# Section I: Applicant Information

Name of Applicant: Kyle Whelan

Project Title: How much fluid should we give to septic patients with heart failure?

What skills do you already have that you will use in this project?

Though I have experience in qualitative research methods and manuscript writing from medical school when I did research in behavior patterns of oncologists in practicing palliative care, my experience in quantitative clinical research is limited. However, I am familiar with basic statistical analysis relevant to medical research from epidemiology in medical school, and from the resident research course in the fall of 2017. I also have the necessary clinical experience and knowledge base from my time in residency to work with the data scientists in our group to perform clinically meaningful data analysis.

What will you learn from this experience?

This experience with further my knowledge of medical research and statistical analysis, and will be the first immersive clinical research experience that will inform my eventual decision of if I want research to be a large part of my career going forward. The process of submitting the manuscripts to journals and performing the necessary edits will also be valuable. Finally, as our group is multidisciplinary and includes data scientists as well as physicians, the experience of working with other professionals with separate skill sets toward a common goal in a research setting will be an important one.

How will this guide your career development?

I plan to apply for a fellowship in Pulmonary & Critical Care medicine, and the time allotted for this project will allow me engage in a meaningful research experience in the field and develop a specific area of interest in the field prior to fellowship. Ideally, I will present the eventual data at a conference, allowing me to network with other members of the field who share my interests.

**Section III: Research Project**

1. **Specific Aims**

This project will have three aims, each with a separate corresponding analysis:

* Evaluate differences in fluid resuscitation in the ICU among septic patients with and without CHF.
* Assess differences in fluid resuscitation among septic patients in the ICU with different types of CHF.
* Examine differences in outcomes among patients with different types of CHF according to amount of fluid received.

1. **Background and Significance**:

Sepsis is among the most common reasons for admission to the intensive care unit. The cornerstones of sepsis treatment include early administration (first one to six hours) of fluid resuscitation, early antibiotics, and supportive care targeted at certain physiologic goals. With respect to fluid resuscitation, current guidelines recommend an initial bolus of 30 milliliters (mL) of crystalloid per kilogram of body weight (Rhodes 2016). However, the ideal amount of fluid to administer is unknown, and recent research has demonstrated that excessive fluid resuscitation is likely to be harmful (Malbrain 2014, Sakr 2017).

Patients with congestive heart failure (CHF) are more likely to suffer the negative impact of excess fluid administration. Fluid accumulation in these patients causes “exacerbation” of CHF - pulmonary edema leading to respiratory failure and poor pump function leading to cardiogenic shock. (Metra 2017). Importantly, CHF is a heterogenous condition, with variations including systolic dysfunction or heart failure with reduced ejection fraction (sCHF or HFrEF) and diastolic dysfunction or heart failure with preserved ejection fraction (dCHF or HFpEF).

Few studies have examined fluid resuscitation in patients with sepsis and CHF (sepsis/CHF patients). Recently, a case-control analysis was performed studying sepsis/CHF patients versus those with sepsis alone; however, specific fluid amounts were not correlated with outcomes (Ouellette 2014). Abstract data reported by one group suggested that under-resuscitation (< 30 mL/kg) in septic patients with heart failure may be associated with increased mortality, but to our knowledge that data has not yet been published in a peer-reviewed journal (Duttuluri 2014). A recent large study of 11,182 patients with severe sepsis and septic shock found that sepsis/CHF patients received, on average, 14 mL/kg *less* fluid resuscitation (around 1L for a 70 kg patient) than patients with sepsis who did not have CHF (Leisman 2017). The findings by Leisman et al suggest that physicians systematically give less IV fluid to sepsis/CHF patients.

The available studies suggest that there is clinical confusion and scientific uncertainty surrounding how much fluid to use when resuscitating sepsis/CHF patients. That there are multiple phenotypes of heart failure (HFrEF and HFpEF) which may respond differently to fluids adds complexity to this question. Given the increasing incidence of both heart failure and sepsis, it is vital that clinicians have appropriate guidance in in fluid resuscitation in these patients.

1. **Research Design and Methods:**

We hypothesize that sepsis/CHF patients receive less fluid resuscitation in cc/kg than sepsis patients without CHF, and that CHF/sepsis patients are at risk of suffering adverse events of mortality, increased length of state, and respiratory failure with over-resuscitation. We will therefore address the following Aims:

**Aim 1**: Using an ICD-9 diagnosis of CHF to identify sepsis/CHF patients, assess whether fluid resuscitation patterns differ between sepsis/CHF patients and those with sepsis alone. This will be a cross sectional analysis: fluid received (cc/kg) by septic patients in first 24 hours of ICU stay, stratified by if ICD 9 diagnosis of CHF.

**Aim 2**: Assess whether fluid resuscitation patterns differ in sepsis/CHF patients depending on category of CHF, using transthoracic echocardiogram (abbreviated “TTE”) within 1 month of ICU admission to identify patients with systolic and diastolic heart failure. This will be a cross sectional analysis: fluid received (cc/kg) by septic in first 24 hours of ICU stay, stratified by type of heart failure determined by TTE parameters (obtained within 1 month of ICU admission).

**Aim 3**: Using the patient cohort and echocardiogram data identified in Aim 2, assess whether amount of fluid resuscitation is associated with outcomes including mortality, length of ICU stay, and initiation of mechanical ventilation for each CHF category. This will be a retrospective cohort study: differences in outcomes e.g mechanical ventilation, stratified by type of heart failure and amount of fluid received.

Data collection:

Data was obtained from the MIMIC database (MIMIC - III V1.4). Data points needed in the study include patient demographics, patient history, lab events, echocardiogram measurements, ICU length of stay, mortality and discharge information.

