Reducing Mortality from Septic Shock Using an Interleukin-1 Receptor Antagonist

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REDUCING MORTALITY FROM SEPTIC SHOCK
USING AN INTERLEUKIN-1 RECEPTOR ANTAGONIST

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

June 2017

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Class of 2017
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ABSTRACT

Septic shock, a severe inflammatory state secondary to a bacterial infection with refractory hypotension and tissue hypoperfusion despite adequate fluid resuscitation, is a leading cause of mortality in intensive care units worldwide. The mortality rate of septic shock patients can exceed 40% in the U.S., highlighting the need for more effective therapies.

Anakinra, an inflammatory cytokine inhibitor, has been identified as a potential therapy for reducing various inflammatory states such as sepsis. Our aim is to evaluate the efficacy of anakinra in reducing mortality in patients with septic shock. This double-blind, randomized control trial will compare the 28-day mortality of patients who receive a 72-hour intravenous infusion of anakinra to a group of patients treated by standard of care alone for septic shock in an intensive care setting. Our goal is to evaluate if the addition of anakinra to standard sepsis care will result in a significant mortality reduction in patients with septic shock.
TABLE OF CONTENTS

ABSTRACT ........................................................................................................................... ii

CHAPTER 1 – INTRODUCTION .............................................................................................. 5

1.1 Background ...................................................................................................................... 5
1.2 Statement of the Problem ............................................................................................... 9
1.3 Goals and Objectives ..................................................................................................... 11
1.4 Hypothesis ..................................................................................................................... 11
1.5 Definitions ...................................................................................................................... 12

Sepsis and Septic Shock ..................................................................................................... 12
SIRS, SOFA and qSOFA – Clinical Criteria for Sepsis ......................................................... 12
Clinical Criteria for Septic Shock ....................................................................................... 13
Standard of Care (for Septic Shock) .................................................................................. 14
Mortality Rate ..................................................................................................................... 15

CHAPTER 2 – REVIEW OF THE LITERATURE ................................................................... 18

2.1 Introduction .................................................................................................................... 18
2.2 Review of empirical studies .......................................................................................... 18

Sepsis and Mortality .......................................................................................................... 19
Inflammatory Cascade and Anti-inflammatory Agents in Sepsis Treatment ...................... 23
Anakinra as Therapy .......................................................................................................... 24

2.3 Confounding Variables in Literature .......................................................................... 31

Infection Control ............................................................................................................... 31
Demographics .................................................................................................................... 32

Immunosuppression .......................................................................................................... 33

The Obesity Paradox ......................................................................................................... 33

Inter-/Intra-facility Transfer .............................................................................................. 34

2.4 Review of relevant methodology ................................................................................. 35

Study Design ..................................................................................................................... 35

Inclusion and Exclusion Criteria (Sepsis-3 definition, SOFA, qSOFA) ............................... 35

Randomization/Sampling/Blinding Techniques .................................................................. 37

Primary Outcome Measures and End Points ..................................................................... 37
<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Data Analysis</th>
<th>2.5 Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

CHAPTER 3 – STUDY METHODS ................................................................. 43

3.1 Study Design .................................................................................. 43
3.2 Study Population and Sampling ...................................................... 43
3.3 Recruitment Timeline ...................................................................... 44
3.4 Subject Protection and Confidentiality .......................................... 45
3.5 Study variables and measures ......................................................... 45
3.6 Blinding of Intervention and Outcome ............................................ 46
3.7 Adherence ....................................................................................... 46
3.8 Monitoring of adverse events .......................................................... 47
3.9 Sample Size Calculation ................................................................. 47
3.9 Analysis ......................................................................................... 48

CHAPTER 4 – CONCLUSION ..................................................................... 50

APPENDICES ......................................................................................... 52

APPENDIX A – Inclusion Criteria Reported by Opal et al. in the 1997 Phase III Trial ............................................. 52
APPENDIX B – Exclusion Criteria Reported by Opal et al. in the 1997 Phase III Trial ............................................. 53
APPENDIX C – Study Flow Chart .............................................................. 54
APPENDIX D – Consent Form for Study Participants ........................................... 55
APPENDIX F – Research Analyst Recruitment Flyer ........................................ 63
APPENDIX G – Sample Size Calculation .................................................. 64

BIBLIOGRAPHY ....................................................................................... 65
CHAPTER 1 – INTRODUCTION

