2019

PROTOCOLIZED VOLUME DE-RESUSCITATION IN CRITICALLY ILL PATIENTS

Brittany Dawn Bissell
University of Kentucky, brittany.bissell@uky.edu
Author ORCID Identifier:
https://orcid.org/0000-0002-7345-9731
Digital Object Identifier: https://doi.org/10.13023/etd.2019.122

STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Brittany Dawn Bissell, Student

Dr. Peter E. Morris, Major Professor

Dr. Hannah Knudsen, Director of Graduate Studies

PROTOCOLIZED VOLUME DE-RESUSCITATION IN CRITICALLY ILL PATIENTS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy
in the College of Medicine at the University of Kentucky

By

Brittany Dawn Bissell

Lexington, Kentucky

Co-Directors: Dr. Peter E. Morris, MD, FACP, FCCP, Professor of Medicine
And: Dr. William W. Stoops, PhD, Professor of Medicine

Lexington, Kentucky

2019

ABSTRACT OF DISSERTATION

PROTOCOLIZED VOLUME DE-RESUSCITATION IN CRITICALLY ILL PATIENTS

While early fluid resuscitation may be a necessary component to decrease mortality in the majority of critically ill patients admitted to the intensive care unit, the benefit of continued administration after the first 24 hours is less clear. Paradoxically, a positive fluid balance secondary to intravenous fluid receipt has been associated with diverse and persistent perpetuating detriment on a multitude of organ systems. Continued clinical harm has been demonstrated on pulmonary and renal function as well as patient outcomes such as rates of mortality and length of stay. Despite the growing body of evidence supporting the potential adverse aspects of positive fluid balances, fluid overload remains common in patients during the early days of critical care admission.

One approach to correcting fluid balance is shifting focus onto the post- or de-resuscitation period with appropriate fluid removal with diuresis once hemodynamic stability is achieved. However, diuresis is often ineffective due to a lack of standardization in identification of fluid-overloaded patients. Further, optimal transition times between fluid resuscitation and fluid removal are not clear and physical signs of fluid overload are delayed relative to onset of organ damage. While administration of diuretics has shown to decrease net volume and improve clinical outcomes in the critically ill, current practice does not reflect clinical trial findings. Most treatment regimens are often inadequate both by nature of time and dosing intensity. Further, as de-resuscitation occurs once the initial instability has resolved, precedence is usually given to other acute or critical needs rather than follow-up for diuresis effectiveness. Additionally, frequent apprehension for medication side effects is seen, despite the preponderance of adverse event data found only in non-critical care populations, frequently non-translatable to patients within the intensive care unit.

Optimization of diuresis in critically ill patients is primed for clinical pharmacy intervention. Clinical pharmacists are experts in the delivery of pharmaceutical care, utilizing specialized therapeutic knowledge, experience, and judgment to ensure optimal patient outcomes. Pharmacist-driven protocols for other conditions have shown improved patient outcomes, reduced adverse events and improved target attainment in before and after studies. A pharmacist-driven diuresis protocol to facilitate de-resuscitation implemented within the multidisciplinary critical care team has the potential to improve patient care by optimizing pharmacotherapy selection, while potentially reducing adverse events, days on mechanical ventilation and length of

intensive care unit stay. Such a protocol rightfully places pharmacist accountability on medication-related outcomes while potentially decreasing critical care resource utilization.

The work within this dissertation aims to accomplish the development of a pharmacist-driven diuresis protocol for implementation in the medical intensive care unit, with national pharmacy organization sponsorship. Further, the protocol aims to be adopted as an innovative practice change for de-resuscitation of critically ill patients to improve clinical outcomes while advancing the pharmacy profession.

KEYWORDS: fluids, critical illness, diuresis, volume status, de-resuscitation, mechanical ventilation

Brittany D. Bissell, PharmD, BCCCP

April 15, 2019

PROTOCOLIZED VOLUME DE-RESUSCITATION IN CRITICALLY ILL PATIENTS

By

Brittany Dawn Bissell

Dr. Peter E. Morris, MD, FACP, FCCP
Co-Director of Dissertation

Dr. William W. Stoops, PhD
Co-Director of Dissertation

Dr. Hannah Knudsen, PhD
Director of Graduate Studies

April 15, 2019

To my grandmother,

who taught me both compassion and perseverance.

ACKNOWLEDGEMENTS

The following dissertation, while an individual work, would not have been possible without the insight, direction, and coordination from multiple collaborators at the University of Kentucky. I must first thank my mentor Dr. Peter E. Morris, for his time, support, and dedication to all research, including my own over the past three years. Without Dr. Morris, Medical intensive care unit research at the University of Kentucky would not be possible. The endless prioritization of advancing practice is constantly evolving and improving the ability of those he trains as well as those patients we care for. I would also like to thank the other members of my research team, including Dr. David Feola, for his inspiration as a PharmD, PhD and his crash course on grant writing and immunology, Dr. William Stoops, with his ever-positive approach and his genuine nature, and Dr. Aaron Cook, who has embraced my drive as a clinician researcher and not only encouraged such, but also nurtured my passions along the way.

I owe many thanks to my pulmonary pharmacy colleagues. First, Alexander Flannery, for his hours of mentorship, refining and cultivating who I am as a practitioner while always remaining a voice of reason. Further, Melissa Thompson-Bastin, for always encouraging my aspirations and creativity, while providing constant guidance to study implementation. I also must thank Melanie Laine, the final key pharmacist author on this project, for providing steadfast support over the past three years, for her unwavering confidence in me, and for inspiring us all with her knowledge and dedication to her patients, students, and trainees. I cannot go without further thanking the entire Medical intensive care unit physician staff, all playing key roles throughout the project development, and the nursing staff and leadership, who played an integral part in the implementation and improvement in the project. I am forever grateful to be surrounded by a group of people whose passion for education and the lives of their patients inspires me daily.

With such, I must also thank the patients who I am blessed to work with and for every day. Your stories, your families, and your tenacity amaze and encourage me. This project, and all future projects, are to better their care, their outcomes, and their lives.

Foremost, I thank my grandmother, Jennifer Jackson, and the rest of my family, Amy, Kristyn, Pam, and Beth as well as my best friend, Brian Gilbert, for keeping me grounded throughout the trials and tribulations and reminding me of my value and capabilities while also always encouraging me to be a better version of myself.

Above all, I thank God, whose blessings have created the person I am today, for giving me the determination, aptitude, and opportunity to undertake this research study and to persevere and complete it. None of these opportunities would be possible if not in His will.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1. INTRODUCTION AND LITERATURE REVIEW

This chapter provides an introduction to both the physiologic and clinical concerns regarding fluid administration and volume status in the intensive care unit (ICU) which motivate the work within this dissertation. This dissertation discusses a protocolized approach to the administration of diuretics for volume removal within the critically ill population.

1.1 Pathophysiology of Shock and Fluid Rationale

1.1.1 Parameters of Perfusion

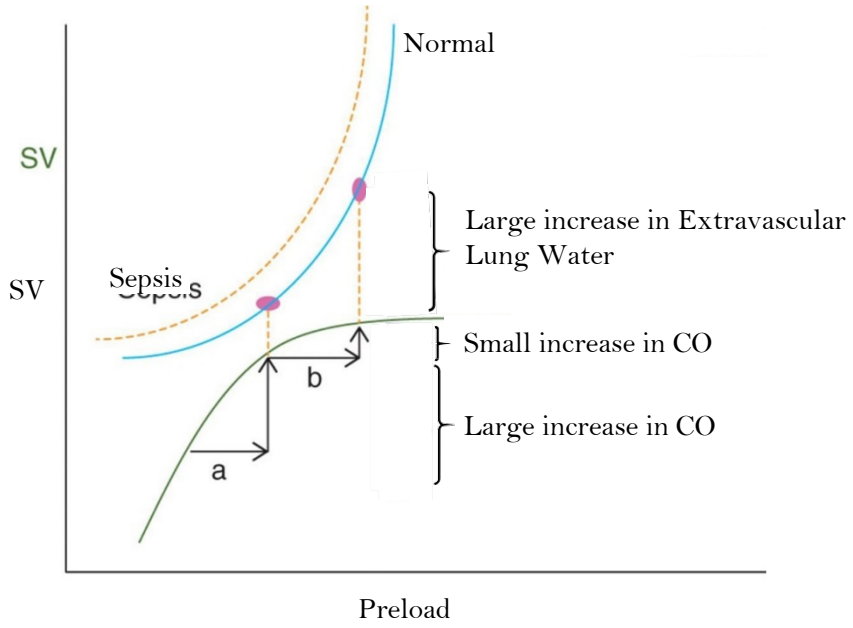
Shock, by definition, is a profound circulatory failure in which the body remains in an overall critical state of low organ perfusion threatening survival. (1) Shock can be secondary to inadequate supply of oxygen as well as impaired oxygen use, either of which may lead to insufficient oxygen delivery (DO_2) relative to oxygen consumption (VO_2). When in balance, the body maintains aerobic metabolism, utilizing energy efficiently to perform bodily functions. When the circulation, consisting of the blood vessels throughout the body, is impaired, tissues and organs can increase oxygen extraction from the blood to compensate. Once a critical threshold is reached, however, the body converts to anaerobic metabolism, a less efficient process for the production of energy, leading to accumulation of breakdown products. If the balance is not restored, organ injury begins. Perfusion of organs and tissue is driven by the DO_2. The amount of oxygen circulating in the blood supply to organs is determined by several key factors, including hemoglobin and the hemoglobin affinity for oxygen, the actual supply of oxygen within the blood, and cardiac output (CO). Once blood supply reaches the tissue level, the amount of delivered oxygen is dependent on perfusion pressure. Perfusion pressure is the energy required to overcome resistance and allow oxygen exchange at the tissue level and is mathematically defined as the difference between the arterial pressure, termed mean arterial pressure (MAP), and the amount of blood flow resistance within the vessel. MAP is the blood flow from the heart to the organs and is the sum of the central venous pressure (CVP) in addition to the mathematical product of

CO multiplied by systemic vascular resistance (SVR). The CVP is the pressure measured in the vena cava prior to right atrium. As the CVP physiologically is typically near 0 mmHg, the calculation is often simplified to MAP = CO × SVR. The SVR is the level of resistance that must be overcome to push blood through the circulatory system and create flow.

1.1.2 Resuscitation Targets in Shock

MAP is most frequently used as a monitoring parameter during the treatment of shock as, while a certain organ-specific autoregulatory range allows small, relatively insignificant fluctuations in MAP, organ perfusion significantly and linearly drops once the MAP is below a critical threshold. Four major types of shock are described, with septic shock found to be the most common in those admitted to the emergency department. (2) In septic shock, both oxygen delivery and consumption may be impaired. Regarding decreased oxygen delivery, a predominant decrease in SVR results in a decrease in MAP, secondary to capillary leak, resulting in extravasation of blood volume from the vascular space to neighboring body cavities. While all organs depend on autoregulation to maintain perfusion pressure, major organs which are most susceptible to these changes include the brain, heart, and kidney. For this reason, studies target increases in SVR utilizing MAP as a surrogate marker and have demonstrated that a MAP between 60-65 mmHg best correlates with survival, resulting in a guideline recommendation for targeted resuscitation in sepsis of a MAP of 65 mmHg. (3, 4) CO, the other key determinant of MAP, is directly correlated with a patient's stroke volume (SV), or the volume of blood pumped from the left ventricle of the heart per beat, as well as heart rate (HR). SV can be increased via contractility of the ventricle, the muscular ability of the heart to contract, or via an increase in left ventricular end-diastolic volume (EDV) just before systole, the phase of the heartbeat when contraction occurs and pumps blood to the arteries and subsequent organs. Hence, intravenous crystalloid fluids remain the hallmark of initial hemodynamic resuscitation in shock, particularly septic shock, within the critically ill via their anticipated impact on EDV, termed preload. This treatment approach has its roots in the rationale of what is termed the Frank-Starling Curve, which

Figure 1.1 Postulated Preload-Stroke Volume Relationship (5)



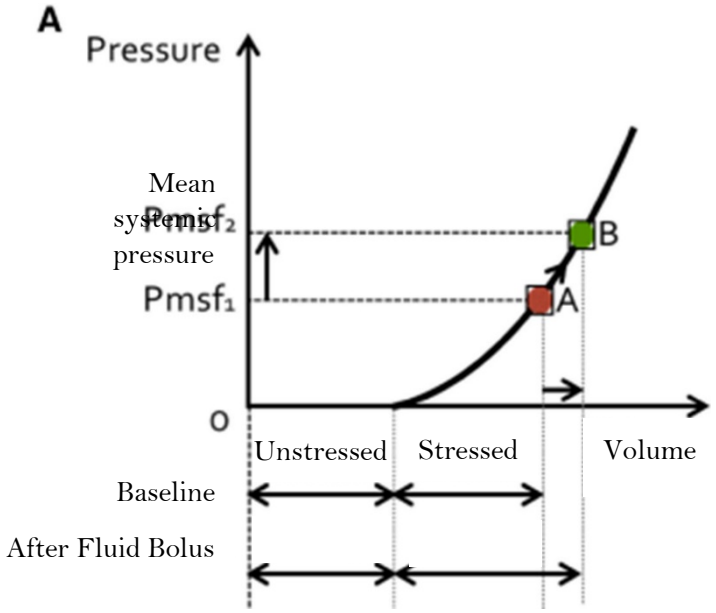
demonstrates that optimizing preload, notably under normal physiologic circumstances, with the administration of fluid, could in turn return stroke volume to normal and increase cardiac output until the optimal preload is achieved, after which stroke volume will remain stagnant (Figure 1.1).

1.1.3 The Venous System

Delving further, when the venous system is evaluated, blood flow is primarily determined by the pressure gradient between the venous periphery, termed mean systemic filling pressure, and the right atrium, the critical back pressure for venous return to the heart. (6) For cardiac output to occur, right atrial pressure should be as low as possible to optimize the pressure gradient. The CVP has been historically used as a surrogate for right atrial pressure. The venous system itself is the primary reservoir for blood flow within the body, holding approximately 70% of the plasma volume.

Theoretically, the venous consists of both stressed and unstressed volume. Unstressed volume is the volume which keeps the vessels minimally open and is the major contributor to total volume, roughly 60-70%. This volume is, however, of decreased significance given minimal

Figure 1.2 Effect of Fluid Bolus on Stressed and Unstressed Volume (7)



contribution to the mean systemic pressure. In sepsis, the unstressed volume increases given the increased dilation of the vascular system (and decreased SVR). It is important to denote the difference in mean systemic pressure and mean arterial pressure. Mean systemic pressure is the pressure in the vascular system that would occur without cardiac output after complete redistribution of pressure, usually 7-10 mmHg. The mean systemic pressure is an indicator of the fullness of the circulatory system and when there is zero flow, the CVP is equal to the mean systemic pressure. (8) The stressed volume does contribute however given its pressure exertion against the vascular walls. The stressed volume is responsible for venous stretch, corresponding to an increase in intravascular pressure, and venous return. In sepsis, as the unstressed volume increases, mean systemic pressure decreases with stressed volume shift and fluid extravasation, given the leakiness of the vasculature at the center of sepsis pathophysiology. Once the unstressed volume maximum is reached, the stressed volume increases, therefore distending vessels to increase intravascular volume. Fluid bolus administration has the potential to increase stressed volume, preload, and therefore cardiac output, but also the CVP (Figure 1.2). In order to improve CO with the administration of fluid, the stressed volume must not only increase, but also this

pressure gradient for venous return must exceed a rise in CVP from such bolus. MAP minus CVP becomes the hallmark equation to determine overall organ blood flow and perfusion pressure, with rising MAP equating to improved organ perfusion and an increased CVP resulting in impeded venous return, stroke volume, and therefore cardiac output. In the situation of septic shock, once the fluid bolus temporizing MAP through CO augmentation is completed, leakiness of the vasculature will allow movement of fluid quickly into the tissue compartments. This results in a practice of continued administration of additional fluid boluses for transitory CO improvement with sustained extravasation.

1.2 Evidence Supporting Fluid Administration

As part of their bundled approach to management, the Surviving Sepsis Campaign recommends aggressive fluid resuscitation with crystalloid therapy of 30 mL/kg minimum in patients presenting in septic shock. (4) Intriguingly, the origin of this recommendation is controversial, with potential derivation from a pediatric study of 34 patients within a single center cohort. This study, performed 30 years ago, demonstrated that children who received 40 mL/kg compared to 20-40 mL/kg and <20 mL/kg of crystalloid therapy within the first hour had improved survival and decreased rates of persistent hypovolemia. (9) Unfortunately, the administration of 30 mL/kg intravenous (IV) fluid versus alternative dosing recommendations has never been studied in prospective adult human models.

1.2.1 Fluid Administration in Landmark Trials

In a study of septic shock patients admitted to a single-center emergency department, administration of 30 mL/kg crystalloid fluid within 30 minutes of presentation compared with 31-60 or 61-180 minutes improved mortality and hospital length of stay. (10) A two-year retrospective cohort study of 594 patients in septic shock demonstrated that the median fluid volume within the first 3 hours was 2058 mL versus 1600 mL in survivors and non-survivors, respectively. (11) Most recently, three large, multinational studies evaluating the aforementioned

bundle-based sepsis therapies failed to demonstrate any benefit with protocolized sepsis interventions versus unguided control arms. (12) What is most notable about these studies, however, is that patients in all groups received roughly 5 liters of fluid within the first 6 hours of arrival. Between group differences in fluid administration was considered a small clinical difference, ranging from -452 mL to 667 mL, and no difference in mortality was seen. These studies oppose a much earlier, smaller single-center study that prompted the adaption of sepsis bundles which compared protocolized therapy versus standard of care. (13) This study showed a dramatic decrease in mortality of 16% (Risk Ratio [RR] 0.58, 95% Confidence Interval [CI] 0.38-0.876) however between-group fluid administration was 1.48 liters, with survivors receiving higher cumulative fluid volumes. While all four of these studies evaluated the end-result of multifaceted protocols, authors argue that the dissimilarity in between-group differences in fluid administration may have resulted in the mortality benefit seen with the older cohort.(14)

1.3 Physiologic Concerns with Fluid Administration

Despite theoretical benefits, excess volume receipt during and following the initial shock stabilization phase may have detrimental effects. CVP elevation from fluid administration not only deleteriously influences cardiac output, but may also increase interstitial pressure of encapsulated organs, which may result in a decrease of microcirculatory blood flow. (5) Particularly with large fluid boluses, volume administration may exceed the heart's ability to compensate and overly rapid increases in filling pressures may counteract compensatory mechanisms within shock resulting in cardiovascular collapse. (15) Despite this evidence, clinical trials demonstrate the majority of hemodynamically unstable patients are not fluid responsive, hence may not benefit from further bolus administration for ongoing shock. (5)

1.3.1 Cardiac Dysfunction and Fluid Administration

Studies specifically examining cardiac function show systolic, diastolic, and combined diastolic and systolic dysfunction occurring in 9-50%, 40-84%, and 14.1% of patients presenting

with septic shock, respectively. (16, 17) Such diastolic dysfunction can align with a decrease in left ventricular compliance which impairs the ability of the left ventricle to subsequently dilate and augment SV in response to fluid loading. (18) Excessive fluid loading to a non-compliant left ventricle may aggravate pulmonary congestion and non-cardiogenic pulmonary edema, potentially leading to pulmonary hypertension, dysfunction of the right ventricle, and a further decrease in left ventricular volumes. (19) In a dilated right ventricle, even a small increase in volume can cause a major increase in end diastolic pressure. A dilated right ventricle also has the ability to result in septal displacement which further impede left ventricular filling and therefore decrease cardiac output. (20)

1.3.2 Effects of Fluid Administration on the Vasculature

Frequent, large volumes of fluid resuscitation have also shown to increase cardiac filling pressures abruptly, increasing the release of natriuretic peptides. These hormones, primarily secreted from cardiac tissue mostly for their natriuretic properties and sodium regulation, cleave proteoglycans and glycoproteins from the endothelial glycocalyx (EGL). The glycocalyx is the inner lining of the vascular endothelium, the key barrier between the intravascular and interstitial spaces. The EGL allows this vascular bed to maintain its patency and function to prevent large molecules and fluid moving out of the vascular system and into the interstitial area. (21, 22) This EGL is damaged in multiple pathophysiologic states, including septic shock, predisposing poor endothelial barricade at baseline. Natriuretic peptides also inhibit the lymphatic system propulsion preventing overall drainage. This results in increased fluid extravasation into the interstitial space and subsequently poor elimination from the tissues.

1.3.3 Effects of Fluid Administration on the Macrocirculation

One cannot forget the basics of hemodynamic physiology in which the rationale of fluids are derived, MAP = CO × SVR. If fluid bolus administration seeks to improve MAP via an increase in cardiac output, a compensatory decrease in SVR may occur, worsening or masking the

actual underlying shock state. Additionally, while a paradoxical increase in CO during shock, termed hyperdynamic cardiac output, has been shown to be associated with improved survival rates compared to low cardiac output states, forced augmentation of the cardiac output via pharmacologic measures has failed to show similar survival benefit as spontaneous rises do. (23, 24) Fluid bolus administration has the potential to decrease SVR via hemodilution, or the lowering of the overall blood concentration. Fluid expansion of blood volume is not synonymous with true plasma expansion which means blood viscosity may decrease leading to decreased vascular resistance with the arterioles. (25) It is plausible that the expansion of circulating volume may only increase distribution of cytokines and worsen organ damage.

1.3.4 Effects of Fluid Administration on the Microcirculation and Oxygen Delivery

While most discussion regarding fluid administration surrounds its hemodynamic effects and the macrocirculation, consisting of systemic pressures and stroke volume responsiveness, less consideration has been made for effects on the microcirculation. Via the augmentation of cardiac output, fluid bolus administration in shock seeks to improve oxygen delivery to the tissues. The microcirculation, the blood flow circulation within the capillaries, the smallest vessels in the organs, responsible for direct exchange with organ tissue, is typically regulated by the macrocirculation. However, in the critically ill, a lack of hemodynamic correlation between macro- and microcirculation is found. Excess fluid extravasation into the interstitial space has the potential to decrease the density of the microvasculature. As a result, an increase in tissue diffusion distance from oxygen carriers is possible. Hemodilution may also worsen oxygen delivery by decreasing availability of oxygen. Further, if the microcirculation is disturbed, local matching of oxygen supply and demand may be altered, resulting in a shunt of microcirculatory flow.(26)

1.4 Evidence Surrounding Fluid Administration

It has been previously stated that absence of evidence is not evidence of absence. Stated simply, if there is no evidence to evaluate harm of a particular therapy, one cannot imply that the

particular therapy has no harm. Fluid administration in the critically ill aligns with this aphorism. This therapy is so ingrained within the management of the critically ill under the assumption of benefit that few have sought clinical repercussions of such. To date, the only evidence critiquing fluid administration versus placebo arises from two African studies. The first, Fluid Expansion as Supportive Therapy (FEAST), evaluated rates of mortality in pediatric patients presenting with fever and impaired perfusion. Patients who received a fluid bolus had a 50% higher risk of mortality versus those who did not (RR 1.45, 95% CI 1.13-1.86), however the population limits generalizability. (27) In a second study, the Simplified Severe Sepsis Protocol (SSSP), adults with sepsis-related organ dysfunction received usual versus protocolized care. (28) Protocolized patients received significantly higher rates of fluid, 2.7 versus 1.7 liters of fluid in the first 6 hours with other therapies equal. The study was stopped early given high mortality rates of those with respiratory failure assigned to protocolized therapy at which point in-hospital mortality was significantly higher with fluid administration (RR 1.05, 95% CI 0.79-1.41). However, as SSSP included patients with nonspecific markers of tissue hypoperfusion rather than only patients with sepsis and overt hypotension for whom the benefit of early intravenous fluid bolus and vasopressor administration may be greatest, a follow-up study, SSSP-2, sought to reconcile these differences. This study demonstrated that patients in protocolized therapy received 1.5 liters more fluid on average in the first 6 hours after presentation to the emergency department and had a higher risk of mortality (RR 1.46, 95% CI 1.04-2.05). (29) Outside of this evidence, no large randomized clinical trials have directly evaluated the impact of fluid therapy compared to placebo for management of shock.

1.5 Monitoring Tools for Fluid Administration

1.5.1 The Utility of Central Venous Pressure for Evaluation of Volume Status

Given concerns for potential error in regards to under or over-administration of crystalloids for septic shock, clinicians have sought invasive and non-invasive tools to optimize fluid administration. Historically, direct measurement of CVP was utilized as a proposed guide to

fluid administration, a practice which dates back to 1959. (30) These authors proposed that right atrial pressure was reflective of an effective circulating blood volume. From these data and because the central venous pressure is the most proximal intravascular pressure obtained proximal to the myocardium, CVP has been proposed as an indicator of right ventricular end-diastolic volume and therefore preload. Previous guidelines for the management of septic shock recommended fluid administration of crystalloid fluid to target a CVP of 8 mmHg. (31) This practice, however, came with assumptions subsequently disproved. The relationship between ventricular pressure and volume is nonlinear. The correlation is reduced in times of diastolic dysfunction and ventricular compliance fluctuations, such characteristics which are frequent in the critically ill. The CVP can also be influenced by thoracic, pericardial, and abdominal pressures, namely positive pressure ventilation. (32) CVP has also shown to have large interpatient variation. Further, as mentioned previously, increases in CVP at times may have the potential to actually decrease venous return and therefore decrease cardiac output. For this reason, CVP without concomitant evaluation of actual cardiac output is now much less often recommended for septic shock. Further, later studies suggest that the CVP is a poor predictor of fluid responsiveness. (33-39) Expanding on notion of poor clinical utility of CVP-drive shock resuscitation, a group of trials comparing the utilization of CVP in the resuscitation versus no use of CVP, found no benefit of CVP use on clinical endpoints and the pontifical for worsened organ function. Conflictingly, CVP-driven patients had increased length of ICU stay and higher cost in protocolized approaches. (40) Evidence concludes that CVP is a poor predictor of volume responsiveness in the critically ill.

1.5.2 Alternative Monitoring Parameters to Guide Fluid Administration

Without clinical support for CVP and decreased recommendation of CVP use from guideline panels, clinicians continue to search for more dynamic measures for monitoring during fluid administration. (4) The concept of fluid responsiveness argues that fluid bolus administration, through increased venous return and augmentation of myocardial stretch, increases contractile force and stroke volume. This practically means fluid responsiveness is

defined a rise in stroke volume by roughly >15% after a fluid challenge, typically of 6 mL/kg, or 250-500 mL. (41) Fluid responsiveness measures include pulse pressure variation, stroke volume variation, inferior vena cava diameter (IVC) variation, superior vena cava variation, passive leg raising, and end-expiratory occlusion testing. (42) Unlike the CVP, these measurements are considered to be dynamic assessments rather than static measurements which focus on point prevalence, demonstrating a single value within one time frame rather than with physiologic change. Fluid responsiveness markers are multifaceted and an exhaustive evaluation is beyond the scope of this chapter, however the key results of the literature evaluating this parameter broadly have demonstrated that roughly 50% of patients are responsive to fluid administration.

1.5.3 Evidence Surrounding Fluid Responsiveness Measures

When fixating on preload-dependence, a study of 60 septic shock patients allocated two groups to either preload dependence indices-guided or CVP-guided fluid administration. Patients in the preload-guided fluid administration group received less daily net volume protocolized fluids compared to the other (917 vs 383 mL, total 1.7 vs 0.9 liters). Of note, patients in this study had already received 25 mL/kg of fluid prior to enrollment; however, no difference was seen in clinical outcomes, including mortality or time to shock resolution. (43) Mortality was numerically, although not statistically, higher in the group of patients who received a higher number fluids, 47% versus 23%. Despite its theoretical appeal, no clinical intervention optimizing fluid responsiveness-directed crystalloid administration has been associated with an improvement in patient outcomes. Another group of authors attempted to stratify fluid administration based purely on fluid responsiveness. A single-center randomized control trial in 82 patients receiving vasoactive support after initial fluid resuscitation randomized patients to usual care or targeted fluid minimization, the latter of which restricted fluid management to those patients who were fluid responsive. (44) Fluid responsiveness was tested via a passive leg raise or administration of a 500 mL bolus. A patient was considered responsive if pulse pressure variability decreased > 13%, the IVC distension index decreased to > 18%, or the stroke volume index difference

increased by > 10%. In those who received targeted fluid minimization, day three and five fluid balances were 1.17 liters and one liter more negative, respectively. However, differences in total volume were not significant nor were clinical outcomes including ventilator days, in-hospital mortality, incidence of renal replacement therapy, or days receiving vasoactive support. (44)

1.5.4 Fluid Responsiveness in the Critically Ill

It is believed only 20% of crystalloid boluses remain intravascular even in healthy humans. Due to fluid redistribution, most fluid boluses even in the responsive patient lose their effect within 30 to 60 minutes. (45) In the critically ill, less than 5% of a total fluid bolus remains in the vascular system after 90 minutes. (46) When evaluated in surgical populations, blood volumes evaluated pre- and post-operatively show net decreases even with positive intraoperative net volume input and output. Fluid responders themselves have large patient-dependent responsiveness. A 1500 mL bolus of balanced crystalloid, 500 mL hydroxyethyl starch, and 1000 mL of hydroxyethyl starch resulted in a change in blood volume of 0-10%, 5-13%, and 15–25%, respectively, demonstrating large interpatient variability with all forms of fluid therapy. (25) To emphasize the potential harm of fluid boluses in critically ill shock patients, even when the expected short-term MAP rise is demonstrated, fluid administration of 500 mL has been shown to decrease the SVR by 10% after infusion. Even with the evolution of optimized monitoring parameters for fluid administration, the totality of evidence still does not provide clarity on how such translates to clinical benefit.

1.6 Current Recommendations Regarding Fluid Administration

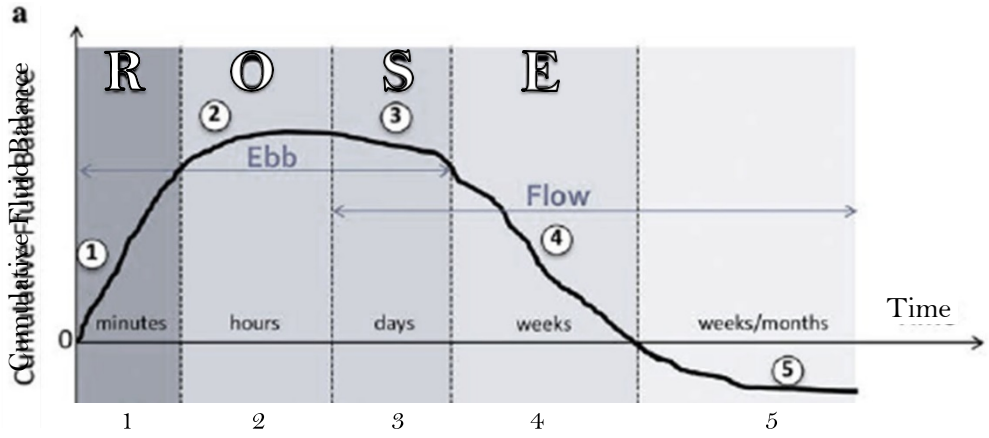
Despite the ongoing concerns with fluid administration and increased understanding of potential harms, multiple national guidelines recommend resuscitation with crystalloid fluids immediately upon admission to the intensive care unit. (4, 47) This practice is commonplace, such that one billion liters of 0.9% sodium chloride, only one of the two key formulations of crystalloid, are purchased in the United States annually. (48) Over 5 million intensive care unit admissions

occur per year, almost all are suspected to expose patients to intravenous fluids. (49) Recently, the scientific community has re-evaluated historical standards of care. (50) Recent publications evaluating compliance with sepsis bundles requiring fluid administration versus non-protocolized resuscitation have shown no difference in mortality rates. However no large clinical trials have specifically evaluated the role of early fluid administration versus no fluids, and therefore utilization remains standard. (20, 51) Current clinical trials addressing this question are ongoing, but given a mean trial duration of 5-10 years in recent septic shock publications and the average 17 year lag between evidence publication and translation to clinical practice, the clinician is currently without timely foreseeable answers. (50, 52-55)

1.7 Late Physiologic Responses to Fluid Resuscitation

Ideally, patients presenting in shock resolve capillary leakage and restore microcirculatory blood flow at 72 hours. In patients who overcome shock, homeostasis of inflammatory cytokines, closure of the capillary leak, normalization of microcirculatory flow and subsequent hemodynamic stabilization with restoration of plasma oncotic pressure have been demonstrated in some patients on day 3 after septic shock. (56) At this time, diuresis, or an augmentation of urine, begins and extravascular fluid mobilizes, resulting in hopefully a more negative fluid balance. This is the optimal progression, however, many patients fail to successfully achieve this augmentation, resulting in global increased permeability syndrome (GIPS). (57) GIPS is an ICU phenomenon first coined by Cordemans and colleagues, consisting of a high capillary leak index (calculated via the laboratory values of c-reactive protein: albumin ratio), failure of achievement of an even-to-negative fluid balance, and progressive organ failure after the first week of ICU stay. The theory behind GIPS is characterized by high capillary leak, excess interstitial fluid, and polycompartment syndrome producing lack of fluid mobilization. For these individuals, it is suspected that fluid increased edema and venous resistance impeding capillary blood flow and oxygen diffusion, resulting in decreased organ perfusion pressure and increased potential for organ failure.

Figure 1.3 ROSE Concept of Fluid Management (57)



Phases of Organ Damage

One model of fluid resuscitation is ROSE consisting of Resuscitation, Optimization, Stabilization, Evacuation, and a potential fifth stage, hypoperfusion. ROSE was conceived to demonstrate this restoration of normal flow throughout what authors describe as ebb and flow states (Figure 1.3). The ebb state occurs from time of septic shock onset to days into acute illness. Ebb is characterized by the need for fluid administration during relative hypovolemia and then normovolemia after fluid resuscitation. There is the possibility for subsequent fluid overload toward the end of the Ebb phase as shock stabilizes. As initial resuscitative measures are made in the ebb phase, organ failure is proposed to decrease. However, continued unnecessary fluid administration as well as failure of subsequent decrease in fluid balance may result in a second potential detriment to organ damage. The latter flow state correlates with the spontaneous resolution of fluid overload, with a decrease in organ damage seen with volume removal. Those patients who do not auto-evacuate fluid, or those with GIPS, may require diuretic augmented diuresis and fluid removal in order to prevent possible worsening of organ failure. The latter portion of this model, when fluid status becomes net negative, demonstrates the potential for a final injury to organ perfusion due to excessive diuresis which harms due to hypoperfusion. This model highlights the critical, time-dependent period in which excess volume is no longer helping and should be removed. The mechanism of removal should be cautious given the potential for additional organ damage with excessive fluid removal and return to a relative hypotension state.

1.8 Clinical Outcomes in the ICU Population Associated with Fluid Overload

Current opinion depicts excess volume receipt during and after the resuscitation phases of shock as potentially detrimental. Some authors have defined fluid overload as 10% fluid accumulation from time of admission. (58) Fluid accumulation is calculated by dividing the cumulative fluid balance by the patient's baseline body weight and multiplying by 100%. Studies dating back to the early 21st century have implicated worse outcomes for patients with persistent positive fluid balances. In 2000, a retrospective review of 36 medical ICU patients with septic shock evaluated patients with at least one day of a negative fluid balance, defined as net volume ≤-500 mL, by day three. In patients which achieved this endpoint, there was an increased chance of survival (RR 5.0, 95% CI 2.3-10.9). (59) Six years later, a prospective multi-center observational study demonstrated an increased risk of ICU mortality with each additional liter of cumulative fluid balance (OR 1.1, 95% CI 1.0–1.1). (60) Ten years later, a strict fluid restriction protocol was studied in patients with septic shock who had already received 30 mL/kg. Despite limiting fluid resuscitation to only 250-500 mL in cases of severe hypoperfusion in the first 2 hours, patients in the fluid restricted group were still 1.7 liters positive after 5 days, compared to 2.7 liters positive in the usual care group. Patients receiving protocolized care had decreased risk of acute kidney injury (OR 0.46, 95% CI 0.23-0.92). (61) A review of a previous randomized controlled trial evaluated clinical outcomes relating to fluid overload in consideration with CVP values. The authors of this study demonstrated that at 12 hours, a CVP <8 mmHg was associated with the lowest mortality and that 3 liters net positive fluid balance was most optimal for survival. (62) In 2017, a multicenter retrospective cohort study of eight medical-surgical ICUs evaluated 18,084 patients and found that a positive fluid balance was associated with increased risk of mortality, a risk sustained up to 178 days after ICU admission. A positive fluid balance was defined as a >4% cumulative fluid balance, calculated as cumulative net fluid volume in liters (L) divided by admission body weight (kg) times 100. Of note, while a negative fluid balance in this cohort was

found to have a decrease in short-term mortality (HR 0.81, 95% CI 0.68-0.96), an increase in long-term mortality was found relative to a net even volume. (63)

A recent meta-analysis evaluated observational or randomized controlled trials of critically ill patients in the intensive care unit receiving an intervention with a target negative or neutral fluid balance after day three of ICU stay. (46) The studies selected looked at intra-abdominal hypertension or mortality as a primary outcome and the comparator group musthave not been targeted to a negative fluid balance. The meta-analysis demonstrated that in the 47 studies evaluated including 19,902 patients, non-survivors had a more positive fluid balance by day 7 of their ICU stay compared to survivors, an average of 4.5 ± 3.6 liters more positive. In patients treated with a more conservative strategy, mortality decreased from 33.2% to 24.7% (OR 0.42, 95% CI 0.32–0.55) irrespective of actual fluid balance. In an even more recent meta-analysis, English cohort studies specific for adult patients with severe sepsis or septic shock were included. The studies selected included high or positive fluid volume/balance compared to low/negative fluid volume/balance after the first 24 hours in the ICU. The resulting literature search found 15 studies comprised of 31,443 patients. (64) A higher fluid balance was associated with a 70% increase in mortality (RR 1.70, 95% CI 1.20-2.41). The average fluid balance after 24 hours in this analysis was 2.3 ± 0.8 liters in survivors and 3.8 ± 0.8 liters in non-survivors. Five of 8 studies looking specifically at mortality based on fluid balance found fluid status to be an independent predictor of mortality. Interestingly, survivors in this cohort had on average a 500 mL higher volume of fluid in the first 3 hours of care compared to non-survivors. This higher fluid receipt early on in ICU admission was associated with improved in-hospital mortality (OR 0.34, 95% CI 0.15–0.75).

The largest observational study to date looking at fluid volume correlation with clinical outcomes was a multinational study of 730 intensive care units of 84 different countries over a one week period. The resulting cohort of 1808 patients was stratified into quartiles based on fluid

Table 1.1 Fluid Quartiles in Study Population

Quartile	Fluid Balance (mL)			Mortality (%)		Length of Stay (days)	
	24 hour	72 hour	ICU	ICU	Hospital	ICU	Hospital
First	2252	-3714	-5375	15.3	25.8	5	16
Second	2444	456	187	21.1	20.5	4	12
Third	3709	3241	3050	32.6	40.8	4	12
Fourth	5398	7904	8307	40.2	50.6	7	14

balance at 24 hours (Table 1.1). While the cumulative fluid balance at 24 hours was not associated with increased mortality, in a multivariable analysis including geographic region, ICU and hospital organizational characteristics, age, sex, comorbidities, severity at ICU admission, type of admission, referring facility, site of infection, and the type of colloid fluid administered, 72-hour fluid balance was significantly higher in the second, third, and fourth quartile in all patients (Hazard Ratio [HR] 1.36, 95% CI 1.03–1.80; 1.47, 1.12–1.92; 1.63, 1.25–2.12, respectively). Intriguingly, cumulative fluid input was similar in survivors and non-survivors; however, fluid output was lower in non-survivors. (65) Evidence continues to accumulate which suggests a correlation between clinical harm and volume status. Of consideration, with the current literature base it is not possible to discern whether increased volume receipt has been secondary to increased severity of illness. Cause and effect analyses are not available and there is the possibility that larger volume of resuscitation cohorts were sicker than those in low volume resuscitation cohorts.

1.9 Pulmonary Dysfunction and Fluid Overload

Blood supply to the pulmonary system is essential for carbon dioxide extraction and back to the body with oxygenated blood. Innervation from the body's nervous system, both sympathetic and parasympathetic, allows for physical control of all pulmonary lobes. Pulmonary blood flow is the blood supply which carries deoxygenated blood to right atrium and subsequently the right ventricle and then lungs via the pulmonary artery. This blood continues until it reaches the pulmonary capillaries, the smallest blood vessels and terminal point of the circulation. Here it circulates within this permeable, pressurized capillary network surrounding bronchial and alveolar ducts containing air circulation, where it undergoes gas exchange with alveolar air.(66)

This blood supply from the right ventricle is a large volume, equal to that of the left ventricle, and different than the bronchial circulation, which is the minute blood supply either direct or indirectly from the aorta, which delivers oxygen to the lungs. (67) Many authors have described the impact of fluid overload on pulmonary physiology. Pulmonary edema occurs when fluid within the lung outside of the vascular system and blood supply begins to accumulate. This fluid first fills up the interstitial space and eventually the alveoli, impairing gas exchange. Pulmonary edema can be caused by particular disease states, insufficient lymphatic drainage, decreased interstitial hydrostatic pressure, increased capillary permeability, increased hydrostatic pressure within the capillaries, and decreased colloid osmotic pressure, with the latter influencers having direct correlation with fluid administration and volume overload. If this volume finds its way into the pleural space, the membrane which surrounds the lungs, it can result in pleural effusions. Pleural effusions, states of excess of fluid within the pleural sac, can result in decreased oxygen in the blood known as hypoxia, potentially by lung collapse. Cardiac tamponade, compression of the heart secondary to continued fluid buildup, specifically within the pericardial space, can prevent cardiac filling and cardiac compliance. (68)

1.9.1 Evidence of Pulmonary Function in Fluid Overload

One of the first studies to trigger the need for consideration of volume status in those with decreased pulmonary function was a 1987 study of 113 patients with acute respiratory distress syndrome (ARDS), also known as acute lung injury. This study showed that patients who lost at minimum 3 kg of body weight, presumably from volume, had a significantly higher rate of survival than those who did not (67% vs 0%). (69) A study of 3147 patients with acute lung injury/acute respiratory distress syndrome evaluated outcomes over a two-week period in 98 European ICUs. A multivariable logistic regression analysis for mortality demonstrated that a higher mean fluid balance was an independent risk factor for death (OR 1.5, 95% CI 1.1-1.9), after accounting for patient acuity and parameters on the mechanical ventilator. (70) In a retrospective study looking at 212 patients with acute lung injury secondary to septic shock, a multivariate

analysis adjusting for illness severity and other markers of acuity, failure to achieve conservative late fluid management, defined as even-to-negative fluid balance for two consecutive days in the first 7 days after septic shock onset, was associated with an increase in hospital mortality (OR 6.13, 95% CI 2.77-13.57). (71) Conservative late fluid management was defined as an even-to-negative fluid balance for 2 consecutive days during the first 7 days after onset of septic shock. However, failure to achieve adequate initial fluid resuscitation, at least 20 mL/kg of fluids within 6 hours of vasoactive therapy, was also associated with increased mortality in the same model (OR 4.94, 95% CI 1.41-4.47). In totals, studies within a population with predominant respiratory failure in the ICU have shown similar result to the general population, with worsened outcomes seen in those patients with higher fluid volumes.

One of the largest indicators of potential impact of fluid on pulmonary function came from a large multicenter study of 1000 patients who had acute lung injury. (72) Acute lung injury was defined as the receipt of positive-pressure ventilation, with a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) <300 and bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema without evidence of left atrial hypertension. Patients in this cohort were randomized to liberal versus conservative fluid management, with the liberal group targeting a CVP >14 versus a target of >8 in the patients in the conservative group. By study day 7, patients in the liberal group had a cumulative fluid balance of 6.9 liters while those in the conservative group were net -136 mL. No difference was seen in the rate of 30-day mortality, however a significant increase was seen in ventilator-free days (14.6 vs 12.1 days, $p<0.001$) and ICU-free days (13.4 vs 11.2 days, $p<0.001$) in those in the conservative group. Acute lung injury, a frequent finding in the ICU, is characterized by direct permeability of the capillaries of the lung, which combined with systemic influences on water balance, increases lung water. (73)

1.10 Monitoring Tools for Pulmonary Complications of Fluid Overload

The extravascular lung water (EVLW) is the water within the lungs outside the

pulmonary circulation and is the summation of interstitial, intracellular, alveolar, and lymphatic fluid excluding pleural effusions. (74). It is the difference between the amounts of water within the blood versus the lung. EVLW is separate from the pulmonary blood supply and typically contains a small amount of fluid, manipulated by either transpulmonary hydrostatic pressure, pulmonary capillary permeability, endothelial changes, or oncotic pressure. Regardless of its cause, an increase in EVLW is directly correlated with the presence of pulmonary edema, with increased lung water correlating to a higher risk of alveolar edema. EVLW accumulation impairs respiratory gas exchange, resulting in worsening respiratory distress. (75) Decreasing blood or plasma intravascular pressures and increasing oncotic pressures via conservative fluid management are believed to decrease the development of pulmonary edema in patients with septic shock and acute respiratory distress syndrome. The pulmonary-artery occlusion pressure (PAOP) is a direct measure of intravascular volume. The PAOP is believed to reflect left ventricular end diastolic volume. Even small volume-induced increases in PAOP can increase EVLW. In patients presenting with congestive heart failure, pulmonary edema can occur secondary to an increase left ventricular end diastolic pressure. Patients with acute respiratory distress syndrome have injured lung capillaries secondary to inflammation which results in the potential for extravasation when intravascular volume is elevated. Regardless of cause, increased pulmonary edema has the potential to worsen outcomes in the ICU population.

