my samples?

Your blood and urine samples will be collected and stored in containers identified only with a code, not your name or other identifying information. Only the researchers and research nurse have access to the code key linking your name to the samples.

Samples are either analysed immediately at the North Shore Hospital laboratory, or stored securely in a freezer in this laboratory. This is a locked area to which only staff working in the laboratory and staff on this study have access. Some of the frozen samples will be sent to researchers in our group who work in Christchurch, as only their laboratory has specialised equipment necessary for some of the kidney function tests.

Some frozen samples will be kept for further analysis of your kidney function should new tests become available after the study. No new research will be conducted on your stored blood samples unless it has been reviewed and approved by The Northern Ethics Committees. If you wish to withdraw from the study, your frozen samples will either be returned to you or destroyed. All unused samples will be destroyed after 10 years.

Alternatively, the can be returned to you at your request at this time.

Benefits, risks and safety

As you are undergoing scheduled surgery your surgeon will explain the benefits and risks of the surgery to you.

Benefits of participating in this research study:
You may not receive any benefit from being in this study. Your kidney function will be monitored more closely than we do currently, ensuring any potential problems are picked up earlier. People undergoing major surgery in the future are likely to benefit from the knowledge that we gain.

Risks and safety:

This study aims to prove that a lower urine output target in people having surgery is safe. Traditionally, it has been thought that a high urine output (0.5 ml/kg/h or more) was the safest target for the kidneys. However, no evidence exists to support this particular target. On the contrary, recent studies indicate that a lower urine output by itself has no harmful effects. Nevertheless, we will monitor kidney function very closely by blood and urine tests along with the sinistrin-PAH test. If the tests show any potential for harm to your kidneys, either from the operation or the study itself, you will be withdrawn from the study immediately. The study group includes expertise in kidney medicine, anaesthesia and surgery.

Allergic reactions to sinistrin (e.g. hives, wheezing, fevers and chills) are possible but extremely rare: two case reports have been published despite its widespread use. PAH administration is not associated with any known risks.

The effects of sinistrin and PAH on the unborn child and on the newborn baby are not known. Because of this you must not take part in the study if you are pregnant or trying to become pregnant, or breast-feeding. If becoming pregnant is a possibility, you will need to undergo a pregnancy test prior to commencing the study.

When cannulae are inserted for blood tests, it may hurt for a short time and you may get a bruise. The total amount of blood taken during the study is approximately 156ml. This is less than half of a blood donation, for example, and you should not notice its loss.

Results
Any results that we find are relevant to your health will be immediately conveyed to you and your GP.
Once the study is complete and the final study report is released, your study doctor will be able to supply you with the study results.

Will taking part in this study cost me anything?

Taking part in this study will not cost you anything, nor will you will be paid for taking part. You will be reimbursed the transport and parking expenses for the extra study visit .You will also be provided with a sandwich lunch at this visit.

What happens if there are any complications or problems with the surgery?

Your surgeon will treat any complications of surgery in the standard way if they occur. After discharge from hospital it is important that you seek medical attention for complications, should they arise, and as you normally would. Accident compensation for injury or medical misadventure works in the same way it whether you are in the study or not.

Confidentiality

All data collected in this study is confidential. No material that could personally identify you will be used in any reports on this study.

Your study information will be coded and stored in a secure, password-protected database only accessible to the researchers and research nurses, in order to protect your confidentiality. These records will be stored for 10 years after the completion of the study, after which they will be destroyed.

Research materials may need to be checked by the ethics committee or auditors appointed by Waitemata District Health Board. Your records will be held in the strictest confidentiality by these persons who will need to have confidentiality approval before having access to them. The records will not be used to identify you personally but to check the integrity of the study as a whole.

General

Will my GP be told I am in the study?

If you agree, your GP will be informed that you are participating in this study.

If I need an interpreter, can one be provided?

Yes. Please let the research staff know and they will arrange for an interpreter through Waitemata District Health Board.

For Maori Participants

To ensure ongoing cultural safety Nga Kai Tataki - Maori Research Review Committee Waitemata DHB encourage those who identify themselves as Maori and who are participating in health research or clinical trials to seek cultural support and advice from either Mo Wai Te Ora - Maori Health Services or their own Kaumatua or Whaea

For assistance please contact the Services Clinical Leader for Mo Wai Te Ora - Maori Health on 09 486 1491 ext: 2324 or the Maori Research Advisor on 09 486 1491 ext: 2553

Kia ora mai.

Cultural Support:

If you would like other cultural support please contact:

The Asian health support service at North Shore Hospital 4868920 ext 2314
Waitakere Hospital 4868920 ext 6017

or ask Dr Puckett or the study research nurse to contact the appropriate service on your behalf.

Where can I get more information about the study?

If you have any questions about this study, please contact:

1. **Dr Jevon Puckett**
   Research Fellow
   Waitemata DHB
   Ph: 021 924 919
   Fax: 488 4662

2. **Mr Mattias Soop**
   Consultant Surgeon
   Department of Surgery
   North Shore Hospital
   Ph: 486 8920 ext: 2459
   Fax: 488 4664

3. **Mr Mark Wade**
   Research Nurse
   Department of Surgery
   North Shore Hospital
   Ph: 486 8920 ext: 7125
   Fax: 488 4664

Compensation: In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

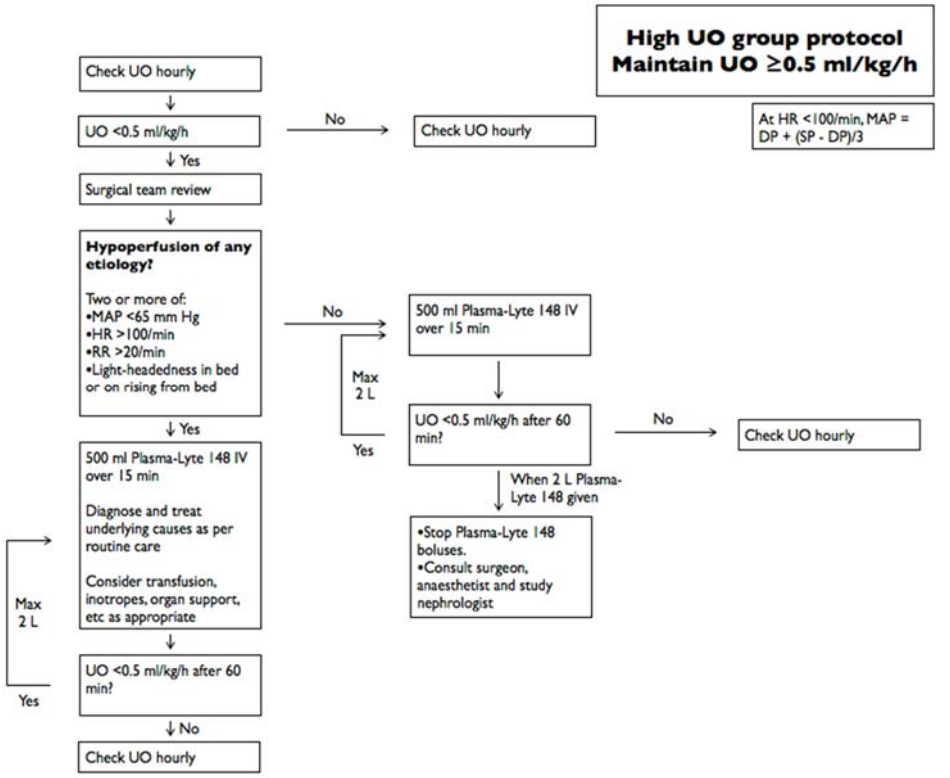
If you have any queries or concerns regarding your rights as a participant in this research study you can contact an Independent Health and Disability Advocate. This is a free service provided under the Health & Disability Commissioner ACT:

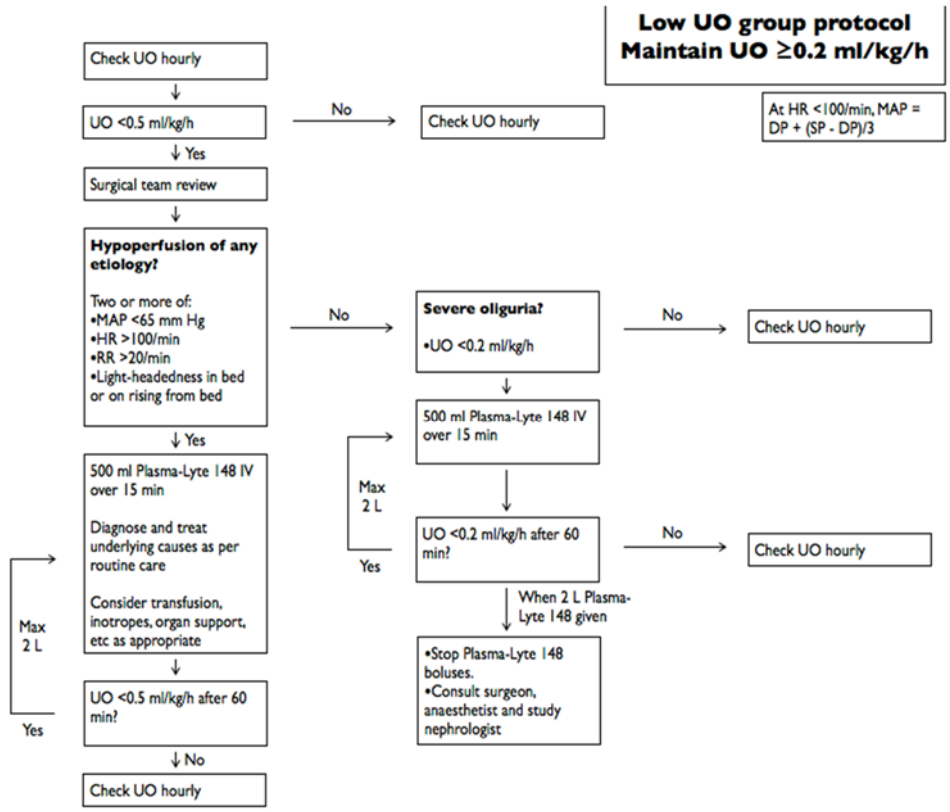
Telephone (NZ Wide): 0800 555 050
Free Fax (ZN Wide): 0800 2787 7678 (0800 2 SUPPORT)
Email: advocacy@hdc.org.nz