1.1 Background

Sepsis persists as a major cause of mortality in intensive care units worldwide. According to a multicenter randomized trial study published by E. Stevenson et al. in 2014, the nationwide 28-day mortality rate of hospitalized adult patients with severe sepsis in the U.S. was 29.2%. The study also identified up to 27 million hospitalizations associated with sepsis in 2009 alone. A 2016 international consensus report on sepsis identified patients with sepsis at critically ill stages marked by hyperlactatemia and hypotension to have mortality rates as high as 54%. Worldwide, there are an estimated 31.4 million cases of sepsis per year, contributing up to 5.3 million deaths worldwide per year. This translates into healthcare costs of billions of dollars per year in the U.S. alone. In 2013, over $23 billion was spent on sepsis care in the U.S., making it the single most expensive condition treated in U.S. hospitals. Readmission rates following hospitalization for sepsis is also high. As compared to common and serious medical conditions such as acute myocardial infarction, heart failure, COPD and pneumonia, sepsis is the leading cause of unplanned 30-day readmission and is associated with a longer mean length of stay than any of the aforementioned conditions.

The high mortality rate and prevalence of sepsis demands a clear and effective approach to treatment that directly translates into improved patient outcome. Understanding the inflammatory response involved with any of the stages of sepsis has been a challenge for healthcare providers as a whole. Numerous research efforts have attempted to shed light into the complex host response that accompanies sepsis. Physicians have continuously attempted to design an effective, systemic approach in treating sepsis. Despite these many efforts, sepsis therapy still remains focused heavily on supportive care without a definitive, directed treatment.
Previous approaches to the critical care of septic patients have focused on early initiation of antibiotic therapy to control the underlying infection. Studies have found that even a delay of 6 hours in the initiation of antibiotics can result in increased hospital mortality. With advances in understanding the pathophysiology of sepsis, however, new therapeutic approaches in targeting the mechanism of the underlying rogue inflammatory response itself have been introduced, namely the development of novel immunomodulatory agents.

It is in the light of this approach that the role of interleukin-1 has been identified as a potential target for therapy. In sepsis, the host produces pro-inflammatory cytokines, one of which is interleukin-1 (IL-1). Upon activation, IL-1 induces fever, inflammation and hemodynamic shock. While the activation of a cytokine such as IL-1 can be beneficial in the host defense cascade against an invading organism, an exaggerated inflammatory response can be equally detrimental to a patient. For example, macrophage activation syndrome (MAS) is a state where inflammatory cytokines such as IL-1 are overexpressed, leading to a “cytokine storm” (Figure 1). The main clinical features of MAS include pancytopenia, liver dysfunction, coagulopathy similar to disseminated intravascular coagulation (DIC), and hyperferritinemia. Clinically and pathologically, MAS bears strong similarity to hemophagocytic lymphohistiocytosis (HLH). In fact, MAS, secondary hemophagocytic lymphohistiocytosis, and sepsis all share the same mechanism of dysregulated inflammation and may exist along a common spectrum.

The acute phase of overwhelming inflammation in MAS can subsequently cause multiorgan dysfunction syndrome (MODS) – a fatal, sepsis-induced state featuring pancytopenia, tissue hemophagocytosis, liver dysfunction, coagulopathy, and/or CNS dysfunction. Such multiple organ dysfunction requires intensive care.
The pathogenesis of this cytokine storm, marked by increased levels of numerous proinflammatory cytokines including IL-1 and ultimate organ dysfunction is also the hallmark of sepsis shock, a state of unregulated host response to an infection. While understanding the intricate balance of cytokines in the cytokine storm of MAS is challenging, the recognition of IL-1 as a major player in the inflammatory cascade supports using the blockade of IL-1 receptors as a therapeutic approach in septic patients.