1.10.1 Extravascular Lung Water and Clinical Outcomes

EVLW in the critically ill has been shown to correlate with worsened clinical endpoints. In a retrospective study of 373 ICU patients, mortality was 67% in patients with increased EVLW (>15 mL/kg) compared to 33% in those without (<10 mL/kg, p=0.001). (76) In a study of 81 surgical patients, an increased EVLW (>9 mL/kg) was associated with a mortality rate of 80% compared to 30% in those with much lower EVLW (9 mL/kg). (77) In another cohort of 48 critically ill patients with targeted management of EVLW, higher EVLW (>14 mL/kg) was associated with a mortality rate of 87% compared to a lesser EVLW, with a mortality rate of 41%

($p<0.05$). (78) A 2008 study of 19 patients with sepsis-induced respiratory distress syndrome demonstrated that a three-day average EVLW exceeding16 mL/kg was 100% specific and 86% sensitive for in-hospital mortality while another of 200 patients with acute respiratory distress syndrome demonstrated 73% specificity and 54% sensitivity with an EVLW over 21 mL/kg. (79, 80) When looking specifically at septic shock, an EVLW greater than 7.5 mL/kg demonstrated 53.8% specificity and 83.3% sensitivity for mortality in a cohort of 50 patients. (81) Oxygenation, as measured by a ratio of PaO_2 to FiO_2, was shown to be significantly correlated with lower EVLW (R^2 0.27, $p< 0.001$) in a prospective study of 29 medical ICU patients with severe sepsis, 11 patients receiving mechanical ventilation (r^2 0.33, $p<0.0001$), and 20 patients admitted with an Acute Physiology and Chronic Health Evaluation (APACHE) II score over 20 receiving mechanical ventilation ($p=0.0004$). (82-84) A prospective study of 101 patients protocolized an approach directed at specifically decreasing EVL. This protocol was associated with less ICU days and duration of mechanical ventilation. (85) The largest compendium of evidence comes from a 2012 meta-analysis of 11 studies which demonstrated a significantly higher EVLW in non-survivors within the ICU, with a mean difference of 5 mL/kg and a diagnostic odds ratio of 8.84, however heterogeneity was significant at 90%. (86) A separate study suggested that the change in EVLW may be most indicative of clinical outcomes, showing that a decrease of EVLW of at least 2.8 correlated with significantly higher survival ($p = 0.008$). (87)

1.10.2 Limitations to Extravascular Lung Water Monitoring

While a practical approach would be to take the EVLW and its monitoring to bedside, several limitations exist. EVLW requires a transpulmonary thermodilution (TPTD) device. In essence, TPTD relies on venous injection of a cold fluid which then mixes with cardiac blood and is then ejected into the arterial circulation. A resistance thermometer within the arterial system then measures blood temperature changes and, through such, is able to give various hemodynamic measurements, including EVLW. EVLW has multiple limitations as it is influenced by the amount of EVLW itself, the PaO_2/FiO_2 ratio, and specific parameters dictated by the mechanical

ventilator. It is also unreliable in cases of pulmonary embolism, lung resection, heterogeneous forms of acute respiratory distress, and pleural effusions. (88) Additionally, because the TPTD itself requires its own system, added adverse events from its placement may occur. (89)

Unfortunately, other attempts at measuring EVLW, such as chest radiography, fail to show the correlation with mortality that is seen with thermodilution methods and have much lower positive predictive values as well as specificity. (90) Alternatively a group of authors attempted to stratify survival via goal directed fluid removal specifically based on PAOP during acute respiratory distress syndrome. (91) They demonstrated that a 25% reduction or more in PAOP was associated with improved survival (75% vs 29%, $p<0.02$), even after stratification for age and severity of illness. A decrease in ICU length of stay of 6 days was also demonstrated, however no statistical significance was found. Measurement of a PAOP, nevertheless, requires a pulmonary arterial catheter (PAC), an even more invasive device as its placement requires direct cardiac entry. Given its increased rates of complications, including but not limited to arrhythmias, misplacement, knotting, valve rupture, perforation, infarction, infection, and thromboembolism, utilization rates in the mechanically ventilated have steadily decreased. (92) Utilization rates have dropped by 2% per year, with only 1% of heart failure patients actually receiving a PAC when last reported in 2012. (93)

1.10.3 Additional Monitoring Tools for Pulmonary Edema and Lung Water

Further, even physical exam findings are difficult to translate into predictions for meaningful outcomes. One study demonstrated a sensitivity of 81% and specificity of 80% regarding the presence of jugular venous distension (a bulge which may occur in the neck secondary to increased pressure within the vena cava) and its correlation to a PAOP >17 mmHg in the heart failure population. Another prospective study combined the measurement of PAOP with rales and edema on physical exam. (94) The latter study found that such physical exam signs were absent in nearly 42% of patients with a PAOP >21 mmHg. (95) On chest radiography, fluid overload can be seen as dilated upper lobe vessels, cardiomegaly, interstitial edema, enlarged

pulmonary artery, pleural effusion, alveolar edema, prominent superior vena cava, and Kerley lines which represent thickened, edematous interlobular septa. (58) However, multiple confounding factors impact chest radiography has a low sensitivity for capture of volume overload. (96) Additionally, pleural effusions can be missed in a patient who is in supine position. Sensitivity and specificity of the chest radiography for intubated patients with pleural effusions have been reported at 60% and 70%, respectively. (97) However, the frequency of volume overload demonstrated on radiography has been shown to increase with severity of fluid overload. (98) Other bedside approaches to visualization of fluid status surround the use of ultrasonography, either through measurement of vena cava diameter or evaluation of sonographic artifacts, both of which require specialized training. (58)

1.11 Incidence of Respiratory Failure and Mechanical Ventilation

With over 50 percent of ICU patients receiving mechanical ventilation (MV), or positive pressure ventilation, within the first 24 hours of ICU admission, this intervention is one of the most common treatment modalities utilized in the intensive care unit. (99) MV is the delivery of air into the central airways with flow to alveoli from an external device. MV can be utilized for the treatment of patients with hypoxia or hypercarbia while also allowing respiratory muscle relaxation. The machine allows for pulmonary gas exchange without normal respiratory work. (100) There are several methods and modes in which mechanical ventilation can be delivered, well beyond the scope of this chapter. While mechanical ventilation is only utilized during 2.8% of all hospital admissions, patients with mechanical ventilation account for over four times the amount of all hospital costs, not limited to ICU care. (99) Adverse events, such as ventilator-associated lung injury, barotrauma, ventilation/perfusion mismatch, hemodynamic instability, muscle weakness, and several others, can occur in these patients. Alarmingly, 19% of adverse events secondary to mechanical ventilation cause serious residual disability or death. (101)

1.11.1 Mechanical Ventilation Weaning and Fluid Status

Weaning from mechanical ventilation does not have a definitive strategy within the literature. (102) However, patients with a longer time to wean from mechanical ventilation have been associated with increased mortality. (103) For this reason, spontaneous breathing trials, a mode of mechanical ventilation which switches from positive-pressure ventilation to allow negative inspiratory pressure, are utilized to test for a patient's readiness for extubation. (104) When protocols for initiation of spontaneous breathing trials are used, a decrease in mechanical ventilation days and decreased rates of complications may be demonstrated. Importantly, ventilator-associated pneumonia risk can increase by 3% every day a patient remains on the ventilator. (105) Once a patient is converted to negative inspiratory pressure, however, hemodynamic changes may occur. Venous return to the right heart may increase as well as central blood volume and left ventricular afterload. In some patients the right ventricle may enlarge, impeding left ventricular filing. (106) This decrease in left ventricular size has the potential to worsen cardiorespiratory function in patients with cardiac dysfunction or those with volume overload. (107)

Studies have attempted to evaluate the impact of fluid balance on timing of successful wean from mechanical ventilation. (106) In an observational study of 87 patients receiving mechanical ventilation, cumulative net negative fluid balance and net negative balance within the 24- or 48-hours prior to breathing trial were associated with success of wean. (108) In another observational study of 900 patients, re-intubation rates were higher in patients with a preceding 24-hour fluid balance prior to extubation (OR 1.70, 95% CI 1.15-2.53). (109) In a third study of 250 patients, a positive fluid balance in the preceding 48-hours was only associated with spontaneous breathing trial failure in patients with chronic obstructive pulmonary disease (OR1.77, 95% CI 1.24 -2.53). (106) Overall, evidence suggests that increased fluid balances in those receiving mechanical ventilation may be associated with a slower wean time.

1.12 Renal Physiology and Pathophysiology

While one of the most obvious detriments of abnormally high fluid status is its effect on the pulmonary dynamics and implications for prolonged mechanical ventilation, the lungs are far from an independent system. In ICU patients with high fluid status, many complex pulmonary-renal interactions occur. Such interactions have been studied in ICU patients, particularly when abnormally high fluid states exist. (110)

The kidney, while accounting for only 1 percent of the entire mass of the body, is a vital organ which has a wide array of functions. Blood flow to the kidneys starts from the renal artery, originating from the abdominal aorta. Blood travels throughout the arteries to the afferent arterioles, the primary providers of blood to the glomerulus. The glomerulus is responsible for the initial filtration of the blood. Here, the glomerular capillaries filter blood into the glomerulus and then unfiltered blood continues to the efferent arterioles until blood makes its way into the renal vein, back to the vasculature. Glomerular filtration rids the blood of excess water, nitrogen waste products, and other nutrients, and glomerular filtration is determined by a balance between the difference of the hydrostatic and osmotic pressures. Hydrostatic pressures are those pressures from the blood vessel which drive filtrate from the blood vessels into the nephron, the individual unit of the kidney, while the osmotic pressure is the intraluminal pressure which counters the hydrostatic pressure and is exerted by large proteins, such as albumin. The glomerular filtration rate (GFR) is increased by vasoconstriction of the efferent arterioles and vasodilation of the afferent arterioles. In order to estimate glomerular filtration, several methods exist. Most commonly, creatinine clearance, measures the amount of creatinine cleared via the kidney. Creatinine is considered to be one of the optimal endogenous substrates for estimation of glomerular filtration as it has less than 10% variability in stable renal function and is freely filtered at the glomerulus with no reabsorption. (111) The renal system, however, does not stop there. A filtered substance, such as creatinine, then travels through the renal tubules, the proximal

convoluted tubule, the loop of Henle, the distal convoluted tubule, and then the collecting duct before it progresses to the ureters through the renal pelvis and finally is expelled via urine output.

1.12.1 Acute Kidney Injury in the Intensive Care Unit

Abrupt insult to native renal function and glomerular filtration is known as acute kidney injury (AKI), or acute renal failure, and occurs in 50-60% of all critically ill patients, with reported mortality up to 80%. (112) This syndrome may be caused by pre-renal, post-renal, or direct renal insult. Pre-renal causes are those most frequently seen in the ICU, accounting for 50-70% of all cases. Examples include cardiac failure, sepsis, hypotension, and intravascular depletion, all resulting in decreased renal blood flow and perfusion. Post-renal causes are the least common in the ICU, consisting of up 15% of cases, and include obstructive causes such as a kidney stone, tubular precipitation, or a blocked catheter. Renal-specific causes of renal injury account for the other 10-30% of patients with AKI in the ICU, consisting of pure renal injury such as tubular necrosis, nephrotoxin damage, namely medications, hepatorenal syndrome, interstitial nephritis, sepsis, and others. (113) In the ICU, if AKI develops to the extent that patients have persistent anuria, or zero urine output, continuous renal replacement therapy (RRT) is often used. RRT use is common, with reported rates of use over 50 percent in the critically ill. (114) The continuous method is often preferred over alternative methods, particularly in patients presenting with shock, given its slow nature of fluid removal and decreased rates of hemodynamic instability. (115, 116) Acute renal failure is defined via the Kidney Disease Improving Global Outcomes (KDIGO) classification criteria. (117) AKI is defined by an increase in the serum creatinine level of atleast 0.3 mg/dL within 48 hours or that has increased by at least 1.5 times the baseline value within the previous 7 days, or a urine output of less than 0.5 mL/kg/hour for a minimum of 6 hours. The definition and understanding of AKI, however, continues to evolve. Over 30 definitions of AKI have been used in the literature, making comparisons challenging. (118)

1.13 Monitoring Tools for Renal Dysfunction

1.13.1 Introduction to Serum Creatinine

Despite guidelines defining AKI via its trend and studies showing a correlation with overall survival, creatinine is known to have many limitations. (119-121) Serum creatinine levels do not only fluctuate with GFR, but creatinine is also secreted by the tubules and variation in secretion can be altered by medications. (122) Further, while serum creatinine is impacted by changes in the kidneys, serum concentrations can also vary based on patient age, gender, race, nutritional status, muscle mass, dietary protein intake, and even volume status itself. Many estimates or measures of body fluid volume are considered more inaccurate in critically ill patients who have AKI. Some authors recommend 20% increases in estimates for dialysis prescriptions based on the lack of correlation. (123) Estimates of total body water with anthropometric measurements have demonstrated over 8 liters of volume difference compared to bioelectrical impedance analysis. (124) Even more perplexing, multiple studies have shown a correlation of improved outcomes with higher serum creatinine values, potentially secondary to a less dilute plasma in patients who have received less volume administration. (125) In one cohort's multivariate analysis evaluating several clinical variables, Mehta and colleagues found that lower creatinine concentrations were associated with an increased risk of death (OR 0.71, 95% CI 0.62-0.80). (126) Uchino and colleagues prospectively looked at the relative impact of serum creatinine for AKI scoring on 1742 patients in a multinational study of those admitted to the ICU with renal failure. They studied six different scoring systems for renal-specific organ failure and general organ failure. All scoring systems included higher serum creatinine values as a predictor for worsened clinical outcomes. A higher creatinine failed to accurately discriminate or calibrate to predict mortality accurately. (127) In a cohort of 134 critically ill patients with AKI requiring initiation of continuous renal replacement therapy, higher serum creatinine was associated with a higher chance of survival in three different multivariate analyses (OR 1.44, 95% CI 1.03-1.99; OR

1.39, p5% CI 0.98-1.96; OR 1.30, 95% CI 0.91-1.86). In the same model, an increase in volume status was associated with a nonsignifcant decrease in chance of survival. (125)

1.13.2 Alternatives to the Use of Serum Creatinine

Given the frequency of fluid overload in the intensive care unit, concomitant influencers of serum creatinine, and evidence pointing to a lack of utility of creatinine to estimate renal function in this population, traditional models of AKI and estimation of GFR are likely not optimal within the ICU setting. The severity of acute kidney injury is affected largely by the urine output which correlates with the degree of injury. Oliguria, defined as a urine output of less than 0.5 mL/kg/hour or less than 500 mL per 24 hour, is at times the body's attempt to conserve salt and water with sympathetic, renin angiotensin aldosterone system (RAAS), and antidiuretic hormone activation as a response to critical illness. (128) Early studies demonstrated when the urine output dropped below 0.5 mL/min, a linear reduction in GFR was seen. (129, 130) However, physiologic oliguria may quickly become pathologic. Requiring oliguria for at least 6 hours to be a criterion for AKI, assists in reporting of transient oliguria appropriately. (131) The 6 hour time frame has been associated with need for renal replacement therapy, mortality, and true AKI. Patients who meet urine output in combination with serum creatinine criteria to meet the definition of AKI have decreased rates of hospital survival and increased rates of need for renal replacement therapy than either method alone. Even without a rise in serum creatinine, oliguria is associated with a decrease in long-term survival. (132)

In a multivariate analysis of 2164 patients with AKI, a combination of creatinine and urine output criteria was the strongest predictor of ICU mortality. (133) In a prospective observational study of 317 critically ill patients, urine output alone as a criterion for AKI had more frequent association for dialysis, longer length of ICU stay, and higher mortality rate than patients without AKI. (134) Sensitivity for AKI was further increased compared to utilization of serum creatinine alone with the incidence of AKI increasing from 24% based on serum creatinine values to 52% with the addition of urine output. Monitoring of urine output has additionally led to earlier

diagnoses of AKI, with a decrease of time to detection seen from 24 hours with serum creatinine to 12 hours with urine output monitoring. (134) In the largest study of 15,274 patients in the ICU over an 8 year period, intensive urine output monitoring was associated with improved rates of survival in patients experiencing AKI. Such urine output monitoring was additionally associated with decreased rates of fluid overload and overall decreases in cumulative fluid volume ($p<0.001$ for all outcomes). (135) For this reason, some authors have advocated that making the definition of AKI as it relates to urine output to be more stringent. It has been reported that a urine output rate of 0.3 mL/kg/hr was best associated with need for dialysis and mortality, as well as predicting both hospital and one-year mortality rates. (131) Of course, urine output monitoring does not come without its limitations. Some types of AKI, such as tubular dysfunction, can lead to increased urine output despite low glomerular filtrate rates. As well, constant urine output monitoring in the ICU requires nursing documentation and monitoring. Several studies have advocated for the use of biomarkers for AKI diagnosis and an exhaustive review can be found in prior publications, however limited studies are available. Bedside applicability is limited, as most methods of monitoring are not readily available. (130) For this reason, authors have suggested the evaluation of 4-6 hour measurements of urine output with consideration for baseline overall volume status and body weight in the ICU as monitoring parameters for renal function. (136)

1.14 Renal and Pulmonary Interactions

The need for mechanical ventilation has been associated with increased risk of acute kidney injury (OR 3.58, 95% CI 1.85-6.92) versus critical illness without mechanical ventilation. Renal dysfunction has associates with prolonged mechanical ventilation and the presence of increased mortality rates. (137) In a study of 63 patients receiving mechanical ventilation, a serum creatinine value greater than 2.5 mg/dL was associated with prolonged ventilation ($p<0.001$). In a study looking at greater than 47 thousand patients in Taiwan receiving positive pressure ventilation, presence of AKI-dependency during admission was associated with prolonged mechanical ventilation days and ICU stay ($p=0.01$, $p<0.001$). (138) A recent 3-year retrospective

cohort study with 167 patients in a long-term care facility showed that a creatinine clearance of <90 mL/min was associated with a significantly higher wean time when compared to a creatinine clearance of >90 mL/min (p=0.04). (139)

1.14.1 Cellular Effects of the Renal and Pulmonary Relationship

At a physiologic level, the lung and kidney have similar cell surface channels for the transport of water and salt. Pulmonary edema is associated with chloride secretion from lung epithelial cells with influx of fluid into the alveolar space via Na+-K+-2Cl− (NKCC) cotransporter 1. This receptor is also found extensively within the kidney which aids in the transport of sodium, potassium, and chloride within the tubules as well. (140)

1.14.2 Oxygenation Parameters and Renal Injury

Certain ventilator strategies such as permissive hypercapnia or low tidal volume strategies may also negatively impact renal function. Potential mechanisms include neurohormonal dysregulations, alterations of cell signaling pathways, remote oxidative stress, and hemodynamics. (110) Acid-base fluctuations and hypoxemia may impact the kidneys. The kidneys, specifically glomerular filtration processes, are high consumers of oxygen. (141) For this reason, the renal system is susceptible to injury in periods of hypoxia resulting from lung injury. Through stimulation of the adrenergic, or sympathetic system and alterations of nitric oxide metabolism, hypoxia has been shown to reduce renal blood flow in a dose-dependent manner. (142, 143) Decreased availability of nitric oxide may impair autoregulation and tubuloglomerular feedback. (144) Hypoxia may alter avidity of the kidney for sodium which may increase renal oxygen consumption and susceptibility to renal tissue dysfunction. (110) However, effects of hypoxia are not always consistently reported as negative, as in a study of ARDS patients receiving mechanical ventilation, short-term mild hypoxemia was associated with increased creatinine clearance and diuresis. Hypercapnia, excess carbon dioxide, will result in reduced renal blood flow and glomerular filtration secondary to direct or indirect renal vasoconstriction and decreased

sodium excretion. Further, if hypercapnia results in increased pulmonary vascular resistance, right ventricular dysfunction can occur. Excess carbon dioxide is likely the more significant determinant of renal function as hypercapnia has been shown to worsen renal function even in states of hyperoxemia. (142) When mechanical ventilation is required, it often is in settings of several of the above factors which can be associated with a worsening of renal function. Mechanical ventilation can disturb systemic hemodynamics, inflammatory mediators, and renal blood flow. (145)

1.14.3 Renal Influence on Pulmonary Function

Contrastingly, renal injury can also have an impact on lung physiology through several mechanisms. Changes in renal function can modulate production or clearance of mediators of pulmonary disorders. (110) Specifically, increased cytokine production, decreases in factors responsible for alveolar water clearance, unbalanced nitric oxide metabolism, increased vascular permeability, and pulmonary hemorrhage are all potential mechanisms in which kidney dysfunction may precipitate worsening of pulmonary function.

1.14.4 Cardiorenal Syndrome and its Implications

Further, the development of cardiorenal syndrome can result in pulmonary congestion and hypertension. Cardiorenal syndrome by definition is a disorder primarily of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the alternative. (146) Five key types of cardiorenal syndrome exist, with types 1 and 2 demonstrating cardiac dysfunction leading to renal injury, acutely and chronically respectively. Types 3 and 4 are instead renal disorders resulting in cardiac dysfunction, similarly divided into acute versus chronic processes. Type 5 includes secondary cardiorenal syndromes in which systemic disorders result in both dysfunction of the cardiac and renal systems simultaneously. As earlier mentioned, cardiac dysfunction is a frequent finding in septic shock as well as other etiologies. Historically, decreases in renal function in the setting of cardiac

dysfunction were thought to be a product of decreased renal blood flow secondary to low cardiac output. However, given the autoregulatory range of the renal system, mild decreases in cardiac index (cardiac output divided by an individual's body surface area) have little impact on renal perfusion. Alternatively, renal function is rarely impacted until the MAP drops below 70 mmHg, with dysfunction resulting from a decrease in systemic pressure rather than poor cardiac output. (147)

1.14.5 Evidence of Hemodynamic Impact on Renal Function

One study of over 500 patients with heart failure demonstrated a weak correlation between cardiac index and glomerular filtration rate and such was actually inverse relationship, demonstrating that a higher cardiac index paradoxically decreased the glomerular filtrate rate ($p = 0.02$). (148) In several other tests to evaluate nonlinear, threshold, and longitudinal relationships between cardiac and renal function, no effect was seen. Alternatively, renal congestion has become increasingly cited for precipitating decreases in renal function. Renal blood flow is dependent on a pressure gradient between the arterial and venous sides. (149) High pressure on the arterial side supplies the glomerulus while low pressure on the venous side allows for a pressure gradient permitting tubule perfusion. In the circumstance of elevated pressure on the venous side of the kidneys, such aswhat is most commonly seen with a rise in central venous pressure, tubule perfusion pressure decreases. Animal models have shown that reduced urine flow is strongly correlated with renal venous pressure and that increased venous pressure decreases renal blood flow more so than decreases in arterial pressure. (150) Increases in venous pressure are associated with sodium and water retention. Elevated venous pressure-induced decreases in renal blood flow and glomerular filtration pressure may be injury mechanisms independent of decreased mean arterial pressure and cardiac output. (151) Because an elevated right atrial and central venous pressure interrupts salt excretion, more sodium retention occurs. Subsequent volume expansion and renal congestion can occur, resulting in cyclical organ damage via volume retention.

1.15 Renal Dysfunction and Fluid Overload

While its utility for fluid responsiveness and guidance of fluid administration has been disproven, the CVP remains a marker of overall venous congestion. Elevated CVP as a surrogate for RV impairment remains an important hemodynamic factors for AKI development and has been associated with high mortality. Right ventricular dysfunction has been shown to be significantly associated with venous congestion ($p=0.009$) and to be predictive of renal outcomes.
(152) Studies examining central venous pressure as a surrogate for volume status have shown a higher CVP to be independently associated with progression of AKI (OR 1.09, 95% CI 1.02-1.16). (153) In 2005, a single-center one year study of patients with sepsis and a serum creatinine less than 2 mg/dL upon admission looked at the relationship between fluid status and development of acute renal failure. Patients who developed renal failure had a higher CVP on day 1 and 2 than those without as well as a higher dose of colloid fluid administration and a lower net diuresis. (154) In heart failure, a high CVP has been inversely associated with glomerular filtration or worsening renal function ($p<0.001$) and directly related to mortality. (149, 155)

1.15.1 Implications of Congestion for Acute Kidney Injury

Intra-abdominal hypertension (IAH) is the state of elevated pressure within the abdominal cavity. (156) Grade 1 includes an abdominal pressure of at least 12 mmHg, with progression of grades occurring with increased pressures. Abdominal compartment syndrome results when there is a combination of intra-abdominal pressure >20 mmHg with new organ dysfunction. While traditionally IAH is more classically associated with surgical and trauma diseases involving abdominal pathology, such can occur in any patient with systemic inflammation who has received large volume resuscitation. (157) In a 2007 prospective study of 40 medical ICU patients with sepsis resuscitation resulting in a minimum net positive fluid balance of 5 liters in the prior 24 hours, 85% developed intra-abdominal hypertension. Of the entire cohort, 25% developed abdominal compartment syndrome. (158) Eight years later, in a study of 53 patients admitted to the medical ICU with at least 2 risk factors for IAH, only 32% of

patients did not develop intra-abdominal hypertension. (159) A prospective review of 81 patients who developed septic shock within a medical-surgical ICU broadened this observation to a mixed population. Surgical patients had a higher incidence of IAH than medical patients (93% vs 73%, $p<0.009$), however 82.7% of the entire cohort developed IAH based on maximal intra-abdominal pressures (IAP) values over a 72 hour time frame. These authors also demonstrated multiple impacted clinical outcomes, including lower abdominal perfusion pressure, survival, and diuresis in patients with IAH, as well as higher lactate, creatinine, norepinephrine doses, and rates of mechanical ventilation ($p<0.05$). (160) Likely secondary to the resulting compression of renal veins and ureters, intra-abdominal pressure is inversely related to renal blood flow. (161-163) A prospective study of general critically ill patients showed that in a cohort of 123 individuals, 30.1% developed IAH and 19% developed renal failure. IAH was associated with renal failure ($p=0.002$), and an IAP of 12 mmHg predicted renal failure with a sensitivity of 91.3% and a specificity of 67%. (164) In an additional cohort study, a multivariate analysis demonstrated that only 24-hour fluid balance and airway pressures were associated with the development of abdominal compartment syndrome. (165)

1.15.2 Significance of the Splanchnic Blood Supply

The splanchnic vascular system, the key source of blood supply for the abdominal cavity, including gastrointestinal blood vessels, receives roughly one-quarter of cardiac output. Splanchnic blood flow is dependent on regulation from endocrine and paracrine systems, but also vasoactive mediators and the sympathetic system. Given the high percentage of the total blood volume that exists within these splanchnic venous vessels, they are often referred to as splanchnic capacitance veins. (162) This specialized vasculature is able to store and release blood volume as effective blood volume changes, optimizing preload at all times. When arterial blood flow decreases, the elastic recoil ability of the splanchnic veins mitigates the arterial pressure decrease acting as a driving force for forward movement into the systemic circulation. The sympathetic system has receptors on all of the vasculature. However, because the venous splanchnic system

contains almost ubiquitously α-receptors, when the sympathetic system is activated, venous constriction occurs. This α-stimulation results in an increase in the circulatory blood volume and a decrease in splanchnic capacitance. (162) The increase in circulatory blood volume based on splanchnic activation by the adrenergic system alone may approximates 2 units of whole blood. (166) It has been widely accepted that the changes to splanchnic circulation decreases gut perfusion during septic shock states; however, a wide range of variability has been demonstrated within patients in sepsis. (167, 168) Very few methods exist to measure splanchnic-related gut perfusion with difficult interpretation of even the most readily available methods, making the interpretation of intra-abdominal pressures as a predictor of outcomes difficult. (169) However, compromised splanchnic vasculature and poor lymphatic flow within the abdominal cavity can worsen interstitial edema within the renal system, adding as another precipitating factor to both increased cardiac filling pressures and renal dysfunction. Increased interstitial pressure can reflect on perfusion changes within the entire capillary bed. Increases in pressure within the tubules can further reduce the transglomerular pressure gradient. Tubular compression will increase the pressure within the tubules which can then add to worsening of the pressure gradient and decrease glomerular filtration.

1.15.3 Hormonal Influencers of Renal Function

Once kidney perfusion pressure decreases, kidney injury progresses via activation of both the sympathetic nervous and RAAS occurs. Further, intra-abdominal hypertension significantly upregulates activation of RAAS. A key RAAS component, angiotensin II (AT-II), and catecholamines vasoconstrict glomerular arterioles, decreasing renal blood flow. (170) AT-II predominately vasoconstricts the efferent arteriole, preserving GFR despite reduced renal blood flow. (171) Initially in kidney injury, filtration and GFR are preserved but eventually diffuse neurohormonal activation of the RAAS system, sympathetic nervous system, ADH, and endothelin system, results in preglomerular vasoconstriction, increased water retention and decreased GFR. (172) The increased reabsorption of both sodium and water by the proximal

tubule leads to more increased widespread and pulmonary congestion, pulmonary hypertension, and RV overload impacting left ventricular filling.

1.15.4 Inflammation and Renal Dysfunction

Systemic inflammation, the hallmark of septic shock, also has a cyclical effect on renal congestion. Common inflammatory mediators, including c-reactive protein (CRP), tumor necrosis factor (TNF)-α, and interleukin-6 (IL-6), have been associated with progression of chronic kidney disease. TNF- α in conjunction with oxidative stress results in intravascular volume rise by the reduction of sodium excretion by the kidneys. The neurohormonal activation from fluid retention can further increase pro-inflammatory cytokines. TNF-α and IL-6 promote inflammatory cell accumulation within the interstitium of the tubules. These cells can then activate proximal tubule cells which respond by further secreting inflammatory mediators. CRP in the renal tubules has been correlated with severity of interstitial fibrosis as well as worsened renal function. (162, 173)

1.16 Evidence Regarding Fluid Overload and Renal Injury

The evidence correlating acute kidney injury and volume overload in the critically ill is vast. The Program to Improve Care in Acute Renal Disease (PICARD) group demonstrated in a prospective cohort of 618 critically ill AKI patients at different medicalcenters, that the adjusted odds ratio for mortality was 2.07 (95% CI 1.27–3.37) in patients with fluid overload versus patients without fluid overload. Fluid overload was defined as a 10% increase in body weight from baseline, at initiation of renal replacement therapy. (174) In non-dialyzed patients, the percent fluid accumulation was lower in survivors versus those who died (OR 3.14, 95% CI 1.18-8.33). Importantly, there was an increased risk of mortality in patients with a higher proportion of days with fluid overload after AKI diagnosis ($p<0.0001$). In a separate cohort of 1453 critically ill patients requiring renal replacement therapy for AKI within a multicenter randomized control trial, a negative mean daily fluid balance was associated with improved 90-day survival (OR 0.318, 95% CI 0.24-0.43) Survivors had a lower mean daily fluid balance, weight-adjusted mean-daily

Table 1.2 Clinical Outcomes and Volume Overload in Acute Kidney Injury

Author	Population	Outcomes
Payen 2008 (175)	Post-hoc analysis of patients with AKI in the SOAP study	• Mean fluid balance was significantly higher in those with AKI throughout the first 7 days of the ICU ($p<0.05$) • Multivariable analysis showed mean fluid balance was associated with 60-day mortality (HR 0.21 per L/day, 95% CI 1.13-1.28) • Patients requiring renal replacement therapy had a higher mean fluid balance ($p<0.01$)
Fülöp T 2010 (176)	Single center prospective 17 month cohort of ICU patients requiring CRRT	• Volume-related weight gain (VRWG) VRWG ≥10% and VRWG ≥20% significantly associated with 30-day mortality ($p=0.049$) • In multivariate analysis accounting for severity, VRWG ≥10% (OR 2.71, 95% CI 1.05-6.99) was associated with mortality
Grams 2011 (177)	Post-hoc analysis of patients with AKI in the FACTT trial	• Significant increase in CVP ($p<0.001$) and average daily fluid balance ($p<0.001$) in non-survivors at 60 days • Multivariable analysis showed significant association of positive fluid balance and 60 day mortality (OR 1.61 per liter/day, 95%CI 1.29-2.0)
Heung 2012 (178)	Single center retrospective cohort of 170 patients with RRT	• Patients with renal recovery had significantly less fluid overload at RRT initiation ($p=0.004$) • In multivariate Cox hazard regression, rise in percent fluid overload (FO) at RRT start was a significant negative predictor of failed renal recovery (HR 0.97, 95% CI 0.95-1.00)
Vaara 2012 (179)	Multicenter observational study of 296 ICU patients receiving CRRT	• 90-day mortality higher in patients with fluid overload at RRT initiation ($p<0.001$) • In a multivariate analysis, FO in RRT was associated with a higher risk of death at 90 days (OR 2.6, 95% CI 1.301-5.299)
Bellomo 2012 (180)	Post-hoc analysis of 1453 adult ICU patients requiring CRRT	• Negative mean daily fluid balance decreased 90-day mortality (OR 0.318, 95% CI 0.24-0.43) • Negative mean daily fluid balance associated with increased RRT-free days ($p=0.0017$), ICU-free days ($p<0.001$), and hospital-free days ($p=0.01$) after adjusting for confounders

Table 1.2 (continued)

Teixeira 2013 (181)	Post-hoc analysis of 601 patients from the NEFROINT study	• Mean fluid balance (MFB) higher in patients with AKI (p = 0.008) • Non-survivor patients with AKI had significantly higher MFB than survivors (p<0.001) • In the multivariate analysis, MFB (HR 1.67 per liter/day, 95%CI 1.33-2.09) was an independent risk factor for 28-day mortality
Raimundo 2015 (182)	Single center retrospective 2-year cohort of 210 ICU patients with AKI stage I	• Patients with >1 liter/day gain had significantly lower urine output (UOP) (p=0.02), MAP (p=0.01), and higher lactate (p<0.001), Sequential Organ Failure Assessment (SOFA) score (p=0.002), and increased risk of AKI progression or ICU mortality (p=0.001) • Multivariable analysis showed fluid intake independently associated AKI progression (OR 1.8 per liter, 95% CI 1.1-8.8)
Wang 2015 (183)	Post-hoc analysis of 2526 patients from the BAKIT trial	• Fluid overload increased incidence of AKI (OR 4.508, 95 % CI 2.900–7.008) • In a multivariate Cox regression cumulative 72 hour fluid balance was associated with 28-day mortality (HR 1.041, 95% CI 1.01-1.07).
Neyra 2016 (184)	Retrospective study of 2632 septic ICU patients	• Independent association between hospital mortality with every liter increase in 72-hour cumulative fluid balance (OR 1.06, 95% CI 1.04–1.08)
Thongpra-yoon 2016 (185)	Retrospective study of 7696 ICU patients	• The risk of 60-day mortality in patients who met criteria after adjustment for fluid balance but not fever was significantly higher than no AKI (OR 2.0, 95 % CI 1.25-3.11)
Salahuddin 2017 (186)	Single center observational study of 339 ICU patients	• Fluid balance significantly higher in AKI (p<0.001) • In multivariate regression, net fluid balance in first 24 hours (OR 1.02, 95% CI 1.01-1.03) and percentage of fluid accumulation adjusted for body weight (OR1.009, 95% CI 1.001-1.017) associated with AKI

fluid balance, mean cumulative fluid balance, and weight-adjusted mean fluid balance (p<0.0001). Further, after adjustment for clinically relevant variables, mean daily fluid balance was also associated with decreased renal replacement free-days at 90 days (p=0.0017). (180) Multiple other post-hoc analyses and prospective trials have tried to evaluate clinical outcomes associated with fluid overload and volume status (Table 1.2). In the largest study to date, a prospective study of 1734 patients admitted to 21 international ICUs demonstrated that not only were the odds of

hospital mortality increased in patients for every 1% increase in fluid overload, but also the speed of fluid accumulation was significantly associated with ICU mortality and fluid accumulation increased significantly in the 72 hours prior to the diagnosis of AKI with a peak 72 hours following. A meta-analysis including 12 cohort studies looking at fluid overload in AKI with 5095 patients showed a positive association between fluid overload and mortality in patients with AKI (OR 3.40, 95% CI 2.50-4.63). (187) Data correlating degree of fluid overload with outcomes in AKI extend to a pediatric patient population. (188-192) In a recent pediatric meta-analysis of 44 studies, fluid overload was associated with an increase in acute kidney injury (OR 2.36, 95% CI 1.27-4.38) and a 6% increase in odds of mortality was seen for every 1% increase in percentage fluid overload (OR 1.06, 95% CI 1.03-1.10). (193)

1.17 Other Implications of Fluid Overload on Organ Dysfunction

While the pulmonary and renal systems are perhaps the most visibly affected by fluid overload, excess volume has been associated with a multitude of effects on other organ systems (Table 1.3). A study of 86 critically ill patients receiving mechanical ventilation and early enteral nutrition showed that the volume of intravenous fluids directly correlated with increased caloric and protein deficits, the latter of which demonstrated a higher rate of mortality. (194) Volume accumulation alters normal immune function homeostasis. (195) In a model of venous congestion to mimic hypervolemia within 24 healthy subjects, IL-6, endothelin-1 (ET-1), AT-II, vascular cell adhesion molecule-1 (VCAM-1), and chemokine (C-X-C motif) ligand 2 (CXCL2) all significantly increased during venous congestion. (196) Similarly, in a model of 20 healthy patients, an increase in venous congestion was correlated to an increase in ET-1. (197) Regarding endothelial function, the glycocalyx may be damaged with vascular congestion. As aforementioned, a volume load of 20 mL/kg colloid has shown to release atrial natriuretic peptides while increasing hyaluronan and syndecan 1 in the serum, components specific to the glycocalyx. (198) Such degradation can occur as soon as within 30 minutes of ischemia. In animal models, this has correlated to an increase in vascular permeability, issue swelling, and further decrease of intravascular volume. (199)

While the majority of this evidence has focused on general ICU patients or those presenting septic shock, surgical and trauma literature has demonstrated similar results. Liberal fluid resuscitation compared to conservative fluid resuscitation has proven to be associated with higher mortality in randomized controlled trials (RR 1.25, 95% CI 1.01-1.55) and observational studies (Odds Ratio [OR] 1.14, 95% CI 1.01-1.28) of trauma populations. (200) In perioperative literature, liberal fluid therapy was associated with an increased risk of pneumonia (RR 2.2, 95% CI 1.0-4.5), pulmonary edema (RR 3.8, 95% CI 1.1-13), longer hospital stay (mean difference 2 days, 95% CI 0.5-3.4), and an increased length of hospital stay (mean difference 4 days, 95% CI 3.4-4.4). (201) Intra- operatively, restrictive fluid volumes are associated with decreased post-operative hospital stay and improved return of bowel function. (202) A positive fluid balance resulting in at least 3 kg weight gain specifically delayed gastric emptying time, stool passage, time to flatus, and hospital day in patients with elective colonic resection. (203) In cardiac surgery, fluid overload was associated with mortality post-operatively and was a more important role in the length of intensive care stay than changes in serum creatinine. (204) Independent from other factors, increased fluid balance post-operatively correlates with an increase need for RRT. (205) A restricted intravenous fluid regimen has shown to significantly reduce postoperative complications including cardiopulmonary and tissue-healing complications in a cohort of elective colorectal resection patients. (206) Additional studies in the cardiac population have correlated a positive volume with the development of acute kidney injury. (207, 208)

Regardless of the organ system, the relationship between fluid accumulation, mortality and clinical outcomes is multifaceted. It is possible that fluid balance does not always affect outcome independently, but instead is a frequent confounder in severity of illness. Frequently, the response to hypotensive episodes within the intensive care unit is the prompt administration of a bolus. In an 8-week prospective study of 235 patients in 5 intensive care units, fluid boluses were administered 65% of the time for the sole purpose of hypotension. (209) It is therefore possible that patients with higher severity of illness may be predisposed to higher fluid administration in

Table 1.3 Physiologic Effects of Volume Overload

Organ System	Pathophysiologic Effect	
	Increased	Decreased
Abdominal	Tissue edema Microcirculatory derangements Pressure ulcers Skin edema	Lymphatic drainage Wound healing Abdominal compliance
Cardiovascular	Myocardial edema Diastolic dysfunction Central venous pressure Pulmonary artery occlusion pressure Pericardial effusion Global end-diastolic volume index Myocardial depression Cardio-abdominal renal syndrome	Contractility Venous return Stroke volume Cardiac output Ejection fraction Conduction normality
Central nervous system	Cerebral edema Delirium Intracranial pressure Intraocular pressure Intracranial hemorrhage Intracranial compartment syndrome Ocular compartment syndrome	Cerebral perfusion pressure Cognition
Endocrine	Pro-inflammatory cytokines	
Gastrointestinal	Ascites formation Gut edema Malabsorption Ileus Intra-abdominal hypertension Intra-abdominal pressure Abdominal compared syndrome Intestinal permeability Bacterial translocation	Abdominal perfusion pressure Bowel contractility Abdominal perfusion pressure Success of enteral feeding Splanchnic microcirculatory flow Regional blood flow Excretory capacity of liver
Hepatic	Hepatic congestion Hepatic compartment syndrome Cholestasis	Cytochrome P450 activity Synthetic function
Renal	Renal interstitial edema Renal venous pressure Interstitial pressure Uremia Renal vascular resistance Salt retention Water retention Renal compartment syndrome	Renal blood flow Glomerular filtration
Respiratory	Pulmonary edema Pleural effusions Alterations of pulmonary and chest wall elastance Hypercarbia Extravascular lung water Ventilation Work of breathing	PO_2/FiO_2 ratio Gas exchange Lung volumes Compliance

the ICU. What can be confirmed reasonably is that control of fluid balance and prevention of fluid overload may help improve clinical outcomes and that a threshold may exist beyond initial resuscitation measures in which additional fluid administration may cause harm.

1.18 Incidence of Fluid Overload in the Intensive Care Unit

One group of investigators sought to stratify outcomes by fluid administration in a retrospective cohort of 405 adults admitted to the medical ICU with severe sepsis or septic shock. (210) Fluid overload was defined as evidence on physical exam, chest radiography on day one. Patients that retained these symptoms on day 3 were considered to have persistent overload. Of these patients, 67% developed fluid overload and 48% went on to develop persistent fluid overload. Patients who had overload and persistent overload had a higher BMI, on average. Patients with chronic kidney disease and liver disease were more likely to have overload and persistent overload, respectively. Increased illness severity as determined by the APACHE IV was associated with increased rate of overload and persistent overload, as well. Persistent overload was associated with increased length of stay (2.4 vs 1.9 days in placebo) while both fluid overload and persistent fluid overload were associated with increased rates of mortality (29.6% and 27%, respectively vs those without overload of 13.5%). Most notable from this study was that the day one fluid balance was 4.9 liters in the fluid overload group versus 5.8 liters in the group without evidence of fluid overload. On day 3, patients with fluid overload had a 6.9 liter net fluid balance compared to 7.1 liter in the group without. This difference in resuscitation volume highlights a key issue of fluid status evaluation in critically ill patients. While most studies have quantitatively evaluated numerical differences in volume receipt and net fluid status, such an approach has shown to, at times, not always correlate with actual signs of fluid overload. In a multivariate analysis, the incidence of persistent fluid overload was associated with a significantly higher need for medical interventions, including ultrafiltration, thoracentesis, and diuretics. Persistent fluid overload was also associated with a significantly higher rate of hospital mortality (OR 1.92, 95% CI 1.16-3.22) once adjusted for APACHE IV, initial lactate, and admission weight.

1.18.1 Non-Resuscitation Fluid Contributors to Volume Status

Unfortunately, careful monitoring of fluid boluses with careful monitoring of fluid resuscitation is not always adequate to predict volume overload. In a recent single-center cohort of 14,654 ICU patients, a self-reported strategy for the reduction of maintenance fluids was utilized. Despite this strategy, maintenance and replacement fluids accounted for a significantly higher portion of the total daily fluid volume compared to resuscitation fluids (24.7% vs 6.5%, respectively). "Fluid creep", defined as the cumulative volumes of administered electrolytes, volumes to keep venous lines open, and volumes administered as part of medication administration, accounted for 32.6% of the mean daily total fluid volume. (211) In a prospective, open-label, sequential period pilot study of 426 patients admitted to the Medical ICU, medication diluents accounted for 63% of the total intravenous volume over the observation period. (212) Fluid overload has been reported frequently, both based on overall net volume status as well as clinical signs and symptoms of overload, showing a lack of perfect synchrony in objective and subjective measures of volume status. Regardless of the measure utilized, volume overload has continued to be associated with worsened clinical outcomes.

1.19 Approaches for the Prevention of Fluid Overload and De-Resuscitation

The World Society of the Abdominal Compartment Syndrome recommends the avoidance of a positive cumulative balance in critically ill patients, particularly those at risk for intra-abdominal hypertension, after completion of acute resuscitation and the rousing insult has been resolved, i.e. incidental fluid administration (Grade 2C). (213) Other authors have taken this thought further, suggesting a zero to negative fluid balance achieved on day three with a day seven fluid balance as low as possible (Grade 2B). These authors recommend the utilization of diuretics or renal replacement therapies for fluid mobilization in patients with a positive cumulative fluid balance once the inciting disease has been addressed and hemodynamic stability has been achieved (Grade 2D). (46) These authors further suggest that de-resuscitation is mandatory when a positive cumulative fluid balance coincides with poor oxygenation (P/F ratio

< 200), increased capillary leak (defined as a pulmonary vascular permeability index >2.5 and EVLW >12 mL/kg), IAP >15 mmHg and abdominal perfusion pressure < 50 mmHg, or a capillary leak index >60. (46) De-resuscitation, the achievement of a net-even to net-negative fluid balance, can be accomplished in three ways: spontaneously, through pharmacologic diuresis, or via the use of mechanical renal replacement therapies or filtration. Other authors suggest clinically evaluating for hemodilution via complete blood counts or signs of worsening right ventricular function on echocardiogram. (214)

1.19.1 Timing of De-Resuscitation

Optimally, the initiation of fluid de-resuscitation would occur before any clinical signs or symptoms present to avoid detriment to organ function. (56) Increased capillary leak, increased intra-abdominal pressure, increased pulmonary lung water, and peripheral edema correlate with the volume or degree of fluid overload, already present. For this reason, some authors suggest that de-resuscitation should be started once a patient is no longer fluid responsive during shock. (215) However, while several fluid responsiveness measures are becoming increasingly encouraged, all have multiple limitations. (42) The most common fluid responsiveness measures, pulse pressure and stroke volume variations have limited applicability in instances of cardiac arrhythmias and the utilization of low tidal volumes during mechanical ventilation. Unfortunately, low tidal volumes have become increasingly utilized in the ICU given evidence supporting that this ventilator strategy consistently improves mortality and decreases time on mechanical ventilation in acute respiratory distress syndrome compared to large tidal volume strategies. (216) In studies which have sought to decrease fluid balance, enrollment was typically not initiated until 12 hours after the discontinuation of vasoactive therapy in order to ensure hemodynamic stability. In a study of diuresis in patients with moderate to high risk kidney injury with 10% fluid overload, fluid removal was started 12 hours within meeting inclusion criteria. (217)

A recent retrospective cohort study of 10 European ICUs, however, attempted to characterize fluid balance and de-resuscitation in a time-dependent manner. (218) In 400 patients receiving mechanical ventilation for at least 24 hours, 276 patients survived. Within the univariate analysis, there was no difference in use of renal replacement, renal replacement with fluid removal, use of furosemide, or total furosemide dose between survivors and non-survivors. Further, average daily fluid balance was significantly greater for non-survivors on day 3 (0.98 liters, 95% CI 0.57–1.37). In the univariate analysis for 30-day mortality, 72 hour fluid balance had the strongest association with mortality per liter of fluid (OR 1.32, 95% CI 1.17-1.50) versus any other day fluid balance or cumulative day fluid balance in the first week of ICU stay. When the group was broken into quartiles based on day 3 fluid balance, a mean fluid balance of 3.1 liters when compared to -1.5 liters was associated with roughly triple the rate of 30-day mortality. When several relevant factors were placed into a multivariate analysis, day 3 fluid balance again had the highest association with 30-day mortality (OR 1.26, 95% CI 1.07-1.46). Of note, this association was even higher than that of severity markers and comorbidities. Further, day 1-2 fluid balance was not significantly associated with mortality. In the ternary regression with the same variables, a fluid balance between -500 mL to 500 mL on day 3 was shown to decrease mortality (OR 0.40, 95% CI 0.21-0.80) as well as a negative fluid balance less than -500 mL (OR 0.17, 95% CI 0.07-0.40). Regarding ICU length of stay and duration of mechanical ventilation in survivors, day 3 fluid balance was also as significant predictor after adjustment for other factors (OR 1.13, 95% CI 1.08-1.19; OR 1.13, 95% CI 1.06-1.20). When evaluating spontaneity of day 3 fluid balance in relation to 30-day mortality, both spontaneously achieved negative fluid balance (OR 0.21, 95% CI 0.08-0.56) and a negative fluid balance achieved with de-resuscitation measures (OR 0.29, 95% CI 0.12-0.69) were associated with decreased mortality. When evaluating day 3 fluid balance as an outcome variable, day 1-2 fluid balances (Coefficient [COEF] 0.14, 95% CI 0.07-0.20) were associated with a higher net volume status while furosemide dose per 10 mg (COEF -0.13, 95% CI -0.18- -0.08) was associated with decreased fluid balance on day 3. Renal

replacement therapy was not associated with a decrease in day 3 fluid balance. Despite a strong correlation demonstrated between day 3 fluid balance and clinical outcomes in this study, no trials have prospectively evaluated the appropriate time to initiate de-resuscitation with pharmacologic measures. More evidence is needed to evaluate augmented de-resuscitation with pharmacotherapy for the achievement of a negative fluid balance 72 hours following shock resolution.