STATEMENT OF APPROVAL

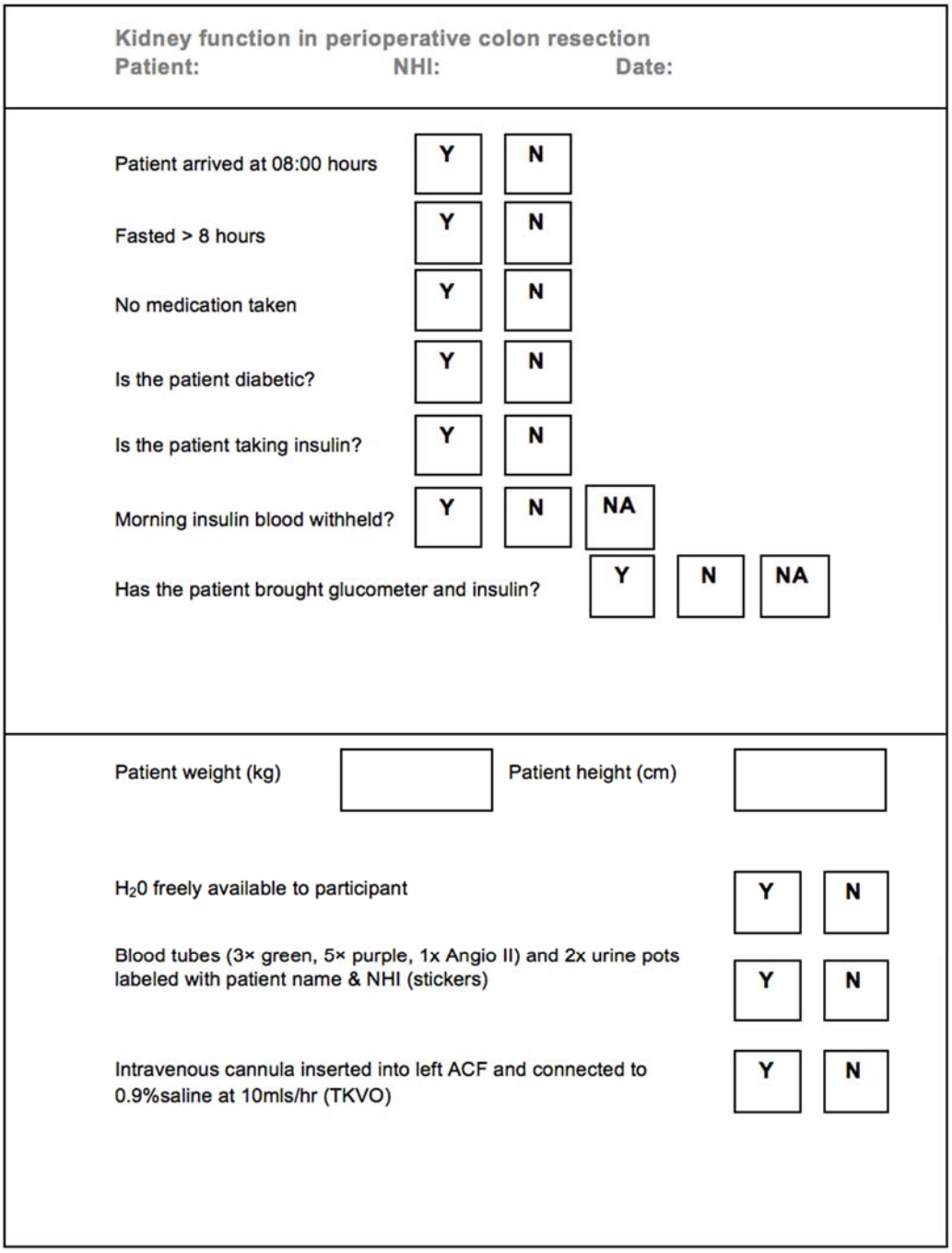
This study has received ethical approval from the Northern X Regional Ethics Committee **(Study number** NTX/11/05/033).

Appendix C – Randomised controlled trial: Trial protocols





Appendix D – Randomised controlled trial: PAH and sinistrin infusion protocols



Kidney function in perioperative colon resection

Patient: NHI: Date:

Patient arrived at 08:00 hours	Y	N	
Fasted > 8 hours	Y	N	
No medication taken	Y	N	
Is the patient diabetic?	Y	N	
Is the patient taking insulin?	Y	N	
Morning insulin blood withheld?	Y	N	NA
Has the patient brought glucometer and insulin?	Y	N	NA

Patient weight (kg) Patient height (cm)

H_20 freely available to participant	Y	N
Blood tubes (3× green, 5× purple, 1x Angio II) and 2x urine pots labeled with patient name & NHI (stickers)	Y	N
Intravenous cannula inserted into left ACF and connected to 0.9%saline at 10mls/hr (TKVO)	Y	N

Kidney function in perioperative colon resection

Patient: **NHI:** **Date:**

Time of last micturition	
Time of current micturition	
Volume of urine (mL)	
MSU taken for urinary NGAL	Y / N

4ml of blood drawn with 5ml syringe and set aside	
Vacutain attached and blood drawn	
3 × EDTA tubes (4mL)	
3 × Lithium heparin tubes (4 mL)	
1 × angiotensin II tubes	
Angiotensin II placed on ice.	
Blood form dated and time bloods taken entered	
4ml blood returned and cannula flushed with 5-10 ml 0.9 % saline	
Bloods taken to lab and processed.	
Plasma separated and placed in plasma tubes	
Plasma tubes placed in -80° C freezer	

Kidney function in perioperative colon resection

Patient: **NHI:** **Date:**

Baseline BP	
Pulse	

PAH and Sinistrin drawn up into 50ml syringe away from patient
Syringes taken to pathology and weighed.

PAH weight (mg)	
Sinistrin weight (mg)	

Inulin lot number	
Inulin expiry date	
P-aminohippurate lot number	
P-aminohippurate expiry date	

Inulin bolus volume *(taken from excel calculation sheet)*	
Inulin bolus dose (mg) *(taken from excel calculation sheet)*	
P-aminohippurate bolus volume (mL) *(taken from excel calculation sheet)*	
P-aminohippurate bolus dose (mg) *(taken from excel calculation sheet)*	

PAH Bolus rate (mL/h)		Sinistrin Bolus rate (mL/h)	
PAH infusion rate (mL/h)		Sinistrin infusion rate (mL/h	

Kidney function in perioperative colon resection
Patient: **NHI:** **Date:**

Extension set primed with PAH to patient ☐

Sinistrin primed to extension set ☐

Infusions started at predetermined rates ☐

Time bolus started ☐

Time infusion started ☐

120 minutes

Mid-point blood ☐ Pulse ☐

Lunch menu offered and ordered (phone ext 2509) ☐

Second cannula inserted into right ACF and connected to 0.9% saline at 10mls/hr (TKVO) ☐

Infusion 160 minutes (2 hours 40 minutes)

Blood drawn 4 ml and set aside ☐

Blood drawn (4 ml) with Vacutain into purple tube, placed on ice and taken to the lab ☐

4ml blood returned to patient and cannula flushed with 10 ml 0.9% saline ☐

Blood sample centrifuged ASAP ☐

Kidney function in perioperative colon resection
Patient: **NHI:** **Date:**

Infusion 180 minutes (3 hours)

Blood drawn 4 ml and set aside	☐
Blood drawn (4 ml) with Vacutain into purple tube, placed on ice and taken to the lab	☐
4ml blood returned to patient and cannula flushed with 10 ml 0.9% saline	☐
Blood sample centrifuged ASAP	☐

3 hours

Stop infusion pumps, lock extensions sets and disconnect	☐
Patient sent for micturation in measuring jug	☐
Time of micturition	☐
Volume of urine (mL)	☐
Urine sample taken for PAH and Sinistrin	☐
Extension set withdrawn into PAH syringe	☐
Sinistrin withdrawn from connection tubing into syringe	☐

Kidney function in perioperative colon resection

Patient: **NHI:** **Date:**

Syringes taken to pathology and weighed	☐
PAH weight (mg) ☐ Sinistrin weight (mg) ☐	
PAH sample taken and stored in -80 freezer	☐
Sinistrin sample taken and stored in – 80 freezer	☐
Cannulas removed both arms	☐

Patient offered lunch/tea and coffee	☐
Taxi/parking voucher offered	☐
Parking coupon held by patient	☐

Kidney function in perioperative colon resection

Patient: **NHI:** **Date:**

Past Medical History:

Past Surgical History:

Drug History:

Renal Disease	Y	N
Smoking		
EtOH		

Appendix E – Randomised controlled trial: Data collection sheets

Patient ID TRENAL Date

Intraoperative Data Collection/POD0 – TRENAL

PATIENT DATA						
Preop weight (kg)	Consultant	Procedures (ERAS code)	Surgery Start	Surgery End	Unplanned Events	EBL (ml)

ASSAYS					
	0 hours	1 hours	2 hours	6 hours	10 hours
Na+ (p)		-			
K+ (p)		-			
Creatinine (p)		-			
Glucose (p)	-	-	-		-
CRP (p)	-	-	-		-
Osmolality (p)	-	-	-		-
Haematocrit (p)	-	-			-
Na+ (u)	-	-			
K+ (u)	-	-			
Creatinine (u)	-	-			
Osmolality (u)	-	-			
Urine Measurement					

Specimen Weight	

Patient ID TRENAL Date

PREOP AND INTRAOP FLUID BALANCE					
Time	Maintenance IV Fluid (ml)	Bolus IV Fluid (ml)	Oral Fluid (ml)	Urine Output (ml)	MAP at start of hour (mmHg)
00:00-01:00					
01:00-02:00					
02:00-03:00					
03:00-04:00					
04:00-05:00					
05:00-06:00					
06:00-07:00					
07:00-08:00					
08:00-09:00					
09:00-10:00					
10:00-11:00					
11:00-12:00					
12:00-13:00					
13:00-14:00					
14:00-15:00					
15:00-16:00					
16:00-17:00					
17:00-18:00					
18:00-19:00					
19:00-20:00					
20:00-21:00					
21:00-22:00					
22:00-23:00					
23:00-24:00					