Interestingly, in sepsis the host also produces its own anti-inflammatory cytokines, such as the interleukin-1 receptor antagonist (IL-1Ra) (Figure 2). IL-1Ra’s role is to inhibit the formation of an IL-1 signaling complex and provide negative regulation to a host’s response to sepsis. The balance between the pro-inflammatory cytokine IL-1 and anti-inflammatory cytokine IL-1Ra is important in the regulated response to an infection. Conversely, an

---


Figure 1. Proinflammatory cytokines, macrophage activation syndrome (MAS) and the cytokine storm.11
imbalance of IL-1 and IL-1Ra has been implicated as the cause or a severity factor in a number of diseases. Therefore, targeting IL-1 in the therapy of inflammatory diseases has been a medical challenge marked by many failures and successes.\textsuperscript{15}

![Figure 2. IL-1 receptor complex and signaling. Binding of the IL-1 receptor antagonist to the IL-1R1 (receptor) inhibits IL-1 binding and signal transduction.\textsuperscript{15}](image)

As efforts continue to understand the complicated pathophysiological role of IL-1 in an inflammatory response, studies have linked gene expression of IL-1 receptors/IL-1 receptor antagonists to outcome in septic shock.\textsuperscript{16-18} One example is a meta-analysis by Fang, F. et al that studied the association between an interleukin-1 receptor antagonist (IL1RN) gene 86-bp VNTR polymorphism and sepsis.\textsuperscript{18} In this meta-analysis, researchers discovered that although IL1RN 86-bp VNTR polymorphism is not associated with sepsis mortality, it is associated with increased risk of sepsis. While the definitive mechanism of the association is not clearly understood, it can be reasoned that an elevated production of anti-inflammatory cytokines can also inadvertently interfere with the host’s natural anti-inflammatory process. Another study by Zhang, A. et al. quantitatively weighed the association between the polymorphisms of IL-1 genes and sepsis. According to this study, polymorphisms of IL-1A-889, IL-1B + 3954 and IL-
IRN VNTR showed significant associations with the risk of sepsis.\textsuperscript{17} Furthermore, a prospective cohort study by Zapata-Tarres, M. et al. showed an increased prevalence of septic shock in childhood acute lymphoblastic leukemia patients with IL-1 receptor antagonist polymorphism (ILrN*1/ILrN*2), again showing the impact of IL-1 related genotype variance on the outcome of sepsis.\textsuperscript{19}

1.2 Statement of the Problem

Anakinra is a recombinant IL-1 receptor antagonist that is proven to be effective in reducing various inflammatory states.\textsuperscript{9,15,20,21} It works by preventing the binding of IL-1a or IL-1b to its receptors, effectively blocking the inflammation cascade from propelling further.\textsuperscript{9} Historically, anakinra has been studied for ameliorating various inflammatory processes such as RA, gout, Type II diabetes, chronic pericarditis, STEMI and autoinflammatory syndromes such as Still’s disease.\textsuperscript{9,21-23}

![Timeline of Anakinra Use in Various Inflammatory Processes](image)

Figure 3. Timeline of Anakinra Use in Various Inflammatory Processes\textsuperscript{9}
While anakinra has been shown to be effective in various inflammatory diseases, its therapeutic role remains unknown. Using the same mechanism as in other inflammatory diseases, blocking the IL-1 receptor and inhibiting the signal transduction may be useful in sepsis. In fact, as early as in the late 1980s, studies suggested correlation between elevated IL-1 levels and increased mortality from sepsis. The most notable early human trial using anakinra as a IL-1 blockade in sepsis was a phase III randomized control trial published in 1997 by Opal et al.\textsuperscript{24} In this double-blinded, randomized control trial, the efficacy of anakinra in patients with severe sepsis was analyzed in comparison with a placebo. According to this study, the 28-day, all-cause mortality rate was 33.1% in the group of subjects treated with anakinra in addition to standard therapy, while the mortality rate in the placebo group was 36.4%. Despite the attempt at a pioneering approach, the researchers concluded a 3.3% difference to be insufficient to demonstrate a statistically significant reduction in mortality when compared with standard therapy.\textsuperscript{24,25}

It wasn’t until almost two decades after Opal’s original study that anakinra was reconsidered as possible treatment for sepsis. In February of 2016, Shakoory et al. published a reanalysis of Opal’s phase III trial in the journal Critical Care Medicine.\textsuperscript{26} The objective of the reanalysis was to reevaluate the efficacy of anakinra in decreasing the 28-day mortality in septic patients, reanalyzing only those patients with features of macrophage activation syndrome as a surrogate for a more severe inflammatory septic response. The investigators discovered that while anakinra did not prove efficacious in Opal’s original trial, regrouping the study subjects according to presence or absence of features associated with macrophage activation syndrome did appear to improve sepsis survival outcomes.\textsuperscript{26}
The reanalysis indicates that patients with septic shock may benefit from interleukin-1 receptor blockade with anakinra given the overlapping clinical features of MAS and septic shock.