1.19.2 Further Considerations for De-Resuscitation Timing

The timing of furosemide administration may depend upon the underlying fluid balance of the patient, the rate of fluid removal desired by the clinical team, and the patient's current kidney function. (219) In the Fluids and Catheters Treatment Trial (FACTT) trial, therapy was started on average 43 hours after ICU admission and roughly one day after the diagnosis of acute lung injury. Others have suggested that a conservative approach for those in shock may be less beneficial compared to those without. (73) However, based on the rationale that resolution of hemodynamic and inflammatory abnormalities should resolve on day three in most patients with ARDS or shock and evidence proposing a significance of day three fluid balance on clinical outcomes, initiation of de-resuscitation at 72 hours is a logical approach to volume management after resolution of shock in the ICU.

1.20 Introduction to Loop Diuretics

Diuretics, by definition, are medications which induce diuresis, reducing both sodium and free water in the body. Loop diuretics, compared to alternative classes, including potassium-sparing diuretics and thiazide diuretics, are the most effective for free water removal. Loop diuretics, including furosemide, bumetanide, and torsemide, act on the NKCC cotransporter on the thick ascending limb on the loop of Henle. Loop diuretics prevent reabsorption of 25% of sodium and chloride filtered from the glomerulus. In the distal tubule, loop diuretic action on the macula densa results in suppression of negative feedback for glomerular filtration and renin secretion. Other NKCC receptors can be found in other organ systems, including the ears, lungs,

vascular smooth muscle, and others. These other receptor sites result in dose-limiting side effects, such as ototoxicity or hypotension. Because loop diuretics are anions and bound to serum proteins, these molecules do not filter through the glomerulus. Organic anion transporters within the proximal tubular cells allow for transportation of the drug into the tubules. (220) Experimental data have shown that loop diuretic use may attenuate metabolic demand within the Loop of Henle via its impairment of tubular sodium reabsorption. (221) Other studies support its role in prostaglandin production resulting in improved oxygen supply and demand as well as the attenuation of apoptosis induced by ischemia-reperfusion injury and gene transcription. (221-224) However, mixed evidence demonstrates an improvement on oxidative stress in acute kidney injury, with some studies showing it may actually worsen such. (225, 226) In normal subjects, an intravenous dose of 40 mg of furosemide results in a maximal urine output response within 3-4 hours, excreting 200-250 mmol of sodium and 3 to 4 liters of free water. (227) However, based on its mechanism, resistance to furosemide can occur. After prolonged drug administration, adaptation within the distal loops of Henle and tubular hypertrophy, results in increased sodium reabsorption after the site of action of the loop. This results in tolerance to the diuretic and diminished effect. (227) Further, the direct stimulation of renin release in the afferent arteriole promotes sodium retention as well. The braking effect demonstrates that continued administration of the same dose of loop diuretic will, overtime, result in less naturiesis. Reportedly, the response to furosemide may fall by as much as 40% by the third day of treatment, depending on the degree of volume depletion. (228) This is potentially caused by an overall decreased extracellular volume, removal of excess sodium, or neurohormonal activation of the sympathetic system and RAAS. Loop diuretics have several probable benefits in the augmentation of renal function in the critically ill, however limitations to use must be considered.

1.21 Comparison of Loop Diuretics

1.21.1 Bumetanide Therapy

Furosemide is the most frequently used diuretic of the loop diuretic class, representing the diuretic of choice in 98% of ICU clinicians. (229, 230) Bumetanide is similar to furosemide in regards to its pharmacodynamic and pharmacokinetic parameters however its chemical structure slightly differs and its potency is 65 times greater. Given its potential secretion into the lumen by a different receptor from furosemide, the organic base transport system, bumetanide was once theorized to be more effective in times of renal injury given that this system is not inhibited in renal injury. However, in a study comparing its use to an equipotent dose of bumetanide, IV furosemide was shown to have a 52% greater effect on naturiesis in patients with renal insufficiency. (231) Authors of this study hypothesized that the nonrenal clearance of bumetanide was double that of furosemide, resulting in its decreased effect. Studies comparing the two agents in the heart failure population have shown no difference in clinical effect or improvement in edema. (232, 233) Of important consideration, intravenous bumetanide has been on shortage since May 2017, limiting its use for a broad ICU population. (234)

1.21.2 Torsemide Therapy

Torsemide has been suggested as a potentially more beneficial loop in the setting of heart failure given its increased bioavailability, hepatic clearance, and prolonged half-life relative to furosemide. In chronic heart failure, torsemide was shown to improve New York Heart Association class while also decreasing readmission and decreasing mortality compared to furosemide, however both studies comparing these cohorts where in a non-critically ill, outpatient setting. (235, 236) In a study of 29 cardiac surgery patients receiving diuresis after continuous renal replacement therapy, furosemide and torsemide were shown to both be efficacious in improving urine output, with torsemide showing a more dose-dependent effect and furosemide demonstrating less pronounced elimination of creatinine and blood urea nitrogen. (237) Of note, while urine output was not significantly different between groups, intragroup urine output was

significantly higher after 6 hours in the furosemide group, however not with the torsemide population. The lack of statistically significant difference in the torsemide group could have been secondary to inadequate dosing. In a separate prospective study of 92 patients with acute renal failure, both torsemide and furosemide resulted in greater diuresis than patients who did not receive diuresis. No between-drug differences were reported, but increase in urine flow was seen in 57% and 48% of torsemide and furosemide groups, respectively. Renal recovery was seen in 28% of patients receiving furosemide and 17% of patients with torsemide. (238) Regardless, the intravenous formulation of torsemide was discontinued by its manufacturer, resulting in no administration form outside of oral tablets. (239)

1.22 Predictors of Loop Diuretic Response

Urine output response to loop diuretics is dependent on underlying renal function. After the creatinine clearance drops below 15 mL/min, 10-20% of the loop diuretic is actually secreted into the tubules. (240) It is noteworthy that a drop in renal function only limits the excretion of the diuretic and not its response. Functioning nephrons still have responsiveness to furosemide administration with decreasing creatinine clearance, but the limitation is in achieving sufficiently high enough tubule concentrations of drug to demonstrate an effect. For this reason, larger doses are utilized in periods of either chronic or acute renal injury. Maximum doses of furosemide via bolus administration have been cited to be between 160-200 mg, however doses as high as 2000 mg have been administered. (231, 241) Despite many studies' efforts, furosemide pharmacokinetics and pharmacodynamics are still poorly understood in the critically ill population. Outside of evaluations in healthy human volunteers, studies of these agents have primarily been performed on patients with chronic renal failure, renal transplants, or those with nephrotic syndrome. One pharmacokinetic study, evaluating 30 critically ill patients without previous renal impairment or diuretic exposure, evaluated urinary output responses to furosemide in patients meeting criteria for acute kidney injury. In a linear mixed model of several predictors of furosemide response, a creatinine clearance of <20 mL/min/1.73m^2 was an independent

predictor of decreased response to furosemide. With a creatinine clearance greater than 40 mL/min/1.73 m^2, the urine output response was primarily determined by the amount of furosemide excreted into the urine. Between 20-40 mL/min/1.73m^2, a significant interaction was found between creatinine clearance and urinary furosemide excretion. (242)

Urea, a nitrogenous waste product eliminated by the kidneys, can potentially interact with the secretion of furosemide into the tubules via organic anion transport. (243) Further, acute tubular necrosis results in necrosis in all tubules, particularly where furosemide is active. (242) Ischemic-reperfusion and inflammation both decrease NKCC. (244, 245) This is an important factor in considering diuretic use in the broad ICU population. While this study was purely limited to AKI, an occurrence found in over half of all ICU patients, it cannot be applied to the totality of critically ill patients. Notably, however, even when adequate perfusion exists, sepsis can result in impairment of tubular function. Specifically, downregulation of the NKCC can occur secondary to inflammatory products. (246)

A small study of 21 critically ill patients evaluated the pharmacodynamic profile of 40 mg IV furosemide administration. (247) In a multivariable linear regression model, MAP and patient age were both significant predictors of urinary output response to furosemide administration. Serum albumin and serum creatinine were significant predictors of a decreased renal response. However, a large interpatient variability was seen. Within the cohort, 28.6% of patients had an increase in urine output of exceeding 1000 mL within 6 hours while 42.8% had less than 500 mL. Six-hour urine output ranges from 240 mL to over 3 liters. Peak effect was seen within 1-2 hours following furosemide administration with a taper close to baseline occurring after 6 hours. Other significant differences after furosemide administration included higher serum bicarbonate and base excess. However, the small sample size limits generalizability of these results to a broad population.

Table 1.4 Furosemide Titration Table per Urine Output in the High BNP Arm

Urine Output	Subsequent Furosemide Dose
<4.5 mL/kg/3 hours	30 mg
4.5–6 mL/kg/3 hours	20 mg
6–7.5 mL/kg/3 hours	15 mg
7.5–9 mL/kg/3 hours	10 mg
>9 mL/kg/3 hours	0 mg

1.23 Evidence-Based Diuretic Dosing in the Critically Ill

Similar to the literature's limitation regarding the timing of de-resuscitation, a paucity of evidence exists to suggest how to pharmacologically achieve volume removal in the general ICU population. Dessap and colleagues randomized 304 patients on mechanical ventilation requiring minimum support to B-type natriuretic peptide (BNP) guided fluid management. (248) Patients were randomized to fluid management driven by serum BNP, requiring diuresis administration for a BNP ≥200 pg/mL, or usual care if BNP was <200 pg/mL. BNP is one of three main types of natriuretic peptides within the body and its release is stimulated by cardiac ventricular stretch. It has been shown to be strongly correlated with left-ventricular dysfunction, elevated left-ventricular filling pressures, and an elevation in BNP is an independent risk for failure of weaning of mechanical ventilation (OR 1.90, 95% CI 1.40–2.62).(249, 250) In the group with BNP-guided management, furosemide was administered every 4 hours according to urine output. The first dose administered was 20 mg followed by a urine output assessment every 3 hours which would dictate the subsequent dose 3 hours following the preceding dose (Table 1.4). The majority of patients received a dose of diuretic, with 72.4% of control patients and 83.6% of BNP-guided therapy having documented pharmacologic de-resuscitation. Patients with BNP-guided therapy had a shorter time to first extubation and successful extubation with a decrease in ventilator-free days at 14, 28, and 60 days. Patients in the BNP-driven group received a median of 40 mg (Interquartile Range [IQR] 9-78) furosemide compared to 14 mg (IQR 0-40) in the control group. No significant differences in adverse events were seen. (248) Worth noting, while high levels of BNP can be seen in patients with volume overload, other clinical conditions may also increase

Table 1.5 FACTT Protocol for Volume Resuscitation

Intravascular Pressure				MAP <60 mmHg or dopamine >5 mcg/kg/min	MAP >60 mmHg off vasopressors			
CVP		PAOP			UOP <0.5 mL/kg/hr		UOP > 0.5 mL/kg/hr	
Group A	Group B	Group A	Group B		Ineffective Circulation	Effective Circulation	Ineffective Circulation	Effective Circulation
Range 1				Vasopressor Fluid Bolus	Dobutamine Furosemide	Furosemide	Dobutamine Furosemide	Furosemide
>13	>18	>18	>24					
Range 2					Dobutamine	Furosemide	Dobutamine	Furosemide
9-13	15-18	13-18	19-24					
Range 3				Fluid Bolus Vasopressor	Fluid Bolus	Fluid Bolus	Fluid Bolus	Group A: Furosemide
4-8	10-14	8-12	14-18					
Range 4					Fluid Bolus	Fluid Bolus	Fluid Bolus	Group B: Fluid Bolus
<4	<10	<8	<14					

BNP values such as chronic heart failure without fluid overload, renal failure and pulmonary embolism. Obese patients may have a low level of BNP. (58)

One of the hallmark studies evaluating fluid status in acute lung injury, known as the FACTT trial, was published in 2006. (72) The study population was randomized to conservative (group A) versus liberal (group B) fluid therapy, with a complex protocol in both groups consisting of furosemide administration, inotropic therapy, fluid administration, or vasopressors depending on signs of circulatory efficacy or safety, pulmonary artery occlusion pressures, or central venous pressures (Table 1.5). Furosemide dosing was started at 3 mg/hr or as a 20 mg bolus if the last effective dose of furosemide was unknown. If urine output remained less than 3 mL/kg after four hours and diuresis was still indicated, the dose was doubled and reassessed in 4 hours continued up to a maximum of 24 mg/hour for 12 hours of 3 doses of 160 mg bolus. Patients in the conservative-strategy group received furosemide more frequently than patients in the liberal-strategy group (41% vs 10%, $p<0.001$), with a total daily dose ranging between 127 mg-167 mg in 24 hours within the conservative group. When evaluating those patients only with AKI, a total of 562 mg was given in the restrictive group compared to 159 mg in the liberal group on average cumulatively ($p<0.001$). (177) Day 7 fluid balance in those patients randomized to the conservative arm was -136 mL compared to a positive 6.9 liters in the liberal arm. Patients in the

Table 1.6 FACTT Lite Protocol

CVP	PAOP	MAP >60 mmHg off Vasopressors	
		UOP <0.5 mL/kg/hr	UOP >0.5 mL/kg/hr
>8	>12	Furosemide; assess in 1 hour	Furosemide; assess in 4 hours
4-8	8-12	Fluid bolus; assess in 1 hour	Furosemide; assess in 4 hours
<4	<8	Fluid bolus; assess in 1 hour	Assess in 4 hours

conservative group had a significant increase in ventilator-free days and ICU-free days compared to the liberal group.

1.23.1 Application of the FACTT Trial to Clinical Practice

Unfortunately, several limitations to this protocol prohibit its quick implementation to every day practice. The complexity of the multiple boxes guiding treatment recommendations limit its ability to be taken bedside. Further, a study specifically evaluating the signs of ineffective circulation utilized in the FACTT trial, found that such are not useful for predicting low cardiac index or mixed venous oxygen saturation given an overall low sensitivity and low positive predictive value. (251) Because of the complexity of the FACTT protocol, the investigators developed a simplified protocol for future studies involving acute respiratory distress syndrome, termed FACTT-LITE, meant to replace the conservative protocol of the latter. (252) Furosemide dosing remained the same, however the signs of ineffective circulation were removed. When compared to FACTT, this protocol resulted in a significantly higher cumulative fluid balance without a change in clinical outcomes (Table 1.6). Even so, as the CVP was in subsequent years following quickly determined to be an inadequate predictor of fluid status and the PAOP, requiring the pulmonary arterial catheter for measurement, became an infrequently used measure within the ICU, this protocol quickly lost applicability to everyday practice as well.

1.23.2 Diuresis Protocols for Treatment and Prevention of Acute Kidney Injury

The remaining evidence, and the majority of evidence validating specific furosemide dosing in the critically ill, is limited to those patients presenting with acute kidney injury. Its use

Table 1.7 Selected Furosemide Dosing in Studies of Acute Kidney Injury

Reference	Route	Furosemide Dosage
Beroniade (253)	Unknown	60–480 mg
Berthelsen (217)	IV infusion	40 mg bolus then 40 mg/hour
Borirakchanyavat (254)	IV	500 mg/day
Brown (255)	IV or oral	2 mg/min or 1000 mg three times daily
Cantarovich (256)	IV infusion	600–3200 mg progression over 30 min-10 hours
Cantarovich (257)	IV infusion	2000 mg/day
Cantarovich (258)	IV or oral	25–35 mg/kg/day
Chandra (259)	IV infusion	200–2000 mg/day
Hager (260)	IV infusion	1 mg/hour
Karayannopoulos (261)	Unknown	1000 mg increased to 3000 mg based on response
Kleinknecht (262)	IV infusion	150-1200 mg
Lassnigg (263)	IV infusion	2.5 mg/hour
Lumlertgul (264)	IV	200 mg every 6 hours
Mehta (265)	Unknown	80 mg
Minuth (266)	IV	40-500 mg
Shilliday (238)	IV	3 mg/kg every 6 hours decreased to 1 mg/kg
Uchino (267)	Unknown	240 mg/day on average
van der Voort (268)	IV infusion	0.5 mg/kg/hour
Vargas Hein (237)	IV infusion	80 mg bolus with 40 mg/hour to 15 mg/day

in this population highlights the ambiguity of diuretic role in the ICU. Early observational studies showed a potential worsening of outcome with the administration of furosemide and acute kidney injury, however confounding by indication often induced uncertainty in interpretation. (269) Within a prospective study of 132 patients admitted to a single center ICU in Brazil, the use of furosemide was a significant predictor of acute kidney injury, with the highest odds ratio in univariate analyses (3.27, 95% CI 1.57-6.80). (373) However, once adjusting for other factors, the statistical significance of this value was lost (OR 2.67, 95% CI 0.89-8.00). Additionally, while others have found furosemide to increase urine output and decrease need for renal replacement therapy in acute kidney injury, mixed results have been seen for overall clinical outcomes such as overall mortality. (230, 270-272) In the previous cohort of 132 patients with AKI in 10 Italian ICUs, diuretic use was associated with better survival in this population (HR 0.25, 95%CI 0.12-0.52). (181) A retrospective observational study of 86 critically ill patients with continuous renal

replacement demonstrated 58.4% of patients received furosemide with weaning of renal therapy. No difference was seen in the number of patients receiving diuresis (56.7% vs 61.8%, p=0.67) or the dose of furosemide utilized (0.5 mg/kg vs 0.6 mg/kg, p=0.52) in those who were successfully weaned versus those who were not. However, urine output for the 6 hours following cessation of CRRT was found to be the main risk factor for lack of successful weaning. The use of furosemide strengthened this association as demonstrated by improved sensitivity and specificity of the area under the receiver operating characteristic curves. Some studies have even shown increased rates of acute kidney injury with utilization of loop diuretics. (273) Doses associated with avoidance of acute kidney injury have included 1-2.5 mg/hour or intermittent doses of 80 mg IV. In the treatment of acute kidney injury, studies have utilized wide ranges of doses, giving total daily doses of up to 3200 mg (average daily dose of 1240 mg) and 3400 mg (Table 1.7). (238, 256) However, in a meta-analysis of studies looking and prevention of treatment of acute kidney injury with furosemide, high doses ranging between 1-3.4 grams per day were associated with increased risk of temporary deafness and tinnitus (RR 3.97, 95% CI 1.00-15.78). (272)

The SPARK study was multi-center randomized controlled study in patients within three intensive care units who experienced early stages of AKI. (229) Patients received 0.2 mg/kg loading dose of furosemide followed by 0.05 mg/kg/hour continuous infusion increased by 0.05 mg/kg/hr every 2 hours up to a maximum of 0.4 mg/kg/hour based on ideal body weight to maintain a urine output of 1-2 mL/kg/hour for at least 24 hours. After enrolling 73 patients, this trial was stopped early. Early termination of the study was reportedly due to feasibility of recruitment given trial interruptions secondary to an influenza pandemic and furosemide shortage in addition to funding limitations. Authors concluded the study was underpowered which likely contributed to the lack of between-group differences seen in clinical outcomes. Notably, protocol deviations occurred in 76% of patients in the furosemide treatment group and 81% of patients in the placebo group, mostly due to deviation from the study algorithm. Further, 10.8% and 30.6% of patients received supplemental furosemide dosing in the furosemide and placebo groups,

respectively. There was no difference in the number of patients who developed an adverse reaction to furosemide infusion compared to placebo, however those that did have side effects had frequent side effects, predominately increases in serum sodium, sodium bicarbonate, or decreases in serum potassium ($p<0.001$).

1.23.3 Furosemide for Assessment of Acute Kidney Injury

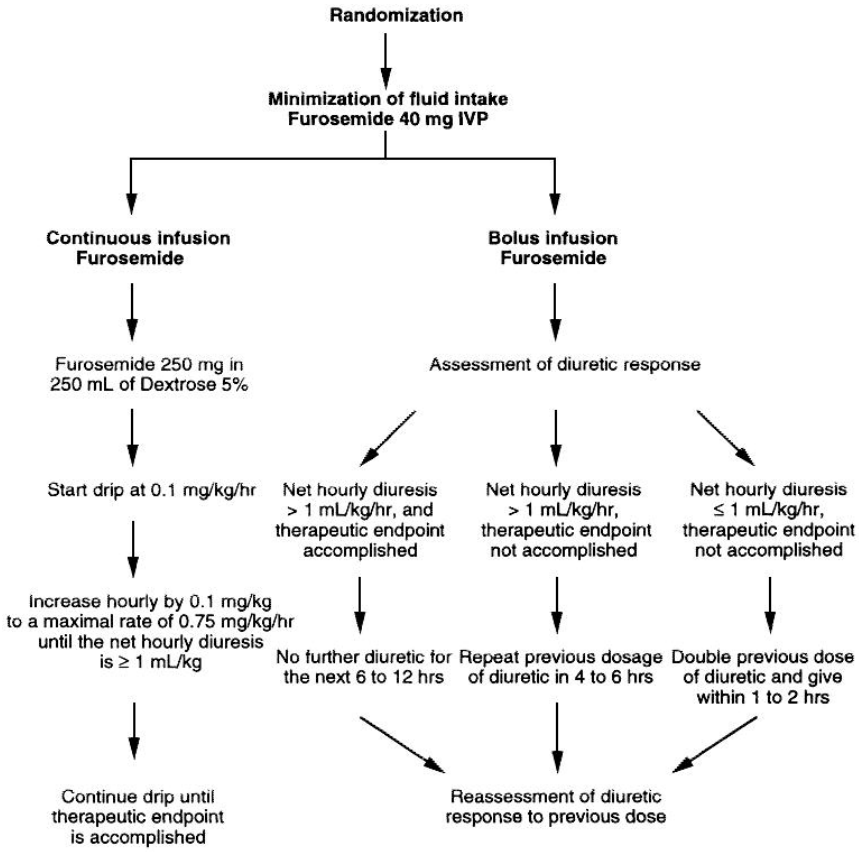
Researchers have extended research utilizing furosemide beyond prevention and treatment of acute kidney injury to testing native renal function with high doses as a method of identifying early renal injury. Chawla and colleagues utilized furosemide as an early assessment of tubular function in acute injury, although tubular injury may account for only up to one-third of patients with acute kidney injury. (273) Given its lack of filtration through the glomerulus and tubular secretion as well as tubular mechanism of action, administration of this loop diuretic was hypothesized to be a clinical assessment tool of tubular function. In one trial, patients were included on the basis of early acute kidney injury after resuscitation. Furosemide was administered at 1 mg/kg or 1.5 mg/kg if the patient had a known previous furosemide exposure. Urine output response was noticeably highest in the first 2-3 hours and the cumulative urine output in the first 2 hours was shown to best predict development of worsened AKI and continued to be associated with progression after adjusting for multiple parameters. (274)

1.23.4 Furosemide Administration Strategies

Beyond the specific dosing of furosemide, the frequency or rate is often debated as well. Continuous infusion furosemide is hypothesized to have a more predictable and constant urine output given minimal fluctuations in serum concentrations relative to intermittent dosing regimens. Consistent serum levels may eliminate instances of compensatory sodium retention possible with intermittent doses. This is hypothesized to prevent large hemodynamic fluctuations as well, decreasing adverse events rates. Early evidence suggests that the duration of furosemide exposure to the tubular receptors has a greater impact on urine output that the route or the total

amount of drug administration. (275) Additionally, the risk of diuretic resistance is believed to decrease with the use of continuous infusion via the prevention of a drop below therapeutic thresholds. The continuous titration, in theory, allows for easier dose adjustments tapered or titrated based on urine output response, however continuous infusion is less convenient, requiring more frequent assessments and constant intravenous access. A prospective study compared the two regimens for the treatment of fluid overload in 59 patients within the ICU. Intermittent furosemide was dosed every 3 hours with escalated mg/kg doses based on urine output response while continuous infusion rates were also escalated every 3 hours based on urine output response. No difference was seen in total urine output, however patients in the intermittent dose group required higher doses to achieve such. (276) A 2018 meta-analysis sought to demonstrate a therapeutic benefit of continuous infusion, evaluating all studies involving continuous infusion compared to bolus furosemide within the intensive care unit. (277) In the 9 studies evaluated, continuous infusion was associated with a total greater urine output (OR 811.19, 95% CI 99.8-1522.5), but also a longer length of hospital stay (OR 2.84, 95% CI 1.74-3.94). No difference was seen in rates of mortality, estimates of renal function, or other safety parameters. However, it is important to note that in the data pool, only a cumulative 464 patients were available for evaluation and the dose ranges varied between groups. Doses of furosemide via intermittent dosing ranged from 25 mg in 24 hours to 24 mg every hour. Continuous infusion dose ranges reported fluctuated from 59.4 mg in 24 hours to 329 mg in 24 hours. Some studies did not report dosing ranges for either group. In a 2018 retrospective study of 1176 patients receiving CRRT, the effect of furosemide on CRRT discontinuation was evaluated. No protocol was specified for dosing however continuous infusion or bolus administration was allowed for a target urine output of at least 0.5 mL/kg/hour. In this study, continuous infusion recipients received a greater dose of furosemide and tended to have a greater urine output on day 3, however a higher increase of serum creatinine was demonstrated if utilized for greater than one day. Multivariable regression analysis identified urine output on the day prior and use of diuretics as significant predictors of

Figure 1.4 Protocolized Furosemide Dosing Strategy (278)



successful discontinuation of CRRT. In a study of 20 patients admitted to the ICU with acute respiratory failure secondary to cardiogenic pulmonary edema, the use of a continuous infusion of 0.1 mg/kg/hour after a 1 mg/kg bolus compared to intermittent doses of 1 mg/kg resulted in a higher hourly urine output ($p<0.05$). (279) In a landmark randomized controlled trial of 308 patients admitted with acute decompensated heart failure, continuous infusion furosemide did not produce any significant benefit on improvement of symptoms, changes in kidney function, or urine output when compared to intermittent dosing. (280)

1.23.5 Protocolized Furosemide Administration

What is likely most proven to be beneficial, and unaccounted for in the aforementioned meta-analysis, is the utilization of goal-directed diuresis compared to standard of care. In a case-

control study of 55 patients, a protocolized continuous infusion furosemide protocol compared to intermittent boluses outside of protocol showed improved net 24 hour fluid balance ($p=0.026$) and cumulative urine output ($p<0.001$). (281) Protocolized bolus administration compared to a protocol of continuous infusion resulted in no difference within clinical outcomes. (282) Specific protocols were not reported here, however the authors mention a goal of -1 mL/kg/hour with a maximum dosing allotted of 0.75 mg/kg/hour in the continuous infusion group and 320 mg per dose in the bolus group. In their prospective study of 90 patients, Shah and colleagues randomized patients to three groups, one with intravenous furosemide bolus 100 mg/24 h in two divided doses and two groups of intravenous furosemide continuous infusion 100 mg/24 h with one of these two including dopamine use. The intermittent dosing protocol correlated with a greater rate of diuresis ($p=0.002$) and a shorter hospital stay ($p=0.023$) compared to continuous infusion. (283) Schuller and colleagues evaluated 33 patients with pulmonary edema or fluid overload and enrolled to either goal directed bolus or continuous infusion furosemide, adjusted based on hourly fluid balance (Figure 1.4). No difference was found in the achievement rates of net hourly fluid balance (0.78) or overall in-hospital mortality. When compared to a nonrandomized cohort, the patients on goal-directed protocol had more diuresis as well as a shorter length of hospital and ICU stay. (278)

Evidence surrounding the utilization of pharmacologic diuresis for de-resuscitation in the ICU is limited, however data does exist evaluating its use in several specific disease states. Evidence suggests that a protocolized approach is likely most efficacious, however a study evaluating a diuresis protocol within the broad ICU population is necessary.

1.24 Diuretic Resistance in the Intensive Care Unit

As eluded thus far, the potential for resistance to loop diuretics may limit their use. Resistance to a loop diuretic is usually termed when a patient does not have adequate clinical response to maximal doses of furosemide, however recommendations for maximum dosing do not agree. (220) Regardless, a patient who receives only 6-8 days of chronic loop therapy can have a

blunted response. For this reason, several adjunct options have been considered in order to improve urine output with the administration of furosemide.

1.24.1 Adjunctive Diuretic Therapy with Albumin

Albumin has been frequently evaluated as an adjunct to furosemide dosing for suspected diuretic resistance. Furosemide delivery to the proximal tubules is dependent on its binding of serum albumin. The ebb phase of the shock state demonstrates increased albumin extravasation out of the intravascular space secondary to increased capillary permeability. When albumin concentrations are low, furosemide binding decreases and its volume of distribution expands. Therefore, the amount of furosemide left within the serum decreases and less drug is able to reach the tubules and site of action. In a study of hypoalbuminemic patients receiving mechanical ventilation for at least 48 hours, patients were randomized to placebo versus albumin and furosemide combination therapy. The addition of albumin did not affect days of mechanical ventilation and total doses of furosemide were not reported. The mean starting rate of furosemide in the both groups was 3.5 mg/hr with a titration up to 4.9 mg/hr in the combination group versus 6.7 mg/hr in the monotherapy group, correlating to a total daily dose of 84-117 mg. (284)‘

A meta-analysis in 2014 attempted to pool data regarding albumin and furosemide co-administration in a broad cohort. (285) A large variation in furosemide dosing regimens were utilized, with a range between 30-220 mg. Studies using smaller furosemide doses were the only protocols resulting in a benefit in combination with albumin therapy, highlighting the importance of adequate furosemide dosing and likely lack of benefit of albumin when optimal furosemide doses are utilized. Of course, this population was very broad, including patients with cirrhosis and nephrotic syndrome, limiting precise interpretation as it relates to the general ICU population. In a 2014 meta-analysis which limited its data pool to only randomized controlled trials evaluating albumin in addition to furosemide in the critically ill, insufficient evidence exists to perform analyses (two eligible trials). (286) Another meta-analysis the same year with less stringent criteria evaluating co-administration of albumin with loop diuretic therapy, significant

heterogeneity was demonstrated in the 10 included trials. A significant increase in 8-hour urine volume was found with albumin use (difference of 231 mL, 95% CI 135.5-326.5) as well as sodium excretion but such differences were not significantly different after the first day. (285)

A 2018 trial evaluating feasibility of albumin addition to clinician-driven diuresis for the treatment of edema secondary to volume overload in hypoalbuminemic ICU patients failed to produce feasibility and furosemide doses went unreported. (287) A recent study utilized what was termed PAL-treatment in patients admitted to the intensive care unit with acute lung injury receiving mechanical ventilation. The first step of this protocol was a 30-minute application of positive end-expiratory pressure to counterbalance an elevated intra-abdominal pressure. After the pressures were equal, albumin 20% solution was administered (twice on day one, then titrated in an attempt to achieve a serum albumin of 3 g/dL). Thirty minutes after the first albumin dose was administered, 60 mg of IV furosemide was administered followed by a continuous infusion of 60 mg/hour for the first four hours then 5–20 mg/hour pending if no shock occurred. For those patients without adequate urine output, continuous renal replacement therapy was used with ultrafiltration in order to obtain either a net-even or negative fluid balance. Patients receiving this therapy showed improvement in ELVW, intra-abdominal pressures, and decreases in cumulative fluid balance; however, the placebo group did not contain furosemide, therefore limiting the interpretation of benefit to albumin alone. (288)

1.24.2 Adjunctive Diuretic Therapy with Thiazide Diuretics

Another potential therapeutic modification to diuresis is the addition of thiazide diuretics to loop therapy within the ICU. Thiazide-type diuretics block the sodium reabsorption in the distal tubules, succeeding the mechanism of action of the loop diuretic therapies. This can result in sequential nephron blockade and may have a synergistic effect with loop diuretic administration. Metolazone, through additional potential action on the proximal tubule, is postulated to have even greater synergy; however, such has never been proven in clinical studies.

(289) The majority of the evidence to support the synergistic effect between metolazone and loop diuretics comes from primarily small observational studies in the acute heart failure population with a reported response rate of up to 90%. (290) In a retrospective study of 242 hospitalized patients receiving diuresis for acute heart failure, the combination of metolazone and intermittent furosemide was more effective than continuous infusion furosemide and bumetanide, demonstrating a mean hourly urine output of 109 mL/hour compared to 48 mL/hour and 90 mL/hour, respectively ($p<0.0001$). (291) Metolazone is available only as an oral form while an alternative thiazide-like diuretic, chlorothiazide is an intravenous option. Given the potential for decreased drug absorption with surrounding gastrointestinal edema, chlorothiazide has been hypothesized to have a greater action in those with refractory edema, such as the critically ill. A group of 45 patients who received chlorothiazide for acute decompensated heart failure after determined to be refractory to metolazone and resistance to diuresis were retrospectively evaluated in a single center study. (292) Chlorothiazide 500 mg IV did not significantly increase urine output compared to metolazone in a heart failure population. One author also demonstrated non-inferiority when metolazone was compared to chlorothiazide. (293) A third study also demonstrated similar responses in urine output between the two options however patients receiving chlorothiazide received higher thiazide and loop diuretic doses ($p<0.01$). (294) Only one study has sought to specifically evaluate metolazone compared to chlorothiazide in the general ICU population. (295) In this retrospective cohort of several ICU types, 122 patients were included. Compared to furosemide monotherapy, chlorothiazide resulted in a significantly higher change in urine output at 6 and 24 hours (1463 mL vs 796 mL, $p<0.01$; 2405 vs 1646 mL, $p+0.01$). However, patients receiving chlorothiazide also required more potassium supplementation and also had a significantly higher cost of therapy ($97 vs $8, $p<0.01$). Further, patients in the chlorothiazide group received a significantly higher amount of furosemide via continuous infusion as well as a numerically higher furosemide receipt with intermittent dosing. No differences were found in renal replacement therapy, ICU length of stay, or survival to discharge.

1.24.3 Adjunctive Diuretic Therapy with Acetazolamide

The final potential adjunct agent for loop diuresis is acetazolamide, a carbonic anhydrase inhibitor whose mechanism relies upon inhibition of the proximal convoluted tubule sodium bicarbonate reabsorption. Via its action, sodium delivery to the NKCC is improved therefore improving loop diuretic efficacy. Thiazide efficacy also improves as it downregulates pendrin, a sodium-independent chloride/iodine transporter, in the distal nephron. Pendrin compensates for sodium and chloride loss in the distal convoluted tubules. Acetazolamide has minimal evidence in the critically ill population, with studies evaluating its use for metabolic alkalosis or mechanical ventilation weaning demonstrating suboptimal results. (296, 297) One single study evaluated acetazolamide in 24 edematous patients, secondary to heart failure, cirrhosis, or nephrotic syndrome. Acetazolamide was shown to improve diuresis in patients with a low fraction excretion of sodium prior to diuretic treatment and when resistance was seen to both thiazides and loop diuretics, however none of these patients studied were critically ill. (298)

1.25 Discrepancies in Approaches to Diuresis

Studies including the administration of furosemide within the ICU show a broad range in the frequency of use, 70%, with equipoise demonstrated in the totality of evidence. (229, 299) In a 2015 survey of 146 intensivists in Australia and New Zealand, concerns regarding current diuretic approaches were raised. (300) Over 60% of the respondents had worked in an ICU for at least 10 years and utilized a positive fluid balance, acute pulmonary edema, or acute lung injury as indications for the administration of a loop diuretic. A minimal number of respondents considered acute kidney injury or elevated central venous pressure to be an indication for volume removal. For all indications, an IV bolus was the preferred route over 60% of the time and several clinicians had no preference in comparison to continuous infusion. Regardless of the indication, the majority started administration of loop diuretics with a 40 mg IV dose or 10 mg/hour infusion, except when acute kidney was present, then physicians stated that at least half of the time an 80 mg IV bolus and 50 mg/hour infusion would be their selection. Most notably, when prompted

about the expected clinical responses to loop therapy based on the clinical indication, the majority of physicians had no set target specified for acute kidney injury, acute pulmonary edema, increased central venous pressure, or acute lung injury. While more physicians did state they most commonly had a set goal in mind when treating positive fluid balance and oliguria, a significant portion of these groups did not, with 27.7% and 11.5% having no goal for the management of fluid balance or oliguria, respectively.

An even larger survey encompassed physicians across 16 countries surveyed diuretic therapy in acute kidney injury specifically. (301) Loop diuretics were administered in 67% of patients most frequently intravenously. Most respondents reported that several considerations were important in the decision for initial dosing regimen, including serum creatinine, urine output, blood pressure, central venous pressure, and toxicity risk. Only 5% of respondents had a protocol to dictate diuretic therapy. Pulmonary edema was a large indicator for diuretic need; however, serum creatinine, oliguria, and metabolic acidosis were not. The use of diuretics for abdominal compartment syndrome was infrequent or almost never in 65.5% of respondents. Use was more common in AKI associated with rhabdomyolysis, major surgery, and cardiogenic shock with respondents reporting 'sometimes' or 'frequently' in 55.6, 56, and 56.2%. Clinicians responded that septic AKI was 'infrequently' or 'almost never' an indication for diuresis in 49.6% of respondents. Most respondents did not believe that diuretics would reduce mortality or improve renal function in this population however roughly 25% were still uncertain about diuretic impact on outcomes. The majority had a set target urine output as their goal for diuresis, but 17% did not have a target fluid balance. Interestingly, 85% of the respondents expressed willingness in the participation of a potential randomized controlled trial evaluating the use of diuretics in patients who are critically ill with acute kidney injury.

Loop diuretics, in general, have been shown to have a large inter-patient variability in urine output response and the standard dose of 40 mg IV has been shown to improve urine output volumes, but does not consistently improve cumulative fluid balances, demonstrating that likely

higher doses are needed in some populations. Multiple patient-specific parameters may need to be considered for optimal outcome.

In a study of 162 patients admitted to the trauma ICU in a single center over a two year timeframe, only 27 patients, 31.8%, received furosemide within the first two weeks of stay in the intensive care unit. (302) While the first day of diuretic administration was within 72 hours of ICU stay, the first day of diuresis in some patients may not have occurred until day 12. The majority of patients received a starting dose of 10 mg with a cumulative dose of 60 mg. The range of cumulative dosing extended from 20 mg to 610 mg, with the average daily dose highest on day 11. Patients who received diuretics had a longer ICU stay (9 vs 5 days, $p<0.001$) as well as longer days on mechanical ventilation (7 vs 2 days, $p=0.005$). It is plausible that the lack of benefit of diuresis was secondary to late initiation of furosemide as well as delayed time to optimized dosing. These possibilities reemphasize the importance of appropriate dosage as well as the team's early recognition of shock resolution in order to transition to the flow state. (302)

In a separate study of patients within the respiratory ICU assigned to a nurse-driven protocolized furosemide continuous infusion over a one year, 43 patients received treatment and were evaluated. (303) Duration of furosemide was widespread, with an average duration of greater than one week with a range between 2-25 days. The average total dose received was 2240 mg (Standard Deviation [SD] 3340 mg), however the average total daily dose received was 251 mg, 10 mg/hour. The majority of patients (89%) stopped receiving furosemide secondary to overall improvement of edema, with a small portion required discontinuation secondary to hypotension (7%). Temporary holds were most frequent for high urine output (44%), with the next highest frequency of temporary holds secondary to hypotension. Worsening kidney function was seen in13 percent of patients with 6% developing high sodium (hypernatremia) or low potassium (hypokalemia), or both. Given the lack of comparator group, no clinical outcomes were compared; however, it was noted that albumin was administered on 22% of days during protocol receipt and acetazolamide was administered on 5% of the days during furosemide infusion. (303) Even in the

prior mentioned multicenter retrospective cohort demonstrating improved mortality with lower 72 hour fluid balances, which was associated with strength of furosemide dosing, the median dose administered on days 1-3 was 0 mg, with an interquartile range extending only to 20 mg. (218)

A retrospective evaluation of 326 patients with acute kidney injury receiving furosemide before consultation of the renal team showed a wide range of diuretic administration and responsiveness. (265) The range extended from 20 mg of furosemide resulting in 1000 mL of urine output to 240 mg of furosemide resulting in only 114 mL of urine. Notably, a ratio of furosemide in mg to urine output in mL on the day of renal consultation ≥1 correlated with a significant increase in death or nonrecovery (OR 2.94, 95% CI 1.61-5.36), however researchers highlighted some limitations in the interpretation of this data, including the use of odds ratios, late nephrology consults, and between-group differences at baseline, including respiratory failure and congestive heart failure. (304-308)

1.25 Expanded Benefits of Diuresis

1.25.1 Potential for Cost Benefit with Diuresis

Beyond improvement in mechanical ventilation, mortality, renal function, and both ICU and hospital length of stay, appropriate management of fluid balance has the potential to impact functional and economic outcomes as well. Intensive care unit costs are three to five times that of stays in alternative hospital floors. One-third of inpatients costs is attributed to the ICU, although these beds accounts for under 10% of the total number of hospital beds within the United States. Specifically, mechanical ventilation increased hospital costs by an average of $18,643 per admission in a retrospective study of 253 United States hospitals, with a mean incremental cost of $1,522 per day with the addition of mechanical ventilation. (309) In a recent Canadian study, mean direct costs of ICU stay were a median of $148,328 (IQR $114,008–$224,611). Acute respiratory failure was associated with the highest costs in multivariate regression (OR 2.44, 95% CI 1.88-3.18). (310) A recent observational study of patients admitted to the ICU with vasopressor

therapy for septic shock sought to evaluate which outcome improvement may decrease overall hospital cost the mot. (311) The median charge for a septic shock hospitalization was $98,583 (IQR $61,177-$136,672). Decreases in ICU length of stay, mechanical ventilation duration, and vasopressor duration of 24 hours were associated with charge reductions of $15,670 (IQR $15,023-$16,317), $15,284 (IQR $13,566-$17,002), and $17,947 (IQR $16,344-$19,549), respectively. Avoidance of new renal replacement therapy was associated with a charge reduction of $36,051 (IQR $22,353-$49,750).