Patient ID TRENAL Date

POD1 Data Collection – TRENAL

PATIENT DATA					
Weight (kg)	Consultant	Operation (ERAS code)	Unplanned Events		

ASSAYS		
	08:00	20:00
Na+ (p)		
K+ (p)		
Creatinine (p)		
Glucose (p)		
CRP (p)		-
Osmolality (p)		
Haematocrit (p)		
Na+ (u)		
K+ (u)		
Creatinine (u)		
Osmolality (u)		
Urine Measurement		

FLUID BALANCE					
Time	Maintenance IV Fluid (ml)	Bolus IV Fluid (ml)	Oral Fluid (ml)	Urine Output (ml)	MAP (mmHg)
00:00-01:00					
01:00-02:00					
02:00-03:00					
03:00-04:00					
04:00-05:00					
05:00-06:00					
06:00-07:00					
07:00-08:00					
08:00-09:00					
09:00-10:00					
10:00-11:00					
11:00-12:00					
12:00-13:00					
13:00-14:00					
14:00-15:00					
15:00-16:00					
16:00-17:00					
17:00-18:00					
18:00-19:00					
19:00-20:00					
20:00-21:00					
21:00-22:00					
22:00-23:00					
23:00-24:00					

Patient ID TRENAL Date

POD2 Data Collection – TRENAL

PATIENT DATA					
Weight (kg)	Consultant	Operation (ERAS code)	Unplanned events		

ASSAYS		
	08:00	20:00
Na+ (p)		
K+ (p)		
Creatinine (p)		
Glucose (p)		
CRP (p)		-
Osmolality (p)		
Haematocrit (p)		
Na+ (u)		
K+ (u)		
Creatinine (u)		
Osmolality (u)		
Urine Measurement		

FLUID BALANCE					
Time	Maintenance IV Fluid (ml)	Bolus IV Fluid (ml)	Oral Fluid (ml)	Urine Output (ml)	MAP (mmHg)
00:00-01:00					
01:00-02:00					
02:00-03:00					
03:00-04:00					
04:00-05:00					
05:00-06:00					
06:00-07:00					
07:00-08:00					
08:00-09:00					
09:00-10:00					
10:00-11:00					
11:00-12:00					
12:00-13:00					
13:00-14:00					
14:00-15:00					
15:00-16:00					
16:00-17:00					
17:00-18:00					
18:00-19:00					
19:00-20:00					
20:00-21:00					
21:00-22:00					
22:00-23:00					
23:00-24:00					

Patient ID TRENAL Date

POD3 Data Collection – TRENAL

PATIENT DATA					
Weight (kg)	Consultant	Operation (ERAS code)	Unplanned Events		

ASSAYS		
		08:00
Na+	(p)	
K+	(p)	
Creatinine	(p)	
Glucose	(p)	
CRP	(p)	
Osmolality	(p)	
Haematocrit	(p)	
Na+	(u)	
K+	(u)	
Creatinine	(u)	
Osmolality	(u)	
Urine Measurement	-	

FLUID BALANCE					
Time	Maintenance IV Fluid (ml)	Bolus IV Fluid (ml)	Oral Fluid (ml)	Urine Output (ml)	MAP (mmHg)
00:00-01:00					
01:00-02:00					
02:00-03:00					
03:00-04:00					
04:00-05:00					
05:00-06:00					
06:00-07:00					
07:00-08:00					
08:00-09:00					
09:00-10:00					
10:00-11:00					
11:00-12:00					
12:00-13:00					
13:00-14:00					
14:00-15:00					
15:00-16:00					
16:00-17:00					
17:00-18:00					
18:00-19:00					
19:00-20:00					
20:00-21:00					
21:00-22:00					
22:00-23:00					
23:00-24:00					

Patient ID TRENAL Date

POD30 Data Collection – TRENAL

PATIENT DATA

Weight (kg)	Consultant	Operation (ERAS code)	Time of last micturition	Time of urinary sample	Urine Volume (ml)

ASSAYS

		a.m
Na+	(p)	
K+	(p)	
Urea	(p)	
Creatinine	(p)	
Glucose	(p)	
CRP	(p)	-
Osmolality	(p)	
Haematocrit	(p)	
Na+	(u)	
K+	(u)	
Creatinine	(u)	
Osmolality	(u)	

Further U&Es Recorded

		Date	Result
Na+	(p)		
K+	(p)		
Urea	(p)		
Creatinine	(p)		
Glucose	(p)		
CRP	(p)		
Osmolality	(p)		
Haematocrit	(p)		

COMPLICATIONS

References

1. Nunoo-Mensha JW, Rosen M, Chan LS, Wasserberg N, Beart RW. Prevalence of intra-abdominal surgery: what is an individual's lifetime risk? South Med J. 2009 Jan 1;102(1):25–9.

2. Tjandra JJ, Chan MKY. Systematic review on the short-term outcome of laparoscopic resection for colon and rectosigmoid cancer. Colorectal Disease. 2006 Jun;8(5):375–88.

3. Thadepalli H, Mandal AK. Antimicrobial Therapy in Abdominal Surgery. Boston, London: CRC Press; 1991. Chapter 6:Prophylaxis for Elective Colonic Surgery; p.31-36.

4. Lassen K, Soop M, Nygren J, Cox P. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Archives of Surgery. 2009 Oct; 144(10):961-969.

5. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. The American Journal of Surgery. Elsevier; 2002 Jun 1; 183(6):630–41.

6. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for Perioperative Care in Elective Colonic Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations. World J Surg. Springer-Verlag; 2012 Oct 6; 37(2):259–84.

7. Asklid D, Segelman J, Gedda C, Hjern F, Pekkari K, Gustafsson UO. The impact of perioperative fluid therapy on short-term outcomes and 5-year survival among patients undergoing colorectal cancer surgery - A prospective cohort study within an ERAS protocol. European Journal of Surgical Oncology. Elsevier Ltd; 2017 Aug 1; 43(8):1433–9.

8. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. Clinical Nutrition. Elsevier Ltd; 2010 Aug 1; 29(4):434–40.

9. Müller S, Zalunardo MP, Hübner M, Clavien PA, Demartines N, Group ZFTS. A Fast-Track Program Reduces Complications and Length of Hospital Stay After Open Colonic Surgery. YGAST. AGA Institute American Gastroenterological Association; 2009 Mar 1; 136(3):842–847.e1.

10. Hannemann P, Lassen K, Hausel J. Patterns in current anaesthesiological peri-operative practice for colonic resections: a survey in five northern-European countries. Acta Anaesthesiol Scand; 2006; 50: 1152-1160.

11. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus “nil by mouth” after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. BMJ Publishing Group Ltd; 2001 Oct 6; 323(7316):773–1421.

12. Han-Geurts IJM, Hop WCJ, Kok NFM, Lim A, Brouwer KJ, Jeekel J. Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg. John Wiley & Sons, Ltd; 2007 May 1; 94(5):555–61.

13. Gustafsson UO, Scott MJ, Schwenk W, Demartines N. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery ERAS® Society recommendations. Clinical Nutrition. 2012.

14. Jorgensen H WJMSDJ. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery (Review). 2013 Jan 1;:1–52.

15. Ljungqvist O, S reide E. Preoperative fasting. Br J Surg. John Wiley & Sons, Ltd; 2003;90(4):400–6.

16. Brady MC KSSPNV. Preoperative fasting for adults to prevent perioperative complications (Review). 2013 Jan 1;:1–156.

17. Smith MD, McCall J, Plank L, Herbison GP. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. The Cochrane Database Syst Rev [Interent]. 2014 [cited 2017 May 15]. Available from http://www.thecochranelibrary.com

18. Mathur S, Plank LD, McCall JL. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. British Journal of Surgery. 2010;97(4):485-494.

19. Guenaga KF MDW-JP. Mechanical bowel preparation for elective colorectal surgery (Review). 2013 Jan 1;:1–59.

20. Mahajna A, Krausz M, Rosin D, Shabtai M, Hershko D, Ayalon A, et al. Bowel Preparation Is Associated With Spillage of Bowel Contents in Colorectal Surgery. Diseases of the Colon & Rectum. 2005 Aug; 48(8):1626–31.

21. Holte K, Nielsen KG, Madsen JL, Kehlet H. Physiologic Effects of Bowel Preparation. Diseases of the Colon & Rectum. 2004 Aug; 47(8):1397–402.

22. Junghans T, Neuss H, Strohauer M, Raue W, Haase O, Schink T, et al. Hypovolemia after traditional preoperative care in patients undergoing colonic surgery is underrepresented in conventional hemodynamic monitoring. Int J Colorectal Dis. Springer-Verlag; 2005 Dec 6; 21(7):693–7.

23. Snchez-Jimnez R, Blanco A, Trebol Lpez J, Snchez A, Gutirrez F, Carmona Sez JA. ERAS (Enhanced Recovery after Surgery) in Colorectal Surgery. In: Colorectal Cancer - Surgery, Diagnostics and Treatment. InTech; 2014. pp. 1–18.

24. Werawatganon T. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. The Cochrane Collaboration, editor. Cochrane Database Syst Review. Chichester, UK: John Wiley & Sons, Ltd; [Interent]. 2005 [cited 2017 May 15]. Available from http://www.thecochranelibrary.com.

25. Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective Effects of Epidural Analgesia on Pulmonary Complications After Abdominal and Thoracic Surgery: A Meta-Analysis. Arch Surg. American Medical Association; 2008 Oct 20; 143(10):990–9.

26. Charlton S CAMPGJ. Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery (Review). 2013 Jan 1;:1–62.

27. Pedrazzani C, Menestrina N, Moro M, Brazzo G, Mantovani G, Polati E, et al. Local wound infiltration plus transversus abdominis plane (TAP) block versus local wound infiltration in laparoscopic colorectal surgery and ERAS program. Surgical Endoscopy. Springer US; 2016 Mar 19; 30(11):5117–25.

28. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Annals of Surgery. 1961.

29. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia. Blackwell Publishing Ltd; 2007 Dec 7; 63(1):44–51.

30. Lobo DN. Fluid Overload and Surgical Outcome. Annals of Surgery. 2009 Feb; 249(2):186–8.

31. Seiler CM, Deckert A, Diener MK, Knaebel H-P, Weigand MA, Victor N, et al. Midline Versus Transverse Incision in Major Abdominal Surgery. Annals of Surgery. 2009 Jun; 249(6):913–20.