1.3 Goals and Objectives

In the light of this intriguing finding, a randomized, controlled trial focusing on septic shock patients may provide insight into the efficacy of anakinra as a therapeutic agent in critically ill septic patients at high risk of death. Our study is designed to focus specifically on patients with septic shock – a subgroup of septic patients with not only end organ dysfunction but also with a dysregulated inflammatory response similar to MAS. We are hopeful that while earlier studies have not found significant improvement in mortality using anakinra in septic patients, our more targeted approach to the most critically ill, septic shock patients will provide a better outcome in reduction of mortality. If effective, this therapy will provide a novel treatment option for patients with septic shock.

1.4 Hypothesis

We hypothesize that adult patients in septic shock treated with anakinra in addition to standard of care therapy will have a decreased 28-day mortality rate as compared to patients treated with standard of care alone.
1.5 Definitions

*Sepsis and Septic Shock*

For decades, defining sepsis has been challenging. In 2001, several international critical care societies convened to define sepsis as a systemic inflammatory process that can be divided into three stages: sepsis, severe sepsis and septic shock. The Sepsis Definitions Conference defined the three stages as follows: “Sepsis is defined as the presence of infection plus some of the listed signs and symptoms of sepsis. Severe sepsis is defined as sepsis complicated by organ dysfunction, and septic shock as severe sepsis with acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.” Despite this definition, defining who would have poor outcomes in sepsis remained difficult until the recent publication in 2016 of the Sepsis-3 guidelines. According to the new guidelines, the term “severe sepsis” has been dropped and the systemic inflammatory state to an infection is categorized into sepsis and septic shock. Sepsis is now defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” and septic shock as “a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.”

*SIRS, SOFA and qSOFA – Clinical Criteria for Sepsis*

There are two widely used methods in clinically identifying sepsis in patients: the SIRS (Systemic Inflammatory Response Syndrome) Criteria and the SOFA (Sequential Organ Failure Assessment) Criteria (Tables 1 and 2). Traditionally, sepsis is defined as 2 or more of the SIRS Criteria with a source of infection. However, the new Sepsis-3 Guidelines recommend...
the use of SOFA scoring to define the organ dysfunction of a potentially septic patient due to higher predictive in-hospital mortality compared to the SIRS criteria. Using SOFA, organ dysfunction is recognized as an increase in the SOFA score of 2 points or more.²

Quick-SOFA (qSOFA) is a new bedside clinical scoring system of three components: 1) respiratory rate of 22/min or greater, 2) altered mentation, or 3) systolic blood pressure of 100 mmHg or less.² The utility of qSOFA lies in its simplicity and the ability to quickly assess potentially septic patients. However, due to its limitations in both sensitivity and specificity, we will not be utilizing this scoring system in our study.

Clinical Criteria for Septic Shock

Sepsis-3 guidelines define septic shock as sepsis plus the need for vasopressor therapy to elevate mean arterial pressure (MAP) to ≥ 65 mmHg and lactate to >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation (Table 1).²

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVIOUS DEFINITIONS</td>
<td></td>
</tr>
<tr>
<td>SIRS (Systemic Inflammatory</td>
<td>Two of the following:</td>
</tr>
<tr>
<td>Response Syndrome)</td>
<td>- Temperature &gt;38°C or &lt;36°C</td>
</tr>
<tr>
<td></td>
<td>- Heart rate &gt; 90 beats/min</td>
</tr>
<tr>
<td></td>
<td>- Respiratory rate &gt;20 breaths/min or arterial carbon dioxide pressure &lt;32 mm Hg</td>
</tr>
<tr>
<td></td>
<td>- White blood cell count &gt;12x10⁹/L or ≤4x10⁹/L</td>
</tr>
<tr>
<td>Sepsis</td>
<td>SIRS with infection (presumed or proven)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis with evidence of acute organ dysfunction (hypotension, lactic acidosis, reduced urine output, reduced Pao₂/Fio₂ ratio, raised creatinine or bilirubin, thrombocytopenia, raised international normalized ratio)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis with persistent hypotension after fluid resuscitation</td>
</tr>
<tr>
<td>REvised DEFINITIONS</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Life threatening organ dysfunction* caused by a dysregulated host response to infection</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis and vasopressor therapy needed to increase mean arterial pressure to ≥65 mm Hg and lactate to &gt;2 mmol/L despite adequate fluid resuscitation</td>
</tr>
</tbody>
</table>