1.25.2 Potential of Impact of Diuresis on Long Term Outcomes

Further, in a retrospective study of 247 patients admitted to an academic medical center within a three year time frame. Fluid overload was associated with post-discharge outcomes. A positive fluid balance was demonstrated in 86% of patients with 35% having volume overload, with an increased in weight from admission of at least 10%. Volume overload upon ICU discharge was independently associated with an inability to ambulate upon hospital discharge (OR 2.29, 95% CI 1.24–4.25) and increased need of discharge to a healthcare facility in those admitted from home (OR 2.34, 95% CI 1.1–4.98). Only 42% of patients received at least one dose of a diuretic during their hospitalization. Patients with volume overload at ICU discharge had a longer duration of mechanical ventilation in the ICU (4.4 days vs 1.8 days, $p<0.01$), were more frequently readmitted to the ICU (14.9% vs 5.6%, $p=0.03$), had a longer duration of an indwelling Foley catheter after ICU discharge (8.3 days vs 3.8 days, $p=0.003$), while also having a longer hospital stay after ICU discharge (9.6 days vs 3.1 days, $p<0.01$) and having higher risk of death before hospital discharge (9.2% vs 1.3%, $p=0.01$). (312) A secondary analysis of the previously mentioned study utilizing BNP for fluid management demonstrated that a fluid depletive strategy was associated with a decreased risk of ventilator association pneumonia as well as ventilator associated complications in addition to a shorter time to extubation, more successful rates of extubation, and more ventilator-free days after adjusting for a competing event of weaning outcome. (313)

1.27 The Role of the Pharmacist in Critical Care

According to the Board of Pharmacy Specialties, a Board Certified Critical Care Pharmacist "has the advanced knowledge and expertise to quickly assess clinical data and deliver direct patient care to the critically ill and injured patient who may require specialized pharmacologic or technological interventions to maintain blood pressure, respiration, nutrition and other homeostatic functions, in addition to the patient's primary condition," as well as "reviews, analyzes and frequently reassesses multifaceted clinical and technological data to make reasoned decisions for patients with life-threatening conditions and complex medication regimens whose pharmacokinetic and pharmacodynamic parameters differ substantially from the non-critically ill patient." (314) In a 2017 study evaluating composition of multidisciplinary teams, 93.6% of teams had a critical care pharmacist at least part-time within the unit, with 74% having a pharmacist always or almost always on the team. (315) A survey specific to the United Kingdom surveying 279 units demonstrated that 98.6% of all critical care units had a designated pharmacist. (316) Many consider a critical care pharmacist to be a basic requirement in the ICU. (317)

1.27.1 The Definition of the Clinical Pharmacist Role

Almost two decades ago, the Society of Critical Care Medicine (SCCM) and the American College of Clinical Pharmacy collaborated to define the fundamental, desirable, and optimal roles of critical care pharmacists (Table 1.8). (318) SCCM guidance documents on optimization of critical care centers recommend pharmacy services in the highest level of critical care services. This organization deems pharmacist services to be essential in the ICU and recommends that dedicated ICU pharmacists should be available to "evaluate all drug therapy orders, review and maintain medication profiles, monitor drug dosing and administration regimens, evaluate adverse reactions and drug/drug interactions, give drug and poison information, and provide recommendation on cost containment issues." Further, SCCM recommends that a pharmacist participates on multidisciplinary rounds, provides drug therapy education to other team members,

Table 1.8 Roles of a Critical Care Clinical Pharmacist (318)

Grade	Definition	Example Activities
Fundamental	Vital to safe provision of pharmaceutical care	• Dedicated time to critical care patients • Prospectively evaluates all drug therapy • Identifies adverse drug events and assists in their management and prevention • Provides drug information • Provides pharmacokinetic monitoring and drug therapy–related education • Implements and maintains departmental policies or procedures related to safe and effective use of drugs • Collaborates with nursing, medical staff, and hospital administration • Participates in quality assurance programs
Desirable	Critical care–specific pharmacotherapeutic services	• Responds to all resuscitation events in the hospital • Rounds with the multidisciplinary team • Clarifies previously effective dosages and regimens • Provides didactic lectures in critical care pharmacology and therapeutics to health professions students • Coordinates development and implementation of drug therapy protocols to maximize drug therapy benefits • Participates in research design and data analysis • Assists in the screening and enrollment of patients and by serving as a study coordinator • Contributes to pharmacy and medical literature
Optimal	Specialized, dedicated and integrated model of critical care that aims to optimize pharmacotherapeutic outcomes via the highest level of teaching, research, and pharmacotherapy practice	• Pharmacist provides formal, accredited educational sessions • Investigates or collaborates with other critical care practitioners to evaluate the impact of guidelines and/or protocols used in the ICU for drug administration and management of common disease states • Develops residencies and/ or fellowships in critical care pharmacy • Proactively designs, prioritizes, and promotes new pharmacy programs and services • Develops and implements pharmacist and pharmacy technician training programs • Publishes in the peer-reviewed pharmacy and medical literature

takes part in multidisciplinary quality activity committees, and implements policies and procedures to provide safe and effective medication practices within the ICU. (319) The therapeutic areas encompassed are ubiquitous, however ACCP specifically recommends expertise in renal diseases, including fluid homeostasis, as well as pulmonary disorders and mechanical ventilation. (320) A study in 2006 demonstrated how closely these recommendations are followed. In a survey of 1034 intensive care units, 43% of ICU pharmacist time was dedicated to patient care with another 26.2% in drug distribution and 12.6% in administration. Educational activities took 10.9% of the overall work time and 7.3% of efforts were dedicated to scholarly activity. The types of services commonly documented included changing drug therapy (90.6%), monitoring therapy (81.7%), preventing adverse drug events (77.5%), providing drug information (71.1%), cost savings (69.2%), and educational activities (53.2%). (321) The three broad areas in which clinical pharmacist workflow can be categorized include pharmacist independent patient review, active participation within the multidisciplinary team, and professional support activities. (322)

1.27.2 Expanding the Role of the Clinical Pharmacist

In the United Kingdom, the role of pharmacy practice is taken even further with the allocation of prescribing rights to critical care pharmacists. In one month, pharmacists contributed roughly 10% of all individual medicine prescriptions with 65.3% of ICU patients receiving at least one medication prescribed by a pharmacist. (323) This was true despite that only 60% of shifts were actually covered by clinical pharmacists. The error rate of pharmacist prescribing in this study was 0.18% compared a provider prescribing error rate of 7-9% in other studies. (324, 325) While the range of medications was broad, no data on diuretic regimens was reported. The critical care profession continues to expand with an over 200% increase in specialized training programs in less than a decade. (326) Rates of acceptance of pharmacist recommendations within the intensive care unit on patient care rounds alone exceed 60% in both academic and non-academic institutions, with a value of service and severity of intervention most

frequently deemed to be significant based on United Kingdom standards. A cost-benefit ratio in this study was 3.2-3.3 depending on type of institution. (327)

1.27.3 Pharmacist-Driven Protocols in the General Population

The benefit of pharmacist-driven protocols is well documented in a multitude of populations. In a pre- and post-intervention study looking at the implementation of a pharmacist-driven protocol (PDP) for discontinuation of proton pump inhibitors in 101 non-ICU patients, pharmacists prospectively evaluated daily lists of hospitalized patients with active medication orders for a proton pump inhibitor and evaluated each for appropriateness and as a result recommended discontinuation of change to an alternative therapy, as appropriate. This PDP was associated with a significantly higher discontinuation rate (absolute risk reduction 24.9%, p=0.001). (328) A PDP for perioperative antibiotic selection allowed the initiation of medication orders in patients with methicillin-resistance *Staphylococcus aureus* colonization undergoing orthopedic surgery. In the 51 patients evaluated, the PDP improved appropriateness of antibiotic selection by 18%. (329) Another study evaluated the use of a PDP for de-escalation of empiric broad spectrum antimicrobials based on patient surveillance screening within in 300 patients in a single center. Those in the post-implementation group had a 2.1 day reduction in the total duration of vancomycin therapy (p<0.0001) while also demonstrating a decrease in the total number of drug levels collected. (330) A pharmacist-driven prothrombin complex concentrate (PCC) protocol for the reversal of warfarin in warfarin-associated intracranial hemorrhage gave pharmacists responsibility in determining the appropriate dose of PCC, preparation, bedside delivery, and order entry into the electronic medical record. This PDP when compared to the historical cohort demonstrated in 48 patients, who presented to the emergency department, decreased time of administration from 70 minutes to 35 minutes, pre- and post-PDP, respectively (p=0.034). (331) PDP-managed warfarin has also shown to be of benefit. In 377 patients receiving warfarin within a single institution, dosing per PDP increased amount of time within therapeutic range (87.8% vs 38.5%), increased total number of patients who received goal therapeutic level

(35% vs 40%), decreased number of subtherapeutic internationalized normalized ratios [INR] (55.3% vs 39%), and decreased supratherapeutic INR values (3.7% vs 2.6%). Time to appropriate INR decreased by 0.5 days. (332) Regarding monitoring of an alternative anticoagulant, enoxaparin, a PDP anti-Xa level protocol increased the number of correctly drawn levels by 22% and follow up to non-therapeutic levels by 36% ($p<0.001$). The number of organizations adopting PDP approaches to therapy is increasing, with multiple recent publications, both demonstrating improved monitoring and increased rates of appropriate therapeutic regimens. (333, 334)

1.27.4 Pharmacist-Driven Protocols in the Critically Ill Population

In the ICU, evidence supporting PDP is more limited. However, PDPs may arguably be more significant regarding total demonstrated impact on clinical outcomes. In a single-center retrospective cohort study of a PDP for discontinuation of acid suppressive therapy, incidence of inappropriate stress ulcer prophylaxis was reduced from 61% versus 24% with PDP ($p<0.0001$). (335) The authors estimated an annual cost savings of $5496. A PDP for antipsychotic medication discontinuation in the ICU led to a significant reduction of antipsychotic medication continuation at hospital discharge of 25.3% ($p<0.001$). (336) In a single-center study of 201 patients with suspected pneumonia within the ICU, a PDP protocol decreased average days of treatment (12.3 vs 15.9 days, $p <0.001$) without any change in clinical outcomes. (337) Further, in the ICU, pharmacist-led interventions have shown to decrease hospital length of stay by 3.7 days (95% CI 5.2-2.3 days), ICU length of stay by 1.4 days (95% CI 2.3-0.5 days), duration of mechanical ventilation by 1.2 days (95% CI 2.1-0.3 days), and overall hospital costs per stay (2560 Euros, 95% CI 3728-1392). (338) In a study evaluating the impact of clinical pharmacists in the ICU in patients with infections, mortality rates in ICUs that did not have clinical pharmacists were 4.8-23.6% higher, ICU length of stay was longer by 7.9-8.1% ($p < 0.05$) and costs were 12% higher ($p < 0.001$). (339) Specifically in a study of 141,079 critically ill patients presenting with a thromboembolic or infarction-related event, mortality rates were higher for both populations without pharmacists during events without bleeding (OR 1.41, 95% CI 1.36-1.46). With bleeding

the odds ratio was 1.35 (95% CI 1.13-1.61) in ICUs which did not have a clinical pharmacist. ICU length of stay was 14.8 to 15.8% longer ($p<0.001$) and additional charges ranged from $2,610,750 to 215,397,354 ($p<0.001$). Bleeding complications were significantly more likely in units without clinical pharmacists (OR 1.53, 95% CI 1.46-1.60) with more patients requiring transfusions (PR 1.47, 95% CI 1.28-1.69) and blood products ($p=0.006$). (340) Outside of PDP, pharmacist presence in the ICU has been associated with a potential cost savings of over $0.5 million per year, reduced rates of ventilator associated pneumonia, decreased ventilator days, decreased medication errors, improved rates of neuromuscular function recovery and spontaneous ventilation, decreased inappropriate serum drug concentrations, and a 66% decrease in adverse events. (341) The only study to date evaluating pharmacists' roles in fluid balance was an evaluation of pharmacist interventions in fluid-restricted patients receiving parenteral nutrition. Pharmacist impact significantly lowered mean fluid intake, fluid balance, and cumulative fluid balance, the latter by over 5.5 liters ($p<0.001$). (342)

1.28 Conclusion

Fluid overload remains an overwhelming and detrimental problem in the ICU and minimal evidence exists to provide guidance on appropriate utilization of diuretics for volume removal. Evidence establishes the detriment of fluid overload; however, current markers for fluid overload and potential monitoring parameters for de-resuscitation are initiated only when overload is present, potentially worsening clinical outcomes. Several surrogate markers have been deemed unreliable, both when monitoring volume status and renal function. Therefore, the clinician is left with urine output monitoring as a surrogate for optimization of therapies in order to achieve a net negative fluid balance. A urine output of 3-4 mL/kg/hour is postulated to provide adequate diuresis without causing intravascular volume depletion given the ability of capillary refill to accommodate. (343) While the timeframe for transition from ebb to flow states is also one of debate, the majority of evidence agrees that 72 hours after shock resolution is an appropriate starting point for the achievement of a net-even to net-negative fluid balance. The approach to

such an achievement is even more unclear. A protocolized approach appears to be better than current standard of care. Loop diuretics, by nature of mechanism of action and strength of drug effect, are likely to be the optimal diuretic for removal of volume, with the potential for adjunct agents in special circumstances. However, specific benefit has not been strongly demonstrated with one specific loop diuretic or mode of administration. The creation of a diuresis protocol to optimize the approach to diuresis is of vital need and is a prime area for pharmacist intervention. Pharmacist impact on clinical outcomes in the ICU is well-documented and previous pharmacist-driven protocols have proven successful. Given the lack of solid evidence, expert-level pharmacotherapy and thorough therapeutic understanding is necessary in order to create, evaluate, and utilize a protocolized approach to diuresis.

CHAPTER 2. NATIONAL STUDY OF THERAPEUTIC DIURESIS PRACTICES WITHIN THE INTENSIVE CARE UNIT

The following chapter outlines the "National Study of Therapeutic Diuresis Practices within the Intensive Care Unit Survey" which is a national survey led by the primary author, Bissell, and colleagues. This survey was distributed to all clinical pharmacists currently practicing within the intensive care unit (ICU) through a national database of the American College of Clinical Pharmacy Critical Care Practice and Research Network (PRN). This is a product of the Critical Care PRN as a network hopes to improve drug therapy outcomes by encouraging excellence as well as innovation in clinical pharmacy practice, research, and education. The main objectives of the PRN are to: provide timely educational updates to members and other pharmacists, participate in multicenter research in partnership with critical care pharmacists, facilitate information exchange among critical care pharmacists, and to provide a venue for informal networking among critical care pharmacists.(344)

2.1 Survey Rationale and Purpose

This research is valuable in order to establish a baseline of perceptions and clinical approaches to diuresis within the critically ill. Several studies have highlighted an association between mortality and fluid balance within the ICU population; however, few have looked at the management of volume status in order to correct positive volume status or facilitate mechanical ventilation wean in the broad ICU population. What is left unknown is how the best take the findings of these baseline evidence base and translate these findings into a truly working practical protocol that is feasible at bedside. A large knowledge gap exists in regards to overall utilization, timing, and monitoring of diuresis within the ICU population. Guidelines steering fluid de-resuscitation within the critically ill do not exist therefore resulting in varied practices. Current evidence on diuresis is limited to indirect evidence within a decompensated heart failure (ADHF) population or patients presenting in acute respiratory distress syndrome. Delaying the application of these studies further is potentially the continued utilization of hemodynamic monitoring

parameters no longer routinely recommended in clinical practice. Previous surveys surrounding diuresis in the critically ill have specific country limitations in which the standard of practice may vary greatly and are limited to very specific patient population subtypes, such as acute kidney injury. This survey is essential in order to develop a baseline understanding of current diuresis practices then implement research providing a more standardized approach to diuresis. The specific aims of this survey were to describe the frequency of pharmacist intervention on ICU diuresis and to evaluate perceptions surrounding efficacy of current diuresis process, particularly apprehension or barriers to diuresis within the ICU. Lastly the survey's aim was to collect diuretic regimens utilized for diuresis in this population. With such, a standardized fluid de-resuscitation protocol after shock resolution could be developed in a multi-center intervention study.

2.2 Survey Design and Validation

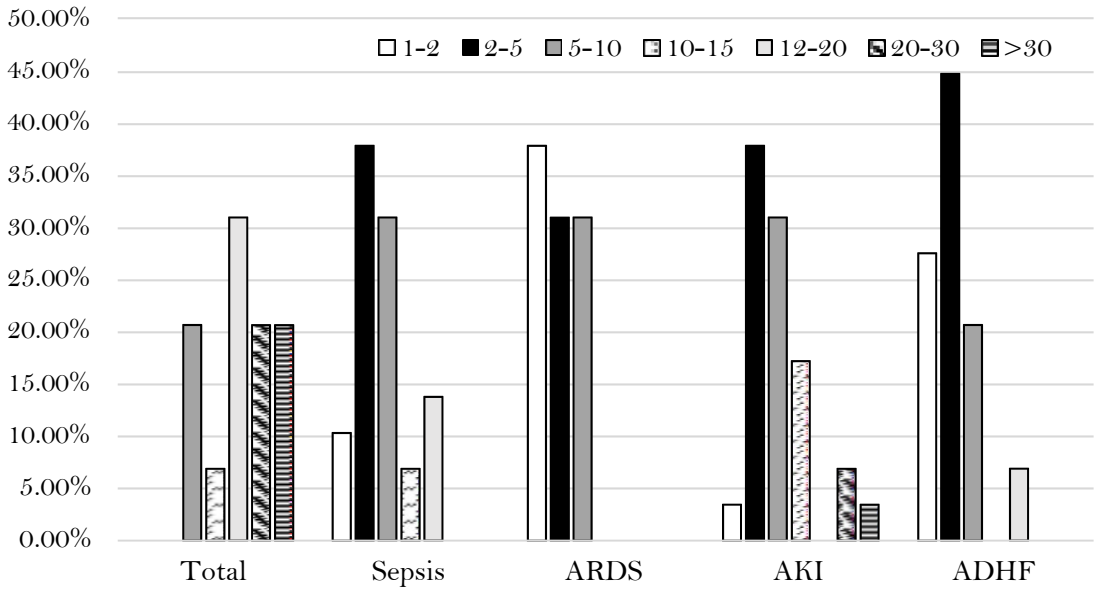
A group of individual pharmacists were responsible for item generation and constructed sample questions. This group checked for redundancy and grouped of items into similar themes based on the survey objectives. The group developed a list of 25 key questions. Given the limited question items and group consensus, factor analysis was deemed unnecessary. SurveyMonkey© internet platform was utilized for questionnaire construction with automatic electronic data exportation to limit inter-rater disagreement. (345) A separate workgroup consisting of 9 pharmacists went through pilot testing of the penultimate version to optimize question relevance, questionnaire flow, and clarity. The first survey was completed September 25, 2018 and the final survey submitted was September 30, 2018. The authors requested that participants share the questionnaire with colleagues. A total of 29 respondents completed the questionnaire (average completion rate of 86%) with a median time of completion of 9.9 minutes (IQR 8.2-25.5 minutes) at the time of data exportation from the database. Clinical sensibility testing was submitted via respondent email within this time frame. Questions were clarified and the addition of "Unsure" responses was included on questions as applicable. Additionally, questions regarding demographics (Q22, 23, 25) were clarified for further inclusion

Table 2.1 Final Survey Respondent Population Demographics

	Percentage	Survey Respondents (n=29)
Current Position		
Pharmacist (Specialist)	86.21%	25
Pharmacist (Staff)	6.90%	2
Pharmacist (Decentralized)	3.45%	1
Resident/fellow pharmacist	3.45%	1
Current Institution		
Academic medical center	55.17%	16
Community medical center	41.38%	12
Government medical center	3.45%	1
ICU Team		
Teaching team	72.41%	21
Rounding hospitalist	3.45%	1
Non-rounding hospitalist	17.24%	5
Rounding intensivist	58.62%	17
Non-rounding intensivist	3.45%	1
Rounding advanced care provider (APP)	27.59%	8
Non-rounding APP	3.45%	1
ICU Type		
Medical ICU	55.17%	16
Non-Trauma Surgical ICU	6.90%	2
Cardiac or Cardiothoracic ICU	13.79%	4
Mixed ICU	20.69%	6
Emergency department	3.45%	1

of a more diverse population. After 2 weeks, the final survey was re-distributed to the same group of pharmacists (Appendix One). This time frame was selected to decrease time for confounding or maturation between test groups and to allow an appropriate amount of time to test selection stability and prevent memorization between cohorts. A total of 6 responses were received with a 100% completion rate and median time of completion of 9.27 minutes (IQR 6.9-29.3 minutes). The first survey in this group was completed October 9, 2018 and the final was completion October 16, 2018. Due to the limited question number and diverse conceptual processes included, direct

Figure 2.1 Study Population Patient Demographics per Day

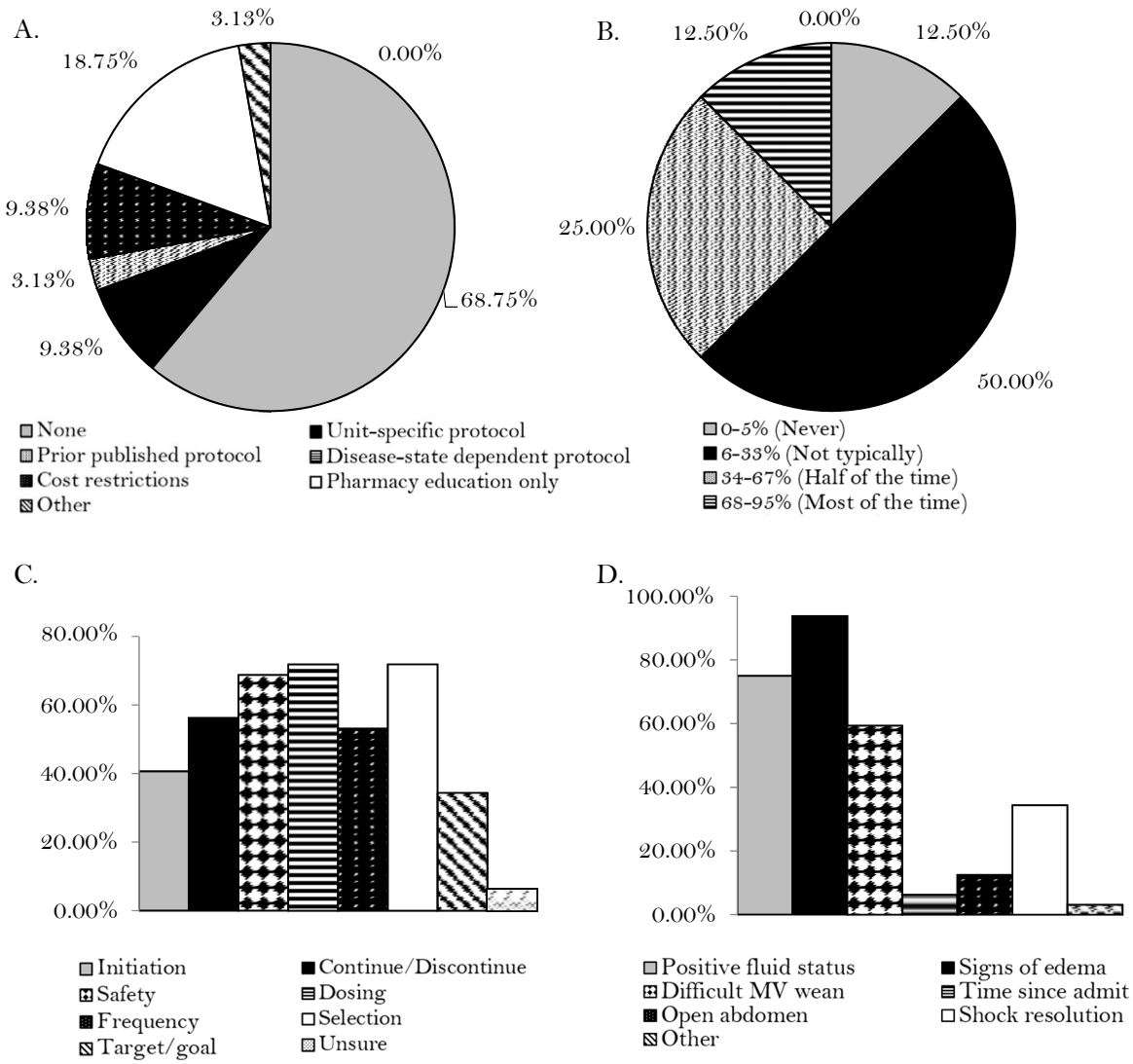


inter-correlation between questions was unanticipated and internal consistency testing was deferred. To evaluate between test-retest reliability, a Pearson Correlation technique was utilized. (346) Overall, the survey was found to have a correlation of 0.854 ($p<0.001$), demonstrating evidence of test-retest reliability.

2.3 Survey Results

Among 32 respondents surveyed, 29 completed the instrument (91%) within a one-week period. The survey remains open given a current response rate of 1.4%, with 2291 individual emails sent via the Critical Care PRN Listserv mailing list in additional to 108 social media exposures. The average survey time was 9.1 minutes with population demographics demonstrated in Table 2.1 Clinical pharmacists were most frequently available during 8-hour daytime shifts (n=20, 69.0%), with 6.9% having 12-hour clinical pharmacy coverage, and another 10.34% having extended daytime hours (n=2 and 3, respectively). Of the cohort, 13.8% had pharmacy coverage 24 hours per day. Exactly half of the population had on-call pharmacy services (n=14), with the majority of these call hours 24 hours per day (n=12). Weekend clinical pharmacy coverage was available in 20.7% of the cohort, while 24.1% of the cohort had decentralized pharmacy services

Figure 2.2 Factors Surrounding Initiation of Diuresis

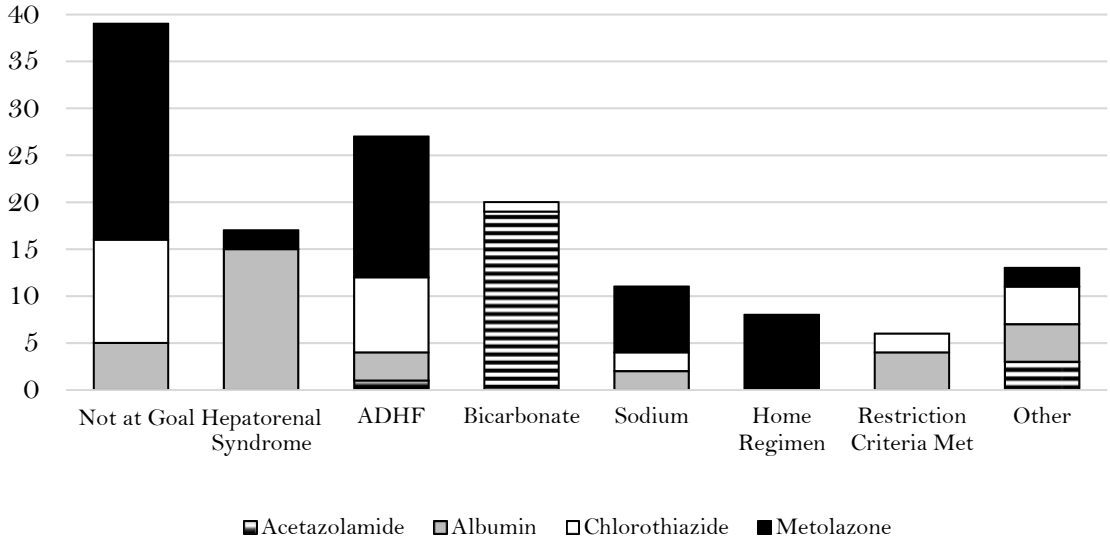


A. Current diuresis approach/protocol within institution B. Percentage of time pharmacist involved in diuresis C. Pharmacist interventions in de-resuscitation D. Most frequent prompter of diuresis initiation

---

Saturday and Sunday and 35.7% had central pharmacy coverage. These demographics are in alignment with previous demographics of the clinical pharmacy services within the ICU population. (321)

Figure 2.3 Adjunctive Agents Utilized in De-Resuscitation



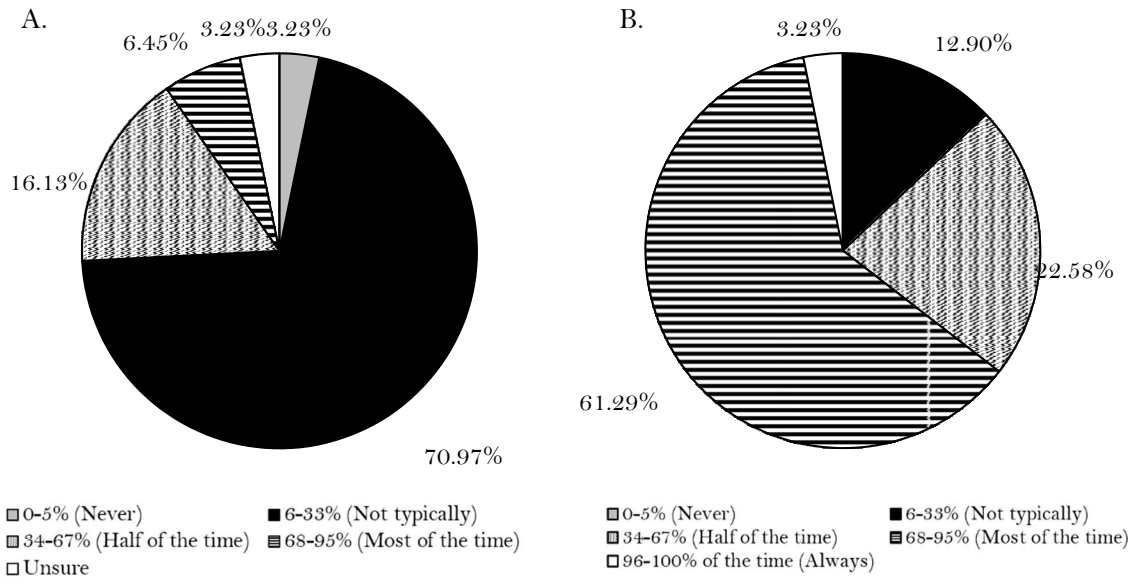
2.3.1 Approach to De-Resuscitation Initiation

As it pertained to the initiation of diuresis, the majority of surveyors did not have a protocol or guideline in place for de-resuscitation (68.8%) and the pharmacist was found to not frequently be involved as 62.5% of the cohort said the pharmacist was involved never or not typically (Figure 2.2) in diuresis initiation. Pharmacist involvement was varied, most frequently involving drug dosing, selection, or safety monitoring. Signs of pulmonary and/or peripheral edema on physical exam or monitoring devices, difficult mechanical ventilation wean, and positive fluid balances were the most frequent reasons for initiation of diuresis. Regimen choice was most frequently driven by fluid balance (n=20) as well as active diagnosis, such as AKI, or home diuretic regimen (n=19 per variable). Serum creatinine was the next most likely parameter for consideration (n=13) followed by nephrology recommendations (n=6).

2.3.2 Diuresis Follow-Up and Modifications

Regarding dosing frequency, every 12 hours and intermittent one-time doses were the most commonly utilized (n=19, 16, respectively). Every 8 hours was the 3rd most frequent

Figure 2.4 Appropriateness of Diuresis Discontinuation



A. Rate in which diuresis is stopped secondary to safety reasons B. Perception of percentage time diuresis stopped appropriately

---

selection with 12 responses. Continuous infusion was utilized less frequently with 6 responses and 5 responses with the latter representing those without an IV bolus prior to infusion start and the former with bolus. Every 24 hour dosing and every 6 hour dosing were also utilized but infrequently (n=2 per variable). The utilization of adjunct therapies is demonstrated in Figure 2.3, with acetazolamide often utilized for serum bicarbonate, albumin for hepatorenal syndrome, and metolazone as a continuation of home regimen, heart failure, or failure to achieve daily goal.

Upon initiation of diuresis, 41.9% of the respondents said the next assessment or regimen was change was typically within 6-8 hours, while 22.6% said after 24 hours, and 19.4% stating within 12 hours. Diuresis follow-up was assessed daily in rounds in 16.1% and within 2 hours in 12.9%. Most respondents stated that typically diuresis was not stopped for safety reasons (70.9%) while 61.3% stated that diuresis was stopped appropriately about half of time overall (Figure 2.4). Despite this, the most common reasons indicated for a decrease in the diuretic regimen occurred for safety reasons were hemodynamic safety, excessive diuresis, and metabolic safety with 18,

Table 2.2 Frequency of Volume Status Consideration

	Percentage	Cohort (n=31)
Only during initial resuscitation	25.81%	8
Multiple times per day	29.03%	9
Daily	54.84%	17
Every 1-2 days	6.45%	2
Once prompted	6.45%	2
Once indicators of volume overload found	51.61%	16
Possibility of extubation	19.35%	6
Unsure	3.23%	1

17, and 15 respondents claiming such within their population. Unresponsiveness to diuresis was stated to be an indication for decrease in the regimen in 8 respondents and conversion to renal replacement therapy was chosen once. Regarding the frequency of volume status monitoring, respondents were permitted to choose more than one answer to the question. The majority of the respondent group stated that volume status is considered only daily and/or when volume overload indicators are displayed (Table 2.2).

2.3.3 Perceptions of Diuresis Efficacy

Regarding the overall effectiveness of de-resuscitation, the majority of the cohort felt as though goal net fluid balance was achieved most of the time (46.7%) while one-third felt as if goal fluid status was achieved only half of the time (36.7%). One respondent each stated that goals were met either never or always and another 10% of the respondents felt as though goals were not typically met. However, when asked specifically about timeframe following shock resolution, most of the respondents felt as though not enough diuresis was given in the first 24 hours following shock resolution and over 50% felt as though this remained true for a total of 48 hours following shock (Figure 2.5). Further, when specifically asked about the rate of appropriateness in diuresis in patients outside of the acute decompensated heart failure population, 36.7% stated that appropriateness was only achieved half of the time. Another 30% felt as though appropriateness was not typical and 3.3% stated never. The remaining 26.7% stated that they felt

Figure 2.5 Appropriateness of Diuresis Quantity Following Shock Resolution

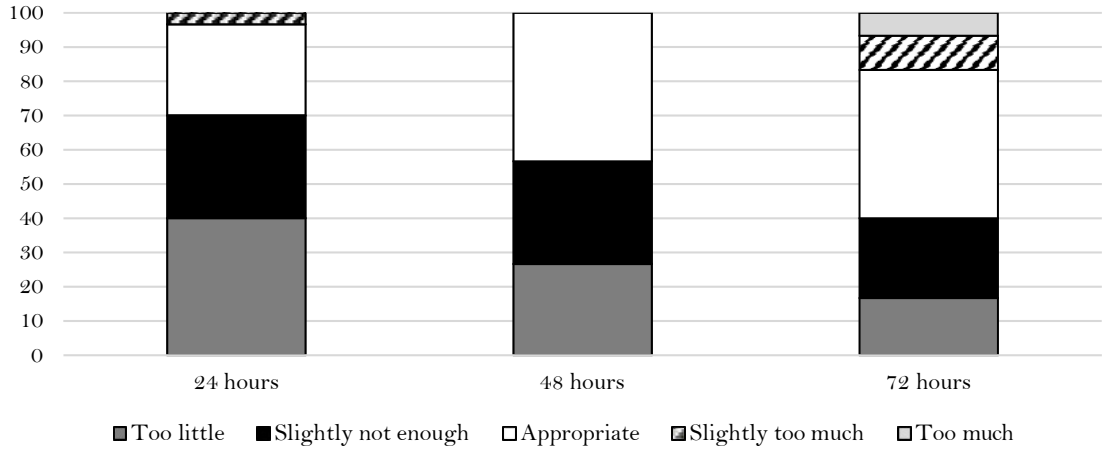
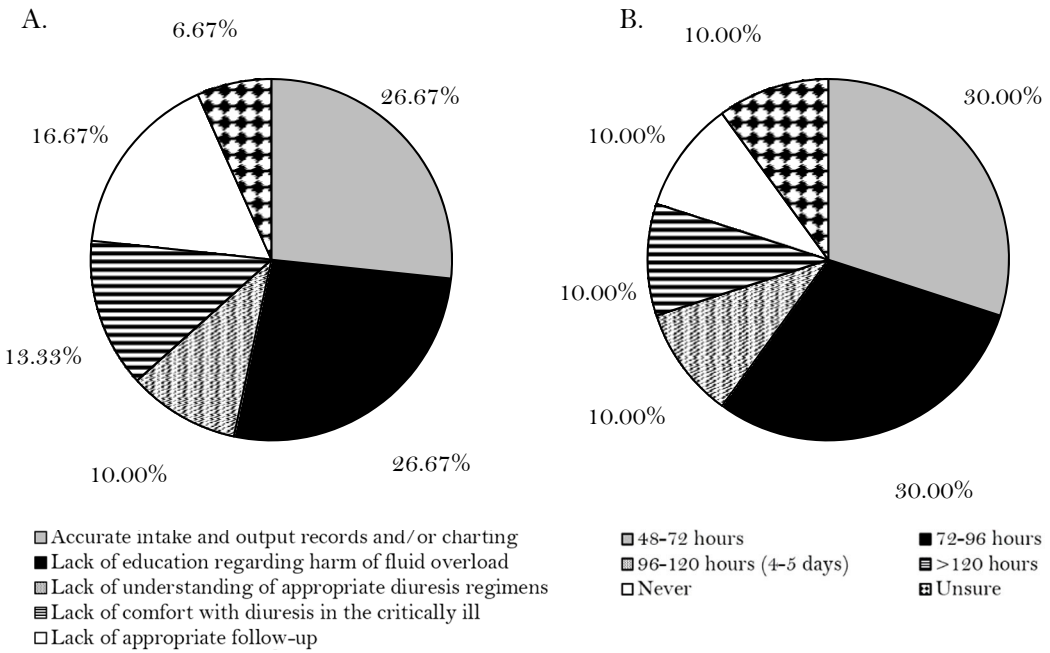


Figure 2.6 Perceptions Surrounding Efficacy of Diuresis



A. Largest perceived barrier to adequate diuresis B. Perception of time in which 50% of ICU population achieves net negative fluid balance

---

diuresis was appropriate most of the time and one individual was unsure (3.3%). The most frequently cited reason for inappropriate diuresis was underdosing (63.3%), followed by incorrect

frequency (40%), incorrect drug (20%), and overdosing (10%). Ten percent of the population felt diuresis was always appropriate while 16.7% were unsure and 3% stated other. When asked, 63.3% of the population felt that if diuresis was performed appropriately then patient outcomes would be improved while another 20% felt outcomes would be significantly approved. The remaining 16.7% felt there would be no difference.

2.4 Discussion

This was the first survey to look at a broad perception of de-resuscitation practices by pharmacists in the general ICU population. This was a diverse cohort, with a wide range in demographic variables as well as patient population and exposure. Most notable is that very few centers had a protocol surrounding de-resuscitation measures and those that did were specific to disease states such as acute kidney injury or acute decompensated heart failure. Further, very limited pharmacy involvement was noted in diuresis initiation; however, pharmacist assistance, when performed, was of a broad variety. A large range of rationale was selected regarding lack of efficacy of diuresis. The population was split with respondents citing lack of comfort with diuresis, lack of understanding of regimens, lack of understanding of fluid overload harms, poor follow-up measurers, or inaccurate intake and output records. All of these areas encompass the fundamental or desirable roles of a critical care pharmacist, including but not limited to collaboration with staff, drug information education, rounding with the multidisciplinary team, and evaluation of all drug therapies. One other desirable role of the clinical pharmacist in the ICU worth considering is the development and implementation of drug therapy protocols to maximize drug therapy benefits. This is a key area in which a pharmacist could assist given the lack of standardized de-resuscitation measures as seen in this cohort. (318) Protocol-driven diuresis has been shown to improve clinical outcomes both regarding diuresis efficacy as well as decreased length of stay. (279) Pharmacy-driven protocols have shown increased rates of target attainment and improved monitoring as well as appropriateness of drug therapy. (327,328,331)

A wide range was also seen in dosing ranges, utilization of adjunctive agents, evaluation

of fluid status, and follow up monitoring. Diuresis appeared to be relatively safe given the limited number of patients in which de-resuscitative measures were discontinued for safety reasons with most patients having appropriate stop times as perceived by the collective group. While discontinuation seemed appropriate, questions surrounding appropriate initiation varied. A high proportion of respondents felt as though not enough diuresis was administered at 24- and 48-hours following shock resolution; however, the respondent group appeared to be confident in achievement rates of fluid goals. This survey's answers highlight two points: the potential for inappropriate fluid balance goals as well as overall confusion regarding the appropriateness of diuresis initiation before the 72 hour mark after shock resolution. Also alarming, survey respondents stated that the most frequent reasons for the initiation of diuresis were signs that fluid overload was already present. These included signs of peripheral or pulmonary edema, positive fluid balance, and difficult wean from mechanical ventilation. A protocolized approach, which would call for inclusion once clinical parameters were met, would assist in timing of protocol initiation to avoid waiting for signs of fluid overload and therefore potentially optimizing patient clinical outcomes such as weaning from mechanical ventilation.

In conclusion, a wide variability was seen in diuresis practices in this cohort. This survey was limited in sample size; however, it was noted that few of the responding institutions have a standardized approach to de-resuscitation and limited pharmacy involvement was noted. The development of a standardized approach is a prime opportunity for the inclusion of clinical pharmacists given the alignment with standard pharmacy roles in the critically ill population.

CHAPTER 3. PROPOSAL FOR FUNDING SUPPORT FOR EVALUATION OF THE EFFECTIVENESS OF PHARMACIST-DRIVEN DIURESIS IN THE INTENSIVE CARE UNIT

This chapter provides rationale and aims to support receipt of investigator-driven funding from the American Society of Health System Pharmacists Foundation 2018 New Investigator Grant. This grant is awarded to new pharmacist investigators to provide funding for specific practice-based research related to advancing pharmacy practice initiatives in hospitals and health systems and are not intended for long-term support of research programs. The goal of this foundation is to support quality research for the advancement of pharmacy practice while developing the research skills of new investigators while also fostering mentorship relationships with senior investigative partners. (347)

3.1 Specific Aims and Hypothesis

A positive fluid balance is associated with worsened outcomes in the ICU, including increased mortality and length of stay. Despite recent studies demonstrating detrimental effects of fluid administration, fluid overload remains prevalent within the ICU. Recently, a shift in approach has started emphasizing de-resuscitation after hemodynamic stability with diuresis. However, diuresis is often ineffective in many institutions, due to a lack of standardization in identification of fluid-overloaded patients, adequate treatment regimens, dysregulated follow-up for effectiveness, and concern for adverse events. Pharmacist-driven protocols have proven to benefit both clinical and therapeutic outcomes in previous cohorts. A pharmacist-driven diuresis protocol implemented in the medical ICU has the potential to optimize clinical- and cost-effectiveness, and safety. In line with the Practice Advancement Initiative's optimal pharmacy practice model recommendations from the American Society of Health-System Pharmacists, a pharmacist-managed diuretic protocol has the ability to advance the pharmacist's role through development of a specific pharmacist-driven order set designed to support pharmacy resources conducted through an existing pharmacist authority policy. Such a protocol may also prevent

adverse events through daily medication review and dose adjustments secondary to monitoring of patient response while placing pharmacist accountability on medication-related outcomes, such as reduction of hospital costs by decreasing ICU resource utilization.

Our objective is to improve patient care via the implementation of a pharmacist-driven diuretic protocol in the medical ICU population and to evaluate the impact on fluid balance 72 hours following hemodynamic stability within ICU stay, as compared to standard of care. We also seek to determine whether the achievement of a net negative fluid status is associated with a decreased duration of mechanical ventilation without an increase in adverse events.

Specific Aim 1: To determine whether a pharmacist-managed diuresis protocol significantly decreases net fluid balance 72 hours following resolution of shock in medically critically ill patients.

Hypothesis 1: A pharmacist-managed diuresis protocol will result in a lower cumulative fluid balance 72 hours after shock resolution, defined as freedom from vasopressor support or bolus crystalloid administration for at least 12 hours, in medically critically ill patients.

Specific Aim 2: To assess the impact of a pharmacist-managed diuresis protocol on mechanical ventilation days in medically critically ill patients.

Hypothesis 2: Patients receiving protocolized pharmacist-managed diuresis will have an increase in ventilator-free days at 28 days, defined as the number of days from day 1 to day 28 in which a patient was able to breathe without assistance.

Specific Aim 3: To address the safety of a pharmacist-managed generalized diuresis protocol via rates of adverse events.

Hypothesis 3: A pharmacist-managed diuresis protocol when compared to standard care will have a similar rate of adverse events, defined as incidence of acute kidney injury (serum creatinine 1.5 times baseline serum creatinine, serum creatinine increase of at least 0.3 mg/dL, or

urine output <0.5 mL/kg/hr for at least 6 hours) and/or the incidence of a severe metabolic disturbance (potassium <3 mmol/L, sodium >150 mmol/L, or bicarbonate >40 mmol/L with a pH <7.3). (117)

3.2 Rationale and Significance

Intravenous fluids remain the hallmark of initial resuscitation in the critically ill. National guidelines recommend aggressive fluid resuscitation in the first 24 hours of ICU stay, however, excess volume receipt during and following the initial shock stabilization phase can be detrimental. (4) Ideally, patients presenting in shock will have an appropriate resolution of capillary leakage and restoration of microcirculatory blood flow at 72 hours, but patients frequently fail to successfully achieve 72 hour resolution, resulting in what some authors refer to as the Global Increased Permeability Syndrome (GIPS). (46) GIPS is an ICU phenomenon characterized by high capillary leak, excess interstitial fluid, and polycompartment syndrome. (288) For these individuals, fluid exposure increases edema impeding capillary blood flow and oxygen diffusion, resulting in decreased organ perfusion pressure and increased potential for organ failure. (348, 349) The edema incurred by overzealous fluid administration increases risk of acute kidney injury, may cause pulmonary edema, and may prolong the need for mechanical ventilator support in critically ill patients admitted to the ICU. (350)

Despite the known consequences of fluid overload, fluid administration in excess continues to remain common practice. Over one-third of patients resuscitated by standard care are fluid overloaded after 24 hours. (210) Fluid overload has been associated with increased ventilator days, mortality and length of stay in the ICU. A large positive fluid balance after the first 48 hours of ICU stay has been reported to be an independent predictor of death (HR 1.10, 95% CI 1.0007-1.022 per mL/kg increase). (351) A recent meta-analysis showed decreased ICU mortality with a negative fluid balance compared to a net positive balance (HR 0.25, 95% CI 0.32-0.55). (46) To further support these findings, an observational cohort study demonstrated that survivors of sepsis had a more negative fluid balance by days 3 and 7 of ICU admission when

compared to non-survivors, regardless of whether they originally presented in shock. (65) Even more alarming, despite a growing amount of disputing literature and protests from the scientific community, a recent mandate from the Centers for Medicare and Medicaid Services (SEP-1) will soon recommend that all patients presenting in sepsis, one of the most common diagnoses for ICU admission, receive a minimum fluid bolus of 30 mL/kg, further increasing the risk for volume overload in this population. (352-354) Our preliminary work in a 4-month prospective observational study of 426 patients in our medical ICU confirmed a daily positive fluid positive balance through ICU day 7 (+1.45 L ± 7L), with only 15 percent of patients receiving diuresis within the first 7 days in the medical ICU. (212) The standard of care, like many institutions, is that the initiation of diuresis therapy begins at clinician discretion.

Protocols for diuresis in a broad medical ICU population have not been extensively studied. A protocolized management diuresis strategy in the heart failure population resulted in significant volume status improvement with marked weight loss without an increase in kidney failure or mortality. (355) However, the most extensive and robust data evaluating a conservative fluid management protocol in critically ill patients focused on patients with acute lung injury or acute respiratory distress syndrome. This protocol reduced ventilator dependent days (12.1 ± 0.5 vs 14.6 ± 0.5 days, $p<0.0001$) and increased ICU-free days (13.4 ± 0.4 vs 11.2 ± 0.4 days, $p<0.001$) without increasing the risk for adverse events. (72) Despite positive results, limitations of this protocol that preclude broad implementation include reliance on invasive hemodynamic monitoring with the use of central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP), parameters no longer commonly used nor recommended in current practice. (4)

The benefits of inpatient clinical pharmacy services, particularly in the ICU, have been described in the literature. These include a reduction in adverse drug events and medication errors, decreased drug costs, facilitation of timely drug administration, and improvement in protocol compliance during medical emergencies. (356) Pharmacist-driven protocols, specifically, within other therapeutic areas have increased appropriateness of medication administration while

increasing rates and timeliness of goal attainment. To date, the impact of a pharmacist-driven diuresis protocol has not been evaluated. A pharmacy-guided protocol for diuretic administration in the ICU has the potential to increase achievement of net negative fluid balance and decrease duration of mechanical ventilation and ICU length of stay. In accordance with the Practice Advancement Initiative recommendations for optimal pharmacy practice models, a pharmacist-managed diuretic protocol will: 1) improve patient care by optimizing fluid balance, 2) advance the clinical pharmacist role, and 3) reduce hospital costs by decreasing per patient ICU resource utilization.

The goal of this research will be to demonstrate the value of pharmacist intervention on fluid balance and duration of mechanical ventilation. This research will lay the framework for a larger multi-center study, and provide preliminary data for a competitive NIH application, specifically a K23 Mentored Patient-Oriented Research Career Development Award (K23; PA-18-375), focused on supporting those with a clinical doctoral degree who are committed to focus their research endeavors on patient-oriented research, or the AHRQ Health Services Research Demonstration and Dissemination Grant (R18; PA-13-046), focused on improvement of health care quality and safety via Patient Center Outcomes Research.