32. Abraham NS, Young JM, Solomon MJ. Meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer. Br J Surg. 2004 Sep 20; 91(9):1111–24.

33. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011.

34. Basse L, Madsen JL, Kehlet H. Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative. Br J Surg. Blackwell Science Ltd; 2001 Nov 1; 88(11):1498–500.

35. Wilmore DW, Kehlet H. Management of patients in fast track surgery. BMJ. British Medical Journal Publishing Group; 2001 Feb 24; 322(7284):473–6.

36. Hendren S, Morris AM, Zhang W. Early discharge and hospital readmission after colectomy for cancer. Diseases of the Colon & Rectum. 2011; 54(11):1362-1367.

37. Madrid E, Urrútia G, Roqué i Figuls M, Pardo-Hernandez H, Campos JM, Paniagua P, et al. Active body surface warming systems for preventing complications caused by inadvertent perioperative hypothermia in adults. Madrid E, editor. Chichester, UK: John Wiley & Sons, Ltd; 1996. 220 p.

38. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. New England Journal of Medicine. 1996; 334(19):1209–16.

39. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc. 2010 Jun 2; 69(04):488–98.

40. Gattas DJ, Dan A, Myburgh J, Billot L. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med. 2013 Jan; 39:558-568.

41. Rochwerg B, Alhazzani W. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Annals of Internal Medicine. 2014 Sept; 161:347-355.

42. Zarychanski R, Abou-Setta A, Turgeon A, Houston B, McIntyre I, Marshall J, Fergusson D. Association of Hydroxyethyl Starch Administration with Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation: A Systematic Review and Meta-Analysis. 2013 Feb 309(7):678-688.

43. Brunkhorst FM, Engel C, Bloos F. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. New England Journal of Medicine. 2008; 358(2):125–39.

44. Perner A, Haase N, Winkel P, Guttormsen AB, Tenhunen J, Klemenzson G, et al. Long-term outcomes in patients with severe sepsis randomised to resuscitation with hydroxyethyl starch 130/0.42 or Ringer's acetate. Intensive Care Medicine. 2014 May 8; 40(7):927–34.

45. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. N Engl J Med. 2014 Apr 10; 370(15):1412–21.

46. Raghunathan K, Bonavia A, Nathanson BH, Beadles CA, Shaw AD, Brookhart MA, et al. Association between Initial Fluid Choice and Subsequent In-hospital Mortality during the Resuscitation of Adults with Septic Shock. Anesthesiology. The American Society of Anesthesiologists; 2015 Dec 1; 123(6):1385–93.

47. JPTUCK. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients. 2011 Mar 7;:1–50.

48. Boersema GSA, van der Laan L, Wijsman JH. A close look at postoperative fluid management and electrolyte disorders after gastrointestinal surgery in a teaching hospital where patients are treated according to the ERAS protocol. Surg Today. 2013 Nov 23; 44(11):2052–7.

49. Warrillow SJ, Weinberg L, Parker F. Perioperative fluid prescription, complications and outcomes in major elective open gastrointestinal surgery. Anaesthesia and intensive care. 2010; 38(2): 259-265.

50. Vaara ST, Parviainen I, Inkinen O, Uusaro A, Group TFS, Laru-Sompa R, et al. Association of oliguria with the development of acute kidney injury in the critically ill. Kidney International. International Society of Nephrology; 2016 Jan 1; 89(1):200–8.

51. Prowle JR, Liu YL, Licari E. Oliguria as predictive biomarker of acute kidney injury in critically ill patients. Critical Care; 2011; 15:R172.

52. Alpert RA, Roizen MF, Hamilton WK, Stoney RJ. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery. 1984.

53. Kheterpal S, Tremper KK, Englesbe MJ. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology. 2007; 107(6):892-902.

54. Burton TP, Mittal A, Soop M. Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence in bowel surgery: systematic review and meta-analysis of randomized, controlled trials. Diseases of the Colon & Rectum. 2013; 56(1):126-134.

55. Lobo DN, Bostock KA, Neal KR, Perkins AC. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. The Lancet. 2002; 359(9320):1812–8.

56. Nisanevich V, Felsenstein I, Almogy G. Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology. 2005; 103(1):25-32.

57. McLatchie G, Borley N, Chikwe J. Oxford Handbook of Clinical Surgery. 3rd ed. Oxford. Oxford University Press; 2013. Chapter 20; General Surgery.

58. Allman K, Wilson I. Oxford Handbook of Anaesthesia. 3rd ed. Oxford. Oxford University Press; 2013. Chapter 2; Principals of Surgery. p.112.

59. Simpson RG, Quayle J, Stylianides N, Carlson G, Soop M. Intravenous fluid and electrolyte administration in elective gastrointestinal surgery: mechanisms of excessive therapy. annals. 2017 Jul; 99(6):497–503.

60. Alves A, Panis Y, Mathieu P, Mantion G. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. Archives of Surgery. 2005; 140:278-283.

61. Ivers N, Jamtvedt G, Flottorp S. Audit and feedback: effects on professional practice and healthcare outcomes. The Cochrane Collaboration, editor. Cochrane Database Syst Review. Chichester, UK: John Wiley & Sons, Ltd; [Interent]. 2012 [cited 2017 May 15]. Available from http://www.thecochranelibrary.com.

62. Folkow B, Langston J. The Interrelationship of Some Factors Influencing Renal Blood Flow Autoregulation. Acta Physiologica. Blackwell Publishing Ltd; 1964 May 1; 61(1-2):165–76.

63. Lobo DN, STANGA Z, SIMPSON JAD, ANDERSON JA, ROWLANDS BJ, ALLISON SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clinical Science. Portland Press Limited; 2001 Aug 1; 101(2):173–9.

64. Kehlet H, Wilmore DW. Evidence-Based Surgical Care and the Evolution of Fast-Track Surgery. Annals of Surgery. 2008 Aug; 248(2):189–98.

65. Choileain NN, Redmond HP. Cell Response to Surgery. Arch Surg. American Medical Association; 2006 Nov 1; 141(11):1132–40.

66. Harmon GD, Senagore DAJ, Kilbride MJ, Warzynski MJ. Interleukin-6 response to laparoscopic and open colectomy. Diseases of the Colon & Rectum. Springer-Verlag; 1994 Aug 1; 37(8):754–9.

67. Christou NV, McLEAN, Meakins JL. Host Defense in Blunt Trauma: Interrelationships of Kinetics of Anergy and Depressed Neutrophil Function, Nutritional Status, and Sepsis. Journal of Trauma and Acute Care Surgery. 1980 Oct 1; 20(10):833.

68. Wu FPK, Sietses C, Blomberg von BME, van Leeuwen PAM, Meijer S, Cuesta MA. Systemic and Peritoneal Inflammatory Response After Laparoscopic or Conventional Colon Resection in Cancer Patients. Diseases of the Colon & Rectum. Springer-Verlag; 2003 Feb 1; 46(2):147–55.

69. Veenhof A, Vlug MS, Van Der Pas M, Sietses C. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Annals of Surgery 2012 Feb; 255(2):216-221.

70. Van der Bij GJ, Oosterling SJ, Beelen RHJ, Meijer S, Coffey JC, van Egmond M. The Perioperative Period is an Underutilized Window of Therapeutic Opportunity in Patients With Colorectal Cancer. Annals of Surgery. 2009 May;249(5):727–34.

71. Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. Clinical Nutrition. Elsevier; 1998 Jan 4; 17(2):65–71.

72. Khan ASA, Gibson JM, Carlson GL, Rooyackers O, New JP, Soop M. Protein kinetics in human endotoxaemia and their temporal relation to metabolic, endocrine and proinflammatory cytokine responses. Br J Surg. 2015 May 7; 102(7):767–75.

73. Wilmore DW. Postoperative Protein Sparing. World J Surg. Springer-Verlag; 1999 Jun 1; 23(6):545–52.

74. Harold Pringle RCBMSP. Clinical effects of ether anaesthesia on renal activity. British Medical Journal. BMJ Group; 1905 Sep 9; 2(2332):542–3.

75. Coller FA, Dick VS, Maddock WG. Mainenance of normal water exchange with intravenous fluids. JAMA. American Medical Association; 1936 Nov 7; 107(19):1522–7.

76. Frederick A Coller KNCHHVLVICAM. Postoperative Salt Intolerance. Annals of Surgery. Lippincott, Williams, and Wilkins; 1944 Apr 1; 119(4):533–41.

77. Wilkinson AW, Nagy G, Billing BH, Stewart CP. Wilkinson: Excretion of chloride and sodium after surgical operations. The Lancet; 1949 April 16; 6555(1):640-646.

78. Wilkinson AW, Nagy G, Billing BH, Stewart CP. Excretion of potassium after partial gastrectomy. The Lancet; 1950 July 22; 6621(2):135-137.

79. Lewis AA, Quesne LL. [Postoperative retention of water and sodium.]. The Lancet; 1953; 6751(261):153-158.

80. Francis DM. Bodily Changes in Surgical Convalescence I—The Normal Sequence—Observations and Interpretation. Ann Surg; 1953; 137(3):289-315.

81. Moore FD. Common patterns of water and electrolyte change in injury, surgery and disease. The New England journal of medicine; 1958.Feb 6; 258(6):277-285.

82. W A Shu'ayb WHMJBZ. Studies of the mechanism of antidiuretic hormone secretion and the post-commissurotomy dilutional syndrome. Annals of Surgery. Lippincott, Williams, and Wilkins; 1965 Oct 1; 162(4):690–701.

83. Moore FD, Haley HB, Bering EA Jr, Brooks L, EDELMAN IS. Further observations on total body water. 2. Changes of body composition in disease. Surgery, Gynecology and Obstetrics. 1952; 95:155–80.

84. Artz C, JM H, JP F. Clinical observations on the use of dextran and modified fluid gelatin in combat casualties. Surgery. 1955 Apr 1; 37(4):612–21.

85. Mills M, McFee AS, Baisch BF. The postresuscitation wet lung syndrome. Ann Thorac Surg; 1967; 187(3).

86. Roth E, Lax L, Malony J. Ringer's lactate solution and extracellular fluid volume in the surgical patient: a critical analysis. 1969 Feb 1; 169(2):1–16.