Study subjects will be identified as those patients in the MIMIC database >18 years of age that had a diagnosis of both sepsis according to the Angus code-based definition, which has been prospectively validated to have a sensitivity of 50.4% and a specificity of 96.3% (Iwashyna 2014). **As sepsis criteria in flux are not uniformly agreed upon, we also plan a similar analysis with a sepsis cohort based on Sepsis-3 criteria. To identify patients within this cohort with a pre-existing diagnosis of CHF, ICD-9 code for CHF will be used. This is imperfect identifier of a true heart failure population, but a reasonable marker of patients who come in to the ICU with a presumed diagnosis of heart failure that may impact clinician behavior.**

In the second and third parts of the of the study, analysis will limited to those patients who fit the above inclusion criteria and also have a TTE within 1 month of ICU admission. Patients with CHF will be identified via measurements obtained from echo reports. Systolic dysfunction will be defined as left ventricular ejection fraction (LVEF) ≤ 40 %; LVEF **can be a categorical variable**. Diastolic dysfunction can be identified from analysis of mitral valve flow patterns and doppler ultrasound of cardiac tissue (reported as E/A and E/E’ ratios).

Patients will be excluded if code status was identified as DNR/DNI. They will also be excluded if they carry a diagnosis of end-stage renal disease on renal replacement therapy, as this could confound the analysis of heart failure. The control group will be septic patients with no ICD-9 CHF diagnosis, at the same age range.

Data analysis:

In the first and second aims of the study, the outcome is amount of intravenous fluid in cc/kg received in the first 24 hours after ICU admission. In the third aim of the study, the primary outcome will be mortality (ICU, hospital, and one year) as evaluated against the continuous variable of bodyweight-normalized fluid resuscitation (**There are several sources of weight in MIMIC, including radiology reports, that we can cross-check)**. Secondary outcomes will include length of stay (ICU, hospital) and respiratory failure (measured by increasing oxygen requirement, initiation of non-invasive ventilation (NIV), or initiation of mechanical ventilation (MV)). Mortality will be identified using the Social Security Death Master file. Length of stay is available via MIMIC. Respiratory failure will be identified by increasing oxygen requirement, or by CPT codes for NIV or MV.

Covariates of interest include: patient demographics at time of ICU admission, lab data (Initial pH, pH at 24 hours, Initial PO2/FiO2, PO2/FiO2 at 24 hours, sodium, WBC, hematocrit, creatinine, etc.), echocardiographic parameters (ejection fraction, measures of diastolic dysfunction). Illness severity score will be determined by the Sequential Organ Failure Assessment (SOFA) score on ICU admission; patients will be subdivided into SOFA categories of mild (SOFA 0-5), moderate (SOFA 6-10), and severe (SOFA ≧ 10) organ dysfunction, based on prior work showing relationship between these categories and mortality (Ferreira 2001).

**The sepsis cohort will be separated according to severity of heart failure based on the most recent echocardiogram report prior to the index admission, and the outcomes analysis will be performed separately for each of the groups.**

**Finally, we hope to perform matched propensity score would allow us to compare outcomes for patients (ideally all within a group of a given severity of heart failure, as above) who got a designated amount of fluids (say, at least x cc/kg) to those of ‘similar’ patients who did not get x cc/k, i.e. ‘similar’ as regards propensity to receive a certain amount of fluid.**

Data analysis will be primarily be performed by Qianxi Li and Sami Elamin, course members in the Collaborative Data Science in Medicine MIT course.

Power calculations:

For aim 1: Presuming 5000 patients admitted with sepsis and ~5% prevalence of heart failure (based national demographic data):

* α = 0.05
* *n*=250
* STD = 1L
* Detect difference of ~180 cc with 80% power

Pitfalls:

One potential pitfall in all three aims of the study is that the MIMIC database does not include fluids given in the Emergency Department, and thus the analysis is limited to fluids received in ICU rather than total fluids in first 24 hours. Though Emergency Department information would be useful, additional fluid resuscitation in ICU is still a clinically significant parameter worth investigating.

Limiting the second and third parts of the study to patients who had a TTE within 1 month of ICU admission may introduce a selection bias, in that patients with a recent TTE could theoretically have greater general disease burden, or with more clinically significant heart failure, then patients with a heart failure diagnosis without a recent TTE. This could limit the generalizability of the results. We feel that a 1 month window for TTE prior to ICU minimizes the selection of sick patients while still providing accurate and current information about cardiac function.

In the third part of the study, respiratory failure will be a secondary outcome of exposure to IV fluids. Respiratory failure could be influenced by conditions other than pulmonary edema, such as the acute respiratory distress syndrome (ARDS) or pneumonia; additionally, those outcomes might be more likely to occur in those with more severe illness (eg, moderate or severe sCHF). However, respiratory failure will be a secondary composite outcome, and this will be noted as a limitation.

**There is a potential problem of confounding in the outcomes part of the study, given that patients with more severe heart failure may both receive less fluid resuscitation and have worse outcomes regardless of IVF received. By separating the cohort into groups according to severity of heart failure, we would only be comparing outcomes according to the exposure of fluid resuscitation within a group of patients with similar cardiac function, hopefully mitigating this confounding.**

Finally, MIMIC is a single-center database, limiting the generalizability of the results to centers unlike BIDMC.

**Protection of Human and Animal Subjects**

The study comprises cross-sectional and retrospective analyses and does not directly involve human subjects. MIMIC database is anonymous and does not contain protected health information.

**Timeline**

I anticipate that the data analysis will take around 1 month. Writing the manuscript after data analysis should take around 1 month as well.

**References**

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