3.3 Innovation

This study is the first of its kind to provide pharmacist-managed diuresis to patients admitted to a medical ICU. Previous studies of diuresis in the ICU have been limited to acute respiratory distress or acute lung injury patients. (72) As the body of evidence builds suggesting the consequences of volume overload are not limited only to lung injured patients, we plan to provide this potentially lifesaving intervention to all eligible patients in our medical ICU.

This study will advance pharmacy practice by allowing pharmacists to practice on a multidisciplinary healthcare team, with interdisciplinary support under a pharmacist authority policy. The results of this study will 1) establish a standardized protocol for diuresis after

shock resolution, 2) elevate the pharmacist role in management of diuresis, and 3) improve outcomes for patients admitted to our medical ICU.

3.4 Investigators and Environment

This proposal is feasible as the research setting is the University of Kentucky Hospital, a 900-bed specialty referral academic medical center. The intervention will be applied in our medical ICU, which cares for over 2,400 patients a year, with a steady yearly increase of 9% (internal data), of which 1,872 (78%) are intubated and eligible for our study. Our institution cares for very critically ill patients; our case-mix index is in the 84th percentile as compared to other academic medical centers.[19]

The Medical ICU at this center includes three separate medical ICU rounding teams and units (designated Pulmonary 1-3). Pulmonary 1-2 are traditional teaching teams, compromised of medical residents, a pulmonary fellow, a clinical pharmacist, all rotating monthly, in addition to an attending physician. Pulmonary 3 is an advanced practice practitioner (APP) driven service, consisting of two APPs or physician assistants, a clinical pharmacist, and an attending physician. Clinical pharmacists are vital members of the medical ICU multidisciplinary healthcare team and attend morning rounds in all units. Patients are admitted to each unit on the basis of open beds and nursing placement, with equal acuity and standards of care across all teams. The assembled research team includes a group of highly capable clinicians for this project. The mentor, Peter E. Morris, MD, an R01-funded investigator, is the Chief of Pulmonary, Critical Care and Sleep Medicine at the University of Kentucky. Three of the full-time Medical ICU clinical pharmacists (Bissell, Flannery, and Bastin) working on this project are current PhD candidates in Clinical and Translational Science. All four Medical ICU pharmacists are board certified, with one holding double board certifications and three holding critical care board certifications through the Board of Pharmacotherapy Specialties. Additional members of our research team include medical ICU advanced practice providers, a biostatistician, nursing administration, and additional board

certified critical care pharmacists, creating a group that is well-poised to carry out this research. This medical ICU-based research team has previously collaborated on outcomes-based research and pharmacy-led protocols. This includes most recently the implementation of novel sedation protocols and a pilot study evaluating clinical outcomes of a diluent change from 0.9% sodium chloride to 5% dextrose. (212, 357) This pilot study enrolled over 400 patients in a 4-month period and received a Society of Critical Care Medicine Star Research Achievement Award, awarded to the top 64 abstracts across all international submissions at the society's annual meeting. The diuresis protocol itself has been developed with medical ICU and nephrology physicians, along with pharmacy and ICU nursing leadership, and will be carried out via the pharmacist authority policy currently in place at our institution.

The current pharmacist authority policy within our institution allows for physician requests for pharmacotherapy evaluations via verbal communication or "Pharmacy to Dose (PTD)" orders within the electronic medical record (EMR). This policy awards the clinical pharmacist the authority to order and adjust medications as well as pertinent laboratory analyses. Specific guidelines exist for anti-infectives and medications with therapeutic drug monitoring, such as antiepileptic medications and anticoagulation, but PTD orders can be placed for any medication, both formulary and non-formulary. Per pharmacy policy, the pharmacist is responsible for providing appropriate and cost-effective pharmacotherapy recommendations. Daily patient-specific medication review will be performed by the primary pharmacist. The pharmacist is responsible for monitoring patient response to medication therapy and making suggestions to the team related to adjustment of doses or regimens. Clinical pharmacists who had documented competency have the authority to manage assigned patient's pharmacotherapy through monitoring and adjustment of regimens to meet defined therapeutic goals. Regarding PTD orders, any physician may request a pharmacist to provide therapeutic dosing or monitoring services for any specified medication. Such a request may be made by submitting a pharmacy to dose (PTD) order in Sunrise Clinical Manager (SCM) or by giving a verbal order

Table 3.1 Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
≥18 years old admitted to the pilot MICU	Comfort care decision to limit support or imminent death, as decided by MICU team
Non-pregnant via serum hCG	Anuric (zero urine output for at least 12 hours)
Receiving mechanical ventilation with net –positive or net-even fluid balance or signs of fluid overload on chest x-ray or physical exam	Nephrology consult for acute renal failure, defined as ≤0.3 mL/kg/hr urine output for at least 12 hours, serum creatinine (SCr) 3 times baseline, a SCr ≥4, or receipt of renal replacement therapy
No vasopressor administration or bolus crystalloid administration within 12 hours, unless cardiogenic shock or norepinephrine <0.05 mcg/kg/min	Acute treatment of any of the following: 1. Diabetic ketoacidosis/Hyperosmolar hyperglycemic state 2. Rhabdomyolysis with a creatine kinase level >5000 units/liter 3. Suspected hepatorenal syndrome

entered on his/her behalf. Such requests by the physician will result in the pharmacist being authorized to write orders for the initial drug dose, laboratory tests relevant to monitoring the drug, or subsequent orders for dosing adjustments as deemed appropriate by the pharmacist.

3.5 Approach

To accomplish these aims, we will implement a sequential period pilot study to evaluate a unit level change in diuresis practice. The protocol (Appendix Two) will be piloted in one of the three medical ICUs, Pulmonary 3, beginning June 1, 2018. This unit was chosen over Pulmonary 1-2 service lines given the established clinical pharmacist-APP relationship and increased continuity within this unit as APPs do not rotate outside of the medical ICU. Patients admitted to the pilot unit receiving mechanical ventilation with a net-positive ICU fluid balance, net-even fluid balance, or signs of fluid overload determined via chest x-ray or physical exam will be included. Patient identification will occur by the clinical pharmacist, in collaboration with the medical team. Inclusion and exclusion criteria are summarized in Table 3.1.

Protocol implementation will occur in the pilot unit, with the clinical pharmacist recommending diuresis based on patient-specific factors: 1) net fluid balance, 2) urine output 3) hemodynamic stability, and 4) metabolic parameters. The other two medical ICUs will maintain

current standard of care, which is diuresis at physician discretion. The pharmacist within both groups will also assist in management of electrolyte abnormalities per the medical ICU electrolyte replacement protocol already established at this institution. The comparator group (Standard Therapy) will be compromised of a retrospective cohort in which we will include all admissions to the medical ICU between June 1, 2016 through December 31, 2016 meeting the above criteria and compared to those patients receiving protocol (Diuresis Protocol).

This protocol will allow for pharmacist guidance in the administration of diuretics based on urine output and daily net fluid status in those patients receiving mechanical ventilation within the medical ICU. After identification of appropriate patients for inclusion during interdisciplinary rounds, pharmacists will establish appropriate urine output goals and initial diuretic dosing. Initial dosing will be based on estimated renal function via glomerular filtration rate (GFR) or previous doses received. Basic metabolic panels will be collected every 6 hours while on protocol and a Foley catheter or external catheter in addition to electrolyte replacement orders will be required concomitantly. The clinical pharmacist will utilize laboratory results, hemodynamic parameters (heart rate, mean arterial pressure), and urine output to titrate diuretic dosing. Pharmacists will utilize an order set within the electronic medical record to allow for nursing assessments and further titration of diuretics overnight while clinical pharmacists are not available for continuity of care (Appendix Three). APPs covering the medical ICU overnight will also be notified of protocol enrollment to avoid duplicate diuresis orders.

This protocol will use a furosemide bolus dosing strategy. Furosemide inhibits reabsorption of sodium and chloride in the ascending loop of Henle and proximal and distal renal tubules, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium. (358) Other available loop diuretics at our institution include bumetanide and torsemide. Given the lack of advantage of bumetanide over furosemide and limited routes of administration for torsemide (oral formulations only), no other loop diuretics aside from furosemide will be administered during this study (unless

equipotent doses of another loop diuretic are required for furosemide sensitivity and/or medication shortage). (359)

Combination diuretic therapy will be considered once the maximum dose of furosemide is reached (200 mg IV) without response, and/or concern for hypernatremia is present, defined as a sodium greater than 145 mmol/L. Available options include: 1) Metolazone 10 mg oral and 2) Chlorothiazide 500 mg IV in instances when no enteral access is available.

Indications for continuous infusion diuresis will include: 1) Lack of response to bolus dose of 200 mg or 2) Lack of sustained diuretic response between dosing intervals, as evidenced by an initial response followed by a decrease in hourly urine output resulting in failure to achieve goal fluid balance. Continuous infusions will be started at 10mg/hr and titrated by 5mg/hr every 30 minutes to goal hourly fluid balance.

Clinical pharmacy specialists within our institution are available from 7 am to 10 pm within the medical ICU. In order to ensure appropriate management between the hours of 10 pm and 7 am, an order set has been created requiring nursing evaluation of urine output at the designated intervals and conditional medication orders based on individual patient response and pharmacist-driven goal parameters. Diuresis hold parameters will also be placed to guarantee safety monitoring outside of clinical pharmacy hours. The pilot ICU has registered nurses designated as research nursing champions who will facilitate the nursing education for the protocol implementation as well as monitoring of adherence to protocol and overall compliance. Bedside nurses in this unit are familiar with research procedures similar to this one, including sedation and analgesia, diabetic ketoacidosis, and anticoagulation. Attending physician education will occur via the clinical pharmacy team in collaboration with the Chief of Pulmonary and Critical Care Medicine. Following implementation of the protocol, clinical pharmacists on all teams will prospectively monitor fluid status and clinical outcomes throughout the ICU stay of patients in the pilot group. Data points are summarized in Table 3.2.

Table 3.2 Data Collection Points

Data Point	Baseline	Hourly	24h	48h	72h	Discharge
Demographics	×					
KDIGO class(117)	×		×	×	×	×
Nephrotoxin use	×		×	×	×	
Electrolyte/labs	×		×	×	×	
Diuretic doses	×				×	
Fluid intake	×		×	×	×	
Urine output	×	×	×	×	×	
RRT Use			×	×	×	×
ICU Length of Stay						×
Hospital Length of Stay						×
Mortality						×

Demographics include age, gender, race, APACHE II score, Vizient mortality risk score, SOFA score, Elixhauser Comorbidity Index, and Charlson Comorbidity Index. Nephrotoxins include intravenous contrast, calcineurin inhibitors, aminoglycosides, amphotericin B, beta-lactam antibiotics, foscarnet, sulfamethoxazole/trimethoprim, ganciclovir, acyclovir, and vancomycin.

The primary outcome of this study will be the net fluid balance 72 hours following resolution of shock, defined as freedom from vasopressor administration or bolus crystalloid administration for at least 12 hours. Secondary outcomes collected will include ICU mortality, ICU length of stay, hospital length of stay, and ventilator-free days (defined as the number of days from day 1 to day 28 in which a patient was able to breathe without assistance). Additional safety outcomes will include incidence of acute kidney injury (defined by KDIGO criteria: serum creatinine 1.5 times serum creatinine prior to diuresis initiation, serum creatinine increase of at least 0.3 mg/dL, or urine output <0.5 mL/kg/hr for at least 6 hours) and the incidence of a severe metabolic disturbance including hypokalemia, hypernatremia, or a new metabolic alkalosis, defined as a potassium <3 mmol/L, sodium >150 mmol/L, or bicarbonate >40 mmol/L with a pH of <7.30, respectively. (117)

3.6 Data Management

Retrospective data will be pulled from the University of Kentucky Medical Center Allscripts based EMR, Sunrise Clinical Manager. This EMR has specific documentation standards which providers uphold and electronic triggers to fill in missing data points. The unit-based quality improvement leadership nurse and coders periodically monitor the daily documentation by the medical team, and errors or omissions are identified. The data is then extracted from the EMR by the UKMC data analytic group.

Data is stored within the Center for Health Services Research/UKMC data management system, which has several quality checks to ensure accuracy. Data extraction analysts ensure data quality and integrity and built-in validation rules ensure reliability. The data are checked for trends, unexpected deviations from previously recorded data and missing data, which then alerts the data analyst for investigation. Subjective data points such as coding and clinical indication are approximately 95% accurate.

Data for the pilot group will be collected prospectively after patient enrollment into the study. A case report form will be created for each patient. The study data will be stored on the REDCap server. (360) REDCap is an encrypted, password protected, online data server (Appendix Four). Only members of the research team will have access to the data, and all protected heath information will be de-identified once a study number is assigned to the patient. The data obtained for this study will be reliable, accurate and safely stored.

3.7 Statistical Analysis

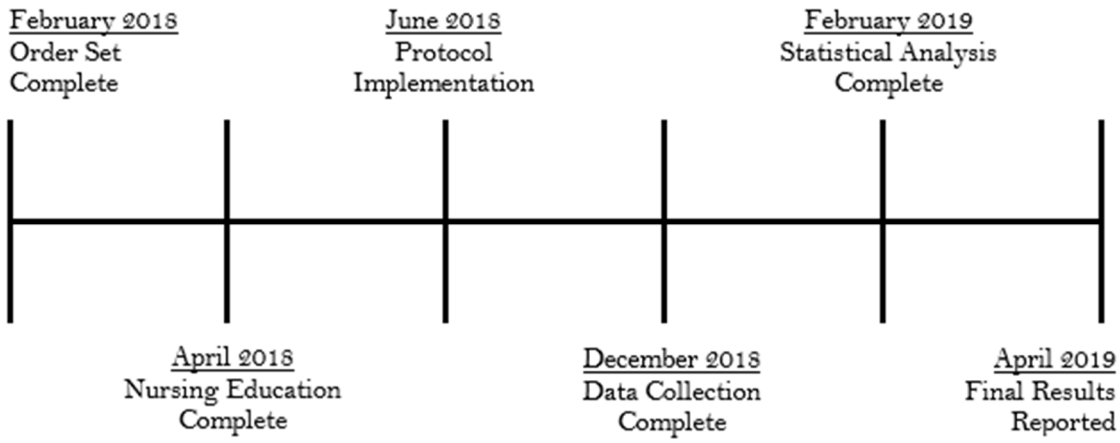
The research team's biostatistician will analyze the data. From our previous study of diluent change in the medical ICU, the average fluid balance in our patients at 72 hours is positive 2.4 ± 5.1 liters (internal data). Based on this figure, we calculate a sample size of 104 patients in each cohort to achieve a decrease in net fluid balance at 72 hours by at least 2 liters, maintaining an 80% power and an alpha of 0.05. On average, patients remain 1.45 liters net positive after the

first week of ICU stay and only 15% receive any type of diuretic within the first 7 days in the intensive care unit. Fluid intake and continuous outcomes will be tested for normality and will be evaluated via t-test or Mann-Whitney U, as appropriate. Chi-square will be utilized for categorical variables and baseline demographics. Protocol-receiving and standard care groups will be matched utilizing end distance matching on parameters including: the net fluid balance of the length of stay prior to furosemide start, the most recent serum creatinine prior to furosemide administration, time from mechanical ventilation to initiation of furosemide (assuming the first record available for those arriving on mechanical ventilation), patient intake source, history of chronic obstructive pulmonary disease (COPD) or pulmonary hypertension, age, use of vasoactive therapy prior to furosemide start, gender, Sequential Organ Failure Assessment score, and diagnosis-related group (DRG) weight, as characterized by the Center for Medicare and Medicaid Services. The primary aim will be evaluated by utilizing multivariable linear regression to account for potential confounders.

3.8 Human Subjects Inclusiveness and Privacy

This study protocol has been approved through the institutional review board at the University of Kentucky. This study presents no more than minimal risk as it is an observational study of a quality improvement initiative within the institution. Legal ramifications of information dissemination will be less than minimal secondary to protection of personal health information PHI) by the members of the research group in a manner conducive with the University of Kentucky and Office of Research Integrity (i.e. compliance with the Health Insurance Portability and Accountability Act). Information will not be removed from the Medical Center in the form of paper or electronic media nor transmitted to non-study personnel. A master list of medical record numbers and assigned IDs will be retained on the password protected computer of the primary investigator in a locked office. All other information will be stored electronically as de-identified data. Patients will not be excluded on the basis of gender, race, or ethnicity. Prisoners will not be excluded as this research is intended to include a broad population and will only incidentally

Figure 3.1 Proposed Study Timeline



include members of this population. Pregnant women and children are not routinely treated within our medical ICU, therefore their inclusion will not be applicable.

3.9 Scope and Timeline

Institutional Review Board approval has been obtained for this study. Additionally, the protocol has been vetted through several members of the medical ICU team, including the Chief of Pulmonary and Critical Care, additional attending physicians, APPs, nursing administration, the information technology (IT) clinical decision support committee, and the clinical pharmacy group. An order set for the institution's electronic medical record has been constructed and is currently under approval for EMR integration by IT administration. With an estimated 200 monthly admissions to the medical ICU who will be applicable for inclusion into this study based on current monthly reports, the timeline is feasible (Figure 3.1).

3.10 Potential Pitfalls

Although highly unlikely, we may see slow enrollment for our prospective data collection. As stated prior, our MICU treats over 200 patients a month, for an average of approximately 2,400 patients/year. Thus, it is highly unlikely we will struggle with slow enrollment. If this were to happen, we would implement this protocol and collect prospective data in other units of our

medical ICU. Additionally, we could extend the data collection period beyond the initial proposed 6 months. Further, given that this study follows a pre-post methodology, there is the potential for confounders and between-group differences affecting interpretation of the final results. For this reason, an end distance matching approach was utilized, matching for multiple parameters that may be potential influencers of fluid balance. Further, joint models of longitudinal and survival data as well as competing risks regression analyses will be utilized for evaluating of secondary outcomes, as appropriate. External generalizability may be decreased given demographic differences. The predominant racial class in the state of enrollment is Caucasian. Racial differences may occur in drug response, however such should be accounted for via the utilization of baseline estimated glomerular fraction. The Modification of Diet in Renal Disease equation (MDRD) is an equation which estimates baseline renal function and includes a race coefficient that raises the calculated eGFR in all Blacks by approximately 21% compared with non-Black persons with the same serum creatinine, age, and sex. (361) Finally, the lack of control group in this prospective trial could contribute to regression toward the mean. It is possible that any changes which may be seen are secondary to chance rather than the treatment itself secondary to awareness and evaluation of volume status in a prospective manner. To prevent this limitation, chosen outcomes measures are objective and will still be recorded retrospectively, meaning chart review will still be utilized even in the prospective group for accuracy. Further, clinical data will be verified by the data analyst for both groups as well as a secondary analyst.

CHAPTER 4. EFFECTIVENESS OF PHARMACIST-DRIVEN DIURESIS IN THE INTENSIVE CARE UNIT INTERIM ANALYSIS

This chapter provides the results of an interim analysis proposed by the doctoral degree advisory committee after successful completion of the qualifying examination, with further request for protocol expansion pending safety results. The independent statistical committee (ISC) and clinical investigators involved in this study opted for an interim analysis with potential for sequential adaption given the paucity of generalizable protocols to the broad critically ill population. Such would allow for re-evaluation of the protocol at the pre-specified time point and allow optimization of relevant therapeutic or monitoring standards with continuation of its use. A data monitoring committee (DMC) was formed, consisting of the chair of the doctoral advisory committee, ISC, and non-committee ICU physicians, pharmacists, and nursing services. After 50% of chronologic study completion, 6 months from study initiation, the ISC performed data extraction and statistical analyses which was brought forward to the DMC. The statistical analyses of the trial remained blinded to the DMC. As the protocol initiation pilot was a quality improvement initiative within the institution, stopping rules were not defined and clinical expertise regarding protocol stop, continuation, modification, and expansion was requested.

4.1 Protocol Assessment and Adherence

After a six month period following protocol implementation, data was extracted from the trial database as well as the electronic medical record and analyzed by the designated study statisticians. Upon extraction, it was found that a total of 139 patients met inclusion criteria. Of these patients, 109 were excluded, most commonly for ongoing vasopressor support or fluid resuscitation for shock (29%), for an active nephrology consult guiding continuous renal replacement or specific diuretic recommendations in the setting of hepatorenal syndrome and/or acute kidney injury (28%), for treatment of rhabdomyolysis (21%), or secondary to intubation solely perioperatively with an excepted ventilator duration of <48 hours (17%). Patients were

Table 4.1 Baseline Characteristics for Selected Matching Variables

	Standard Therapy (n=63)	Diuresis Protocol (n=21)
Mean Net Fluid Balance (mL)	2508	2493
Pressors prior to Furosemide	50.8%	47.6%
Mean Time MV prior to Furosemide (hours)	36.01	36.47
Mean DRG Weight	5.73	5.95
Mean Age (years)	57.6	57.6
Mean Prior SCr (mg/dL)	1.06	1.12
Mean SOFA Score	7.71	7.67
History of COPD	23.8%	19.0%
From Emergency Department (ED)	20.6%	19.0%
From Outside Hospital	31.7%	42.9%
From Outside Hospital via ED	23.8%	19.0%
From Other Intensive Care Unit	1.6%	0.0%
Other Admission Source	22.2%	19.0%
Male Gender	54.0%	57.1%

additionally excluded given terminal care or withdrawal of life sustaining support (3%) or treatment of diabetic ketoacidosis or diabetic hyperglycemic hyperosmolar syndrome.

The most frequent reason for admission in those patients in the diuresis protocol group (n=30) was primarily secondary to respiratory failure, with 41% of the cohort admitted for this indication. Septic shock was the second highest admission reason, accounting for 20% of the ICU admissions with altered mental status and acute kidney injury rounding off the most frequent reasons for admission with 11% and 7%, respectively. In the protocol group, 26.7% had been on furosemide as an outpatient and 43.3% had received furosemide at least once during the hospital stay prior to the initiation of the study protocol. Hours since shock resolution were also collected for those patients receiving the diuresis protocol. Almost half of patients, 46.7%, were non-applicable, given no vasoactive therapy was received during the admission. Another 43% received the protocol 12 hours from the completion of hemodynamic support and 13% received less than 12 hours from achievement of hemodynamic stability, despite protocol inclusion criteria. A total

Table 4.2 Selected Clinical Outcomes of Interim Population

	Standard Therapy (n=63)	Diuresis Protocol (n=21)
72 Hour Fluid Balance (mL)	+139	-1739
Mean Ventilator Days	9.25	8.43
Median Ventilator Days	8	7
Mean ICU Days	9.81	9.34
Median ICU Days	8.10	7.76
Mean Ventilator Free Days ± SD	15.10 ± 9.54	18.71 ± 5.54
Median Ventilator Free Days	20	21
Range Ventilator Free Days	0-26	0-24
Mean ICU Free Days	14.16 ± 9.11	17.57 ± 5.25
Median ICU Free Days	16	20
Range ICU Free Days	0-26	0-23
In-Hospital Mortality	22.2%	4.8%
72 Hour Fluid Balance (mL)	+139	-1739
Mean Vent Days	9.25	8.43
Any Adverse Event	33.3%	38.1%
Acute Kidney Injury	23.8%	28.6%
Hypokalemia	0%	0%
Hypernatremia	14.3%	14.3%
Metabolic alkalosis	1.6%	0%

of 18 protocol violations were noted in the protocol-receiving group, 10 of which were secondary to a change in furosemide dosing frequency. Furosemide was inappropriately held in 2 instances, while one incorrect administration based on safety goals met, and 5 patients had a noted deviation without a documented rationale. In the majority of patients, n=28, there was at least one hold of furosemide during protocol administration with 80% appropriateness based on protocol. The majority of holds (66.7%) were performed as daily fluid balance goal had been met or mechanical ventilation was discontinued, or both. Pertinent safety holds included: rise in serum creatinine (7.1%), excessive urine output (9.5%), elevated serum sodium (2.4%), mean arterial pressure < 65 mmHg (19.1%), increase in heart rate (21.4%), and the others for unknown reason (14.3%).

4.2 Results of the Interim Analysis

Baseline matching criteria are listed in Table 4.1 Due to incomplete coding at time of evaluation, the total number included from diuresis protocol group for between-group comparison in the interim analysis was narrowed to 21. Tests of significance were not performed given lack of sample size attainment, however the DMC found the groups to be well matched based on clinical experience. Notably, both groups had over half of patients admitted as transfers from outside hospitals.

For the primary outcome of 72 hour fluid balance, patients receiving the diuresis protocol were on average 1878 mL more net negative on day 3 compared to those receiving standard care (Table 4.2). Clinical outcomes, including ventilator days, ICU length of stay, ventilator-free days, and ICU-free days appeared similar between groups. The only notable difference between groups was a higher rate of mortality in the control group, potentially secondary to chance given the early analysis relative to anticipated study duration. For safety outcomes, less than 5 percent difference was seen in any occurrence between groups. Acute kidney injury was slightly more frequent in the protocol group and the control arm had a higher incidence of metabolic alkalosis while receiving furosemide therapy.

4.3 Protocol Modification and Rationale

Upon interim analysis and completion of statistical analysis per request of the doctoral committee, the DMC was asked to evaluate the data accumulated while also providing decisions regarding protocol dosing and monitoring parameters while evaluating overall safety. Decisions regarding protocol modification were made by majority vote upon group discussion (Appendix Five) and brought to the primary investigator. Protocol revisions were approved by the Institutional Review Board, institutional nursing practice council. Subsequent education was completed for physicians, advanced practice providers, nurses, and pharmacy personnel prior to implementation, one month following the completion of interim analysis. All attending physicians

in the respective ICUs were permitted time for feedback and suggestion before final execution of protocol change.

4.3.1 Standardization of Monitoring Parameter Frequency

Upon survey of the pilot nursing unit, registered nursing personnel expressed frequent misunderstanding of target urine output goal and the first urine output assessment at 2 hours. The electronic medical record at this institution auto-calculates 8-hour shift fluid balances, including net input, net output, and net volume status for the 8 hours, computed at the hours of 00:00, 08:00, and 16:00 per day. In order to rid the protocol of potential error in urine output calculation and/or evaluations, the committee modified the hourly urine output goal to become an 8-hour shift fluid balance goal, rather than the six hour nursing observation. Further, the additional workload of every 6 hour basic metabolic panels was noted to be a significant addition in time requirements for the nursing staff. Given the lack of clinically important difference in adverse events rates seen within the interim analysis and the relatively constant 24 hour production of serum creatinine in normal physiologic states, the committee further opted to modify the basic metabolic panel collection to an every 8 hour frequency as requested by hospital laboratory administration. (362, 363) The committee still found this uphold a cautious approach as previous trials have utilized daily monitoring of such assessments. (72) Additionally, time to serum creatinine change in the incidence of acute kidney injury has wide patient variability, ranging from 4 to 27 hours based on baseline renal function. (364, 365) As nursing staff within this institution enter the room at a standardized times, 06:00, 14:00, and 22:00, in order to document net intake volume for the shift, the basic metabolic panels were timed in correlation with room entry at these interval points in order to decrease workload. For the initial urine output monitoring at 2 hours, it was deemed that the clinical pharmacist was most frequently the primary medical professional taking responsibility for this follow-up evaluation step in the interim phase, therefore the protocol was modified to reflect such.

4.3.2 Modification of Furosemide Dosing Frequency

When assessing protocol adherence, 55.6% of patients had a protocol violation secondary to a change in furosemide frequency from every 6 hours to every 8 hours, with the population still remaining net negative at 72 hours despite non-adherence. Given the proportion of protocol violations, standardization of aforementioned monitoring parameters, and efficacy of every 8 hour dosing found within those, patients included in the interim analysis, furosemide administration times were standardized to 00:00, 08:00, and 16:00. The standard administration times were selected to further facilitate nursing workflow and to allow for activation of higher doses as applicable in circumstances in which 8-hour shift fluid balance goals were not met. Given that protocol initiation could happen outside of these times, the new protocol's first dose defaulted to STAT-level administration time, with the next dose to follow the schedule above. In circumstances in which there was less than 4 hours (half the dosing interval) between the STAT medication administration and the next scheduled dose, the first administration after the STAT dose would be omitted. Given the wide range of furosemide dosing frequency in the literature, ranging from a continuous infusion to once daily dosing, the committee supported the dosing frequency change.

4.3.3 Modification of Safety Parameters

Protocol furosemide hold rules were two additional sources of uncertainty for nurses. There was a hold for a heart rate percentage increase and a 10 mL/kg/hour urinary output hold parameter. Upon further investigation of the daily maximum heart values, there were 31 instances in which a heart rate met stopping criteria of at least a 25% increase if the difference between minimum heart rate and maximum heart rate was calculated. However the dose was given based on patient clinical stability. In comparison to the 9 patients who received a hold for heart rate in the cohort, none of these patients actually developed hemodynamic instability or a new tachyarrhythmia secondary to this heart rate change. For ease of monitoring and clarification, the committee deemed a heart rate of greater than 150 bpm to be an appropriate stopping parameter

to replace the percentage change rule. Additionally, given the shift away from urine output goals for nursing tasks within the protocol, the committee further simplified the stopping criterion of 10 mL/kg/hour to a daily net volume that exceeded greater than 1 liter negative beyond goal. The net volume status for the 24 hour period is also calculated within the electronic medical record, easing evaluation of the safety parameter.

4.3.4 Expansion of Protocol to Additional Medical Intensive Care Units

Upon analysis of the interim data, the more negative net volume status was deemed to be a clinically important difference by the DMC. Supporting rationale included previous studies demonstrating 1) at least one day of a negative fluid balance, ≤-500 mL, by day three was associated with increased survival, and 2) increased rates of ICU mortality occur with each additional liter of cumulative fluid balance during ICU stay. (59, 60) The committee proposed expansion of the protocol to the other medical ICUs, including the Pulmonary 1 and Pulmonary 2 service lines. Given that attending physicians, nurses, advanced practice providers, and pharmacy equally rotate among ICUs, this expansion was deemed feasible and found to likely benefit achievement of timeline goals. Education was provided, however, to fellow-level physicians, resident-level physicians, and additional nursing staff who had limited presence within the Pulmonary 3 ICU. Expansion was approved by the aforementioned parties and initiated one month following interim analysis completion.

4.3.5 Clarification of Exclusion Parameters

Based on previous clinical trials and clinical experience, the following additions were made to the exclusion criteria per request of the attending ICU physicians: 1) Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, secondary polycythemia, severe pulmonary hypertension (mean PAP > 40 mmHg), or respirator dependency preventing further mechanical ventilation wean and 2) neuromuscular

disease that impairs ability to ventilate spontaneously, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre Syndrome, and myasthenia gravis. (72)

CHAPTER 5. EFFECTIVENESS OF PHARMACIST-DRIVEN DIURESIS IN THE INTENSIVE CARE UNIT

The final chapter provides results for the completion of the study at the end of the study timeline, considerations in the evaluation of these endpoints and the study methodology, and such implications for practice.

5.1 Study Methods

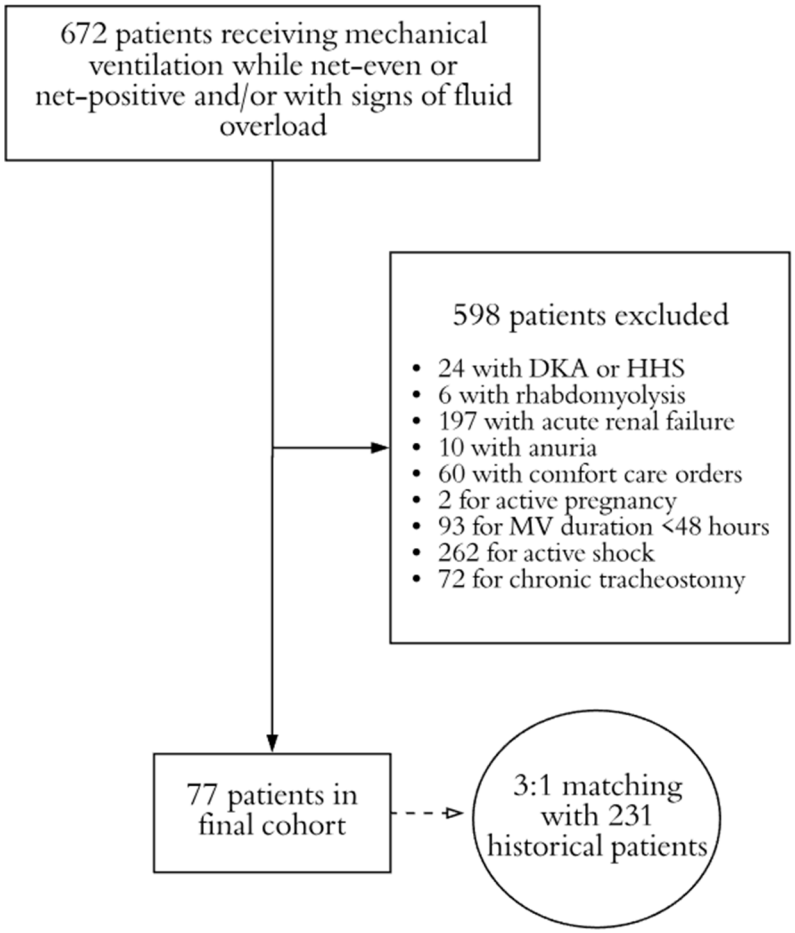
In order to approximate an experimental design using observational electronic medical record data, each protocol patient visit was matched to three patient visits from the pre-protocol time period of January 2016 through December 2017 admission. The same inclusion and exclusion criteria used to enroll patients in the protocol were applied when developing this pre-protocol group of potential control patient visits. Mahalanobis distance matching was used as the similarity measure to assess how similar each patient visit in the control group was to each protocol patient visit. Age, gender, insurance type, home county classification, admission source, DRG weight, SOFA score, baseline creatinine, pre-furosemide fluid balance, time from ventilator to furosemide administration, pre-furosemide vasopressor administration, COPD diagnosis, and ARDS diagnosis were used as matching variables in the distance calculation. Nearest neighbor matching was then used to select the three control visits 'closest' to each protocol visit, based on the distance calculation. This resulted in a control group of patient visits that were balanced with the protocol group on the variables used in the matching algorithm (Table 5.1). Further, we utilized used linear regression analysis to test for an interaction between treatment group and pre- versus post-protocol modification in order to determine whether there was a differential effect on 72 hour fluid balance.

5.2 Study Results

This was a quasi-experimental pre-post single center pilot study of a pharmacist-driven multidisciplinary protocol within the medical intensive care unit overa 12 month period. Within that time frame, 672 met criteria for inclusion, while 598 met exclusions criteria (Figure 5.1).

5.2.1 Baseline Characteristics and Concomitant Therapies

Figure 5.1 Study Flow Diagram



The 77 patients who met criteria for inclusion without an exclusion (Diuresis Protocol) were matched 3:1 from the retrospective cohort (Standard Therapy, n=231) for a total of 308 patients within study. Matching criteria showed no statistically significant difference between groups (Table 5.1). Further, no major difference in other baseline criteria were found with the exception of a higher arterial pH at baseline in the protocol group as well as a higher incidence of rhabdomyolysis upon admission. No difference was demonstrated in the utilization of concomitant nephrotoxic medications between groups for any therapy other than a higher incidence of use of intravenous anti-viral medications in the protocol group compared to the historical cohort

Table 5.1 Baseline Characteristics

	Standard Therapy (n=231)	Diuresis Protocol (n=77)	p-Value
Matching Criteria			
Net Fluid Balance (mL)*	2291 (0-5537)	1784 (-17-4438)	0.199
Vasopressors prior to Furosemide†	106 (45.8)	41 (53.2)	0.263
Time MV prior to Furosemide (hours)*	46.9 (24.2-84.0)	52.3 (30.5-107.4)	0.319
DRG Weight*	5.3 (2.3-6.1)	5.3 (2.4-6.3)	0.414
Age (years)*	59 (48-69)	60 (48-71)	0.564
Prior SCr (mg/dL)*	1 (0.75-1.31)	0.96 (0.77-1.44)	0.685
SOFA Score*	6 (4-8)	5 (4-7)	0.726
History of COPD†	57 (24.6)	21 (27.3)	0.650
From Emergency Department (ED)‡	51 (22.1)	13 (16.9)	0.729
From Outside Hospital‡	80 (34.6)	32 (41.6)	
From Outside Hospital via ED‡	54 (23.4)	20 (25.9)	
From Other Intensive Care Unit‡	5 (2.1)	1 (1.3)	
From floor‡	41 (14.8)	11 (14.3)	
Male Gender†	119 (51.5)	42 (54.6)	0.645
Medicare Payer‡	121 (52.4)	35 (45.5)	0.716
Medicaid Payer‡	78 (33.8)	31 (40.3)	
Commercial Payer‡	25 (10.8)	8 (10.4)	
Self-Pay or Government Payer‡	7 (3.0)	3 (3.9)	
Rural County†	26 (11.3)	9 (11.7)	0.309
Urban Area†	91 (39.4)	23 (29.9)	
Urban Cluster†	114 (49.4)	45 (58.4)	
Past Medical History			
Chronic Kidney Disease†	37 (16.0)	11 (14.3)	0.717
Cirrhosis†	34 (14.7)	7 (9.1)	0.208
Chronic Respiratory Failure†	80 (34.6)	25 (32.5)	0.729
DKA or HHS‡	0 (0)	1 (1.3)	0.250
Hepatorenal Syndrome‡	3 (1.3)	0 (0)	0.420
Pulmonary Hypertension‡	0 (0)	0 (0)	
Renal Transplant‡	0 (0)	0 (0)	
Admission Parameters			
Admission Weight (kilograms [kg])*	89.7 (73.6-104)	88.2 (68-112.3)	0.975

Table 5.1 (continued)

	Standard Therapy (n=231)	Diuresis Protocol (n=77)	p-Value
Admission Height (centimeters)*	170.1 (162.5-177.8)	170.1 (162.5-177.8)	0.678
Rhabdomyolysis‡	0 (0)	8 (10.4)	<0.0001
Acute Respiratory Distress Syndrome‡	13 (5.6)	1 (1.3)	0.202
Pre Furosemide Parameters			
Mean Arterial Pressure (mmHg)*	81 (73-91)	82 (71-91)	0.849
Heart Rate (bpm)*	91 (79-103)	88 (75-102)	0.254
Weight Prior to Furosemide Start (kg)*	91.7 (75-104.4)	88.2 (67.1-113)	0.806
Change in Weight Prior to Furosemide (kg)*	0 (0-7.1)	0 (-3.1-4.9)	0.103
Laboratory Results			
Serum Creatinine*	0.88 (063-1.30)	0.79 (0.65-1.19)	0.259
Blood Urea Nitrogen*	24 (16-36)	25 (14-36)	0.881
pH, Arterial*	7.38 (7.29-7.44)	7.43 (7.39-7.47)	0.002
pH, Venous§	7.37 (0.08)	7.40 (0.07)	0.221
Sodium*	143 (139-145)	142 (140-145)	0.569
Potassium*	4.1. (3.8)	4.1 (3.6-4.4)	0.215
Bicarbonate§	27.2 (6.9)	287 (5.6)	0.268
Chloride§	105.4 (6.0)	105.7 (6.2)	0.731
Albumin§	2.1 (0.6)	1.9 (0.5)	0.091

*Wilcoxon Rank Sum, Median (Interquartile Range); †Chi Square Test; Number (Percentage); Fisher's Exact, Number (Percentage); § Student's T-test, Average (Standard Deviation)

(Table 5.2). The starting dose of furosemide was found to be significantly higher in the protocol group while the total daily doses and cumulative doses were significantly higher in this group. A higher frequency of metolazone and acetazolamide use were found in the protocol group, contrasted to a higher rate of albumin usage in the historical cohort.

5.2.2 Specific Aim 1

For the primary aim which sought to determine whether a pharmacist-managed diuresis protocol significantly decreases net fluid balance 72 hours following resolution of shock in medically critically ill patients, the average mean fluid balance at 72 hours post-shock resolution

Table 5.2 Concomitant Therapies

	Standard Therapy (n=231)	Diuresis Protocol (n=77)	p-Value
Furosemide Dosing Strategy			
Starting Dose (mg)§	41.9 (21.2)	45.7 (15.1)	0.007
Day One Total Daily Dose (mg)*	40 (40-60)	80 (40-120)	<0.0001
Day Two Total Daily Dose (mg)*	0 (0-40)	60 (0-120)	<0.0001
Day Three Total Daily Dose (mg)*	0 (0-20)	0 (0-80)	0.0008
Total Cumulative Dose *	80 (40-200)	240 (120-400)	<0.0001
Adjunctive Agents			
Metolazone†	14 (6.1)	27 (35.1)	<0.0001
Chlorothiazide‡	13 (5.6)	3 (3.9)	0.553
Acetazolamide†	12 (5.2)	10 (13.0)	0.021
Albumin‡	23 (10.0)	2 (2.6)	0.041
Concomitant Nephrotoxins			
Total Nephrotoxin Exposure*	2 (1-3)	2 (1-3)	0.321
Aminoglycoside†	23 (10.0)	7 (9.1)	0.824
Beta-Lactam†	194 (83.9)	65 (84.4)	0.928
Intravenous Antiviral†	10 (4.3)	12 (15.6)	0.001
ACE Inhibitor†	39 (16.9)	12 (15.6)	0.729
Amphotericin B‡	4 (1.7)	3 (3.9)	0.372
Intravenous Bactrim‡	16 (6.9)	3 (3.9)	0.338
Intravenous Vancomycin†	131(56.7)	42 (54.6)	0.740
Initiation of Infusion	28 (12.1)	8 (10.4)	0.682

*Wilcoxon Rank Sum, Median (Interquartile Range); †Chi Square Test; Number (Percentage); ‡Fisher's Exact, Number (Percentage); §Student's T-test, Average (Standard Deviation)

was – 2403 mL in the protocol group and + 765 mL in the standard therapy cohort, a difference found to be statistically significant (Table 5.3). There was also a significant difference in 24- and 48-hour volumes in the protocol group. Further, a test of interaction was performed for patient enrollment pre- and post- protocol modification, demonstrating a lack of statistical significance regarding those enrolled in the protocol before or after this time point. (Table 5.4)

Table 5.3 Clinical Outcomes

	Standard Therapy (n=231)	Diuresis Protocol (n=77)	p-Value
72 Hour Fluid Balance (mL)§	252.4 (4021.7)	-2412.5 (4198.0)	<0.0001
48Hour Fluid Balance (mL)§	479.4 (3170.2)	-1481.5 (3307.8)	<0.0001
24 Hour Fluid Balance (mL)§	326.6 (2024.3)	-607 (2227.5)	0.0007
Ventilator-Free Days (days)*	18 (5-22)	20 (14-23)	0.071
Ventilator Days (days)*	8 (6-14)	8 (5-12)	0.387
Furosemide to Extubation (hours)*	68.1 (23.6-144.4)	49.8 (22.5-141.1)	0.298
Re-intubation Rate	44 (19.0)	16 (20.8)	0.740
ICU-Free Days (days)*	16 (4-21)	19 (13-22)	0.018
ICU Days (days)*	9.4 (6.4-14.5)	8.1 (5.8-13.7)	0.310
In-Hospital Mortality	43 (18.6)	5 (6.5)	0.011
Serum Creatinine Rise	49 (21.2)	19 (24.7)	0.526
Hypokalemia	0 (0)	3 (3.9)	0.015
Hypernatremia	17 (7.4)	17 (22.1)	0.001
Metabolic Alkalosis	1 (0.4)	1 (1.3)	0.438
Overall Adverse Event	58 (25.1)	32 (41.6)	0.006
Comfort Care Order†	37 (16.0)	8 (10.4)	0.226

*Wilcoxon Rank Sum, Median (Interquartile Range); †Chi Square Test; Number (Percentage); ‡Fisher's Exact, Number (Percentage); §Student's T-test, Average (Standard Deviation)

5.2.3 Specific Aim 2

For the secondary aim of assessment of the impact of a pharmacist-managed diuresis protocol on mechanical ventilation days in medically critically ill patients, it was demonstrated that while patients had 2 more ventilator-free days in the protocol group versus those in the historical cohort, this difference was not statistically significant. Rates of re-intubation, defined as any repeat incidence of mechanical ventilation after the initial extubation while receiving diuresis within 180 minutes of original extubation, were not significantly different between groups.

5.2.4 Specific Aim 3

Finally, we sought to address the safety of a pharmacist-managed generalized diuresis protocol via rates of adverse events. Within the study cohort, there was a statistically significant

Table 5.4 Subgroup Analysis of Post-Modification

	Coefficient	95% CI	p-Value
Protocol	-3347.3	-4815.3 – -1879.3	<0.0001
Post Modification	1221.865	-612.3 – 3055.9	0.191

increase in the rate of metabolic disturbances compared to the historical cohort. This was primarily driven by an increase in hypernatremia as well as hypokalemia.

5.2.5 Other Outcomes of Interest

Mortality within the protocolized cohort in this study was lower compared to the historical cohort group. There was also a higher rate of ICU-free days in the protocol group, with protocolized patients having 3 days more free of ICU care. In multivariable logistic regression for overall mortality, protocolized therapy was associated with an OR of 0.29 (0.10-0.85) after adjustment for illness severity, fluid balance upon furosemide start, time on mechanical ventilation prior to furosemide therapy, and vasoactive therapy. In regards to ICU length of stay, no significant difference was seen between groups.

5.2.6 Protocol Adherence

When evaluating protocol compliance, data for 74 patients were available for evaluation. A total of 65 patients had their furosemide stopped appropriately by the protocol secondary to goal achievement. There were also 14 stops for safety reason, 9 of which were also designated to have goal achievement simultaneously as an indication for stopping, and 5 stops for pure safety reasons. Zero stops were accounted for by death or initiation of renal replacement therapy. Upon initiation, 34 had received a prior dose of furosemide during admission, with an average dose of 50.6 mg ± 19.2 mg IV. Of those who did not have furosemide during admission, 11 patients received furosemide prior to admission, with an average dose of 32.7 mg ± 18.4 mg orally. Upon inclusion, 40 patients had both a positive fluid balance with signs of fluid overload on physical exam. A total of 13 had only a net or positive fluid balance without signs of fluid overload and 21 patients had signs of fluid overload without a positive fluid balance. The majority of fluid intake

was from intravenous medications, continuous infusion medications, and enteral feedings (Table 5.5), rather than shock resuscitation.

Of the 74 patients on protocol, there were 23 patients with a protocol duration of 24 hours. The majority of patients were on protocol for 48 hours (n=26 patients), while 10 patients received protocol for 3 days. Another 10 patients required 4 days of protocol, while 3 patients required 6 days and 2 patients required a total of 8 days of therapy. Overall, there were 179 patient days on protocol for evaluation, 77 of which were prior to the protocol modification. Of these 179 days, the goal most frequently selected was -1000 mL, with 67 patient days targeting this goal. Further, 61 patient days had a goal of -2000 mL and 41 had a goal of -1500 mL. A much smaller number had goals outside of this range with 3, 1, and 4 days with a goal of net even, -500 mL, and greater than -2000 mL, respectively.