87. Sawyer KC Jr, Sawyer RB, Robb WC. Postoperative renal failure. The American Journal of Surgery. 1963; 106(4):668–72.

88. Figdor PP, Höltl G, Zinnbauer B. Diagnostic differentiation between advanced functional and acute organic renal failure. International Urology and Nephrology. Kluwer Academic Publishers; 1972 Mar 1; 4(1):71–81.

89. Sinnatamby C, Edwards CR, Irving MH. Antidiuretic hormone response to high and conservative fluid regimes in patients undergoing operation. Surgery, Gynaecology, Obstertrics. 1974; 139:715-719.

90. Josephs SA, Thakar CV. Perioperative risk assessment, prevention, and treatment of acute kidney injury. International anesthesiology clinics. 2009; 47(4):89-105.

91. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Critical Care Medicine. 2009 Jun; 37(6):2079–90.

92. Golden D, Corbett J, Forni LG. Peri-operative renal dysfunction: prevention and management. Anaesthesia. 2015 Dec 1; 71:51–7.

93. Berger K, Moeller MJ. Mechanisms of Epithelial Repair and Regeneration After Acute Kidney Injury. Seminars in Nephrology. Elsevier; 2014 Jul 1; 34(4):394–403.

94. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac SurgeryToward an Empirical Definition of Hypotension. Anesthesiology. The American Society of Anesthesiologists; 2013 Sep 1; 119(3):507–15.

95. Sun LY, Wijeysundera DN, Tait GA, Scott Beattie W. Association of Intraoperative Hypotension With Acute Kidney Injury After Elective Noncardiac Surgery. Survey of Anesthesiology. 2016 Jun 1; 60(3):120–1.

96. Salmasi V, Maheshwari K, Yang D, Mascha EJ. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after non cardiac surgery. Anesthesiology. 2017; 126(1):47-65.

97. Pearse R, Dawson D, Fawcett J, Rhodes A. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Critical Care. 2005 Nov 5; 9(6):R687-R693.

98. Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. Critical Care Medicine. 1993 Jul 1; 21(7):977.

99. Huddart S, Peden CJ, Swart M, McCormick B, Dickinson M, Mohammed MA, et al. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. Br J Surg. 2014 Nov 10; 102(1):57–66.

100. Estrada CA, Murugan R. Hydroxyethyl starch in severe sepsis: end of starch era? Crit Care. BioMed Central; 2013 Mar 13; 17(2):310.

101. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major Complications, Mortality, and Resource Utilization After Open Abdominal Surgery. Annals of Surgery. 2012 May; 255(5):821–9.

102. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. Intensive Care Medicine. 2014 Dec 18; 41(2):257–64.

103. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults. JAMA. American Medical Association; 2012 Oct 17; 308(15):1566–72.

104. Self WH, Semler MW, Wanderer JP, Ehrenfeld JM, Byrne DW, Wang L, et al. Saline versus balanced crystalloids for intravenous fluid therapy in the emergency department: study protocol for a cluster- randomized, multiple-crossover trial. Trials; 2017 Apr 11;:1–8.

105. Severs D, Hoorn EJ, Rookmaaker MB. A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence. Nephrology Dialysis Transplantation. 2015 Jan 28; 30(2):178–87.

106. Scheingraber S, Rehm M. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. The Journal of Anesthesiology. 1999; 90:1265-1270.

107. Sugrue M, Jones F, Deane SA, Bishop G, Bauman A, Hillman K. Intra-abdominal Hypertension Is an Independent Cause of Postoperative Renal Impairment. Arch Surg. American Medical Association; 1999 Oct 1; 134(10):1082–5.

108. Zimmermann B. Postoperative management of fluid volumes and electrolytes. Current Problems in Surgery. Elsevier; 1965 Dec; 2(12):1–46.

109. Minto G, Mythen MG. Perioperative fluid management: science, art or random chaos?: Fig 1. British Journal of Anaesthesia. 2015 Apr 22; 114(5):717–21.

110. Harris B, Schopflin C, Khaghani C, Edwards M. Perioperative intravenous fluid prescribing: a multi-centre audit. Perioperative Medicine. Perioperative Medicine; 2016 Nov 3;:1–11.

111. Cronin RM, VanHouten JP, Siew ED, Eden SK, Fihn SD, Nielson CD, et al. National Veterans Health Administration inpatient risk stratification models for hospital-acquired acute kidney injury. Journal of the American Medical Informatics Association. The Oxford University Press; 2015 Sep 1; 22(5):1054–71.

112. Bellomo R, Ronco C, Kellum JA, Mehta RL. Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQL) Group Crit Care. 2004; 8:R204-R212.

113. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute Renal Failure in Critically Ill Patients: A Multinational, Multicenter Study. JAMA. American Medical Association; 2005 Aug 17; 294(7):813–8.

114. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. American Journal of Kidney Diseases. 2002 Nov 30; 39(5):930-936.

115. Turner N, Goldsmith D, Winearls C, Lamiere N, Himmelfarb J, Remuzzi G. Oxford Textbook of Clinical Nephrology. Oxford University Press; 2015. Chapter 221; Pathophysiology of acute kidney injury. p 1844.

116. Miller BF, Alving AS, Rubin J. The renal excretion of inulin at low plasma concentrations of this compound, and its relationship to the glomerular filtration rate in normal, nephritic and hypertensive individuals. Journal of Clinical Investigation. 1940; 19(1): 89-94.

117. Richards AN. Physiology of the kidney. Bull. New York Acad. Med. 1938; 14:5-20.

118. Cole BR, Giangiacomo J, Ingelfinger JR. Measurement of renal function without urine collection: a critical evaluation of the constant-infusion technic for determination of inulin and para-aminohippurate. New England Journal of Medicine. 1972 Nov 30; 287(22):1109-1114.

119. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Ann Intern Med. American College of Physicians; 1999 Mar 16; 130(6):461–70.

120. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using Serum Creatinine To Estimate Glomerular Filtration Rate: Accuracy in Good Health and in Chronic Kidney Disease. Ann Intern Med. American College of Physicians; 2004 Dec 21; 141(12):929–37.

121. Michels WM, Grootendorst DC, Verduijn M. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clinical Journal of the American Society of Nephrology. 2010 Feb 15; 5:1003-1009.

122. Ichai C, Vinsonneau C, Souweine B, Armando F, Canet E, Clec'h C, et al. Acute kidney injury in the perioperative period and in intensive care units (excluding renal replacement therapies). Annals of Intensive Care 2016 6:1. 5 ed. Springer Paris; 2016 May 27; 6(1):1.

123. Moore E, Bellomo R, Nichol A. Biomarkers of acute kidney injury in anesthesia, intensive care and major surgery: from the bench to clinical research to clinical practice. Minerva anestesiologica. 2010 Jun; 76(6):425-440.

124. Laterza OF, Price CP, Scott MG. Cystatin C: An Improved Estimator of Glomerular Filtration Rate? Clinical Chemistry. American Association for Clinical Chemistry; 2002 May 1; 48(5):699–707.

125. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, Group NM-AI. Haase. American Journal of Kidney Diseases. Elsevier Inc; 2009 Dec 1; 54(6):1012–24.

126. Dent CL, Ma Q, Dastrala S, Bennett M. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care. 2007 Dec 10; 11(6):R127.

127. Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, et al. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Critical Care Medicine. 2008 Apr; 36(4):1297–303.

128. Kusaka M, Iwamatsu F, Kuroyanagi Y, Nakaya M, Ichino M, Marubashi S, et al. Serum Neutrophil Gelatinase Associated Lipocalin During the Early Postoperative Period Predicts the Recovery of Graft Function After Kidney Transplantation From Donors After Cardiac Death. JURO. Elsevier Inc; 2012 Jun 1; 187(6):2261–7.

129. Bolignano D, Lacquaniti A, Coppolino G, Campo S, Arena A, Buemi M. Neutrophil Gelatinase-Associated Lipocalin Reflects the Severity of Renal Impairment in Subjects Affected by Chronic Kidney Disease. Kidney Blood Press Res. 2008; 31(4):255–8.

130. Haase-Fielitz A, Haase M, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. Annals of Clinical Biochemistry: An international journal of biochemistry and laboratory medicine. 2014 Apr 10; 51(3):335–51.

131. Han WK, Bailly V, Abichandani R, Thadhani R. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney International. 2002 Jul; 62(1):237-244.

132. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney International. 2008 Apr; 73(7):863–9.

133. Kamijo-Ikemori A, Sugaya T, Kimura K. Urinary fatty acid binding protein in renal disease. Clinica Chimica Acta. 2006 Dec; 374(1-2):1–7.

134. Manabe K, Kamihata H, Motohiro M, Senoo T, Yoshida S, Iwasaka T. Urinary liver-type fatty acid-binding protein level as a predictive biomarker of contrast-induced acute kidney injury. European Journal of Clinical Investigation. 2011 Nov 10; 42(5):557–63.

135. Eynatten von M, Baumann M, Heemann U, Zdunek D, Hess G, Nawroth PP, et al. Urinary L-FABP and anaemia: distinct roles of urinary markers in type 2 diabetes. European Journal of Clinical Investigation. 2010 Feb; 40(2):95–102.

136. Fiseha T, Tamir Z. Urinary Markers of Tubular Injury in Early Diabetic Nephropathy. International Journal of Nephrology. 2016; 2016(4):1–10.

137. Melnikov VY, Ecder T, Fantuzzi G, Siegmund B, Lucia MS, Dinarello CA, et al. Impaired IL-18 processing protects caspase-1–deficient mice from ischemic acute renal failure. Journal of Clinical Investigation. American Society for Clinical Investigation; 2001 May 1; 107(9):1145–52.

138. Chirag R Parikh MD P, Charles L Edelstein MD P. Urinary interleukin-18 is a marker of human acute tubular necrosis. American Journal of Kidney Diseases. National Kidney Foundation, Inc; 2004 Feb 17; 43(3):405–14.

139. Parikh CR. Urine IL-18 Is an Early Diagnostic Marker for Acute Kidney Injury and Predicts Mortality in the Intensive Care Unit. Journal of the American Society of Nephrology. 2005 Aug 24; 16(10):3046–52.