Table 1. Previous and Revised Sepsis and Septic Shock Definitions²⁹
Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score²

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td>≥400 (33.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td>≤1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)b</td>
<td>Dopamine 5.1-15 or epinephrine ≥0.1 or norepinephrine ≤0.1a</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1b</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td>Creatinine, mg/dL (μmol/L)</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
</tr>
<tr>
<td><strong>Urine output, ml/d</strong></td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FiO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.
² Adapted from Vincent et al.³³
³³ Catecholamine doses are given as μg/kg/min for at least 1 hour.
³ Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Table 2. Sequential [Sepsis-Related] Organ Failure Assessment Score²

**Standard of Care (for Septic Shock)**

Current standard of care for septic shock in intensive care and emergency care settings include 1) rapidly treating the underlying infection with broad-spectrum antibiotic therapy followed by subsequent narrowing of antibiotics to appropriate antimicrobial agents, 2) hemodynamic support through improving stroke volume and intravascular volume resuscitation, and 3) the use of vasopressors to counteract vasoplegic shock. However, septic shock management remains largely variable and is dependent on the severity of the disease and individual response of the patient. For example, recent studies have shown a more “flexible” or “conservative” approach to fluid resuscitation rather than an aggressive, universal approach may be more beneficial to patients in septic shock.⁷ Practice variation still exists and it is important to recognize the diversity of the population we intend to treat.⁷,³³,³¹
Mortality Rate

For the purposes of our study, we define mortality rate as the percentage of subjects that achieve the outcome of death from all causes within 28 days of study enrollment. The percentage will be calculated by the number of deceased subjects divided by the number of living subjects at 28 days.
References:


CHAPTER 2 – REVIEW OF THE LITERATURE

2.1 Introduction

An electronic literature review was conducted using the MeSH database system of PubMed, Ovid, and Cochrane Review. We used a comprehensive list of combinations of the key terms: “sepsis”, “septic shock”, “interleukin-1”, “IL-1”, “anakinra”, “mortality”, and “28-day mortality”. We included both retrospective and prospective studies as well as meta-analyses, dating back to 1991. Editorials or non-systematic reviews were excluded from our references. The reason for such expanded retrospective research of literature in time was due to lack of studies conducted in the use of anakinra for sepsis and to evaluate the evolution of sepsis treatment.

2.2 Review of empirical studies

Our empirical literature review focused on three things:

1) studies that identified the mortality of sepsis, to highlight the weight of the problem we wanted to address;

2) research in understanding the mechanism behind sepsis, septic shock and the potential anti-inflammatory therapies; and

3) studies using anakinra as therapy.

An abbreviated chart of the main articles discussed will be included at the end of each section.
As mentioned previously, observed mortality rates from sepsis can exceed 40%. We looked at three main articles that discussed sepsis-associated mortality rates and the factors that affected the outcome, if relevant.

The earliest study we reviewed was a meta-analysis of retrospective and prospective studies published by Friedman et al. in 1998, looking at mortality rates in septic shock patients between 1958-1997. The review focused on changes in mortality in septic shock over time. To achieve this goal, Friedman and his colleagues reviewed literature from 1958-1997 on the MEDLINE database and identified 131 studies (99 prospective and 32 retrospective) involving a total of 10,694 patients. The study reported the overall mortality rate of patients in septic shock across the 131 studies to be an astonishing 49.7%. The study also noted a decreasing trend of mortality over the study period, at $r = 0.49$ with $p < 0.05$. The study also looked at variability in mortality according to site of infection and changes in the most common organisms over time.

While the study raises significant alarm in the high mortality rate identified, it was confounded by the lack of consistency among the studies in defining severe sepsis and septic shock and the varying entry criteria for each study. Also, the researchers did not standardize the studied population by using a severity score for sepsis, thus were unable to stratify or control for the severity of the illness which limited their analysis. The analysis included studies with different designs and different aims, further limiting the internal validity of the study. Finally, the researchers also did not specify the countries from which the studies were conducted.