The most frequently utilized starting dose was 40 mg (n=131), followed by 80 mg (n=26), 60 mg (n=13), and 20 mg (n=11). The majority of days did not need dose adjustments with only 11 patient days with 1 adjustment and 1 patient day each regarding a total of 2 or 3 adjustments. Nine of the dose adjustments were via activatable orders per nursing. The 40 mg dose was found to be effective in 126 patients, with 38 of these patient days on every 6 hour therapy versus 66 with every 8 hour, 14 with every 12 hour, and 2 with every 24 hours frequency. In the 13 patients requiring 60 mg to meet goal, 2 patient days were on every 6 hour frequency, and 10 were on every 8 hour therapy. An effective dose of 80 mg was found in 28 patients, with 12 patients receiving every 6 hours, 14 receiving every 8 hours and 2 receiving every 12 hours. There was one patient who required 120 mg and two patients who required 160 mg for effectiveness every 8 hours. In nine patients the effective dose and interval were not found as goal was never met. Within this time, 84 protocol days did not require a protocol hold. The most frequent reason for holding of the protocol was for achievement of goal (n=58) followed by urine output exceeding goal (Figure 5.2). Of the holds, 77 were deemed appropriate and 13 were inappropriate stops.

Table 5.5 Fluid Intake Source

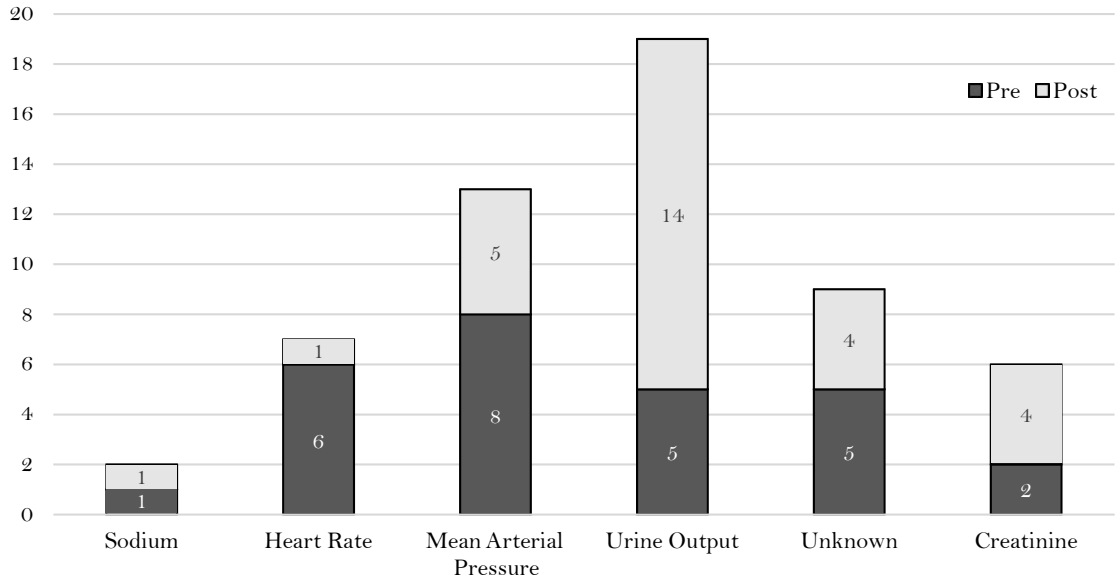
	Baseline (n=74)	Patient Days (n = 179)
Fluids	13 (17.6)	21 (11.7)
Intermittent Medications	69 (92.0)	162 (90.5)
Continuous Medications	60 (81.1)	125 (69.8)
Enteral Feeding	59 (79.7)	155 (86.6)
Free water	21 (28.4)	77 (43.0)
Other oral fluids	7 (9.5)	36 (20.1)
Other fluid source	2 (2.7)	5 (2.8)

Outside of inappropriate stops, there were 12 protocol deviations for doses given despite hold parameters. There were 7 deviations secondary to decrease dose and 21 patients with an interval change. The average percentage decrease in dose was 56.2% (Range 50-67%). The daily goal was met 80.5% of the time, with 144 patient days at goal. Of the interval changes, a high proportion of these patients were patients decreased from every 6 hours to every 8 hours (n=21). Eight patients required a decrease to every 12 hour dosing and 2 patients were decreased to every 24 hour dosing. Two patients required initiation of continuous infusion. Two protocol deviations were secondary to failed nursing activation of orders.

5.3 Discussion

We hypothesized that a pharmacist-managed diuresis protocol would result in a lower cumulative fluid balance 72 hours after shock resolution, defined as freedom from vasopressor support or bolus crystalloid administration for at least 12 hours, in medically critically ill patients. Given the high number of outside hospital transfers at this institution as well as the proportion of patients admitted without shock criteria, the statistical team opted to calculate this 72 hour post-shock volume beginning with the last dose of vasoactive therapy or upon time of ICU admission for those patients without vasopressor support during their stay. We found a significant decrease in day 3 fluid volume with the addition of this protocol in patients' care. We further hypothesized that patients receiving protocolized pharmacist-managed diuresis would

Figure 5.2 Indications for Protocol Hold Pre- and Post- Protocol Modification



have an increase in ventilator-free days at 28 days, defined as the number of days from day 1 to day 28 in which a patient was able to breathe without assistance. While a numeric difference in duration of mechanical ventilation wean was seen, there was no statistically significant difference found. Of note, ventilation wean procedures are not standardized at this institution. Daily spontaneous breathing trials are performed in all patients who meet criteria which is taken into consideration for extubation; however, extubation orders are left to attending discretion. This lack of ventilator wean protocolization may have affected total ventilator duration and ventilator-free days between groups. Reintubation rates were not significantly different between groups which supports relative uniformity on ventilator wean strategies. The reported reintubation rates are in alignment with previous studies showing ranges from 13.8-22.6%, depending on weaning method. (366)

For the third aim regarding metabolic derangements in the patient, we anticipated that a pharmacist-managed diuresis protocol when compared to standard care will have a similar rate of adverse events. Adverse events were defined as acute kidney injury (serum creatinine 1.5 times baseline serum creatinine, serum creatinine increase of at least 0.3 mg/dL, or urine output <0.5

mL/kg/hr for at least 6 hours), or the incidence of a severe metabolic disturbance (potassium <3 mmol/L, sodium >150 mmol/L, or bicarbonate >40 mmol/L with a pH <7.3). (119) We saw within the protocol group, however, a significant increase in the rates of adverse events. Of note, while a nursing-driven electrolyte replacement protocol had been in place within this institution, changes to the protocol occurred mid-protocol implementation. These electrolyte protocol changes potentially may have increased the rates of hypokalemia, particularly within the post-modification period. In regards to rates of hypernatremia, it is worth nothing that 12 patient days had protocol noncompliance secondary to dose administration despite hold parameters. At our institution, providers at times request continuation of furosemide despite elevated sodium levels, often with the addition of metolazone for augmentation in patient situations with an elevated sodium. There was an increased rate in metolazone use. No severe adverse events were reported over the course of protocol implementation within the protocol population. Overall, there was a significant difference in net fluid status that was likely due to a higher furosemide exposure. A significant increase in episodes of hypernatremia and hypokalemia are not unsurprising given this furosemide strategy. Future protocol design will reflect these episodes of hypernatremia and hypokalemia with creation of more explicit electrolyte rules.

Other key considerations to this study include a decrease in mortality and increased ICU-free days in the protocol group. Diligence in the selection of potential impactful parameters on outcomes was pursued. These included baseline weight and admission source as there have been correlated with rates of mortality in the sepsis population. (367, 368) A recent meta-analysis of 65 randomized controlled trials of septic shock evaluated mortality rates based on baseline characteristics and inclusion criteria. (369) When evaluating the control groups, a significant amount of heterogeneity was found in mortality rates with an overall mortality rate of 38.6% and a prediction limit ranging from 13.5% to 71.7% When evaluating parameters influencing mortality ranges, a combination of severity scores, incidence of mechanical ventilation, and mean serum creatinine could only account for 41% of the total heterogeneity in mortality rates.

Vasopressor, mechanical ventilation, and definitions of sepsis or infection did not affect mortality rates. Other parameters such as size of trial, number of centers, blinding, and quality did not affect rates of mortality either. Variables such as fluid balance and diuretic therapy were not included in that meta-analysis. It is possible that the implication of volume de-resuscitation seen in the current study is directly correlated with mortality, in line with previous studies examining the impact of fluid status. The variables which have been consistently correlated with mortality, such as the aforementioned study, were accounted for in the matching criteria of this cohort. However, these findings need to be replicated in a larger population for confirmation. (71, 177)

A key limitation to this study is the lack of randomization and blinding. Given the nature of the protocol, blinding to the medical staff was not possible. A pre-post intervention study was chosen given the lack of blinding within the study. As all pharmacists, physicians, and nurses at this institution rotate among the medical ICUs, it was anticipated that an overall change in practice may occur over the study timeframe given increased awareness of fluid balance and approach to diuretic dosing with its use in the pilot unit. To demonstrate the potential for such phenomenon, a recent debate regarding sepsis management illustrates this point. While a landmark trial by Rivers and colleagues in 2001 demonstrated a significant improvement in sepsis mortality with utilization of an early goal directed therapy (EGDT) protocol, large clinical trials 15 years later have failed to demonstrate an improvement in mortality when EGDT was compared to usual care. (13, 370) Authors have proposed that usual care has, with time, improved given the popularity of the EGDT trial, guideline incorporation, and by nature of increased recognition. Such a phenomenon is possible with implementation of this protocol. However, given the limited time lapse between the pre-group and the protocol implementation within these time periods and lack of emergence of any randomized control trial or change of clinical guideline regarding fluid management between the pre- and post-phases, changes in overall approaches to care based on factors external to the protocol were unlikely. When considering the aforementioned survey (Chapter 2) which indicated a broad range in approaches to diuresis, a

practice drift among control patients was unlikely as objective differences were observed using the protocol. To limit potential bias further, patients were matched on a large number of clinically relevant variables and no subjective outcome measures were utilized.

Protocol modifications in the study may also be seen as a potential limiting factor in study interpretation. However, in the subgroup analysis performed, protocol inclusion pre- or post-modification did not appear to significantly impact the primary result. This supports the result that a pharmacist-driven multi-disciplinary protocol would improve fluid balance at 72 hours compared to standard of care.

Other considerations within this study were overall protocol adherence and pharmacist hours. Evening critical care pharmacy services are provided daily within the Medical ICU at our institution until 22:00, leaving a 9 hour gap without coverage. Van Berkel and colleagues showed that 42% of institutions have evening critical care services with pharmacist-to-patient ratios greater than 1:15 and 1:25 in 92% and 58.3% of hospitals, respectively. (371) In this cohort, 50% of respondents expressed concerns regarding the appropriateness of the workload and ability to provide adequate patient care. Pharmacist-to-patient ratios at our institution range from 1:13 to 1:16 minimum and a minimum of 1:75 during evening hours (16:00-22:00). For this reason, we opted to utilized nursing-activatable furosemide orders for those patients not at fluid balance goals. However, utilization rates of these orders accounted for only 56% of the adjustments, with the primary pharmacist activating or increasing orders the remaining percentage of the time. The feasibility of this study without activatable orders is likely; however, pharmacist staffing ratios must be considered in such a design alteration.

Lastly, the selection of outcome parameters are likely worth mentioning. We evaluated 72 hour fluid balance in accordance with previous literature, however evidence suggests that fluid balance documentation is not always accurate. Perren and colleagues found in a cohort of 147 ICU patients, cumulative fluid balances were inaccurate over 33% of the time with errors ranging from -3606 mL to 2020 mL. A poor correlation was found between body weight changes and net

cumulative fluid balance. While adjusting the fluid balance for sensible or insensible fluid losses, febrile states, or diarrhea, correlation was only slightly better. Standard deviations of the average difference of body weight fluctuations and fluid balance changes were always greater than 1 liter total. (372) In another cohort evaluating 504 ICU admissions, only 160 patients had complete data. In this cohort, changes in body weight and fluid balance demonstrated weak correlation both prior to as well as after correlation for insensible losses (r^2=0.34 for both). The 95% limits of agreement had a large range from -5.8 kg up to 6 kg total. (373) In our study, patient daily body weights were unreliable. Because this practice is not tightly protocolized, we did not utilize body weight as a monitoring parameter. However, it is possible that daily weights would assist in providing stronger clinical outcomes.

This study does have several strengths; however, including the utilization of easily obtainable bedside monitoring parameters, the multi-disciplinary approach to protocol development, utilization, and modification, and selection of matching parameters. Several potential confounders on 72-hour fluid balance were matched between groups, decreasing between-group difference. Objective outcome measures were utilized to limit overall bias in the interpretation of both efficacy and safety. This sequential period pilot study demonstrated that a pharmacist-driven diuresis protocol was significantly associated with a negative fluid balance at 72 hours; however increased rates of adverse events were found, namely hypernatremia and hypokalemia. The increased mortality and decreased number of ICU-free days in the standard therapy group is hypothesis-generating, particularly given the lack of difference between-groups in ventilator-free days.

5.4 Further Investigation

While we were able to show a pharmacist-driven protocolized approach to diuresis was associated with 72-hour negative fluid balance post-shock resolution, as well as a decrease in mortality with an increase in ICU-free days, questions surrounding administration of diuretics in the intensive care unit still remain.

5.4.1 Diuretic Considerations and Renal Function Assessment by Biomarkers

Much of the furosemide literature furosemide in the critically ill population surrounds its use as a predictor of acute kidney injury, diagnosis of acute kidney injury, or even as a causative factor in the development of acute kidney injury. Potentially deleterious effects of furosemide on overall renal function include an increased risk of acute tubular injury secondary to medullary ischemia with a decrease in medullary flow relative to the cortex. There is activation of RAAS and sympathetic stimulation resulting in venodilation, in conjunction with volume loss leading to decreased preload and renal vasoconstriction. The use of furosemide in our population demonstrated no difference in rates of AKI between treatment groups as defined via the KDIGO criteria. (117) However, such was defined via serum creatinine, as the majority of other available studies, which is a highly limited biomarker of renal function given its long half-life and delay in diagnosis of acute kidney injury up to 36 hours. The utilization of biomarkers for renal function in the ICU may better assist the clinician in the administration of furosemide as it relates to effects on the kidneys. More novel biomarkers of renal function include biomarkers of actual function, including cystatin C, galectin-3, and proenkephalin. Biomarkers of renal damage include neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding proteins, interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) and biomarkers of cycle arrest include tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein-7. Additional biomarkers of nephrotoxicity include N-acetyl-glucosaminidase, Glutathione-S-transferase, and Gamma-glutamyl transpeptidase and alkaline phosphatase. (374) Various combinations of these biomarkers can demonstrate progression of acute kidney injury and progression of acute injury and pre-renal injury from tubular injury. (375) IL-18, NGAL, and KIM-1 have all shown to correlate significantly with acute tubular injury in comparison to pre-renal injury and other types of renal dysfunction. (375-378) Specifically, NGAL is not affected by the administration of diuresis. (375) Utilizing these biomarkers and their trends may assist in

timing for the initiation of diuresis, appropriateness of its use, and even the decision to discontinue in the critically ill. (379)

5.4.2 Diuretic Dosing Considerations

More evidence regarding the optimization of furosemide dosing in the critically ill is likely necessary. The range of furosemide utilized in our study included 20-320 mg per day; however, a high incidence of concomitant diuretics were found. Loop diuretics have a known threshold dose which must be achieved in order to see an effect on urine output. (240) This threshold has a wide range based on underlying renal function, starting at 10 mg IV in a naive patient with normal renal function up to 80 to 160 mg in patients with acute kidney injury or chronic kidney disease. Similarly, a dose ceiling effect has been defined in patients with chronic kidney disease, nephrotic syndrome, cirrhosis, and heart failure, ranging from 40 mg to 200 mg depending on underlying disease state. However such a ceiling has not been found in the broad critically ill population. The half-life of furosemide also changes depending on renal function. Low serum albumin and increased organic anion transport receptor competitors can decrease furosemide delivery while increased tubular albumin, increased RAAS activation and elevated sodium and water intake can diminish the furosemide effect. A recent study demonstrated that within 7724 critically ill patients in a single center ICU, body mass index was independently correlated with an increased risk of diuretic receipt, with every 5 kg/m^2 associated with a 1.19 increase risk of diuretic administration in the ICU. Additionally, every 5 kg/m^2 associated with a 2.75 mg higher daily diuretic dose. The authors attribute this to the sodium-retentive state of obesity; however, were unable to differentiate this affect independent of comorbidities of obesity such as insulin resistance, pulmonary hypertension, and heart failure. (380) A large model accounting for all of the known baseline parameters, concurrent diseases, physiologic state and variables, and pharmacokinetic variables is necessary in order to determine which factors are most influential on the optimal furosemide dose for those individuals in the ICU. Additionally

concomitant therapies such as nephrotoxins, fluid administration, and the sodium or other composition variates of such are also likely impactful.

5.4.3 Diuretic Timing Considerations

Timing of furosemide administration is a highly ambiguous area within this population. In our study, we opted to evaluate 72 hour fluid balance after shock resolution; however, 24- and 48-hours were also significantly lower in the protocol group. It is possible that in some patients early initiation is better. A recent study evaluated the utilization of diuretic therapy early in critically ill patients receiving vasoactive therapy using the Medical Information Mart for Intensive Care III database. (381) This is an online database that contains over 40,000 critically ill patients over a 12 year period. In patients with a positive fluid balance 48 hours after ICU admission diuretic use was significantly associated with decreased mortality (OR 0.64, 95% CI 0.51-0.78). (382) In the negative fluid balance subgroup, there was no statistical difference in mortality (OR 0.73, 95% CI 0.47-1.14). This study is the first to demonstrate a benefit of diuretic therapy in patients still found to be in active shock outside of an acute decompensated heart failure population. In line with the physiologic rationale of ebb and flow phases, most literature has evaluated fluid balance around 72 hours after shock onset. However, there are several other considerations. This diuretic administration relative to shock timing concept makes several assumptions. The first of which that all patients have the same pattern of shock onset and resolution timing. The second is that we are not able to account for the exact time of shock onset in a presenting patient, considering other key factors such as outside hospital transfers, time of symptom onset, and patient presentation time.

Further, other factors may contribute to ongoing vasoactive therapy support that is independent of fluid balance. Patients in septic shock may develop septic cardiomyopathy, resulting in a continuation of vasoactive support for maintenance of cardiac output. Additionally, if fluid overload results in an elevated central venous pressure, cardiac output may decrease therefore decreased mean arterial pressure or a decrease in microcirculatory flow and overall

perfusion pressure may be seen. Both situations which may be mitigated at bedside by continued vasoactive support when undifferentiated from a pure decrease in systemic vascular resistance. (383) This study did not specifically evaluate whether a baseline vasopressor dose impacted benefit of diuresis; therefore, it is possible that certain patients may be able to tolerate volume offloading during shock while others cannot. Loop diuretics such as furosemide may activate RAAS, which can result in vasodilation. Loop diuretics may also increase secretion of vasodilatory prostaglandins that result in increased proximal tubule pressure. (384, 385) For this reason, IV furosemide may decrease or increase arterial pressure, stroke volume, and renal blood flow. (220) While invasive hemodynamic monitoring is no longer standard of care, a study evaluating non-invasive hemodynamic parameters, such as markers of volume responsiveness and bedside ultrasonography, as triggers for initiation of volume removal, may assist in resolving ongoing questions regarding optimal timing of diuretic initiation.

New data demonstrates that septic shock additionally can be stratified into subphenotypes. The most recent data suggested six subphenotypes of sepsis, including uncomplicated septic shock, pneumonia with acute respiratory distress syndrome, postoperative abdominal, severe septic shock, pneumonia with acute respiratory distress syndrome plus multiorgan dysfunction syndrome, and late septic shock. (386) In another meta-analysis on 349 studies, 29 variants of 23 genes were associated with the risk of sepsis. (387) Neither of these studies, however evaluated the impact of volume and fluid status on outcomes based on genetic or phenotypic factors. A retrospective study of 14,993 patients admitted to a single center over a 12 year period, however, did in fact look at fluid resuscitation and response based on sepsis subclasses. That study identified four distinct sepsis profiles including profile 1, considered to be the baseline type; profile 2, consisting of respiratory dysfunction; profile 3, with multiple organ dysfunction; and profile 4 with neurologic dysfunction. Mortality was highest in profile 3 (45.4%) and lowest in profile 1 (16.9%). In a multivariable regression model adjusting for several concomitant factors, a higher cumulative fluid input volume within the first 48 hours was found

to decrease overall mortality in profile 3 (OR 0.89 per 1L, 95% CI 0.83-0.95) while increasing mortality in those patients in profile 4 (OR 1.20, 95% CI 1.11-1.30). (388) Lest we forget, with less than 5 randomized controlled trials evaluating fluid resuscitation in sepsis and actual physiology outcomes, there are more questions than answers regarding which patients may benefit from fluid resuscitation and when. (389) If such solutions can be found, selection of patients for diuresis and volume removal as well as timing can be evaluated more lucidly.

5.4.4 Diuretic Considerations and Pulmonary Function

All of these considerations must further be explored within the cohort of acute respiratory distress syndrome as these patients may have alternative optimal timeframes and de-resuscitation goals compared to the shock and general ICU population. A recent secondary analysis of all randomized controlled trial conducted by the Acute Respiratory Distress Syndrome Network from the year 1996 to 2013 took an additional look at mortality rates in patients with ARDS. These authors found in a multivariable logistic regression model that day one fluid balance was significantly associated with mortality (OR 1.07 per 1 L, 95% CI 1.04-1.11). Further, day one fluid balance was additionally associated with a decreased rate of discharge home with unassisted breathing (HR 0.918 per 2 L, 95% CI 0.895-0.941). Most intriguingly, when looking at rates of mean daily fluid balance, days 1-7 showed a decrease in averages over time. However, day zero fluid balance has steadily risen in the past 15 years. Further, the average fluid balance on day one still remains positive, above 1000 mL. (390) How loop diuretics play a role in fluid balance and these outcomes has yet to be definitively determined. Literature has demonstrated that the administration of furosemide may improve pulmonary gas exchange, decrease edema formation, and improve intrapulmonary shunt fraction in early phases of pulmonary edema in mechanisms that are not direct to its diuretic action. Instead furosemide effects relating to pulmonary vasodilation, attributing to redirection of blood flow to nonedematous alveolar regions may become important. (391-396) Specifically, continuous infusion furosemide has shown to improve lung injury scores, pO_2/FiO_2, and shunt fractions in animal models while decreasing the amount

of pulmonary end expiratory pressure required when initiated 2 hours after the onset of acute lung injury. (397) Other models have demonstrated that furosemide administration in later stages of pulmonary edema may actually worsen pulmonary gas exchange without having any effect on the edema itself. (398-400)

Recent evidence in acute respiratory distress syndrome also has taken to the use of biomarkers. A latent class analysis of baseline clinical and plasma biomarker data within the aforementioned FACTT trial was performed in a recent publication. (401) Two phenotypes were found, consisting of different cutoffs for interleukin-8, serum bicarbonate, and tumor necrosis receptor factor-1. Subphenotype 2, identified in 2 previous trials, was associated with increased levels of inflammatory biomarkers, acidosis, and shock and was present in similar frequency in the two earlier trials, In this analysis, within phenotype 1, a fluid conservative approach resulted in a mortality rate of 26% versus 18% in a fluid liberal group, whereas a fluid conservative approach resulted in a mortality rate of 40% compared to 50% in a fluid liberal approach in the phenotype 2 group. When looking beyond the defining laboratory parameters, other laboratory differences are seen, with an increase in Ang-2, a mediator of endothelial cell injury, RAGE, a marker of lung epithelial cell injury, and serum creatinine. Hemodynamic variables at baseline do not appear to be significantly different between phenotypes, with the exception of a significantly higher central venous pressure in those patients with phenotype 2 ($p=0.005$). The impact of furosemide as well as fluid management strategies potentially needs to potentially be stratified based on phenotype of ARDS.

Outside of the acute respiratory distress population, pulmonary edema secondary to other causes may also potentially benefit from furosemide. In an animal model of cardiogenic pulmonary edema, inhibition of pulmonary NKCC blocked alveolar fluid secretion. (140) Inhibition of epithelial sodium channels increased alveolar fluid which was dependent on NKCC. Given furosemide's effect on NKCC, administration has shown to decrease alveolar fluid transport and secretion while alveolar fluid clearance. However, the administration of furosemide in this study

was via inhalation. Additionally, multiple types of edema were not considered such as those in neurogenic diseases states or altered altitudes. The effect of furosemide on edema in these states as well as in relation to volume status must also be further considered before broadening its application to a generalized pulmonary edema population.

5.5 Conclusion

Fluid administration is ubiquitous within the critically ill population. The number of patients presenting with severe sepsis, just one indication for fluid administration in the ICU, has surpassed one million annually. There is minimal evidence to guide initiation of de-resuscitation within the general ICU population. This study was the first to evaluate a pharmacist-drive de-resuscitation protocol utilizing pharmacologic diuresis in the intensive care unit. We were able to demonstrate a significant improvement in fluid balance at 72 hours following shock resolution, with potential benefit on mortality and ICU length of stay. Volume overload states may be a marker of severity rather than a parameter for early diuresis intervention. Although this study provided support for a pharmacist-driven protocol, prospective randomized trials may not demonstrate efficacy of this intervention for such clinical outcomes. Further evidence is needed to optimize those who may benefit. Questions remain regarding patient selection, timing, concomitant disease considerations, and role of phenotypic profiling as well as serum biomarkers to optimize furosemide dosing regimens.

APPENDIX ONE

* 1. Does your ICU have a standardized approach to diuresis administration specifically for volume removal to target net-even or net-negative fluid status/de-resuscitation? [Select all that apply]

- [ ] Institutional or unit-based protocol (mandated)
- [ ] Institutional or unit-specific guideline (preferred but not mandated)
- [ ] Utilization of prior published protocol (not institution or unit-specific)
- [ ] Disease-state dependent protocol/guideline (i.e. heart failure, acute kidney injury)
- [ ] Cost restrictions to diuretic use
- [ ] Pharmacy provided education (only, no protocols/guidelines)
- [ ] Unsure
- [ ] None
- [ ] Other (please specify)

* 2. Which percentage of the time is the pharmacist involved with making decisions surrounding diuresis?

- ( ) 0-5% (Never)
- ( ) 6-33% (Not typically)
- ( ) 34-67% (Half of the time)
- ( ) 68-95% (Most of the time)
- ( ) 96-100% of the time (Always)
- ( ) Unsure

* 3. Pharmacist intervention as it relates to de-resuscitation surrounds which of the following? [Select all that apply]

- [ ] Recommends initiation of diuresis
- [ ] Recommends continuation or discontinuation of diuresis
- [ ] Recommendations regarding diuretic safety (metabolic changes, hemodynamics)
- [ ] Recommendations regarding dosing
- [ ] Recommendations regarding frequency
- [ ] Recommendations regarding drug selection
- [ ] Recommendations regarding diuresis target/goal
- [ ] Unsure

* 4. Once deciding to initiate de-resuscitation, which of the following factors most frequently impact diuretic regimen choice? [Select up to three]

- [ ] Active medical disorder (renal failure, cardiorenal syndrome, etc.)
- [ ] Home diuretic regimen/historical use
- [ ] Age
- [ ] Weight
- [ ] Serum creatinine (SCr) trend
- [ ] Net volume status
- [ ] Expected daily input
- [ ] Nephrology consult recommendation
- [ ] Metabolic parameters and/or derangement (other than SCr)
- [ ] Standardized Method for Estimating Creatinine Clearance (MDRD, Cockcroft-Gault, etc)
- [ ] Unsure

* 5. Which of the following most frequently prompts initiation of diuresis in your ICU (not including ADHF, AKI stress tests, re-initiation of home medications, ascites management? [Select all that apply]

- [ ] Net positive fluid status
- [ ] Signs of peripheral and/or pulmonary edema (imaging, Swan-Ganz)
- [ ] Difficult ventilator wean
- [ ] Time since ICU admission
- [ ] Other (please specify)
- [ ] Open abdomen
- [ ] Shock resolution
- [ ] Unsure

* 6. Multiple medications are listed below that could be used in conjunction with loop diuretics based on the indication. Please select which of the following adjuncts are utilized at least one-third of the time in conjunction with loop diuretics your ICU?

	Not at net fluid balance goal	Hepatorenal syndrome	Acute decompensated heart failure	Serum bicarbonate	Serum sodium	Home regimen	Restriction criteria met	Other
Acetazolamide	☐	☐	☐	☐	☐	☐	☐	☐
Albumin	☐	☐	☐	☐	☐	☐	☐	☐
Chlorothiazide	☐	☐	☐	☐	☐	☐	☐	☐
Metolazone	☐	☐	☐	☐	☐	☐	☐	☐

Other (please specify)

* 7. What is the most common frequency of loop diuretic administration in your ICU once de-resuscitation is initiated? [Select up to three]

- ☐ Scheduled less than every 6 hours
- ☐ Scheduled every 6 hours
- ☐ Scheduled every 8 hours
- ☐ Scheduled every 12 hours
- ☐ Scheduled every 24 hours
- ☐ Intermittently as one-time doses
- ☐ Continuous infusion following IV bolus
- ☐ Continuous infusion without IV bolus
- ☐ Loop diuretics are not utilized
- ☐ Other (please specify)

* 8. In the majority of patients, once diuresis is initiated, when would you say the next assessment and therapeutic change is made?

- ☐ Within 2 hours
- ☐ Within 6-8 hours
- ☐ Within 12 hours
- ☐ Within 24 hours
- ☐ Shift change
- ☐ Subsequent (next day) patient care rounds
- ☐ Unsure

* 9. What are the most common reasons for a decrease in the diuretic regimen (dose decrease, frequency increase, etc) within your ICU after de-resuscitation is initiated? [Select up to two]

- ☐ Low urine output/unresponsive to diuresis
- ☐ Over-diuresis determined by urine output
- ☐ Hemodynamic safety (low blood pressure, elevated heart rate)
- ☐ Metabolic safety (pH, bicarbonate, BUN, serum creatinine, electrolytes)
- ☐ Initiation of renal replacement therapy
- ☐ Unsure

* 10. What percent of the time is diuresis stopped for safety reasons (metabolic safety, hemodynamic safety)?

- ◯ 0-5% (Never)
- ◯ 6-33% (Not typically)
- ◯ 34-67% (Half of the time)
- ◯ 68-95% (Most of the time)
- ◯ 96-100% of the time (Always)
- ◯ Unsure

* 11. What percentage of the time do you feel diuresis is stopped appropriately ?

- ◯ 0-5% (Never)
- ◯ 6-33% (Not typically)
- ◯ 34-67% (Half of the time)
- ◯ 68-95% (Most of the time)
- ◯ 96-100% of the time (Always)
- ◯ Unsure

* 12. In your current practice, how frequently do you consider volume status in patients admitted with shock? [Select up to three]

- ☐ Only during initial resuscitation to ensure prescriptive goals met (i.e. 30 mL/kg in septic shock)?
- ☐ Multiple times per day
- ☐ Daily
- ☐ Every 1-2 days
- ☐ Once prompted
- ☐ After indicators of volume overload are found
- ☐ Possibility of extubation
- ☐ Unsure

* 13. What percentage of the time does diuresis achieve the desired net fluid balance within your ICU?

- ◯ 0-5% (Never)
- ◯ 6-33% (Not typically)
- ◯ 34-67% (Half of the time)
- ◯ 68-95% (Most of the time)
- ◯ 96-100% of the time (Always)
- ◯ Unsure

* 14. Do you feel that patients in your ICU are more likely to receive too much or too little diuresis...

	Too little	Slightly not enough	Roughly the appropriate amount	Slightly too much	Too much
At 24 hours after shock resolution?	◯	◯	◯	◯	◯
At 48 hours after shock resolution?	◯	◯	◯	◯	◯
At 72 hours after shock resolution?	◯	◯	◯	◯	◯

* 15. Which of the following do you find to be the most frequent reason that diuresis selection is inappropriate during de-resuscitation? [Select all that apply]

- ☐ Utilization of more expensive drugs than necessary or incorrect drug choice
- ☐ Underdosed
- ☐ Overdosed
- ☐ Incorrect frequency
- ☐ Selection is always appropriate
- ☐ Unsure
- ☐ Other (please specify)

* 16. What is the biggest barrier to adequate diuresis during de-resuscitation?

- ◯ Accurate intake and output records and/or charting
- ◯ Lack of appropriate follow-up
- ◯ Lack of education regarding harm of fluid overload
- ◯ None
- ◯ Lack of understanding of appropriate diuresis regimens
- ◯ Unsure
- ◯ Lack of comfort with diuresis in the critically ill
- ◯ Other (please specify)

* 17. Complete this statement: At least 50% of my patients achieve net negative fluid status _____ after resolution of shock?

- ◯ <24 hours
- ◯ 96-120 hours (4-5 days)
- ◯ 24-48 hours
- ◯ >120 hours (>5 days)
- ◯ 48-72 hours
- ◯ Never
- ◯ 72-96 hours
- ◯ Unsure

* 18. What percentage of the time do you feel diuresis is administered appropriately in non-ADHF patients (right drug, dose, interval)?

- ◯ 0-5% (Never)
- ◯ 68-95% (Most of the time)
- ◯ 6-33% (Not typically)
- ◯ 96-100% of the time (Always)
- ◯ 34-67% (Half of the time)
- ◯ Unsure

* 19. Complete this statement: If diuresis were performed as appropriately as possible in my ICU, patient outcomes would be

- ◯ Significantly improved
- ◯ Worse
- ◯ Improved
- ◯ Significantly worse
- ◯ No difference

* 20. Which title best applies to your current position?

- ◯ Pharmacist (Specialist)
- ◯ Physician in training
- ◯ Pharmacist (Staff)
- ◯ Advanced practice practitioner
- ◯ Pharmacist (Decentralized)
- ◯ Registered Nurse
- ◯ Resident/fellow pharmacist
- ◯ Dietitian
- ◯ Physician
- ◯ Respiratory Therapist

* 21. Which of the following best classifies your current institution?

- ◯ Academic medical center
- ◯ Government medical center
- ◯ Community medical center
- ◯ Other (please specify)

* 22. Which best describes your ICU team? [Select all that apply]

- ☐ Teaching team (students, fellows, residents)
- ☐ Non-rounding intensivist
- ☐ Rounding hospitalist
- ☐ Rounding advanced care provider team
- ☐ Non-rounding hospitalist
- ☐ Non-rounding advanced care provider team
- ☐ Rounding intensivist
- ☐ Other (please specify)

* 23. In which type of ICU do you most frequently practice?

- ○ Medical ICU
- ○ Trauma ICU
- ○ Non-Trauma Surgical ICU
- ○ Burn ICU
- ○ Cardiac ICU
- ○ Other (please specify)
- ○ Cardiothoracic ICU
- ○ Immunocompromised ICU
- ○ Neurosurgical ICU
- ○ Medical-Surgical ICU
- ○ Emergency department

* 24. On average, how many patients does your ICU see per day?

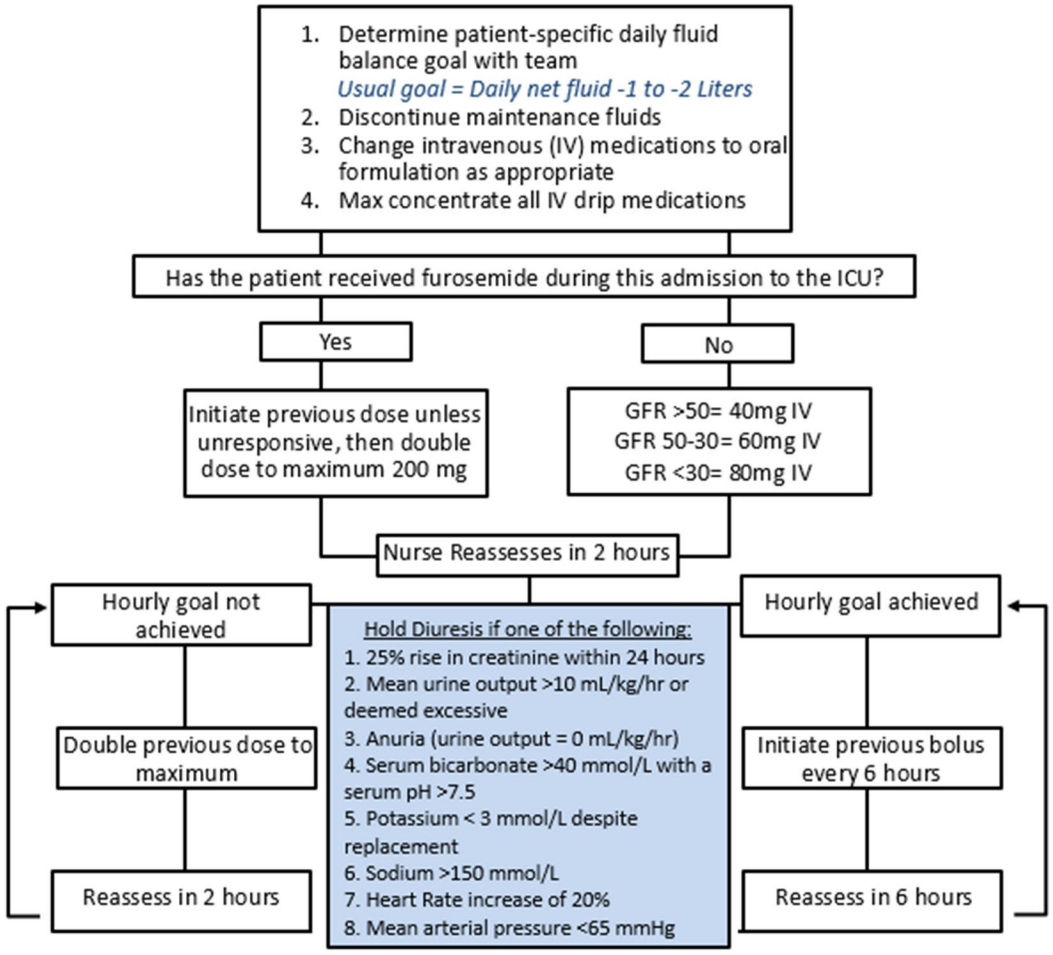
	1-2	2-5	5-10	10-15	12-20	20-30	>30
Overall ICU	○	○	○	○	○	○	○
Septic Shock	○	○	○	○	○	○	○
Acute Respiratory Distress Syndrom	○	○	○	○	○	○	○
Renal Failure	○	○	○	○	○	○	○
Acute Decompensated Heart Failure	○	○	○	○	○	○	○

* 25. What hours are the following pharmacy services available in your respective ICU? Please select the variables that most closely represent your practice.

	8-Hour Daytime (i.e. 0700-1600)	12-Hour Daytime (i.e. 0700-1900)	Extended Daytime Hours (i.e. 0700-2300)	Second Shift (i.e. 1500-2300)	Third Shift (i.e. 2300-0700)	24 hours per day	M-F	Weekend	N/a
Rounding/Clinical pharmacist	☐	☐	☐	☐	☐	☐	☐	☐	☐
Decentralized pharmacist	☐	☐	☐	☐	☐	☐	☐	☐	☐
Central pharmacist	☐	☐	☐	☐	☐	☐	☐	☐	☐
On-call pharmacist	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other (please specify)

APPENDIX TWO



Goal Parameters

Order	Date	Priority	Special Instructions
Daily Fluid Balance Goal	14-Mar-2018	Routine	Goal Hourly Fluid Balance = _____ mL/hour

Medications

Select from the following 3 lasix orders

Order	Start Date	Priority	Low Dose	High Dose	Set Dose	Unit of Measure	Dosage Form	Route	Frequency	PRN	PRN Reason	Special Instructions
Furosemide Inj.	T	Routine			40	MG	Solution	IntraVenously	every 6 hours	☐		
Furosemide Inj.	T	Routine			60	MG	Solution	IntraVenously	every 6 hours	☐		
Furosemide Inj.	T	Routine			80	MG	Solution	IntraVenously	every 6 hours	☐		
Nurse Activated Orders - 4 item(s)												
Furosemide Inj.	T	Routine			80	MG	Solution	IntraVenously	every 6 hours	☐		
Furosemide Inj.	T	Routine			160	MG	Solution	IntraVenously	every 6 hours	☐		
Furosemide Inj.	T	Routine			120	MG	Solution	IntraVenously	every 6 hours	☐		
Furosemide Inj.	T	Routine			200	MG	Solution	IntraVenously	every 6 hours	☐		
Combination Diuretics - 2 item(s)												
Metolazone	T	Routine			10	MG	Tablet	Oral	Once a day	☐		
Chlorothiazide Inj.	T	Routine			500	MG	Powder for...	IntraVenous...	once	☐		
Continuous Infusion - 1 item(s)												
Furosemide Inj. (Drip)	T	Routine			10	MG/hr	Solution	IntraVenous				Titrate every 30 minutes by 5 mg/hour to goal hourly fluid balance

Vital Signs

Order	Date	Priority	Frequency	Special Instructions
Intake & Output - 3 item(s)				
Weight	14-Mar-2018	Routine	daily	
Urine Output	14-Mar-2018	Routine	q2h	Every 2 hours after initial furosemide dose or dose increase, then every 6 hours until within goal x2, then daily AM assessment
Intake & Output	14-Mar-2018	Routine		
Hemodynamic Monitoring - 2 item(s)				
Heart Rate	14-Mar-2018	Routine	q1h	
Blood Pressure	14-Mar-2018	Routine	q1h	

Nursing Orders

Order	Date	Priority	Frequency	Special Instructions
Hemodynamic Monitoring - 11 item(s)				
COM - Electrolyte Replacement (0...				
COM - Adult - Foley Orders (4 orders of...				
Foley to Straight Drain	14-Mar-2018	Routine	<Continuous>	
Foley Care	14-Mar-2018	Routine		
Adult Post Foley Removal Protocol...	14-Mar-2018	Routine		To access Adult Post Foley Removal Instructions:...
Special Order - Nursing	14-Mar-2018	Routine		Follow the approved nursing urinary catheter removal protocol for adult patients with a Foley catheter....
Notify Physician For	14-Mar-2018	Routine		
D/C IV Fluids	14-Mar-2018	Routine		Discontinue Maintenance Fluids
Special Order - Nursing	14-Mar-2018	Routine	<Continuous>	Hold furosemide for:...
Special Order - Nursing	14-Mar-2018	Routine	AM	Hold furosemide for:...
Special Order - Nursing	14-Mar-2018	Routine	<Continuous>	Request maximum concentration IV drips as appropriate

Laboratory

Order	Date	Priority	Lab Special Instructions
Hemodynamic Monitoring - 1 item(s)			
Basic Metabolic Panel	14-Mar-2018	Routine	

APPENDIX FOUR

Patient Origin	▼
Primary Reason for Admission	☐ Septic shock ☐ Acute liver failure ☐ Acute respiratory failure ☐ Acute kidney injury ☐ Seizures ☐ GI Bleed ☐ Oncologic emergency ☐ Overdose/toxicology ☐ Metabolic, other ☐ Infection, other ☐ Pulmonary, other ☐ Cardiac arrest ☐ Altered mental status ☐ Hepatic, other ☐ Cardiac, other Select all that apply
Pertinent PMH	☐ Heart Failure with Reduced EF ☐ Cirrhosis ☐ COPD ☐ Renal transplant ☐ Pulmonary hypertension ☐ Chronic respiratory failure ☐ CKD
Home diuresis dose (Furosemide equivalents)	"0" if no diuretic PTA
Date of birth	Today M-D-Y
Race	▼
Gender	○ Female ○ Male reset
Height (cm)	
Weight (kilograms)	
Indication for Diuresis	☐ Net-positive or net-even fluid balance ☐ Signs of fluid overload on CXR or physican exam
Net Fluid Balance to Date	On day of protocol initiation - From 24h I/O on Rounding Report
Hours Since Shock Resolution	○ N/a ○ <12 hours ○ 12 hours ○ 12-24 hours ○ 24-48 hours ○ >48 hours reset Shock resolution = No bolus crystalloid or vasopressor administration
Date of Protocol Start	Today M-D-Y
Previous Effective Dose this ICU Admission	☐ 40 mg IV ☐ 60 mg IV ☐ 80 mg IV ☐ 120 mg IV ☐ 160 mg IV ☐ 200 mg IV ☐ 20 mg IV ☐ N/a Furosemide Equivalents

Protocol Stopped or Held	☐ No holds required ☐ 25% rise in serum creatinine within 24 hours ☐ Urine output >10 mL/kg/hr or deemed excessive ☐ Anuria ☐ Serum bicarbonate >40 with pH > 7.5 ☐ K < 3 after replacement ☐ Sodium >150 ☐ Heart rate increase of 20% ☐ MAP < 65 ☐ Death ☐ Renal replacement therapy ☐ Goal achieved ☐ Other/unknown (please comment) Daily indication for hold/stop of protocol
Was Protocol Stop/Hold Appropriate	○ Yes ○ No reset
Maximum BUN	For the 24 hour period/day
Minimum Creatinine (mg/dL)	For the 24 hour period/day
Maximum Creatinine (mg/dL)	For the 24 hour period/day
Maximum Serum Sodium	For the 24 hour period/day
Minimum Serum Potassium	For the 24 hour period/day
Maximum Serum Bicarbonate	For the 24 hour period/day
Serum Albumin	For the 24 hour period/day
Maximum Venous pH	For the 24 hour period/day
Maximum Arterial pH	For the 24 hour period/day
Maximum Heart Rate	For the 24 hour period/day
Minimum Mean Arterial Pressure	
Daily Fluid Intake	From 24h I/O on Rounding Report
Daily Fluid Intake Source	☐ IV Fluids ☐ Medications ☐ Drip Medications ☐ Enteral feeding ☐ Free water ☐ Other PO fluids ☐ Other
Daily Urine Output	From 24h I/O on Rounding Report
Daily Net Volume	From 24h I/O on Rounding Report
Comments	