140. Washburn KK, Zappitelli M, Arikan AA, Loftis L, Yalavarthy R, Parikh CR, et al. Urinary interleukin-18 is an acute kidney injury biomarker in critically ill children. Nephrology Dialysis Transplantation. 2007 Oct 30; 23(2):566–72.

141. Jia H-M, Huang L-F, Zheng Y, Li W-X. Prognostic value of cell cycle arrest biomarkers in patients at high risk for acute kidney injury: A systematic review and meta-analysis. Nephrology. 2017 Oct 17; 22(11):831–7.

142. Gocze I, Koch M, Renner P, Zeman F, Graf BM, Dahlke MH, et al. Urinary Biomarkers TIMP-2 and IGFBP7 Early Predict Acute Kidney Injury after Major Surgery. Zarbock A, editor. PLoS ONE. 2015 Mar 23; 10(3):e0120863–11.

143. Murray PT, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, et al. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. Kidney International. Elsevier Masson SAS; 2013 Jan 1; 85(3):513–21.

144. Xue JL. Incidence and Mortality of Acute Renal Failure in Medicare Beneficiaries, 1992 to 2001. Journal of the American Society of Nephrology. 2006 Mar 8; 17(4):1135–42.

145. Chertow GM. Acute Kidney Injury, Mortality, Length of Stay, and Costs in Hospitalized Patients. Journal of the American Society of Nephrology. 2005 Nov 1; 16(11):3365–70.

146. Carmichael P, Carmichael AR. Acute renal failure in the surgical setting. ANZ Journal of Surgery. Blackwell Science Pty; 2003; 73(3):144–53.

147. Kellum JA, Lameire N, Aspelin P, Barsoum RS. KDIGO clinical practice guideline for acute kidney injury 2012. Kidney International. 2012.

148. Susantitaphong P, Cruz DN, Cerda J. World incidence of AKI: a meta-analysis. Clinical Journal of the American Society of Nephrology. 2013 Sept; 8:1482-1493.

149. Hoste E, Clermont G, Kersten A. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006 April 1;10:R73.

150. Mehta RL, Kellum JA, Shah SV, Molitoris BA. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007 Mar 1; 11:R31.

151. Remuzzi G, Horton R. Acute renal failure: an unacceptable death sentence globally. The Lancet. Elsevier; 2013 Dec 21; 382(9910):2041–2.

152. Huen SC, Parikh CR. Predicting Acute Kidney Injury After Cardiac Surgery: A Systematic Review. ATS. Elsevier Inc; 2012 Jan 1; 93(1):337–47.

153. Thakar CV. Perioperative Acute Kidney Injury. Advances in Chronic Kidney Disease. Elsevier; 2013 Jan 1; 20(1):67–75.

154. Vanmassenhove J, Kielstein J, Jörres A, Biesen WV. Management of patients at risk of acute kidney injury. The Lancet. 2017 May; 389(10084):2139–51.

155. Moher D, Liberati A, Tetzlaff J. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):1-7.

156. Howick J. The Philosophy of Evidence-Based Medicine. 1st ed. Oxford, UK: Wiley-Blackwell, 2011. Chapter 3: What is good evidence for a clinical decision; p.28.

157. Abdullah HR, Tan TP, Vaez M, Deb C, Farag N, Jackson TD, et al. Predictors of Perioperative Acute Kidney Injury in Obese Patients Undergoing Laparoscopic Bariatric Surgery: a Single-Centre Retrospective Cohort Study. Obesity Surgery. Springer US; 2015; 26(7):1493–9.

158. Aveline C, Leroux A, Vautier P, Cognet F, Le Hetet H, Bonnet F. Facteurs prédictifs de dysfonction rénale postopératoire après arthroplasties totales de hanche. Annales Françaises d'Anesthésie et de Réanimation. 2009 Sep; 28(9):728–34.

159. Biteker M, Dayan A, Tekkeşin Aİ, Can MM, Taycı İ, İlhan E, et al. Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery. The American Journal of Surgery. Elsevier; 2014 Jan 1; 207(1):53–9.

160. Kim CS, Oak CY, Kim HY, Kang YU, Choi JS, Bae EH. Incidence, predictive factors, and clinical outcomes of acute kidney injury after gastric surgery for gastric cancer. PLoS ONE. 2013 Dec 9; 8(12):e82289.

161. Lee E-H, Ryul Kim H, Baek S-H, Kim K-M, Chin J-H, Choi D-K, et al. Risk Factors of Postoperative Acute Kidney Injury in Patients Undergoing Esophageal Cancer Surgery. Journal of Cardiothoracic and Vascular Anesthesia. Elsevier; 2014 Aug 1; 28(4):948–54.

162. Naik BI, Colquhoun DA, McKinney WE. Incidence and risk factors for acute kidney injury after spine surgery using the RIFLE classification: Clinical article. Journal of Neurosurgery: Spine. 2014 May; 20:505-511.

163. Sehgal V, Jit Singh Bajwa S, sehgal R, Eagan J, Reddy P, M Lesko S. Predictors of Acute Kidney Injury in Geriatric Patients Undergoing Total Knee Replacement Surgery. Int J Endocrinol Metab. Kowsar; 2014 Jul 1; 12(3).

164. Sharma SK, McCauley J, Cottam D, Mattar SG, Holover S, Dallal R, et al. Acute changes in renal function after laparoscopic gastric surgery for morbid obesity. Surg Obes Relat Dis. Elsevier; 2006 May; 2(3):389–92.

165. Slankamenac K, Breitenstein S, Held U. Development and validation of a prediction score for postoperative acute renal failure following liver resection. Annals of Surgery. 2009 Nov; 250(5):720-728.

166. Tateda T, Ohji M, Yokozuka M, Masumori Y, Sakamoto M. Acute kidney injury after hepatic surgery: 12AP1-8. European Journal of Anaesthesiology (EJA). 2011 Jun 1; 28:168.

167. Teixeira C, Rosa R, Rodrigues N, Mendes I, Peixoto L, Dias S, et al. Acute Kidney Injury after Major Abdominal Surgery: A Retrospective Cohort Analysis. Critical Care Research and Practice. Hindawi Publishing Corporation; 2014; 2014(1):1–8.

168. Thakar CV, Kharat V, Blanck S, Leonard AC. Acute Kidney Injury after Gastric Bypass Surgery. Clinical Journal of the American Society of Nephrology. 2007 Apr 11; 2(3):426–30.

169. Weingarten TN, Gurrieri C, Jarett PD, Brown DR, Berntson NJ, Calaro RD, et al. Lésion rénale aiguë après arthroplastie totale: une analyse rétrospective. Can J Anesth/J Can Anesth. 2012 Sep 29; 59(12):1111–8.

170. Weingarten TN, Gurrieri C, McCaffrey JM, Ricter SJ. Acute kidney injury following bariatric surgery. Obesity Surgery. 2012 Sept 13; 23:64-70.

171. Zhang J, Feng G, Yang Y, Zhang P, Pu C. Acute kidney injury after radical gastrectomy: a single center study. International urology and neprhology. 2014; 46:973-977.

172. Kim H-J, Koh W-U, Kim S-G, Park H-S, Song J-G, Ro Y-J, et al. Early postoperative albumin level following total knee arthroplasty is associated with acute kidney injury. Medicine. 2016 Aug; 95(31):e4489–7.

173. Long TE, Helgason D, Helgadottir S. Acute Kidney Injury After Abdominal Surgery: Incidence, Risk Factors, and Outcome. Anesthesia & analgesia. 2016 Jun; 122(6):1912-1920.

174. Kambakamba P, Slankamenac K. Epidural analgesia and perioperative kidney function after major liver resection. British Journal of Surgery. 2015; 102:805-812.

175. Bekelis K, Kalakoti P, Nanda A, Missios S. A Predictive Model of Unfavorable Outcomes After Benign Intracranial Tumor Resection. World Neurosurgery. Elsevier Inc; 2015 Jul 1; 84(1):82–9.

176. Squires M, Lad N, Fisher S, Kooby D, Weber S, Brinkman A, Scoggins C, Egger M, Cardona K, Cho C, Martin R, Russell M, Winslow E, Staley C, Maithel S. The Effect of Preoperative Renal Insufficiency on Postoperative Outcomes after Major Hepatectomy: A Multi-Institutional Analysis of 1,170 Patients. Journal of the American College of Surgeons. Elsevier Inc; 2014 Nov 1; 219(5):914–22.

177. Taylor RS, Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. European Journal of Pain. 2005 Mar 28; 10:91-101.

178. Biccard B. Proposed Research Plan for the Derivation of a New Cardiac Risk Index. Anesthesia & Analgesia. 2015 Mar; 120(3):543–53.

179. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. Anesthesiology. 1978 Oct; 49(4):239-43.

180. Astrup A, Finer N. Redefining Type 2 diabetes: 'Diabesity' or 'Obesity Dependent Diabetes Mellitus'? Obesity Reviews. Blackwell Science Ltd; 2000 Oct 1; 1(2):57–9.

181. Liu C, Cripe TP, Kim MO. Statistical issues in longitudinal data analysis for treatment efficacy studies in the biomedical sciences. Molecular Therapy. 2010 Sept; 18(9):1724-30.

182. Palevsky PM. Renal replacement therapy in acute kidney injury. Advances in Chronic Kidney Disease. 2013 Jan; 20(1):76-84.

183. Thakar CV, Worley S, Arrigain S, Yared J-P, Paganini EP. Improved Survival in Acute Kidney Injury After Cardiac Surgery. American Journal of Kidney Diseases. 2007 Nov; 50(5):703–11.

184. Morgera S, Schneider M, Neumayer HH. Long-term outcomes after acute kidney injury. Critical Care Medicine. 2008 April; 36(4):s193-197.

185. Varrier M, Forni LG, Ostermann M. Long-term sequelae from acute kidney injury: potential mechanisms for the observed poor renal outcomes. Crit Care. BioMed Central; 2015 Mar 16; 19(1):102.

186. Heung M, Chawla LS. Acute Kidney Injury: Gateway to Chronic Kidney Disease. Nephron Clin Pract. 2014; 127(1-4):30–4.

187. Doyle JF, Ostermann M, Forni LG. Goal-directed therapy and acute kidney injury: as good as it gets? Crit Care. Critical Care; 2016 May 31;:1–3.

188. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney International. Elsevier Masson SAS; 2012 Jan 1; 82(5):516–24.

189. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney International. Nature Publishing Group; 2011 Nov 23; 81(5):442–8.

190. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS. Nonrecovery of Kidney Function and Death after Acute on Chronic Renal Failure. Clinical Journal of the American Society of Nephrology. 2009 May 4; 4(5):891–8.

191. Haanschoten MC, van Straten AHM, Bouwman A, Bindels AJGH, van Zundert AAJ, Soliman Hamad MA. The Impact of Postoperative Renal Replacement Therapy on Long-Term Outcome After Cardiac Surgery Increases with Age. J Card Surg. 2014 Apr 18; 29(4):464–9.

192. Wu HC, Lee LC, Wang WJ. Incidence and mortality of postoperative acute kidney injury in non-dialysis patients: comparison between the AKIN and KDIGO criteria. Ren Fail. 2016; 38(2):330-9.

193. Wu VC, Wu PC, Wu CH, Huang TM, Chang CH, Tsai PR, et al. The Impact of Acute Kidney Injury on the Long-term Risk of Stroke. Journal of the American Heart Association. 2014 Jun 30; 3(4):e000933–3.

194. Fortrie G, Stads S, Aarnoudse A, Zietse R. Long-term sequelae of severe acute kidney injury in the critically ill patient without comorbidity: a retrospective cohort study. PLoS ONE. 2015 Mar 23; 10(3):e0121482.

195. Cohen SD, Kimmel PL. Long-term sequelae of acute kidney injury in the ICU. Current Opinion in Critical Care. 2012 Dec; 18(6):623-628.

196. Wald R, Shariff SZ, Adhikari NKJ, Bagshaw SM, Burns KEA, Friedrich JO, et al. The Association Between Renal Replacement Therapy Modality and Long-Term Outcomes Among Critically Ill Adults With Acute Kidney Injury. Critical Care Medicine. 2014 Apr; 42(4):868–77.

197. National Ethics Advisory Committee. Streamlined ethical guidelines for health and disability research. [Internet]. 2006 [cited 2014 Sep 27]. Available from: http://neac.health.govt.nz/publications-and-resources/neac-publications/streamlined-ethical-guidelines-health-and-disability.

198. Eckardt K-U, Berns JS, Rocco MV, Kasiske BL. Definition and Classification of CKD: The Debate Should Be About Patient Prognosis—A Position Statement From KDOQI and KDIGO. American Journal of Kidney Diseases. Elsevier; 2009 Jun 1; 53(6):915–20.

199. Ministry of Health. My DHB [Internet]. 2016 [cited 2014 Sep 27]. Available from http://www.health.govt.nz/new-zealand-system-my-dhb.

200. Child CG. The Liver and Portal Hypertension. Major problems in clinical surgery. 1964; 1:1-85.

201. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic Dialysis and Death Among Survivors of Acute Kidney Injury Requiring Dialysis. JAMA. American Medical Association; 2009 Sep 16; 302(11):1179–85.

202. Grams M, Sang Y, Coresh J, Ballew S, Matsushita K, Molnar M, Sazbo Z, Kalantar-Zadeh K, Kovesdy C. Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data. American Journal of Kidney Diseases. Elsevier Inc; 2016 Jun 1; 67(6):872–80.

203. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failurein U.S. veterans: focus on acute tubular necrosis. Kidney International. Nature Publishing Group; 2009 Sep 9; 76(10):1089–97.

204. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute Kidney Injury Increases Risk of ESRD among Elderly. Journal of the American Society of Nephrology. 2009 Jan 1; 20(1):223–8.

205. Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications. Kidney International. 2005 Sept; (98):S7-S10.

206. Zimmet P, Alberti K, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001; 414(6865):782–7.

207. Bracco D, Dubois M-J. Hemodynamic support in septic shock: Is restoring a normal blood pressure the right target? Critical Care Medicine. 2005 Sep; 33(9):2113–5.

208. Gholipour C. Using an Artificial Neural Networks (ANNs) Model for Prediction of Intensive Care Unit (ICU) Outcome and Length of Stay at Hospital in Traumatic Patients. JCDR. 2015;:1–5.

209. Lipsett PA, Swoboda SM, Dickerson J, Ylitalo M, Gordon T, Breslow M, et al. Survival and Functional Outcome After Prolonged Intensive Care Unit Stay. Annals of Surgery. 2000 Feb 1; 231(2):262.

210. Strunden MS, Heckel K, Goetz AE, Reuter DA. Perioperative fluid and volume management: physiological basis, tools and strategies. Annals of Intensive Care 2016 6:1. 2011 Dec 1; 1(1):2.

211. Corcoran T, Emma Joy Rhodes J, Clarke S, Myles PS, Ho KM. Perioperative Fluid Management Strategies in Major Surgery. Anesthesia & Analgesia. 2012 Mar; 114(3):640–51.

212. Egal M, de Geus HRH, van Bommel J, Groeneveld ABJ. Targeting oliguria reversal in perioperative restrictive fluid management does not influence the occurrence of renal dysfunction. European Journal of Anaesthesiology (EJA). 2016 Jun; 33(6):425–35.

213. Egal M, Erler NS, de Geus HRH, van Bommel J, Groeneveld ABJ. Targeting Oliguria Reversal in Goal-Directed Hemodynamic Management Does Not Reduce Renal Dysfunction in Perioperative and Critically Ill Patients. Anesthesia & Analgesia. 2016 Jan; 122(1):173–85.

214. Van der Zee EN, Egal M, Gommers D, Groeneveld ABJ. Targeting urine output and 30-day mortality in goal-directed therapy: a systematic review with meta-analysis and meta-regression. BMC Anesthesiology; 2017 Feb 9;:1–12.

215. Brandstrup B, Tønnesen H, Beier-Holgersen R. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Annals of Surgery. 2003 Nov; 238(5):641-648.

216. McArdle GT, McAuley DF, McKinley A, Blair P. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. Annals of Surgery. 2009 Jul; 250(1):28-34.

217. ERAS CG. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Annals of Surgery. 2015 Jun; 261(16):1153-9.

218. Keats AS. The ASA Classification of Physical Status-A Recapitulation. Anesthesiology. 1978 Oct 1; 49(4):233.

219. Buzby GP, Williford WO, Peterson OL, Crosby LO, Page CP, Reinhardt GF, et al. A randomized clinical trial of total parenteral nutrition in malnourished surgical patients: the rationale and impact of previous clinical trials and pilot study on protocol design. Am J Clin Nutr. American Society for Nutrition; 1988 Feb 1; 47(2):357–65.

220. Clavien PA, Strasberg SM. Severity Grading of Surgical Complications. Annals of Surgery. 2009 Aug; 250(2):197–8.

221. Coresh J, Stevens LA. Kidney function estimating equations: where do we stand? Current opinion in nephrology and hypertension. 2006; 15:276-284.

222. Kheterpal S, Tremper KK, Heung M. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. Anesthesiology. 2009; 110(3):505-515.

223. Abelha FJ, Botelho M, Fernandes V, Barros H. Determinants of postoperative acute kidney injury. Crit Care. 2009; 13(3):1-10.

224. Calvert S, Shaw A. Perioperative acute kidney injury. Perioperative Medicine. 2012; 1(6):1-11.

225. Kateros K, Doulgerakis C, Galanakos SP, Sakellariou VI, Papadakis SA, Macheras GA. Analysis of kidney dysfunction in orthopaedic patients. BMC Nephrology. BMC Nephrology; 2012 Sep 3; 13(1):1–1.

226. Ramadan I. Acute Kidney Injury Network: report of an initiative to improveoutcomes in acute kidney injury. 2014 Mar 2;:1–8.

227. Marjanovic G, Villain C, Juettner E, Hausen AZ, Hoeppner J, Hopt UT, et al. Impact of Different Crystalloid Volume Regimes on Intestinal Anastomotic Stability. Annals of Surgery. 2009 Feb; 249(2):181–5.

228. Aguilar-Nascimento JE, Diniz BN, do Carmo AV, Silveira EAO, Silva RM. Clinical Benefits After the Implementation of a Protocol of Restricted Perioperative Intravenous Crystalloid Fluids in Major Abdominal Operations. World J Surg. 2009 Feb 21; 33(5):925–30.

229. Wenkui Y, Ning L, JianFeng A, Weigin L, Shaoqiu T, Zhihui T, Tao G, Juanjuan Z, Fengchan X, Hui S, Weiming Z, Jie-Shou L. Restricted peri-operative fluid administration adjusted by serum lactate level improved outcome after major elective surgery for gastrointestinal malignancy. Surgery. Mosby, Inc; 2010 Apr 1; 147(4):542–52.

230. Booi DI. Perioperative fluid overload increases anastomosis thrombosis in the free TRAM flap used for breast reconstruction. Eur J Plast Surg. 2010 Jun 22; 34(2):81–6.

231. Kambhampati G, Ross EA, Alsabbagh MM, Asmar A, Pakkivenkata U, Ejaz NI, et al. Perioperative fluid balance and acute kidney injury. Clin Exp Nephrol. 2012 Mar 29; 16(5):730–8.

232. Le Quesne LP. Some Aspects of Fluid and Electrolyte Problems in the Post-operative Period. Proceedings of the Royal Society of Medicine. 1952 Jun;45(6):393-394.

233. Sweny P. Is postoperative oliguria avoidable? British Journal of Anaesthesia. 1991;67(2):137–45.

234. Mirenda JV, Grissom TE. Anesthetic implications of the renin-angiotensin system and angiotensin-converting enzyme inhibitors. Anesthesia & Analgesia. 1991 May; 72(5):667-83.

235. Bonnet F, Harari A, Thibonnier M. Suppression of antidiuretic hormone hypersecretion during surgery by extradural anaesthesia. Journal of anaesthesia. 1982; 54(29):29-36.

236. Hübner M, Schäfer M, Demartines N, Müller S. Impact of Restrictive Intravenous Fluid Replacement and Combined Epidural Analgesia on Perioperative Volume Balance and Renal Function Within a Fast Track Program. Journal of Surgical Research. 2012 Mar; 173(1):68-74.

237. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A Prospective Randomized Controlled Trial of Multimodal Perioperative Management Protocol in Patients Undergoing Elective Colorectal Resection for Cancer. Annals of Surgery. 2007 Jun; 245(6):867–72.

238. Bourgeois É, Bataille A, Jacob L. Modifications péri-opératoires de la fonction rénale. La Presse Médicale. 2009 Nov; 38(11):1621–9.

239. Nygård P, Jansman FGA, Kruik-Kollöffel WJ, Barnaart AFW, Brouwers JRBJ. Effects of short-term addition of NSAID to diuretics and/or RAAS-inhibitors on blood pressure and renal function. Int J Clin Pharm. 2012 May 24; 34(3):468–74.

240. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. Crit Care. BioMed Central; 2011 Aug 15; 15(4):R197.

241. Chesley LC. Renal excretion at low urine volumes and the mechanism of oliguria. Journal of Clinical Investigation. 1938 Sep 1; 17(5):591–7.

242. Le Quesne LP, Lewis A. POstoperative water and sodiu retention. The Lancet. 1953 Jan 24;1(6752):153-158.

243. Springberg PD, Garrett LE, Thompson AL, Collins NF, Lordon RE, Robinson RR. Fixed and Reproducible Orthostatic Proteinuria: Results of a 20-Year Follow-up Study. Ann Intern Med. American College of Physicians; 1982 Oct 1; 97(4):516–9.

244. Burton C, Harris K. The role of proteinuria in the progression of chronic renal failure. American Journal of Kidney Diseases. 1996; 27(6):765–75.

245. Makris K, Kafkas N. Neutrophil Gelatinase-Associated Lipocalin in Acute Kidney Injury. Advances in Clinical Chemistry. 2012. 58:131-91.

246. Shemin D, Dworkin LD. Neutrophil gelatinase– associated lipocalin (NGAL) as a Biomarker for Early Acute Kidney Injury. Critical Care Clinics. 2011 Apr 1; 27(2):379–89.

247. Haase M, Haase-Fielitz A. NGAL—From discovery to a new era of "Acute Renal Disease" diagnosis? Clinical Biochemistry. 2011 May 1; 44(7):499–500.

248. Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, et al. Dual Action of Neutrophil Gelatinase-Associated Lipocalin. Journal of the American Society of Nephrology. 2007 Jan 17; 18(2):407–13.

249. Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, Devarajan P. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care. 2007; 11(6):R127.

250. Doi K, Negishi K, Ishizu T, Katagiri D, Fujita T, Matsubara T, et al. Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit*. Critical Care Medicine. 2011 Nov; 39(11):2464–9.

251. Cruz DN, Bolgan I, Perazella MA, Bonello M, de Cal M, Corradi V, et al. North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEiPHROS-AKI): Targeting the Problem with the RIFLE Criteria. Clinical Journal of the American Society of Nephrology. 2007 Apr 11; 2(3):418–25.

252. de Geus H, Bakker J, Lesaffre EM, le Noble JL. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med. 2001 Apr 1; 183(7):907-14.

253. Di Somma S, Magrini L, De Berardinis B, Marino R, Ferri E, Moscatelli P, et al. Additive value of blood neutrophil gelatinase- associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department. Crit Care. BioMed Central Ltd; 2013 Feb 12; 17(1):R29.

254. Bagshaw SM, Bennett M, Haase M, Haase-Felitz A, Egi M, Morimatsu H, D'amico G, Goldsmith D, Deverajan P, Bellomo R. Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med. 2010 Mar; 36(3):452-61.

255. Nickolas TL, O'Rourke MJ, Yang J. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase–associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008 Jun 3; 148(11):810-9.

256. Buckmans FC. Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry. 2016 Nov 7;:1–56.

257. Ralib AM, Pickering JW, Shaw GM, Than MP, George PM, Endre ZNH. The clinical utility window for acute kidney injury biomarkers in the critically ill. 2014 Nov 25;:1–12.

258. Moghadamyeghaneh Z, Hanna MH, Carmichael JC, Mills SD, Pigazzi A, Nguyen NT, Stamos MJ. Nationwide Analysis of Outcomes of Bowel Preparation in Colon Surgery. Journal of the American College of Surgeons. American College of Surgeons; 2015 May 1; 220(5):912–20.

259. Makris K, Markou N, Evodia E, Dimopoulou E, Drakopoulos I, Ntetsika K, et al. Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. Clinical Chemistry and Laboratory Medicine. 2009; 47(1):79-82.

260. Herget-rosenthal S, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, et al. Early detection of acute renal failure by serum cystatin C. Kidney International. Elsevier Masson SAS; 2004 Jan 1; 66(3):1115–22.

261. Mehta RL, Pascual MT, Soroko S, Savage BR. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney International. 2004; 66(4):1613–21.

262. Mishra J, Ma Q, Prada A, Mitsnefes M. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. Journal of the American Society of Nephrology. 2003; 14:2534-2543.

263. Fredman B, Zohar E, Golan E, Tillinger M, Bernheim J, Jedeikin R. Diclofenac Does Not Decrease Renal Blood Flow or Glomerular Filtration In Elderly Patients Undergoing Orthopedic Surgery. Anesthesia & Analgesia. 1999 Jan 1; 88(1):149–54.

264. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR. Incidence and associations of acute kidney injury after major abdominal surgery. Intensive Care Medicine. Springer Berlin Heidelberg; 2015 Nov 23; 42(4):521–30.

265. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Continuous renal replacement therapy: A worldwide practice survey. Intensive Care Medicine. Springer-Verlag; 2007 Jun 27; 33(9):1563–70.

266. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, et al. Cost and Mortality Associated With Postoperative Acute Kidney Injury. Annals of Surgery. 2015 Jun; 261(6):1207–14.

267. Prowle JR, Kam EPY, Ahmad T, Smith NCE, Protopapa K, Pearse RM. Preoperative renal dysfunction and mortality after non-cardiac surgery. Br J Surg. 2016 Jun 27; 103(10):1316–25.

268. Goren O, Matot I. Update on perioperative acute kidney injury. Current Opinion in Critical Care. 2016 Aug; 22(4):370–8.

269. Koeze J, Keus F, Dieperink W, van der Horst ICC, Zijlstra JG, van Meurs M. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. BMC Nephrology; 2017 Feb 16;:1–9.

270. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol. American Society of Nephrology; 2006 Jan; 1(1):19–32.

271. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation. American Heart Association, Inc; 2009 Feb 3; 119(4):495–502.

272. Englberger L, Suri RM, Connolly HM, Li Z, Abel MD, Greason KL, et al. Increased risk of acute kidney injury in patients undergoing tricuspid valve surgery. European Journal of Cardio-Thoracic Surgery. 2013 Apr 8; 43(5):993–9.

273. Medve L, Antek C, Paloczi B, Kocsi S, Gartner B, Marjanek Z, et al. Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study. BMC Nephrology. BioMed Central; 2011 Sep 13; 12(1):43.

274. Romagnoli S, Zagli G, Tuccinardi G, Tofani L, Chelazzi C, Villa G, Cianchi F, Coratti A, De Gaudio AR, Ricci Z. Postoperative acute kidney injury in high-risk patients undergoing major abdominal surgery. Journal of Critical Care. 2016 Oct 1; 35(C):120–5.

275. Causey MW, Maykel JA, Hatch Q, Miller S, Steele SR. Identifying Risk Factors for Renal Failure and Myocardial Infarction Following Colorectal Surgery. Journal of Surgical Research. 2011 Sep 1; 170(1):32–7.

276. Kelz RR, Reinke CE, Zubizarreta JR, Wang M, Saynisch P, Even-Shoshan O, et al. Acute Kidney Injury, Renal Function, and the Elderly Obese Surgical Patient. Annals of Surgery. 2013 Aug; 258(2):359–63.

277. Sabaté S, Gomar C, Canet J, Sierra P. [Risk factors for postoperative acute kidney injury in a cohort of 2378 patients from 59 hospitals]. Revista espanola de Anestesiol Reanime. 2011; 58(9):548–55.

278. Masoomi H, Carmichael JC, Dolich M. Predictive factors of acute renal failure in colon and rectal surgery. The American Surgeon. 2012 Jan 22; 78:1019-1023.

279. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. The Lancet. 2012 Aug 25; 380(9843):756–66.

280. AKIN Group. Acute Kidney Injury Network Crieteria [Internet]. 2013 [cited 2014 Sep 24]. Available from: http://www.akinet.org/akinstudies.php

281. Wald R, Deshpande R, Bell CM, Bargman JM. Survival to discharge among patients treated with continuous renal replacement therapy. Hemodialysis International. 2nd ed. Blackwell Science Inc; 2006 Jan 1; 10(1):82–7.

282. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Medicine. 2009 Jun 23; 35(10):1692–702.

283. Garzotto F, Piccinni P, Cruz D, Gramaticopolo S, Dal Santo M, Aneloni G, et al. RIFLE-Based Data Collection/Management System Applied to a Prospective Cohort Multicenter Italian Study on the Epidemiology of Acute Kidney Injury in the Intensive Care Unit. Blood Purif. 2011; 31(1-3):159–71.

284. Flaatten H, Kvåle R. Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. Intensive Care Medicine. 2001 May 12; 27(6):1005–11.

285. Timmers TK, Verhofstad MH, Moons KG, Leenen LP. Long-term Survival After Surgical Intensive Care Unit Admission. Annals of Surgery. 2011 Jan; 253(1):151–7.

286. Wlodzimirow KA, Abu-Hanna A, Slabbekoorn M, Chamuleau RA, Schultz MJ, Bouman CS. A comparison of RIFLE with and without urine output criteria for acute kidney injury in critically ill patients. Crit Care. BioMed Central; 2012 Oct 18; 16(5):R200.

287. Macedo E, Malhotra R, Claure-Del Granado R, Fedullo P, Mehta RL. Defining urine output criterion for acute kidney injury in critically ill patients. Nephrology Dialysis Transplantation. 2011 Jan 27; 26(2):509–15.

288. Salgado G, Landa M, Masevicius D, Gianassi S, San-Román JE, Silva L, et al. Acute renal failure according to the RIFLE and AKIN criteria: A multicenter study. Medicina Intensiva (English Edition). SEGO; 2014 Jun 4; 38(5):271–7.