In 2014, a more thorough meta-analysis was published by Stevenson, E et al., reviewing 36 sepsis trials from 1993-2009. The study was conducted in response to an observation that
there appeared to be a declining sepsis mortality, leading researchers to question whether the decline was due to advances in practices or merely a mirage reflecting changes in classification of patients with “severe sepsis”. The new classification could have possibly led to the inclusion of less critically ill patients in its definition and therefore falsely reflecting better outcomes. In this meta-analysis, researchers reviewed 36 multi-centered, randomized prospective trials that included a total of 14,418 adult (>18 years old) participants with severe sepsis or septic shock in hospitals across the U.S and abroad. Single-center trials were excluded to reduce bias from center-specific outcomes. The primary outcome explored in this study was 28-day all-cause mortality, as planned in our study. The nearly two-decade span of data showed a mortality rate of 29-46.9%, with a decreasing trend over time consisting of a 3.0% drop annually (95% CI, 0.8%–5.0%; p = 0.009). The average 28-day mortality rate across all trials was 33.2%. The researchers also calculated standardized mortality ratios for each trial using observed and predicted mortality rates to identify whether discrepancies existed from differing sepsis identification criteria. The study showed decline in mortality ratio over time, confirming the decrease in mortality rates. They also observed a similar trend among trials using different sepsis identification criteria, suggesting the downtrend in mortality rate was not a result of the simple re-classification of patients.

While the analysis was useful in reviewing mortality rates and trends leading up to 2009, the study had its limitations in reflecting true mortality rates in severe sepsis/septic shock. Due to the nature of a meta-analysis, data regarding potential confounders at individual patient-by-patient level were unavailable and thus unadjusted for. Also, although the multi-national, multi-centered trials allowed for larger sample sizes, the results are vulnerable to internal validity due to variability in practices between different nations. Furthermore, the large
number of participants may falsely represent statistically significant results while being exposed to a greater number of confounding biases that are not controlled for. Nonetheless, Stevenson et al.’s study draws attention to the high mortality rate associated with sepsis worldwide and despite the downturn at the turn of the century, it shows that mortality rates in critically-ill septic patients remains high.

Most recently, in 2016, Fleischmann, C. and his colleagues made another attempt at evaluating global mortality rates in septic patients. In this systematic review, researchers investigated the incidence and the mortality rate of sepsis and severe sepsis between 1979-2015, using 15 international citation databases in an attempt to assess the global burden of sepsis. They searched any relevant literature on sepsis that reported evidence-based epidemiologic data within a given time frame but excluded studies that were limited to subgroups of sepsis or certain patient populations such as cancer patients or pediatric patients. Ultimately the study included 27 international sepsis trials from 18 different countries. According to their study, the global population incidence for in-hospital sepsis cases was estimated to be 288 per 100,000 person-years. Individually, the studies reviewed showed sepsis incidence ranging from 73.6 per 100,000 inhabitants in the United States (1979) to 1,180 per 100,000 inhabitants in Australia (2007–2008). When limiting the data to more recent years (2003–2015) the study revealed an even higher incidence at 437 per 100,000 person-years. For in-hospital severe sepsis cases, including septic shock, the investigators reported an incidence of 148 per 100,000 person-years. During the last decade, the incidence rate for severe sepsis was 270 per 100,000 person-years. The investigators used 95% confidence intervals for their analysis with $t=0.55-0.99$. 
28-day in-hospital mortality rates from sepsis showed great variability between studies, ranging from 5% to 42.5%, to an estimate of 21% worldwide. For severe sepsis, the estimated worldwide mortality rate was higher at 28%. Only looking at 2003-2015, the analysis showed a slightly decreased 28-day mortality rate of 17% in sepsis and 29% in severe sepsis.

The investigators in this study recalculated the population-level incidence rates from each study using the number of hospital sepsis cases provided in each study and census data reported for the time of that study. This reduced the variability in reported rates from different calculation methods in the original studies. However, the wide range of t values (0.55-0.99) shows the great difference in rates between studies as original publications were of different populations in different countries. While it may be impossible to control for the variables between studies from different countries, patient populations and practices, we also note that the great range in incidence and mortality rates may also reflect the heterogeneity of identification of sepsis cases among administrations. Achieving a consensus on defining sepsis has been an ongoing challenge and the difference in definition criteria for sepsis and severe sepsis among coding systems make global epidemiologic assessment challenging.

The most prominent limitation of this study lies in the fact that only 18 higher-income countries were included in the study due to lack of sufficient sepsis data from lower-income countries, limiting its predictive value as a true assessment of sepsis cases worldwide. We can assume sepsis incidence and mortality rates may be higher in lower-income countries, if we assume these countries also suffer from higher prevalence of infectious diseases and less efficient infection control.