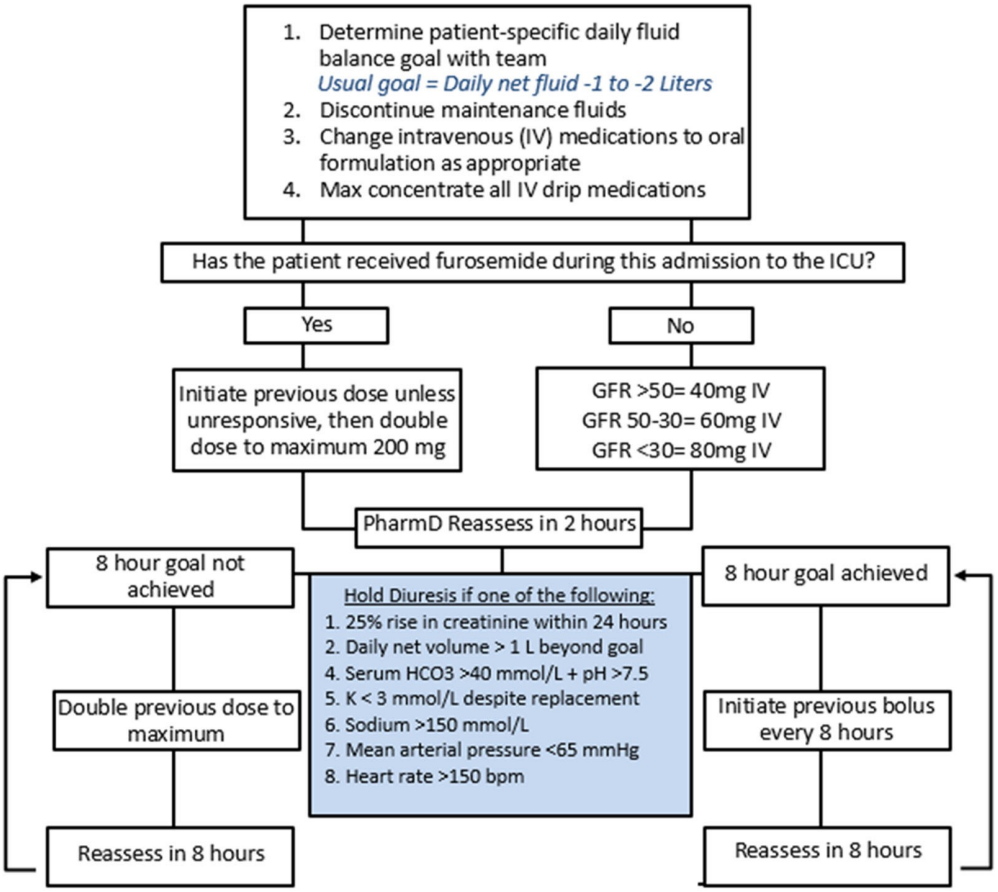
Daily Net Fluid Goal	☐ Net even ☐ -500 mL ☐ -1000 mL ☐ -1500 mL ☐ -2000 mL ☐ Greater than -2000 mL
Daily Net Fluid goal achieved?	○ Yes ○ No reset Was daily net fluid goal achieved (if < 24 hours from first dose of diuretic but based on extrapolation, goal achieved anticipated and no further titration of diuretics - say yes)
Protocol Deviation	○ Yes ○ No reset
Reason for Deviation	Expand
Starting Dose (mg)	
Dose Decrease Required	○ Yes ○ No reset
Dose Decrease Utilized	Percentage of Original Dose
Dose Interval Changed	○ Yes ○ No reset
Dose Interval Change	☐ Decreased to q8h ☐ Decreased to q12h ☐ Decreased to q24h ☐ n/a
Total Daily Dose (mg)	For the 24 hour period/day
Number of Dose Increases	○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ None reset
Nursing Driven Dose Adjustment?	○ Yes ○ No reset Did RN utilize activatable orders
Effective Dose	☐ 40 mg IV ☐ 60 mg IV ☐ 80 mg IV ☐ 120 mg IV ☐ 160 mg IV ☐ 200 mg IV ☐ Never found ☐ 20 mg IV Minimum effective dose (if found)
Effective Interval	☐ q6h ☐ q8h ☐ q12h ☐ q24h ☐ Never found

Adjunct Diuretic	☐ Metolazone ☐ Chlorothiazide ☐ Acetazolamide ☐ Albumin ☐ Other ☐ None
Initiation of continuous infusion	○ Yes ○ No reset
Concomitant Nephrotoxin	☐ aminoglycosides ☐ amphotericin B ☐ beta-lactams ☐ calcineurin inhibitors ☐ intravenous contrast ☐ foscarnet ☐ ganciclovir ☐ sulfamethoxazole/trimethoprim, ☐ vancomycin ☐ acyclovir ☐ none ☐ ACEi

Primary Reason for Admission	☐ Septic shock ☐ Acute liver failure ☐ Acute respiratory failure ☐ Acute kidney injury ☐ Seizures ☐ GI Bleed ☐ Oncologic emergency ☐ Overdose/toxicology ☐ Metabolic, other ☐ Infection, other ☐ Pulmonary, other ☐ Cardiac arrest ☐ Altered mental status ☐ Hepatic, other ☐ Cardiac, other ☐ ESRD
Exclusion Criteria Met	☐ Diabetic ketoacidosis/ Hyperosmolar hyperglycemic state ☐ Rhabdomyolysis with a CK above 5000 ☐ Diagnosis of hepatorenal syndrome (i.e. failure to respond to albumin challenge and withdrawal of diuretics for 48 hours) in the first 72 hours of active treatment including albumin + vasopressors or midodrine/octreotide ☐ Acute renal failure with active consult to nephrology consult team ☐ Anuric (Zero UOP x 12 hours) ☐ Comfort care decision to limit support or imminent death ☐ Pregnancy ☐ Intubated for procedure or anticipated vent duration < 48 hours ☐ Vasopressor administration or crystalloid administration for non-cardiogenic shock in the last 12, unless cardiogenic shock or norepinephrine doses < 0.05 mcg/kg/min ☐ Chronic vent/trach with no further wean
Comments	

Data Collection Instrument	Enrollment and Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Outcomes
Demographics	○											
Labs and Urine Output		○	○	○	○	○	○	○	○	○	○	
Diuretics		○	○	○	○	○	○	○	○	○	○	
Completion Data												○
Labs and Urine Output Baseline	○											
Exclusion Reason	○											

APPENDIX FIVE



REFERENCES

1. Marik PE: **The Physiology of Volume Resuscitation**. *Current Anesthesiology Reports* 2014, **4**(4):353-359.
2. Smith N, Silberman M: **Shock, Distributive**. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2018.
3. Beloncle F, Radermacher P, Guerin C, Asfar P: **Mean arterial pressure target in patients with septic shock**. *Minerva anestesiologica* 2016, **82**(7):777-784.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME *et al*: **Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016**. *Crit Care Med* 2017, **45**(3):486-552.
5. Marik PE, Lemson J: **Fluid responsiveness: an evolution of our understanding**. *British journal of anaesthesia* 2014, **112**(4):617-620.
6. Arshed S, Pinsky MR: **Applied Physiology of Fluid Resuscitation in Critical Illness**. *Critical care clinics* 2018, **34**(2):267-277.
7. Jacobs R, Lochy S, Malbrain M: **Phenylephrine-induced recruitable preload from the venous side**. *Journal of clinical monitoring and computing* 2018.
8. Wijnberge M, Sindhunata DP, Pinsky MR, Vlaar AP, Ouweneel E, Jansen JR, Veelo DP, Geerts BF: **Estimating mean circulatory filling pressure in clinical practice: a systematic review comparing three bedside methods in the critically ill**. *Annals of intensive care* 2018, **8**(1):73.
9. Carcillo JA, Davis AL, Zaritsky A: **Role of early fluid resuscitation in pediatric septic shock**. *Jama* 1991, **266**(9):1242-1245.
10. Leisman D, Wie B, Doerfler M, Bianculli A, Ward MF, Akerman M, D'Angelo JK, Zemmel D'Amore JA: **Association of Fluid Resuscitation Initiation Within 30 Minutes of Severe Sepsis and Septic Shock Recognition With Reduced Mortality and Length of Stay**. *Annals of emergency medicine* 2016, **68**(3):298-311.
11. Lee SJ, Ramar K, Park JG, Gajic O, Li G, Kashyap R: **Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: a retrospective cohort study**. *Chest* 2014, **146**(4):908-915.
12. Nguyen HB, Jaehne AK, Jayaprakash N, Semler MW, Hegab S, Yataco AC, Tatem G, Salem D, Moore S, Boka K *et al*: **Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE**. *Critical care (London, England)* 2016, **20**(1):160.
13. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early goal-directed therapy in the treatment of severe sepsis and septic shock**. *The New England journal of medicine* 2001, **345**(19):1368-1377.
14. Jaehne AK, Rivers EP: **Early Liberal Fluid Therapy for Sepsis Patients Is Not Harmful: Hydrophobia Is Unwarranted but Drink Responsibly**. *Crit Care Med* 2016, **44**(12):2263-2269.
15. Maitland K, George EC, Evans JA, Kiguli S, Olupot-Olupot P, Akech SO, Opoka RO, Engoru C, Nyeko R, Mtove G *et al*: **Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial**. *BMC medicine* 2013, **11**:68.
16. Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, Avidan A, Beeri R, Weissman C, Jaffe AS *et al*: **Diastolic dysfunction and mortality in severe sepsis and septic shock**. *European heart journal* 2012, **33**(7):895-903.
17. Rolando G, Espinoza ED, Avid E, Welsh S, Pozo JD, Vazquez AR, Arzani Y, Masevicius FD, Dubin A: **Prognostic value of ventricular diastolic dysfunction in patients with severe sepsis and septic shock**. *Revista Brasileira de terapia intensiva* 2015, **27**(4):333-339.
18. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP *et al*: **Role of left ventricular stiffness in heart failure with normal ejection fraction**. *Circulation* 2008, **117**(16):2051-2060.

19. Schneider AJ, Teule GJ, Groeneveld AB, Nauta J, Heidendal GA, Thijs LG: **Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study**. *American heart journal* 1988, **116**(1 Pt 1):103-112.
20. Elbers P, Rodrigus T, Nossent E, Malbrain ML, Vonk-Noordegraaf A: **Fluid therapy in critically ill patients: perspectives from the right heart**. *Anaesthesiology intensive therapy* 2015, **47 Spec No**:s38-43.
21. Edwards MR, Mythen MG: **Fluid therapy in critical illness**. *Extreme Physiology & Medicine* 2014, **3**(1):16.
22. Jacob M, Chappell D, Rehm M: **The 'third space'--fact or fiction?** *Best practice & research Clinical anaesthesiology* 2009, **23**(2):145-157.
23. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R: **A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group**. *The New England journal of medicine* 1995, **333**(16):1025-1032.
24. Velmahos GC, Demetriades D, Shoemaker WC, Chan LS, Tatevossian R, Wo CC, Vassiliu P, Cornwell EE, 3rd, Murray JA, Roth B *et al*: **Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial**. *Annals of surgery* 2000, **232**(3):409-418.
25. Ueyama H, Kiyonaka S: **Predicting the Need for Fluid Therapy-Does Fluid Responsiveness Work?** *Journal of intensive care* 2017, **5**:34.
26. Bennett VA, Vidouris A, Cecconi M: **Effects of Fluids on the Macro- and Microcirculations**. *Critical care (London, England)* 2018, **22**(1):74.
27. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T *et al*: **Mortality after fluid bolus in African children with severe infection**. *The New England journal of medicine* 2011, **364**(26):2483-2495.
28. Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Bernard GR: **Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia**. *Crit Care Med* 2014, **42**(11):2315-2324.
29. Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Mabula C, Bwalya M, Bernard GR: **Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: A Randomized Clinical Trial**. *Jama* 2017, **318**(13):1233-1240.
30. Hughes RE, Magovern GJ: **The relationship between right atrial pressure and blood volume**. *AMA archives of surgery* 1959, **79**(2):238-243.
31. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R *et al*: **Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012**. *Crit Care Med* 2013, **41**(2):580-637.
32. De Backer D, Vincent JL: **Should we measure the central venous pressure to guidefluid management? Ten answers to 10 questions**. *Critical care (London, England)* 2018, **22**(1):43.
33. Belloni L, Pisano A, Natale A, Piccirillo MR, Piazza L, Ismeno G, De Martino G: **Assessment of fluid-responsiveness parameters for off-pump coronary artery bypass surgery: a comparison among LiDCO, transesophageal echochardiography, and pulmonary artery catheter**. *Journal of cardiothoracic and vascular anesthesia* 2008, **22**(2):243-248.
34. Eskesen TG, Wetterslev M, Perner A: **Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness**. *Intensive care medicine* 2016, **42**(3):324-332.
35. Lee JH, Kim JT, Yoon SZ, Lim YJ, Jeon Y, Bahk JH, Kim CS: **Evaluation of corrected flow time in oesophageal Doppler as a predictor of fluid responsiveness**. *British journal of anaesthesia* 2007, **99**(3):343-348.
36. Marik PE, Cavallazzi R: **Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense**. *Crit Care Med* 2013, **41**(7):1774-1781.

37. Marik PE, Cavallazzi R, Vasu T, Hirani A: **Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature**. *Crit Care Med* 2009, **37**(9):2642-2647.
38. Rex S, Brose S, Metzelder S, Huneke R, Schalte G, Autschbach R, Rossaint R, Buhre W: **Prediction of fluid responsiveness in patients during cardiac surgery**. *British journal of anaesthesia* 2004, **93**(6):782-788.
39. Wagner JG, Leatherman JW: **Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge**. *Chest* 1998, **113**(4):1048-1054.
40. Wang X, Chen H, Liu D, Zhang Q, Su L: **The correlation between CVP-derived parameters and the prognosis of critically ill patients**. *Journal of critical care* 2017, **40**:257-264.
41. Miller A, Mandeville J: **Predicting and measuring fluid responsiveness with echocardiography**. *Echo research and practice* 2016, **3**(2):G1-g12.
42. Monnet X, Marik PE, Teboul JL: **Prediction of fluid responsiveness: an update**. *Annals of intensive care* 2016, **6**(1):111.
43. Richard JC, Bayle F, Bourdin G, Leray V, Debord S, Delannoy B, Stoian AC, Wallet F, Yonis H, Guerin C: **Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial**. *Critical care (London, England)* 2015, **19**:5.
44. Chen C, Kollef MH: **Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study**. *Chest* 2015, **148**(6):1462-1469.
45. Nunes TS, Ladeira RT, Bafi AT, de Azevedo LC, Machado FR, Freitas FG: **Duration of hemodynamic effects of crystalloids in patients with circulatory shock after initial resuscitation**. *Annals of intensive care* 2014, **4**:25.
46. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, Van Regenmortel N: **Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice**. *Anaesthesiology intensive therapy* 2014, **46**(5):361-380.
47. Kayilioglu SI, Dinc T, Sozen I, Bostanoglu A, Cete M, Coskun F: **Postoperative fluid management**. *World journal of critical care medicine* 2015, **4**(3):192-201.
48. Glassford NJ, Bellomo R: **The Complexities of Intravenous Fluid Research: Questions of Scale, Volume, and Accumulation**. *Korean J Crit Care Med* 2016, **31**(4):276-299.
49. Daniels LM, Johnson AB, Cornelius PJ, Bowron C, Lehnertz A, Moore M, Shen Y, Schulte PJ, Pendegraft RS, Hall KR *et al*: **Improving Quality of Life in Patients at Risk for Post-Intensive Care Syndrome**. *Mayo Clinic proceedings Innovations, quality & outcomes* 2018, **2**(4):359-369.
50. Self WH, Semler MW, Bellomo R, Brown SM, deBoisblanc BP, Exline MC, Ginde AA, Grissom CK, Janz DR, Jones AE *et al*: **Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial**. *Annals of emergency medicine* 2018, **72**(4):457-466.
51. Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, Anderson DJ, Warren DK, Dantes RB, Epstein L *et al*: **Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care HospitalsPrevalence, Underlying Causes, and Preventability of Sepsis-Associated MortalityPrevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality**. *JAMA Network Open* 2019, **2**(2):e187571-e187571.
52. Morris ZS, Wooding S, Grant J: **The answer is 17 years, what is the question: understanding time lags in translational research**. *Journal of the Royal Society of Medicine* 2011, **104**(12):510-520.
53. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C *et al*: **Hydrocortisone plus Fludrocortisone for Adults with Septic Shock**. *The New England journal of medicine* 2018, **378**(9):809-818.

54. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M *et al*: **Adjunctive Glucocorticoid Therapy in Patients with Septic Shock**. *The New England journal of medicine* 2018, **378**(9):797-808.
55. Macdonald SPJ, Taylor DM, Keijzers G, Arendts G, Fatovich DM, Kinnear FB, Brown SGA, Bellomo R, Burrows S, Fraser JF *et al*: **REstricted Fluid REsuscitation in Sepsis-associated Hypotension (REFRESH): study protocol for a pilot randomised controlled trial**. *Trials* 2017, **18**(1):399.
56. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, Malbrain ML: **Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance**. *Annals of intensive care* 2012, **2**(Suppl 1 Diagnosis and management of intra-abdominal hyperten):S1.
57. Malbrain MLNG, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal P-J, Joannes-Boyau O, Teboul J-L, Rice TW, Mythen M, Monnet X: **Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy**. *Annals of intensive care* 2018, **8**(1):66.
58. Claure-Del Granado R, Mehta RL: **Fluid overload in the ICU: evaluation and management**. *BMC nephrology* 2016, **17**(1):109.
59. Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA: **Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study**. *Chest* 2000, **117**(6):1749-1754.
60. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D: **Sepsis in European intensive care units: results of the SOAP study**. *Crit Care Med* 2006, **34**(2):344-353.
61. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V, Aaen A, Lodahl D, Berthelsen RE, Christensen H *et al*: **Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial**. *Intensive care medicine* 2016, **42**(11):1695-1705.
62. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA: **Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality**. *Crit Care Med* 2011, **39**(2):259-265.
63. Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA: **Both Positive and Negative Fluid Balance May Be Associated With Reduced Long-Term Survival in the Critically Ill**. *Crit Care Med* 2017, **45**(8):e749-e757.
64. Tigabu BM, Davari M, Kebriaeezadeh A, Mojtahedzadeh M: **Fluid volume, fluid balance and patient outcome in severe sepsis and septic shock: A systematic review**. *Journal of critical care* 2018, **48**:153-159.
65. Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, Schroeder ME, Marshall JC, Vincent JL: **Higher Fluid Balance Increases the Risk of Death From Sepsis:Results From a Large International Audit**. *Crit Care Med* 2017, **45**(3):386-394.
66. Assaad S, Kratzert WB, Shelley B, Friedman MB, Perrino A, Jr.: **Assessment of Pulmonary Edema: Principles and Practice**. *Journal of cardiothoracic and vascular anesthesia* 2018, **32**(2):901-914.
67. **Blood Flow to the Lung.** . In: *Pulmonary Physiology*. Edited by Levitzky MG, 9e edn. New York, NY: McGraw-Hill; 2018.
68. Maslove DM, Chen BT, Wang H, Kuschner WG: **The diagnosis and management of pleural effusions in the ICU**. *Journal of intensive care medicine* 2013, **28**(1):24-36.
69. Simmons RS, Berdine GG, Seidenfeld JJ, Prihoda TJ, Harris GD, Smith JD, Gilbert TJ, Mota E, Johanson WG, Jr.: **Fluid balance and the adult respiratory distress syndrome**. *The American review of respiratory disease* 1987, **135**(4):924-929.
70. Sakr Y, Vincent JL, Reinhart K, Groeneveld J, Michalopoulos A, Sprung CL, Artigas A, Ranieri VM: **High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury**. *Chest* 2005, **128**(5):3098-3108.

71. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, Micek ST, Kollef MH: **The importance of fluid management in acute lung injury secondary to septic shock**. *Chest* 2009, **136**(1):102-109.
72. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Jr., Hite RD, Harabin AL: **Comparison of two fluid-management strategies in acute lung injury**. *The New England journal of medicine* 2006, **354**(24):2564-2575.
73. Rivers EP: **Fluid-management strategies in acute lung injury--liberal, conservative, or both?** *The New England journal of medicine* 2006, **354**(24):2598-2600.
74. Jozwiak M, Teboul JL, Monnet X: **Extravascular lung water in critical care: recent advances and clinical applications**. *Annals of intensive care* 2015, **5**(1):38.
75. Tagami T, Ong MEH: **Extravascular lung water measurements in acute respiratory distress syndrome: why, how, and when?** *Current opinion in critical care* 2018, **24**(3):209-215.
76. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A: **Prognostic value of extravascular lung water in critically ill patients**. *Chest* 2002, **122**(6):2080-2086.
77. Sturm JA. Entwicklung und Bedeutung der Lungenwassermessung in Klinik und Experiment. In: Bergmann H GH, Steinbereithner K, et al, eds. Beitra¨ge zur Ana¨sthesiologie und Intensivmedizin. Wien, Austria: Verlag Wilhelm Maudrich, 1984; 15–39.
78. Eisenberg PR, Hansbrough JR, Anderson D, Schuster DP: **A prospective study of lung water measurements during patient management in an intensive care unit**. *The American review of respiratory disease* 1987, **136**(3):662-668.
79. Phillips CR, Chesnutt MS, Smith SM: **Extravascular lung water in sepsis-associated acute respiratory distress syndrome: indexing with predicted body weight improves correlation with severity of illness and survival**. *Crit Care Med* 2008, **36**(1):69-73.
80. Jozwiak M, Silva S, Persichini R, Anguel N, Osman D, Richard C, Teboul JL, Monnet X: **Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome**. *Crit Care Med* 2013, **41**(2):472-480.
81. Yang CS, Qiu HB, Liu SQ, Yang Y, Huang YZ, Liu L: **[The prognostic value of extravascular lung water index in critically ill septic shock patients]**. *Zhonghua nei ke za zhi* 2006, **45**(3):192-195.
82. Bhattacharjee A, Pradhan D, Bhattacharyya P, Dey S, Chhunthang D, Handique A, Barman A, Yunus M: **How Useful is Extravascular Lung Water Measurement in Managing Lung Injury in Intensive Care Unit?** *Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine* 2017, **21**(8):494-499.
83. Davey-Quinn A, Gedney JA, Whiteley SM, Bellamy MC: **Extravascular lung water and acute respiratory distress syndrome--oxygenation and outcome**. *Anaesthesia and intensive care* 1999, **27**(4):357-362.
84. Martin GS, Eaton S, Mealer M, Moss M: **Extravascular lung water in patients with severe sepsis: a prospective cohort study**. *Critical care (London, England)* 2005, **9**(2):R74-82.
85. Mitchell JP, Schuller D, Calandrino FS, Schuster DP: **Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization**. *The American review of respiratory disease* 1992, **145**(5):990-998.
86. Zhang Z, Lu B, Ni H: **Prognostic value of extravascular lung water index in critically ill patients: a systematic review of the literature**. *Journal of critical care* 2012, **27**(4):420.e421-428.
87. Tagami T, Nakamura T, Kushimoto S, Tosa R, Watanabe A, Kaneko T, Fukushima H, Rinka H, Kudo D, Uzu H *et al*: **Early-phase changes of extravascular lung water index as a prognostic indicator in acute respiratory distress syndrome patients**. *Annals of intensive care* 2014, **4**:27.
88. Monnet X, Teboul JL: **Transpulmonary thermodilution: advantages and limits**. *Critical care (London, England)* 2017, **21**(1):147.

89. Belda FJ, Aguilar G, Teboul JL, Pestana D, Redondo FJ, Malbrain M, Luis JC, Ramasco F, Umgelter A, Wendon J *et al*: **Complications related to less-invasive haemodynamic monitoring**. *British journal of anaesthesia* 2011, **106**(4):482-486.
90. Brown LM, Calfee CS, Howard JP, Craig TR, Matthay MA, McAuley DF: **Comparison of thermodilution measured extravascular lung water with chest radiographic assessment of pulmonary oedema in patients with acute lung injury**. *Annals of intensive care* 2013, **3**(1):25.
91. Humphrey H, Hall J, Sznajder I, Silverstein M, Wood L: **Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure**. *Chest* 1990, **97**(5):1176-1180.
92. **Pulmonary Artery Catheter Consensus conference: consensus statement**. *Crit Care Med* 1997, **25**(6):910-925.
93. Pandey A, Khera R, Kumar N, Golwala H, Girotra S, Fonarow GC: **Use of Pulmonary Artery Catheterization in US Patients With Heart Failure, 2001-2012**. *JAMA internal medicine* 2016, **176**(1):129-132.
94. Butman SM, Ewy GA, Standen JR, Kern KB, Hahn E: **Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension**. *Journal of the American College of Cardiology* 1993, **22**(4):968-974.
95. Marantz PR, Kaplan MC, Alderman MH: **Clinical diagnosis of congestive heart failure in patients with acute dyspnea**. *Chest* 1990, **97**(4):776-781.
96. Peacock WF, Soto KM: **Current techniques of fluid status assessment**. *Contributions to nephrology* 2010, **164**:128-142.
97. Ruskin JA, Gurney JW, Thorsen MK, Goodman LR: **Detection of pleural effusions on supine chest radiographs**. *AJR American journal of roentgenology* 1987, **148**(4):681-683.
98. Chait A, Cohen HE, Meltzer LE, VanDurme JP: **The bedside chest radiograph in the evaluation of incipient heart failure**. *Radiology* 1972, **105**(3):563-566.
99. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM: **The epidemiology of mechanical ventilation use in the United States**. *Crit Care Med* 2010, **38**(10):1947-1953.
100. Dries DJ: **Mechanical Ventilation: History and Harm**. *Air medical journal* 2016, **35**(1):12-15.
101. Kamio T, Masamune K: **Mechanical Ventilation-Related Safety Incidents in General Care Wards and ICU Settings**. *Respiratory care* 2018, **63**(10):1246-1252.
102. Tobin MJ: **Principles of Mechanical Ventilation**. In: *Fishman's Pulmonary Diseases and Disorders, 5e*. Edited by Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, Siegel MD. New York, NY: McGraw-Hill Education; 2015.
103. Epstein SK: **Extubation**. *Respiratory care* 2002, **47**(4):483-492; discussion 493-485.
104. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF: **Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously**. *The New England journal of medicine* 1996, **335**(25):1864-1869.
105. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, Jaeschke RZ, Brun-Buisson C: **Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients**. *Annals of internal medicine* 1998, **129**(6):433-440.
106. Antonio AC, Teixeira C, Castro PS, Savi A, Oliveira RP, Gazzana MB, Knorst M: **48-Hour Fluid Balance Does Not Predict a Successful Spontaneous Breathing Trial**. *Respiratory care* 2015, **60**(8):1091-1096.
107. Perren A, Brochard L: **Managing the apparent and hidden difficulties of weaning from mechanical ventilation**. *Intensive care medicine* 2013, **39**(11):1885-1895.
108. Upadya A, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA: **Fluid balance and weaning outcomes**. *Intensive care medicine* 2005, **31**(12):1643-1647.

109. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguia C, Gonzalez M, Hill NS, Nava S, D'Empaire G *et al*: **Risk factors for extubation failure in patients following a successful spontaneous breathing trial**. *Chest* 2006, **130**(6):1664-1671.
110. Husain-Syed F, Slutsky AS, Ronco C: **Lung-Kidney Cross-Talk in the Critically Ill Patient**. *American journal of respiratory and critical care medicine* 2016, **194**(4):402-414.
111. Traynor J, Mactier R, Geddes CC, Fox JG: **How to measure renal function in clinical practice**. *BMJ (Clinical research ed)* 2006, **333**(7571):733-737.
112. Maxwell RA, Bell CM: **Acute Kidney Injury in the Critically Ill**. *The Surgical clinics of North America* 2017, **97**(6):1399-1418.
113. Flood L, Nichol A: **Acute kidney injury and the critically ill**. *Anaesthesia & Intensive Care Medicine* 2018, **19**(3):113-118.
114. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, Paganini EP, Chertow GM: **Spectrum of acute renal failure in the intensive care unit: the PICARD experience**. *Kidney international* 2004, **66**(4):1613-1621.
115. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, Kaplan RM: **A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure**. *Kidney international* 2001, **60**(3):1154-1163.
116. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T,Pallot JL, Chiche JD, Taupin P, Landais P *et al*: **Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial**. *Lancet (London, England)* 2006, **368**(9533):379-385.
117. Khwaja A: **KDIGO clinical practice guidelines for acute kidney injury**. *Nephron Clinical practice* 2012, **120**(4):c179-184.
118. Bellomo R, Kellum JA, Ronco C: **Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria**. *Intensive care medicine* 2007, **33**(3):409-413.
119. Hoste EA, Kellum JA: **Acute kidney injury: epidemiology and diagnostic criteria**. *Current opinion in critical care* 2006, **12**(6):531-537.
120. Lamb EJ, Tomson CR, Roderick PJ: **Estimating kidney function in adults using formulae**. *Annals of clinical biochemistry* 2005, **42**(Pt 5):321-345.
121. Levy EM, Viscoli CM, Horwitz RI: **The effect of acute renal failure on mortality. A cohort analysis**. *Jama* 1996, **275**(19):1489-1494.
122. Delanaye P, Cavalier E, Pottel H: **Serum Creatinine: Not So Simple!** *Nephron* 2017, **136**(4):302-308.
123. Ikizler TA, Sezer MT, Flakoll PJ, Hariachar S, Kanagasundaram NS, Gritter N, Knights S, Shyr Y, Paganini E, Hakim RM *et al*: **Urea space and total body water measurements by stable isotopes in patients with acute renal failure**. *Kidney international* 2004, **65**(2):725-732.
124. Himmelfarb J, Evanson J, Hakim RM, Freedman S, Shyr Y, Ikizler TA: **Urea volume of distribution exceeds total body water in patients with acute renal failure**. *Kidney international* 2002, **61**(1):317-323.
125. Cerda J, Cerda M, Kilcullen P, Prendergast J: **In severe acute kidney injury, a higher serum creatinine is paradoxically associated with better patient survival**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2007, **22**(10):2781-2784.
126. Mehta RL, Pascual MT, Gruta CG, Zhuang S, Chertow GM: **Refining predictive models in critically ill patients with acute renal failure**. *Journal of the American Society of Nephrology : JASN* 2002, **13**(5):1350-1357.
127. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A *et al*: **External validation of severity scoring systems for acute renal failure using a multinational database**. *Crit Care Med* 2005, **33**(9):1961-1967.

128. Glassford NJ, Bellomo R: **Does Fluid Type and Amount Affect Kidney Function in Critical Illness?** *Critical care clinics* 2018, **34**(2):279-298.
129. Kellum JA, Lameire N: **Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1)**. *Critical care (London, England)* 2013, **17**(1):204.
130. Legrand M, Payen D: **Understanding urine output in critically ill patients**. *Annals of intensive care* 2011, **1**(1):13.
131. Md Ralib A, Pickering JW, Shaw GM, Endre ZH: **The urine output definition of acute kidney injury is too liberal**. *Critical care (London, England)* 2013, **17**(3):R112.
132. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G: **Classifying AKI by Urine Output versus Serum Creatinine Level**. *Journal of the American Society of Nephrology : JASN* 2015, **26**(9):2231-2238.
133. Cruz DN, Bolgan I, Perazella MA, Bonello M, de Cal M, Corradi V, Polanco N, Ocampo C, Nalesso F, Piccinni P *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 : CJASN* 2007, **2**(3):418-425.
134. Macedo E, Malhotra R, Bouchard J, Wynn SK, Mehta RL: **Oliguria is an early predictor of higher mortality in critically ill patients**. *Kidney international* 2011, **80**(7):760-767.
135. Jin K, Murugan R, Sileanu FE, Foldes E, Priyanka P, Clermont G, Kellum JA: **Intensive Monitoring of Urine Output Is Associated With Increased Detection of Acute Kidney Injury and Improved Outcomes**. *Chest* 2017, **152**(5):972-979.
136. Fulop T, Zsom L, Tapolyai MB, Molnar MZ, Rosivall L: **Volume-related weight gain as an independent indication for renal replacement therapy in the intensive care units**. *Journal of renal injury prevention* 2017, **6**(1):35-42.
137. van den Akker JP, Egal M, Groeneveld AB: **Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis**. *Critical care (London, England)* 2013, **17**(3):R98.
138. Chao CT, Hou CC, Wu VC, Lu HM, Wang CY, Chen L, Kao TW: **The impact of dialysis-requiring acute kidney injury on long-term prognosis of patients requiring prolonged mechanical ventilation: nationwide population-based study**. *PloS one* 2012, **7**(12):e50675.
139. Datta D, Foley RJ, Wu R, Grady J, Scalise P: **Renal Function, Weaning, and Survival in Patients With Ventilator-Dependent Respiratory Failure**. *Journal of intensive care medicine* 2017:885066617696849.
140. Solymosi EA, Kaestle-Gembardt SM, Vadasz I, Wang L, Neye N, Chupin CJ, Rozowsky S, Ruehl R, Tabuchi A, Schulz H *et al*: **Chloride transport-driven alveolar fluid secretion is a major contributor to cardiogenic lung edema**. *Proceedings of the National Academy of Sciences of the United States of America* 2013, **110**(25):E2308-2316.
141. Ricksten SE, Bragadottir G, Redfors B: **Renal oxygenation in clinical acute kidney injury**. *Critical care (London, England)* 2013, **17**(2):221.
142. Hemlin M, Ljungman S, Carlson J, Maljukanovic S, Mobini R, Bech-Hanssen O, Skoogh BE: **The effects of hypoxia and hypercapnia on renal and heart function, haemodynamics and plasma hormone levels in stable COPD patients**. *The clinical respiratory journal* 2007, **1**(2):80-90.
143. Sharkey RA, Mulloy EM, O'Neill SJ: **Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects**. *The European respiratory journal* 1998, **12**(3):653-657.
144. Anand IS: **Cardiorenal syndrome: a cardiologist's perspective of pathophysiology**. *Clinical journal of the American Society of Nephrology : CJASN* 2013, **8**(10):1800-1807.
145. Kuiper JW, Groeneveld AB, Slutsky AS, Plotz FB: **Mechanical ventilation and acute renal failure**. *Crit Care Med* 2005, **33**(6):1408-1415.
146. House AA, Anand I, Bellomo R, Cruz D, Bobek I, Anker SD, Aspromonte N, Bagshaw S, Berl T, Daliento L *et al*: **Definition and classification of Cardio-Renal Syndromes: workgroup**

statements from the 7th ADQI Consensus Conference. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2010, **25**(5):1416-1420.
147. Hermoye L, Annet L, Lemmerling P, Peeters F, Jamar F, Gianello P, Van Huffel S, Van Beers BE: **Calculation of the renal perfusion and glomerular filtration rate from the renal impulse response obtained with MRI**. *Magnetic resonance in medicine* 2004, **51**(5):1017-1025.
148. Hanberg JS, Sury K, Wilson FP, Brisco MA, Ahmad T, Ter Maaten JM, Broughton JS, Assefa M, Tang WHW, Parikh CR *et al*: **Reduced Cardiac Index Is Not the Dominant Driver of Renal Dysfunction in Heart Failure**. *Journal of the American College of Cardiology* 2016, **67**(19):2199-2208.
149. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW: **Importance of venous congestion for worsening of renal function in advanced decompensated heart failure**. *Journal of the American College of Cardiology* 2009, **53**(7):589-596.
150. Winton FR: **The influence of venous pressure on the isolated mammalian kidney**. *The Journal of physiology* 1931, **72**(1):49-61.
151. Blake WD, Wegria R, et al.: **Effect of increased renal venous pressure on renal function**. *The American journal of physiology* 1949, **157**(1):1-13.
152. Testani JM, Khera AV, St John Sutton MG, Keane MG, Wiegers SE, Shannon RP, Kirkpatrick JN: **Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure**. *The American journal of cardiology* 2010, **105**(4):511-516.
153. Raimundo M, Crichton S, Syed Y, Martin JR, Beale R, Treacher D, Ostermann M: **Low Systemic Oxygen Delivery and BP and Risk of Progression of Early AKI**. *Clinical journal of the American Society of Nephrology : CJASN* 2015, **10**(8):1340-1349.
154. Van Biesen W, Yegenaga I, Vanholder R, Verbeke F, Hoste E, Colardyn F, Lameire N: **Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: a prospective analysis**. *Journal of nephrology* 2005, **18**(1):54-60.
155. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL: **Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease**. *Journal of the American College of Cardiology* 2009, **53**(7):582-588.
156. Patel DM, Connor MJ, Jr.: **Intra-Abdominal Hypertension and Abdominal Compartment Syndrome: An Underappreciated Cause of Acute Kidney Injury**. *Advances in chronic kidney disease* 2016, **23**(3):160-166.
157. Ortiz-Diaz E, Lan CK: **Intra-abdominal hypertension in medical critically ill patients: a narrative review**. *Shock (Augusta, Ga)* 2014, **41**(3):175-180.
158. Daugherty EL, Hongyan L, Taichman D, Hansen-Flaschen J, Fuchs BD: **Abdominal compartment syndrome is common in medical intensive care unit patients receiving large-volume resuscitation**. *Journal of intensive care medicine* 2007, **22**(5):294-299.
159. Anvari E, Nantsupawat N, Gard R, Raj R, Nugent K: **Bladder Pressure Measurements in Patients Admitted to a Medical Intensive Care Unit**. *The American journal of the medical sciences* 2015, **350**(3):181-185.
160. Regueira T, Bruhn A, Hasbun P, Aguirre M, Romero C, Llanos O, Castro R, Bugedo G, Hernandez G: **Intra-abdominal hypertension: incidence and association with organ dysfunction during early septic shock**. *Journal of critical care* 2008, **23**(4):461-467.
161. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH: **Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function?** *Journal of the American College of Cardiology* 2008, **51**(3):300-306.

162. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W: **Abdominal contributions to cardiorenal dysfunction in congestive heart failure**. *Journal of the American College of Cardiology* 2013, **62**(6):485-495.
163. Bloomfield GL, Blocher CR, Fakhry IF, Sica DA, Sugerman HJ: **Elevated intra-abdominal pressure increases plasma renin activity and aldosterone levels**. *The Journal of trauma* 1997, **42**(6):997-1004; discussion 1004-1005.
164. Dalfino L, Tullo L, Donadio I, Malcangi V, Brienza N: **Intra-abdominal hypertension and acute renal failure in critically ill patients**. *Intensive care medicine* 2008, **34**(4):707-713.
165. McNelis J, Marini CP, Jurkiewicz A, Fields S, Caplin D, Stein D, Ritter G, Nathan I, Simms HH: **Predictive factors associated with the development of abdominal compartment syndrome in the surgical intensive care unit**. *Archives of surgery (Chicago, Ill : 1960)* 2002, **137**(2):133-136.
166. Gelman S, Mushlin PS: **Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics**. *Anesthesiology* 2004, **100**(2):434-439.
167. Sakka SG, Reinhart K, Wegscheider K, Meier-Hellmann A: **Variability of splanchnic blood flow in patients with sepsis**. *Intensive care medicine* 2001, **27**(8):1281-1287.
168. Sam AD, 2nd, Sharma AC, Law WR, Ferguson JL: **Splanchnic vascular control during sepsis and endotoxemia**. *Frontiers in bioscience : a journal and virtual library* 1997, **2**:e72-92.
169. Jakob SM: **Clinical review: splanchnic ischaemia**. *Critical care (London, England)* 2002, **6**(4):306-312.
170. Blankstein R, Bakris GL: **Renal hemodynamic changes in heart failure**. *Heart failure clinics* 2008, **4**(4):411-423.
171. Sambandam KK: **Effective use of loop diuretics in heart failure exacerbation: a nephrologist's view**. *The American journal of the medical sciences* 2014, **347**(2):139-145.
172. Ruggenenti P, Remuzzi G: **Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney**. *European heart journal* 2011, **32**(20):2476-2478.
173. Colombo PC, Ganda A, Lin J, Onat D, Harxhi A, Iyasere JE, Uriel N, Cotter G: **Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome**. *Heart failure reviews* 2012, **17**(2):177-190.
174. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL: **Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury**. *Kidney international* 2009, **76**(4):422-427.
175. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL: **A positive fluid balance is associated with a worse outcome in patients with acute renal failure**. *Critical care (London, England)* 2008, **12**(3):R74.
176. Fulop T, Pathak MB, Schmidt DW, Lengvarszky Z, Juncos JP, Lebrun CJ, Brar H, Juncos LA: **Volume-related weight gain and subsequent mortality in acute renal failure patients treated with continuous renal replacement therapy**. *ASAIO journal (American Society for Artificial Internal Organs : 1992)* 2010, **56**(4):333-337.
177. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD: **Fluid balance, diuretic use, and mortality in acute kidney injury**. *Clinical journal of the American Society of Nephrology : CJASN* 2011, **6**(5):966-973.
178. Heung M, Wolfgram DF, Kommareddi M, Hu Y, Song PX, Ojo AO: **Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2012, **27**(3):956-961.
179. Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, Laurila JJ, Mildh L, Reinikainen M, Lund V *et al*: **Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study**. *Critical care (London, England)* 2012, **16**(5):R197.

180. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, Lo S, McArthur C, McGuiness S, Norton R *et al*: **An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial**. *Crit Care Med* 2012, **40**(6):1753-1760.
181. Teixeira C, Garzotto F, Piccinni P, Brienza N, Iannuzzi M, Gramaticopolo S, Forfori F, Pelaia P, Rocco M, Ronco C *et al*: **Fluid balance and urine volume are independent predictors of mortality in acute kidney injury**. *Critical care (London, England)* 2013, **17**(1):R14.
182. Raimundo M, Crichton S, Martin JR, Syed Y, Varrier M, Wyncoll D, Ostermann M: **Increased Fluid Administration After Early Acute Kidney Injury is Associated with Less Renal Recovery**. *Shock (Augusta, Ga)* 2015, **44**(5):431-437.
183. Wang N, Jiang L, Zhu B, Wen Y, Xi XM: **Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study**. *Critical care (London, England)* 2015, **19**:371.
184. Neyra JA, Li X, Canepa-Escaro F, Adams-Huet B, Toto RD, Yee J, Hedayati SS: **Cumulative Fluid Balance and Mortality in Septic Patients With or Without Acute Kidney Injury and Chronic Kidney Disease**. *Crit Care Med* 2016, **44**(10):1891-1900.
185. Thongprayoon C, Cheungpasitporn W, Srivali N, Ungprasert P, Kittanamongkolchai W, Kashani K: **The impact of fluid balance on diagnosis, staging and prediction of mortality in critically ill patients with acute kidney injury**. *Journal of nephrology* 2016, **29**(2):221-227.
186. Salahuddin N, Sammani M, Hamdan A, Joseph M, Al-Nemary Y, Alquaiz R, Dahli R, Maghrabi K: **Fluid overload is an independent risk factor for acute kidney injury in critically Ill patients: results of a cohort study**. *BMC nephrology* 2017, **18**(1):45.
187. Zhang L, Chen Z, Diao Y, Yang Y, Fu P: **Associations of fluid overload with mortality and kidney recovery in patients with acute kidney injury: A systematic review and meta-analysis**. *Journal of critical care* 2015, **30**(4):860.e867-813.
188. Flores FX, Brophy PD, Symons JM, Fortenberry JD, Chua AN, Alexander SR, Mahan JD, Bunchman TE, Blowey D, Somers MJ *et al*: **Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group**. *Pediatric nephrology (Berlin, Germany)* 2008, **23**(4):625-630.
189. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, Rogers K, Reid C, Tanner AJ, Easley KA: **Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis**. *Crit Care Med* 2004, **32**(8):1771-1776.
190. Gillespie RS, Seidel K, Symons JM: **Effect of fluid overload and dose of replacement fluid on survival in hemofiltration**. *Pediatric nephrology (Berlin, Germany)* 2004, **19**(12):1394-1399.
191. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R: **Outcome in children receiving continuous venovenous hemofiltration**. *Pediatrics* 2001, **107**(6):1309-1312.
192. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, Bunchman TE, Baker C, Mottes T, McAfee N *et al*: **Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy**. *Kidney international* 2005, **67**(2):653-658.
193. Alobaidi R, Morgan C, Basu RK, Stenson E, Featherstone R, Majumdar SR, Bagshaw SM: **Association Between Fluid Balance and Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis**. *JAMA pediatrics* 2018, **172**(3):257-268.
194. Arantes SS, Silva JM, Jr., De Aguilar-Nascimento JE, Dock-Nascimiento DB: **Effects of intravenous fluid overload on caloric and protein deficit in critically ill patients**. *Nutricion hospitalaria* 2018, **35**(5):1017-1023.
195. Colbert GB, Szerlip HM: **Euvolemia-A critical target in the management of acute kidney injury**. *Seminars in dialysis* 2019, **32**(1):30-34.

196. Colombo PC, Onat D, Harxhi A, Demmer RT, Hayashi Y, Jelic S, LeJemtel TH, Bucciarelli L, Kebschull M, Papapanou P *et al*: **Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation**. *European heart journal* 2014, **35**(7):448-454.
197. Lin J, Chudasama N, Hayashi Y, Hawk C, Ramnauth SD, Wong KY, Harxhi A, Onat D, Wakabayashi M, Uriel N *et al*: **Peripheral venous congestion causes time- and dose-dependent release of endothelin-1 in humans**. *Physiological reports* 2017, **5**(6).
198. Chappell D, Bruegger D, Potzel J, Jacob M, Brettner F, Vogeser M, Conzen P, Becker BF, Rehm M: **Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx**. *Critical care (London, England)* 2014, **18**(5):538.
199. Bruegger D, Jacob M, Rehm M, Loetsch M, Welsch U, Conzen P, Becker BF: **Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts**. *American journal of physiology Heart and circulatory physiology* 2005, **289**(5):H1993-1999.
200. Wang CH, Hsieh WH, Chou HC, Huang YS, Shen JH, Yeo YH, Chang HE, Chen SC, Lee CC: **Liberal versus restricted fluid resuscitation strategies in trauma patients: a systematic review and meta-analysis of randomized controlled trials and observational studies***. *Crit Care Med* 2014, **42**(4):954-961.
201. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM: **Perioperative fluid management strategies in major surgery: a stratified meta-analysis**. *Anesthesia and analgesia* 2012, **114**(3):640-651.
202. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I: **Effect of intraoperative fluid management on outcome after intraabdominal surgery**. *Anesthesiology* 2005, **103**(1):25-32.
203. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP: **Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial**. *Lancet (London, England)* 2002, **359**(9320):1812-1818.
204. Stein A, de Souza LV, Belettini CR, Menegazzo WR, Viegas JR, Costa Pereira EM, Eick R, Araujo L, Consolim-Colombo F, Irigoyen MC: **Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study**. *Critical care (London, England)* 2012, **16**(3):R99.
205. Haase-Fielitz A, Haase M, Bellomo R, Calzavacca P, Spura A, Baraki H, Kutschka I, Albert C: **Perioperative Hemodynamic Instability and Fluid Overload are Associated with Increasing Acute Kidney Injury Severity and Worse Outcome after Cardiac Surgery**. *Blood purification* 2017, **43**(4):298-308.
206. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH *et al*: **Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial**. *Annals of surgery* 2003, **238**(5):641-648.
207. Dass B, Shimada M, Kambhampati G, Ejaz NI, Arif AA, Ejaz AA: **Fluid balance as an early indicator of acute kidney injury in CV surgery**. *Clinical nephrology* 2012, **77**(6):438-444.
208. Kambhampati G, Ross EA, Alsabbagh MM, Asmar A, Pakkivenkata U, Ejaz NI, Arif AA, Ejaz AA: **Perioperative fluid balance and acute kidney injury**. *Clinical and experimental nephrology* 2012, **16**(5):730-738.
209. Parke RL, McGuinness SP, Gilder E, McCarthy LW: **Intravenous fluid use after cardiac surgery: a multicentre, prospective, observational study**. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2014, **16**(3):164-169.
210. Kelm DJ, Perrin JT, Cartin-Ceba R, Gajic O, Schenck L, Kennedy CC: **Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death**. *Shock (Augusta, Ga)* 2015, **43**(1):68-73.

211. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG: **Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population**. *Intensive care medicine* 2018, **44**(4):409-417.
212. Magee CA, Bastin MLT, Laine ME, Bissell BD, Howington GT, Moran PR, McCleary EJ, Owen GD, Kane LE, Higdon EA *et al*: **Insidious Harm of Medication Diluents as a Contributor to Cumulative Volume and Hyperchloremia: A Prospective, Open-Label, Sequential Period Pilot Study**. *Crit Care Med* 2018, **46**(8):1217-1223.
213. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC *et al*: **Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome**. *Intensive care medicine* 2013, **39**(7):1190-1206.
214. Monnet X, Teboul JL: **My patient has received fluid. How to assess its efficacy and side effects?** *Annals of intensive care* 2018, **8**(1):54.
215. Jacobs R, Jonckheer J, Malbrain M: **Fluid overload FADEs away! Time for fluid stewardship**. *Journal of critical care* 2018, **48**:458-461.
216. Petrucci N, De Feo C: **Lung protective ventilation strategy for the acute respiratory distress syndrome**. *The Cochrane database of systematic reviews* 2013(2):Cd003844.
217. Berthelsen RE, Perner A, Jensen AK, Rasmussen BS, Jensen JU, Wiis J, Behzadi MT, Bestle MH: **Forced fluid removal in intensive care patients with acute kidney injury: The randomised FFAKI feasibility trial**. *Acta anaesthesiologica Scandinavica* 2018, **62**(7):936-944.
218. Silversides JA, Fitzgerald E, Manickavasagam US, Lapinsky SE, Nisenbaum R, Hemmings N, Nutt C, Trinder TJ, Pogson DG, Fan E *et al*: **Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness**. *Crit Care Med* 2018, **46**(10):1600-1607.
219. Goldstein S, Bagshaw S, Cecconi M, Okusa M, Wang H, Kellum J, Mythen M, Shaw AD: **Pharmacological management of fluid overload**. *British journal of anaesthesia* 2014, **113**(5):756-763.
220. Ellison DH, Felker GM: **Diuretic Treatment in Heart Failure**. *The New England journal of medicine* 2018, **378**(7):684-685.
221. Sward K, Valsson F, Sellgren J, Ricksten SE: **Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans**. *Intensive care medicine* 2005, **31**(1):79-85.
222. Aravindan N, Aravindan S, Riedel BJ, Weng HR, Shaw AD: **Furosemide prevents apoptosis and associated gene expression in a rat model of surgical ischemic acute renal failure**. *Renal failure* 2007, **29**(4):399-407.
223. Aravindan N, Shaw A: **Effect of furosemide infusion on renal hemodynamics and angiogenesis gene expression in acute renal ischemia/reperfusion**. *Renal failure* 2006, **28**(1):25-35.
224. Kramer HJ, Schuurmann J, Wassermann C, Dusing R: **Prostaglandin-independent protection by furosemide from oliguric ischemic renal failure in conscious rats**. *Kidney international* 1980, **17**(4):455-464.
225. Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE: **Acute renal failure is NOT an "acute renal success"--a clinical study on the renal oxygen supply/demand relationship in acute kidney injury**. *Crit Care Med* 2010, **38**(8):1695-1701.
226. Silbert BI, Ho KM, Lipman J, Roberts JA, Corcoran TB, Morgan DJ, Pavey W, Mas E, Barden AE, Mori TA: **Does Furosemide Increase Oxidative Stress in Acute Kidney Injury?** *Antioxidants & redox signaling* 2017, **26**(5):221-226.
227. Brater DC: **Diuretic therapy**. *The New England journal of medicine* 1998, **339**(6):387-395.

228. Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, Souney PF: **Response of the kidney to furosemide. I. Effects of salt intake and renal compensation**. *The Journal of laboratory and clinical medicine* 1983, **102**(3):450-458.
229. Bagshaw SM, Gibney RTN, Kruger P, Hassan I, McAlister FA, Bellomo R: **The effect of low-dose furosemide in critically ill patients with early acute kidney injury: A pilot randomized blinded controlled trial (the SPARK study)**. *Journal of critical care* 2017, **42**:138-146.
230. Bagshaw SM, Delaney A, Haase M, Ghali WA, Bellomo R: **Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis**. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2007, **9**(1):60-68.
231. Voelker JR, Cartwright-Brown D, Anderson S, Leinfelder J, Sica DA, Kokko JP, Brater DC: **Comparison of loop diuretics in patients with chronic renal insufficiency**. *Kidney international* 1987, **32**(4):572-578.
232. Brater DC, Day B, Burdette A, Anderson S: **Bumetanide and furosemide in heart failure**. *Kidney international* 1984, **26**(2):183-189.
233. Konecke LL: **Clinical trial of bumetanide versus furosemide in patients with congestive heart failure**. *Journal of clinical pharmacology* 1981, **21**(11):688-690.
234. **Bumetanide Injection** [https://www.ashp.org/drug-shortages/current-shortages/Drug-Shortage-Detail.aspx?id=307]
235. Di Somma S, Magrini L: **Drug Therapy for Acute Heart Failure**. *Revista espanola de cardiologia (English ed)* 2015, **68**(8):706-713.
236. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA: **Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy**. *Nature reviews Cardiology* 2015, **12**(3):184-192.
237. Vargas Hein O, Staegemann M, Wagner D, von Heymann C, Martin M, Morgera S, Spies C: **Torsemide versus furosemide after continuous renal replacement therapy due to acute renal failure in cardiac surgery patients**. *Renal failure* 2005, **27**(4):385-392.
238. Shilliday IR, Quinn KJ, Allison ME: **Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study**. *Nephrology Dialysis Transplantation* 1997, **12**(12):2592-2596.
239. **Torsemide Injection** [https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=168]
240. Oh SW, Han SY: **Loop Diuretics in Clinical Practice**. *Electrolyte & blood pressure : E & BP* 2015, **13**(1):17-21.
241. van Olden RW, van Meyel JJ, Gerlag PG: **Sensitivity of residual nephrons to high dose furosemide described by diuretic efficiency**. *European journal of clinical pharmacology* 1995, **47**(6):483-488.
242. Silbert BI, Ho KM, Lipman J, Roberts JA, Corcoran TB, Morgan DJ, Pavey W, Mas E, Barden AE, Mori TA: **Determinants of Urinary Output Response to IV Furosemide in Acute Kidney Injury: A Pharmacokinetic/Pharmacodynamic Study**. *Crit Care Med* 2016, **44**(10):e923-929.
243. Rose HJ, O'Malley K, Pruitt AW: **Depression of renal clearance of furosemide in man by azotemia**. *Clinical pharmacology and therapeutics* 1977, **21**(2):141-146.
244. Rosen S, Heyman SN: **Difficulties in understanding human "acute tubular necrosis": limited data and flawed animal models**. *Kidney international* 2001, **60**(4):1220-1224.
245. Rosen S, Stillman IE: **Acute tubular necrosis is a syndrome of physiologic and pathologic dissociation**. *Journal of the American Society of Nephrology : JASN* 2008, **19**(5):871-875.
246. Morrell ED, Kellum JA, Hallows KR, Pastor-Soler NM: **Epithelial transport during septic acute kidney injury**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2014, **29**(7):1312-1319.

247. Huang A, Luethi N, Martensson J, Bellomo R, Cioccari L: **Pharmacodynamics of intravenous frusemide bolus in critically ill patients**. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2017, **19**(2):142-149.
248. Mekontso-Dessap A, de Prost N, Girou E, Braconnier F, Lemaire F, Brun-Buisson C, Brochard L: **B-type natriuretic peptide and weaning from mechanical ventilation**. *Intensive care medicine* 2006, **32**(10):1529-1536.
249. Friedl W, Mair J, Thomas S, Pichler M, Puschendorf B: **Relationship between natriuretic peptides and hemodynamics in patients with heart failure at rest and after ergometric exercise**. *Clinica chimica acta; international journal of clinical chemistry* 1999, **281**(1-2):121-126.
250. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M: **Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction**. *American heart journal* 1998, **135**(5 Pt 1):825-832.
251. Grissom CK, Morris AH, Lanken PN, Ancukiewicz M, Orme JF, Jr., Schoenfeld DA, Thompson BT: **Association of physical examination with pulmonary artery catheter parameters in acute lung injury**. *Crit Care Med* 2009, **37**(10):2720-2726.
252. Grissom CK, Hirshberg EL, Dickerson JB, Brown SM, Lanspa MJ, Liu KD, Schoenfeld D, Tidswell M, Hite RD, Rock P *et al*: **Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome***. *Crit Care Med* 2015, **43**(2):288-295.
253. V B: **Furosemide in acute and chronic renal failure**. *Dialysis Renal Transplant* 1969(5):241–245.
254. Borirakchanyavat V, Vongsthongsri M, Sitprija V: **Furosemide and acute renal failure**. *Postgraduate medical journal* 1978, **54**(627):30-32.
255. Brown CB, Ogg CS, Cameron JS: **High dose frusemide in acute renal failure: a controlled trial**. *Clinical nephrology* 1981, **15**(2):90-96.
256. Cantarovich F, Fernandez JC, Locatelli A, Perez Loredo J: **Frusemide in high doses in the treatment of acute renal failure**. *Postgraduate medical journal* 1971, **47**:Suppl:13-17.
257. Cantarovich F, Galli C, Benedetti L, Chena C, Castro L, Correa C, Perez Loredo J, Fernandez JC, Locatelli A, Tizado J: **High dose frusemide in established acute renal failure**. *British medical journal* 1973, **4**(5890):449-450.
258. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL: **High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo-controlled, multicenter trial**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2004, **44**(3):402-409.
259. Chandra M, Agarwal SS, Mitra MK, Tandon NN, Gupta NN: **Some observations in the management of acute renal failure by massive intravenous frusemide therapy**. *The Journal of the Association of Physicians of India* 1975, **23**(7):415-422.
260. Hager B, Betschart M, Krapf R: **Effect of postoperative intravenous loop diuretic on renal function after major surgery**. *Schweizerische medizinische Wochenschrift* 1996, **126**(16):666-673.
261. **Letter: High-dose frusemide in renal failure**. *British medical journal* 1974, **2**(5913):278-279.
262. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, Fermanian J: **Furosemide in acute oliguric renal failure. A controlled trial**. *Nephron* 1976, **17**(1):51-58.
263. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M: **Lack of renoprotective effects of dopamine and furosemide during cardiac surgery**. *Journal of the American Society of Nephrology : JASN* 2000, **11**(1):97-104.
264. Lumlertgul D, Keoplung M, Sitprija V, Moollaor P, Suwangool P: **Furosemide and dopamine in malarial acute renal failure**. *Nephron* 1989, **52**(1):40-44.
265. Mehta RL, Pascual MT, Soroko S, Chertow GM: **Diuretics, mortality, and nonrecovery of renal function in acute renal failure**. *Jama* 2002, **288**(20):2547-2553.

266. Minuth AN, Terrell JB, Jr., Suki WN: **Acute renal failure: a study of the course and prognosis of 104 patients and of the role of furosemide**. *The American journal of the medical sciences* 1976, **271**(3):317-324.
267. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E *et al*: **Acute renal failure in critically ill patients: a multinational, multicenter study**. *Jama* 2005, **294**(7):813-818.
268. van der Voort PH, Boerma EC, Koopmans M, Zandberg M, de Ruiter J, Gerritsen RT, Egbers PH, Kingma WP, Kuiper MA: **Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial**. *Crit Care Med* 2009, **37**(2):533-538.
269. Wu VC, Lai CF, Shiao CC, Lin YF, Wu PC, Chao CT, Hu FC, Huang TM, Yeh YC, Tsai IJ *et al*: **Effect of diuretic use on 30-day postdialysis mortality in critically ill patients receiving acute dialysis**. *PloS one* 2012, **7**(3):e30836.
270. Bove T, Belletti A, Putzu A, Pappacena S, Denaro G, Landoni G, Bagshaw SM, Zangrillo A: **Intermittent furosemide administration in patients with or at risk for acute kidney injury: Meta-analysis of randomized trials**. *PloS one* 2018, **13**(4):e0196088.
271. Sampath S, Moran JL, Graham PL, Rockliff S, Bersten AD, Abrams KR: **The efficacy of loop diuretics in acute renal failure: assessment using Bayesian evidence synthesis techniques**. *Crit Care Med* 2007, **35**(11):2516-2524.
272. Ho KM, Sheridan DJ: **Meta-analysis of frusemide to prevent or treat acute renal failure**. *BMJ (Clinical research ed)* 2006, **333**(7565):420.
273. Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R *et al*: **Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study**. *Intensive care medicine* 2013, **39**(3):420-428.
274. Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, Tumlin JA, Trevino SA, Kimmel PL, Seneff MG: **Development and standardization of a furosemide stress test to predict the severity of acute kidney injury**. *Critical care (London, England)* 2013, **17**(5):R207.
275. Martin SJ, Danziger LH: **Continuous infusion of loop diuretics in the critically ill: a review of the literature**. *Crit Care Med* 1994, **22**(8):1323-1329.
276. Ostermann M, Alvarez G, Sharpe MD, Martin CM: **Frusemide administration in critically ill patients by continuous compared to bolus therapy**. *Nephron Clinical practice* 2007, **107**(2):c70-76.
277. Jeon J, Kim DH, Baeg SI, Lee EJ, Chung CR, Jeon K, Lee JE, Huh W, Suh GY, Kim YG *et al*: **Association between diuretics and successful discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury**. *Critical care (London, England)* 2018, **22**(1):255.
278. Schuller D, Lynch JP, Fine D: **Protocol-guided diuretic management: comparison of furosemide by continuous infusion and intermittent bolus**. *Crit Care Med* 1997, **25**(12):1969-1975.
279. Makhoul N, Riad T, Friedstrom S, Zveibil FR: **Frusemide in pulmonary oedema: continuous versus intermittent**. *Clinical Intensive Care* 1997, **8**(6):273-276.
280. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO *et al*: **Diuretic strategies in patients with acute decompensated heart failure**. *The New England journal of medicine* 2011, **364**(9):797-805.
281. Yeh DD, Van Der Wilden GM, Cropano C, Chang Y, King DR, De Moya M, Fagenholz P, Kaafarani H, Lee J, Velmahos G: **Goal-directed diuresis: A case - control study of continuous furosemide infusion in critically ill trauma patients**. *Journal of emergencies, trauma, and shock* 2015, **8**(1):34-38.
282. Mojtahedzadeh M, Salehifar E, Vazin A, Mahidiani H, Najafi A, Tavakoli M, Nayebpour M, Abdollahi M: **Comparison of hemodynamic and biochemical effects of furosemide by**

continuous infusion and intermittent bolus in critically ill patients. *Journal of infusion nursing : the official publication of the Infusion Nurses Society* 2004, **27**(4):255-261.
283. Shah RA, Subban V, Lakshmanan A, Narayanan S, Udhayakumaran K, Pakshirajan B, Krishnamoorthy J, Latchumanadhas K, Janakiraman E, Mullasari AS: **A prospective, randomized study to evaluate the efficacy of various diuretic strategies in acute decompensated heart failure**. *Indian heart journal* 2014, **66**(3):309-316.
284. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR: **Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury**. *Crit Care Med* 2002, **30**(10):2175-2182.
285. Kitsios GD, Mascari P, Ettunsi R, Gray AW: **Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis**. *Journal of critical care* 2014, **29**(2):253-259.
286. Oczkowski SJ, Mazzetti I: **Colloids to improve diuresis in critically ill patients: a systematic review**. *Journal of intensive care* 2014, **2**:37.
287. Oczkowski SJW, Klotz L, Mazzetti I, Alshamsi F, Chen ML, Foster G, Meade MO, Hamielec C: **Furosemide and Albumin for Diuresis of Edema (FADE): A parallel-group, blinded, pilot randomized controlled trial**. *Journal of critical care* 2018, **48**:462-467.
288. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Martin G, Huber W, Malbrain ML: **Aiming for a negative fluid balance in patients with acute lung injury and increased intra-abdominal pressure: a pilot study looking at the effects of PAL-treatment**. *Annals of intensive care* 2012, **2 Suppl 1**:S15.
289. Jentzer JC, DeWald TA, Hernandez AF: **Combination of loop diuretics with thiazide-type diuretics in heart failure**. *Journal of the American College of Cardiology* 2010, **56**(19):1527-1534.
290. Verbrugge FH: **Editor's Choice-Diuretic resistance in acute heart failure**. *European heart journal Acute cardiovascular care* 2018, **7**(4):379-389.
291. Ng TM, Konopka E, Hyderi AF, Hshieh S, Tsuji Y, Kim BJ, Han SY, Phan DH, Jeng AI, Lou M *et al*: **Comparison of bumetanide- and metolazone-based diuretic regimens to furosemide in acute heart failure**. *Journal of cardiovascular pharmacology and therapeutics* 2013, **18**(4):345-353.
292. Cardinale M, Altshuler J, Testani JM: **Efficacy of Intravenous Chlorothiazide for Refractory Acute Decompensated Heart Failure Unresponsive to Adjunct Metolazone**. *Pharmacotherapy* 2016, **36**(8):843-851.
293. Shulenberger CE, Jiang A, Devabhakthuni S, Ivaturi V, Liu T, Reed BN: **Efficacy and Safety of Intravenous Chlorothiazide versus Oral Metolazone in Patients with Acute Decompensated Heart Failure and Loop Diuretic Resistance**. *Pharmacotherapy* 2016, **36**(8):852-860.
294. Moranville MP, Choi S, Hogg J, Anderson AS, Rich JD: **Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance**. *Cardiovascular therapeutics* 2015, **33**(2):42-49.
295. Michaud CJ, Mintus KC: **Intravenous Chlorothiazide Versus Enteral Metolazone to Augment Loop Diuretic Therapy in the Intensive Care Unit**. *The Annals of pharmacotherapy* 2017, **51**(4):286-292.
296. Marik PE, Kussman BD, Lipman J, Kraus P: **Acetazolamide in the treatment of metabolic alkalosis in critically ill patients**. *Heart & lung : the journal of critical care* 1991, **20**(5 Pt 1):455-459.
297. Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, Schneider F, Duguet A, Gibot S, Lerolle N *et al*: **Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial**. *Jama* 2016, **315**(5):480-488.
298. Knauf H, Mutschler E: **Sequential nephron blockade breaks resistance to diuretics in edematous states**. *Journal of cardiovascular pharmacology* 1997, **29**(3):367-372.

299. Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Nacedo E, Gibney N *et al*: **Diuretics and mortality in acute renal failure**. *Crit Care Med* 2004, **32**(8):1669-1677.
300. Jones SL, Martensson J, Glassford NJ, Eastwood GM, Bellomo R: **Loop diuretic therapy in the critically ill: a survey**. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2015, **17**(3):223-226.
301. Bagshaw SM, Delaney A, Jones D, Ronco C, Bellomo R: **Diuretics in the management of acute kidney injury: a multinational survey**. *Contributions to nephrology* 2007, **156**:236-249.
302. Yeh DD, Tang JF, Chang Y: **The use of furosemide in critically ill trauma patients: A retrospective review**. *Journal of emergencies, trauma, and shock* 2014, **7**(2):83-87.
303. Thomsen G, Bezdjian L, Rodriguez L, Hopkins RO: **Clinical outcomes of a furosemide infusion protocol in edematous patients in the intensive care unit**. *Critical care nurse* 2012, **32**(6):25-34.
304. Emmett M: **Diuretics in critically ill patients with acute renal failure**. *Jama* 2003, **289**(11):1379; author reply 1380-1371.
305. Kalantar-Zadeh K: **Diuretics in critically ill patients with acute renal failure**. *Jama* 2003, **289**(11):1380; author reply 1380-1381.
306. Stefanec T: **Diuretics in critically ill patients with acute renal failure**. *Jama* 2003, **289**(11):1380; author reply 1380-1381.
307. Tedesco JV: **Diuretics in critically ill patients with acute renal failure**. *Jama* 2003, **289**(11):1379; author reply 1380-1371.
308. Unnikrishnan D, Lanewala A, Krishnan S: **Diuretics in critically ill patients with acute renal failure**. *Jama* 2003, **289**(11):1379-1380; author reply 1380-1371.
309. Dasta JF, McLaughlin TP, Mody SH, Piech CT: **Daily cost of an intensive care unit day: the contribution of mechanical ventilation**. *Crit Care Med* 2005, **33**(6):1266-1271.
310. Reardon PM, Fernando SM, Van Katwyk S, Thavorn K, Kobewka D, Tanuseputro P, Rosenberg E, Wan C, Vanderspank-Wright B, Kubelik D *et al*: **Characteristics, Outcomes, and Cost Patterns of High-Cost Patients in the Intensive Care Unit**. *Critical Care Research and Practice* 2018, **2018**:7.
311. Self WH, Liu D, Strayer N, Russ S, Ward MJ, Shapiro NI, Rice TW, Semler MW: **Charge Reductions Associated With Shorter Time to Recovery in Septic Shock**. *Chest* 2019, **155**(2):315-321.
312. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL: **Volume Overload: Prevalence, Risk Factors, and Functional Outcome in Survivors of Septic Shock**. *Annals of the American Thoracic Society* 2015, **12**(12):1837-1844.
313. Mekontso Dessap A, Katsahian S, Roche-Campo F, Varet H, Kouatchet A, Tomicic V, Beduneau G, Sonneville R, Jaber S, Darmon M *et al*: **Ventilator-associated pneumonia during weaning from mechanical ventilation: role of fluid management**. *Chest* 2014, **146**(1):58-65.
314. **BPS Critical Care Fact Sheet - Board of Pharmacy Specialties** [https://www.bpsweb.org/wp-content/uploads/factsheet_criticalcare.pdf]
315. Bhatt M, Lizano D, Carlese A, Kvetan V, Gershengorn HB: **Severe Burnout Is Common Among Critical Care Physician Assistants**. *Crit Care Med* 2017, **45**(11):1900-1906.
316. Borthwick M, Barton G, Bourne RS, McKenzie C: **Critical care pharmacy workforce: UK deployment and characteristics in 2015**. *The International journal of pharmacy practice* 2018, **26**(4):325-333.
317. Chant C: **How critical are critical care pharmacists?** *The Canadian journal of hospital pharmacy* 2012, **65**(1):5-6.
318. **Position paper on critical care pharmacy services. Society of Critical Care Medicine and American College of Clinical Pharmacy**. *Pharmacotherapy* 2000, **20**(11):1400-1406.
319. Haupt MT, Bekes CE, Brilli RJ, Carl LC, Gray AW, Jastremski MS, Naylor DF, Pharm DM, Md AS, Wedel SK *et al*: **Guidelines on critical care services and personnel:**

Recommendations based on a system of categorization of three levels of care. *Crit Care Med* 2003, **31**(11):2677-2683.
320. Dager W, Bolesta S, Brophy G, Dell K, Gerlach A, Kristeller J, Micek S, Hess M, Bentley M, Juang P *et al*: **An Opinion Paper Outlining Recommendations for Training, Credentialing, and Documenting and Justifying Critical Care Pharmacy Services**. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2011, **31**(8):829-829.
321. Maclaren R, Devlin JW, Martin SJ, Dasta JF, Rudis MI, Bond CA: **Critical care pharmacy services in United States hospitals**. *The Annals of pharmacotherapy* 2006, **40**(4):612-618.
322. Borthwick M: **The role of the pharmacist in the intensive care unit**. *Journal of the Intensive Care Society*, **0**(0):1751143718769043.
323. Cross VJ, Parker JT, Law Min M-CYL, Bourne RS: **Pharmacist prescribing in critical care: an evaluation of the introduction of pharmacist prescribing in a single large UK teaching hospital**. *European Journal of Hospital Pharmacy* 2018, **25**(e1):e2.
324. Klopotowska JE, Kuiper R, van Kan HJ, de Pont AC, Dijkgraaf MG, Lie AHL, Vroom MB, Smorenburg SM: **On-ward participation of a hospital pharmacist in a Dutch intensive care unit reduces prescribing errors and related patient harm: an intervention study**. *Critical care (London, England)* 2010, **14**(5):R174.
325. Ryan C, Ross S, Davey P, Duncan EM, Francis JJ, Fielding S, Johnston M, Ker J, Lee AJ, MacLeod MJ *et al*: **Prevalence and causes of prescribing errors: the PRescribing Outcomes for Trainee Doctors Engaged in Clinical Training (PROTECT) study**. *PloS one* 2014, **9**(1):e79802.
326. Benedict N, Hess MM: **History and future of critical care pharmacy practice**. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2015, **72**(23):2101-2105.
327. Bosma BE, van den Bemt P, Melief P, van Bommel J, Tan SS, Hunfeld NGM: **Pharmacist interventions during patient rounds in two intensive care units: Clinical and financial impact**. *The Netherlands journal of medicine* 2018, **76**(3):115-124.
328. Michal J, Henry T, Street C: **Impact of a pharmacist-driven protocol to decrease proton pump inhibitor use in non-intensive care hospitalized adults**. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2016, **73**(17 Suppl 4):S126-132.
329. Hyde BB, Ogden RK, Jr., Berger RD, VanBrimmer BW, Stach LM: **Preoperative Antibiotic Orders: Protocol-Initiated Pharmacist Order Entry**. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG* 2016, **21**(5):432-435.
330. Willis C, Allen B, Tucker C, Rottman K, Epps K: **Impact of a pharmacist-driven methicillin-resistant Staphylococcus aureus surveillance protocol**. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2017, **74**(21):1765-1773.
331. Corio JL, Sin JH, Hayes BD, Goldstein JN, Fuh L: **Impact of a Pharmacist-Driven Prothrombin Complex Concentrate Protocol on Time to Administration in Patients with Warfarin-associated Intracranial Hemorrhage**. *The western journal of emergency medicine* 2018, **19**(5):849-854.
332. Downing A, Mortimer M, Hiers J: **Impact of a pharmacist-driven warfarin management protocol on achieving therapeutic International Normalized Ratios**. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2016, **73**(5 Suppl 1):S69-73.
333. Baucom A, Brizendine C, Fugit A, Dennis C: **Evaluation of a Pharmacy-to-Dose Pneumococcal Vaccination Protocol at an Academic Medical Center**. *The Annals of pharmacotherapy* 2019, **53**(4):364-370.
334. Nagy MW, Gruber S, McConnell M: **Implementation of a Pilot Pharmacist Testosterone Therapy Management Service**. *Journal of pharmacy practice* 2019:897190019830251.

335. Kaifer C GM: **538: IMPACT OF A PHARMACIST-DRIVEN STRESS ULCER PROPHYLAXIS DISCONTINUATION PROTOCOL IN THE ICU** *Critical Care Medicine* 2019, **47**(1):B11-B87.
336. Stuart M, Martz C, Payter K, McDonnell J, Vinay S, Swiderek J, Coba V, To L, Smith Z, Peters M: **908: PHARMACIST-DRIVEN DISCONTINUATION OF ANTIPSYCHOTICS STARTED FOR ICU DELIRIUM**. *Critical Care Medicine* 2019, **47**(1):433.
337. Campion M SK, Stock AH, Shawa I, Need R, Cheatham SC: **Optimization of pneumonia treatment in an intensive care unit utilizing a pharmacist-driven protocol**. In: *ID Week 2016*. New Orleans, LA; 2016.
338. Leguelinel-Blache G, Nguyen TL, Louart B, Poujol H, Lavigne JP, Roberts JA, Muller L, Kinowski JM, Roger C, Lefrant JY: **Impact of Quality Bundle Enforcement by a Critical Care Pharmacist on Patient Outcome and Costs**. *Crit Care Med* 2018, **46**(2):199-207.
339. MacLaren R, Bond CA, Martin SJ, Fike D: **Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections**. *Crit Care Med* 2008, **36**(12):3184-3189.
340. MacLaren R, Bond CA: **Effects of pharmacist participation in intensive care units on clinical and economic outcomes of critically ill patients with thromboembolic or infarction-related events**. *Pharmacotherapy* 2009, **29**(7):761-768.
341. Kane SL, Weber RJ, Dasta JF: **The impact of critical care pharmacists on enhancing patient outcomes**. *Intensive care medicine* 2003, **29**(5):691-698.
342. Broyles JE, Brown RO, Vehe KL, Nolly RJ, Luther RW: **Pharmacist interventions improve fluid balance in fluid-restricted patients requiring parenteral nutrition**. *DICP : the annals of pharmacotherapy* 1991, **25**(2):119-122.
343. Bellomo R, Prowle JR, Echeverri JE: **Diuretic therapy in fluid-overloaded and heart failure patients**. *Contributions to nephrology* 2010, **164**:153-163.
344. **Practice and Research Networks** [https://www.accp.com/about/prns.aspx]
345. [www.surveymonkey.com]
346. IBM SPSS Statistics for Windows VA, NY: IBM Corp.
347. **New Investigator Research Grant** [http://www.ashpfoundation.org/MainMenuCategories/ResearchResourceCenter/FundingOpportunities/JuniorInvestigatorResearchGrant]
348. Marik PE: **Iatrogenic salt water drowning and the hazards of a high central venous pressure**. *Annals of intensive care* 2014, **4**:21.
349. Boerma EC, van der Voort PH, Spronk PE, Ince C: **Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis**. *Crit Care Med* 2007, **35**(4):1055-1060.
350. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R: **Fluid balance and acute kidney injury**. *Nature reviews Nephrology* 2010, **6**(2):107-115.
351. Acheampong A, Vincent JL: **A positive fluid balance is an independent prognostic factor in patients with sepsis**. *Critical care (London, England)* 2015, **19**:251.
352. Klompas M, Rhee C: **The CMS Sepsis Mandate: Right Disease, Wrong Measure**. *Annals of internal medicine* 2016, **165**(7):517-518.
353. Marik PE, Malbrain M: **The SEP-1 quality mandate may be harmful: How to drown a patient with 30 mL per kg fluid!** *Anaesthesiology intensive therapy* 2017, **49**(5):323-328.
354. Rhee C, Gohil S, Klompas M: **Regulatory mandates for sepsis care--reasons for caution**. *The New England journal of medicine* 2014, **370**(18):1673-1676.
355. Barsuk JH, Gordon RA, Cohen ER, Cotts WG, Malkenson D, Yancy CW, Williams MV: **A diuretic protocol increases volume removal and reduces readmissions among hospitalized patients with acute decompensated heart failure**. *Congestive heart failure (Greenwich, Conn)* 2013, **19**(2):53-60.

356. Laine ME, Flynn JD, Flannery AH: **Impact of Pharmacist Intervention on Selection and Timing of Appropriate Antimicrobial Therapy in Septic Shock**. *Journal of pharmacy practice* 2018, **31**(1):46-51.
357. Flannery AH, Thompson Bastin ML, Montgomery-Yates A, Hook C, Cassity E, Eaton PM, Morris PE: **Multidisciplinary Prerounding Meeting as a Continuous Quality Improvement Tool: Leveraging to Reduce Continuous Benzodiazepine Use at an Academic Medical Center**. *Journal of intensive care medicine* 2018:885066618769015.
358. **Furosemide**. In: *Lexicomp Online*. 2019.
359. Buggey J, Mentz RJ, Pitt B, Eisenstein EL, Anstrom KJ, Velazquez EJ, O'Connor CM: **A reappraisal of loop diuretic choice in heart failure patients**. *American heart journal* 2015, **169**(3):323-333.
360. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: **Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support**. *Journal of Biomedical Informatics* 2009, **42**(2):377-381.
361. 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. Modification of Diet in Renal Disease Study Group**. *Annals of internal medicine* 1999, **130**(6):461-470.
362. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP: **Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C**. *Clinical journal of the American Society of Nephrology : CJASN* 2008, **3**(2):348-354.
363. Hosten AO: **BUN and Creatinine**. In: *Clinical Methods: The History, Physical, and Laboratory Examinations*. Edited by rd, Walker HK, Hall WD, Hurst JW. Boston: Butterworths Butterworth Publishers, a division of Reed Publishing.; 1990.
364. Prowle JR, Kolic I, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ: **Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI**. *Clinical journal of the American Society of Nephrology : CJASN* 2014, **9**(6):1015-1023.
365. Waikar SS, Bonventre JV: **Creatinine kinetics and the definition of acute kidney injury**. *Journal of the American Society of Nephrology : JASN* 2009, **20**(3):672-679.
366. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, Fernandez R, de la Cal MA, Benito S, Tomas R *et al*: **A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group**. *The New England journal of medicine* 1995, **332**(6):345-350.
367. Motzkus CA, Chrysanthopoulou SA, Luckmann R, Rincon TA, Lapane KL, Lilly CM: **ICU Admission Source as a Predictor of Mortality for Patients With Sepsis**. *Journal of intensive care medicine* 2018, **33**(9):510-516.
368. Pepper DJ, Demirkale CY, Sun J, Rhee C, Fram D, Eichacker P, Klompas M, Suffredini AF, Kadri SS: **Does Obesity Protect Against Death in Sepsis? A Retrospective Cohort Study of 55,038 Adult Patients**. *Crit Care Med* 2019.
369. de Grooth HJ, Postema J, Loer SA, Parienti JJ, Oudemans-van Straaten HM, Girbes AR: **Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates**. *Intensive care medicine* 2018, **44**(3):311-322.
370. Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, Canter RR, Coats TJ, Delaney A, Gimbel E, Grieve RD *et al*: **Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis**. *The New England journal of medicine* 2017, **376**(23):2223-2234.
371. Van Berkel M, Rabinovich M, Newsome A: **913: EVALUATION OF CRITICAL CARE PHARMACIST-TO-PATIENT RATIOS IN INTENSIVE CARE UNITS**. *Critical Care Medicine* 2018, **46**(1):440.

372. Perren A, Markmann M, Merlani G, Marone C, Merlani P: **Fluid balance in critically ill patients. Should we really rely on it?** *Minerva anestesiologica* 2011, **77**(8):802-811.
373. Schneider AG, Baldwin I, Freitag E, Glassford N, Bellomo R: **Estimation of fluid status changes in critically ill patients: fluid balance chart or electronic bed weight?** *Journal of critical care* 2012, **27**(6):745.e747-712.
374. Teo SH, Endre ZH: **Biomarkers in acute kidney injury (AKI)**. *Best practice & research Clinical anaesthesiology* 2017, **31**(3):331-344.
375. Parikh CR, Mansour SG: **Perspective on Clinical Application of Biomarkers in AKI**. *Journal of the American Society of Nephrology : JASN* 2017, **28**(6):1677-1685.
376. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV: **Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury**. *Kidney international* 2002, **62**(1):237-244.
377. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J *et al*: **Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury**. *Annals of internal medicine* 2008, **148**(11):810-819.
378. Parikh CR, Butrymowicz I, Yu A, Chinchilli VM, Park M, Hsu CY, Reeves WB, Devarajan P, Kimmel PL, Siew ED *et al*: **Urine stability studies for novel biomarkers of acute kidney injury**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2014, **63**(4):567-572.
379. Xu K, Rosenstiel P, Paragas N, Hinze C, Gao X, Huai Shen T, Werth M, Forster C, Deng R, Bruck E *et al*: **Unique Transcriptional Programs Identify Subtypes of AKI**. *Journal of the American Society of Nephrology : JASN* 2017, **28**(6):1729-1740.
380. de Louw EJ, Sun PO, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ, Danziger J: **Increased incidence of diuretic use in critically ill obese patients**. *Journal of critical care* 2015, **30**(3):619-623.
381. Shen Y, Zhang W, Shen Y: **Early diuretic use and mortality in critically ill patients with vasopressor support: a propensity score-matching analysis**. *Critical care (London, England)* 2019, **23**(1):9.
382. Johnson AEW, Pollard TJ, Shen L, Lehman L-wH, Feng M, Ghassemi M, Moody B, Szolovits P, Anthony Celi L, Mark RG: **MIMIC-III, a freely accessible critical care database**. *Scientific Data* 2016, **3**:160035.
383. Vellinga NA, Ince C, Boerma EC: **Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis**. *BMC anesthesiology* 2013, **13**:17.
384. Oppermann M, Hansen PB, Castrop H, Schnermann J: **Vasodilatation of afferent arterioles and paradoxical increase of renal vascular resistance by furosemide in mice**. *American journal of physiology Renal physiology* 2007, **293**(1):F279-287.
385. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN: **Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis**. *Annals of internal medicine* 1985, **103**(1):1-6.
386. Gardlund B, Dmitrieva NO, Pieper CF, Finfer S, Marshall JC, Taylor Thompson B: **Six subphenotypes in septic shock: Latent class analysis of the PROWESS Shock study**. *Journal of critical care* 2018, **47**:70-79.
387. Lu H, Wen D, Wang X, Gan L, Du J, Sun J, Zeng L, Jiang J, Zhang A: **Host genetic variants in sepsis risk: a field synopsis and meta-analysis**. *Critical care (London, England)* 2019, **23**(1):26.
388. Zhang Z, Zhang G, Goyal H, Mo L, Hong Y: **Identification of subclasses of sepsis that showed different clinical outcomes and responses to amount of fluid resuscitation: a latent profile analysis**. *Critical care (London, England)* 2018, **22**(1):347.

389. Hilton AK, Bellomo R: **A critique of fluid bolus resuscitation in severe sepsis**. *Critical care (London, England)* 2012, **16**(1):302.
390. Zhang Z, Spieth PM, Chiumello D, Goyal H, Torres A, Laffey JG, Hong Y: **Declining Mortality in Patients With Acute Respiratory Distress Syndrome: An Analysis of the Acute Respiratory Distress Syndrome Network Trials**. *Crit Care Med* 2019, **47**(3):315-323.
391. Ali J, Chernicki W, Wood LD: **Effect of furosemide in canine low-pressure pulmonary edema**. *The Journal of clinical investigation* 1979, **64**(5):1494-1504.
392. Ali J, Duke K: **Colloid osmotic pressure in pulmonary edema clearance with furosemide**. *Chest* 1987, **92**(3):540-546.
393. Ali J, Unruh H, Skoog C, Goldberg HS: **The effect of lung edema on pulmonary vasoactivity of furosemide**. *The Journal of surgical research* 1983, **35**(5):383-390.
394. Ali J, Wood LD: **Pulmonary vascular effects of furosemide on gas exchange in pulmonary edema**. *Journal of applied physiology: respiratory, environmental and exercise physiology* 1984, **57**(1):160-167.
395. Baltopoulos G, Zakynthinos S, Dimopoulos A, Roussos C: **Effects of furosemide on pulmonary shunts**. *Chest* 1989, **96**(3):494-498.
396. Waugh JB, Op't Holt TB, Gadek JE, Clanton TL: **High-dose furosemide alters gas exchange in a model of acute lung injury**. *Journal of critical care* 1996, **11**(3):129-137.
397. Reising CA, Chendrasekhar A, Wall PL, Paradise NF, Timberlake GA, Moorman DW: **Continuous dose furosemide as a therapeutic approach to acute respiratory distress syndrome (ARDS)**. *The Journal of surgical research* 1999, **82**(1):56-60.
398. Schuster DP: **ARDS: clinical lessons from the oleic acid model of acute lung injury**. *American journal of respiratory and critical care medicine* 1994, **149**(1):245-260.
399. Schuster CJ, Weil MH, Besso J, Carpio M, Henning RJ: **Blood volume following diuresis induced by furosemide**. *The American journal of medicine* 1984, **76**(4):585-592.
400. Demling RH, Will JA: **The effect of furosemide on the pulmonary transvascular fluid filtration rate**. *Crit Care Med* 1978, **6**(5):317-319.
401. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, Calfee CS: **Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy**. *American journal of respiratory and critical care medicine* 2017, **195**(3):331-338.

VITA

BRITTANY D. BISSELL, PHARMD, BCCCP

EDUCATION AND POST-GRADUATE TRAINING

2015-2016	**ASHP Accredited PGY-2 Critical Care Residency** Jackson Memorial Hospital | Miami, Florida Residency Director: Mayela Castillo, Pharm.D., BCPS, BCCCP
2014-2015	**ASHP Accredited PGY-1 Residency** UF Health Jacksonville | Jacksonville, Florida Residency Director: Bernadette Belgado, Pharm.D
2011- 2014	**Midwestern University College of Pharmacy- Glendale** | Glendale, Arizona Doctor of Pharmacy | Valedictorian | *Summa cum Laude* Cumulative GPA: 3.97 out of 4.0
2007-2011	**University of Rio Grande Evans School of Business** | Rio Grande, Ohio Bachelor of Science in Health Care Administration; *Summa cum Laude* Associate of Science in Chemistry; *Summa cum Laude* Major GPA: 4.0 out of 4.0

ACADEMIC APPOINTMENTS

2017-present	**Assistant Adjunct Professor** University of Kentucky College of Pharmacy | Lexington, Kentucky

PROFESSIONAL EXPERIENCE

2016-present	**Pulmonary/Medical ICU Clinical Pharmacist** Emergency Medicine PRN Clinical Pharmacist Surgical ICU PRN Clinical Pharmacist University of Kentucky Medical Center | Lexington, Kentucky Supervisor: Aaron Cook, Pharm.D., BCPS, BCCCP
2015-2016	**Clinical Critical Care Pharmacist** Jackson Memorial Hospital | Miami, Florida Supervisor: Mayela Castillo, Pharm.D., BCPS, BCCCP
2014-2015	**Clinical Pharmacist** UF Health Jacksonville | Jacksonville, Florida Supervisor: Stephanie McCormick, Pharm.D.
2012-2014	**Pharmacy Intern** Cigna Paseo Pharmacy | Glendale, Arizona Supervisor: Suzanne Banasek, Pharm.D.
2010	**Health Care Administrative Intern** Holzer Consolidated Health Systems | Gallipolis, Ohio Supervisor: Teresa Remy-Detty, MHA, LNHA, BSN, RN

PUBLICATIONS

2018	**Ehrlichiosis presenting as severe sepsis and meningoencephalitis in an immunocompetent adult** Buzzard S, **Bissell BD,** Bastin MLT. *JMM Case Rep.* 201827;5(9):e005162.
2018	**Development of a Co-Precepting Model for a Preceptor-in-Training Program for New Practitioners**

McCleary E, Bastin MLT, **Bissell BD,** Cook AM, Pierce C, Flannery A. *Hosp Pharm.* [Epub ahead of print]

2018 **Insidious Harm of Medication Diluents as a Contributor to Cumulative Volume and Hyperchloremia: A Prospective, Open-Label, Sequential Period Pilot Study.**
Magee CA, Bastin MLT, Laine ME, **Bissell BD,** Howington GT, Moran PR, McCleary EJ, Owen GD, Kane LE, Higdon EA, Pierce CA, Morris PE, Flannery AH. *Crit Care Med.* 2018;46(8):1217-1223

2018 **A Multicenter, Prospective, Observational Study to Determine Predictive Factors for Multidrug-Resistance Pneumonia in Critically Ill Adults: The DEFINE Study**
Lat I, Daley MJ, Shewale A, Pangrazzi MH, Hammond D, Olsen KM, **DEFINE Study Group**. *Pharmacotherapy.* 2018. [Epub ahead of print]

2018 **Evaluation of Vancomycin Continuous Infusion in the Intensive Care Unit**
Bissell BD, Riggi G, Morrison C. *J Intensive Care Med.* 2018. [Epub ahead of print]

2018 **A Blast From the Past: Revival of Angiotensin II for Vasodilatory Shock**
Bissell BD, Browder K, McKenzie M, Flannery AH. *Ann Pharmacother.* 2018. [Epub ahead of print]

2018 **Aggressive Treatment of Life-Threatening Hypophosphatemia During Recovery From Fulminant Hepatic Failure: A Case Report**
Bissell BD, Davis JE, Flannery AH, Adkins DA, Bastin ML. *J Intensive Care Med.* 2018;33(6):375-379.

2018 **Misdirected Sympathy: The Role of Sympatholysis in Sepsis and Septic Shock**
Ferreira JA, **Bissell BD**. *J Intensive Care Med.* 2018;33(2):74-86

2017 **Hemodynamic Instability Secondary to Vasopressin Withdrawal in Septic Shock.**
Bissell BD, Magee C, Moran P, Bastin MLT, Flannery AH. *J Intensive Care Med.* 2017. [Epub ahead of print]

2015 **Impact of Endocrine Supplementation on Adverse Events in Septic Shock**
Bissell BD, Erdman MJ, Smotherman C, Kraemer DF, Ferreira JA. *J Crit Care.* 2015 Dec;30(6):1169-73.

BOOK CHAPTERS

In progress **Pharmacology in Clinical Neuroscience | Corticosteroid Chapter**
Co-Author

In progress **Essentials of Neurocritical Care | Oxford Clinical Practice Series**
Co-Author, Neurocritical Care Society

2018 **Side Effects of Drugs Annual | Corticosteroid Chapter**
Co-Author

2016-present **Critical Care Pharmacotherapy Literature Update**
Co-Author, Society of Critical Care Medicine Clinical Pharmacy and Pharmacology
Reviewer, Society of Critical Care Medicine Clinical Pharmacy and Pharmacology

SCHOLASTIC AND PROFESSIONAL HONORS

2019 Society of Critical Care Medicine 48th Annual Congress Star Award, co-investigator
2018 Society of Critical Care Medicine Presidential Citation Recipient
2018 American College of Clinical Pharmacy Critical Care PRN Junior Investigator of the Year
2018 Society of Critical Care Medicine 47th Annual Congress Star Award, co-investigator
2018 Omicron Delta Kappa Inductee, *University of Kentucky*
2015 Society of Critical Care Medicine Clinical Pharmacy and Pharmacology Travel Grant

2014	College of Pharmacy- Glendale Class Valedictorian, *Midwestern University*
2013	Phi Lambda Sigma Inductee, *Midwestern University*
2012	The Rho Chi Society Inductee, *Midwestern University*
2011	School of Sciences Outstanding Chemistry Graduate, *University of Rio Grande*
2007	Alpha Lambda Delta Inductee, *University of Rio Grande*