While the studies by Friedman, Stevenson, and Fleischmann each showed its own strengths and weaknesses, they all showed an alarmingly high mortality among the populations
studies. Despite the declining hospital mortality rates shown in the study by Stevenson, E. et al., the study by Fleischmann demonstrated the continuing burden of sepsis worldwide, encouraging the need for continued research in treatment for sepsis.\textsuperscript{2,3}

<table>
<thead>
<tr>
<th>Date of Study</th>
<th>Author</th>
<th>Type of Study</th>
<th>Study Population</th>
<th>Primary Outcome</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Friedmann, G</td>
<td>Meta-analysis</td>
<td>131 studies (99 prospective, 32 retrospective) involving a total of 10,694 patients</td>
<td>Overall mortality</td>
<td>Overall mortality rate 49.7%</td>
</tr>
<tr>
<td>2014</td>
<td>Stevenson, E</td>
<td>Meta-analysis</td>
<td>36 sepsis trials globally from 1993-2009, total of 14,418 participants with severe sepsis and septic shock</td>
<td>28-day mortality</td>
<td>Observed mortality rate between 1993-2009: 29-46.9%, ave. 33.2%</td>
</tr>
<tr>
<td>2016</td>
<td>Fleischmann, C</td>
<td>Meta-analysis</td>
<td>27 international sepsis trials from 1979-2015 in 18 countries, total of &gt;2.8 million sepsis cases</td>
<td>Incidence and in-hospital mortality</td>
<td>Incidence, mortality rate for: sepsis - 437 per 100,000 person-years, 17%; severe sepsis - 270 per 100,000 person-years, 29% (2003-2015)</td>
</tr>
</tbody>
</table>

Table 3. Sepsis Mortality in Literature

**Inflammatory Cascade and Anti-inflammatory Agents in Sepsis Treatment**

While the previous studies mentioned exposed the high disease burden of sepsis, the next group of studies supports our understanding of the physiologic mechanism that lies behind the high mortality of sepsis as well as the use of anti-inflammatory agents as treatment.

In 1991, Charles A. Dinarello published an article discussing the role of proinflammatory cytokines in treatment of septic shock.\textsuperscript{4} The article focused mainly on two cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF). In his article, Dinarello argued that treating septic shock by either blocking the endotoxins secreted by the causative organisms or by neutralizing the antibodies was not an effective method. He suggested the direct inhibition of IL-1 or TNF would be a possible treatment strategy for sepsis by blocking the inflammation process and therefore a potential solution to reducing the high mortality associated with septic shock. He supported his argument by proving that an endogenous IL-1
receptor antagonist blocks shock and death due to *Escherichia coli* as well as its efficacy in treating a variety of inflammatory diseases.

Three years later, Charles Natanson presented a study at the 1994 NIH Conference highlighting the limitations of the new approach to sepsis therapy. In this study, Natanson analyzed preclinical and clinical trial data of antiendotoxin antibodies and anti-cytokine therapies for sepsis. The 10 clinical trials discussed in this study did not produce conclusive results to establish the safety or benefit of using antiendotoxin antibodies or anti-cytokines in septic shock.\(^5\) Natanson noted that although IL-1 inhibition studies have shown some benefit in animal models, it has not shown clear improvement in human trials. He also discussed the limitations of searching for a therapy when the exact mechanism of the inflammatory response is yet poorly understood. While inhibiting the host inflammatory response may be a premise for new therapy, the complexity of the mechanism in which the cytokines function greatly limits identifying a successful target for therapy.

**Table 4. Literature on IL-1 Blockade**

<table>
<thead>
<tr>
<th>Date of Study</th>
<th>Author</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991, 1993</td>
<td>Dinarello, C</td>
<td>Review of the role of IL-1 in septic shock and its blockade</td>
</tr>
<tr>
<td>1994</td>
<td>Natanson, C.</td>
<td>Review of potential therapies for septic shock using IL-1 inhibition</td>
</tr>
</tbody>
</table>

*Anakinra as Therapy*

Anakinra, a recombinant interleukin-1 receptor antagonist, has been most popularly used in treating chronic inflammatory diseases such as rheumatoid arthritis.\(^6,7\) As such, there have not been many studies conducted which focus on anakinra as a therapy for sepsis. The most notable study that introduced anakinra as a potential new treatment was a randomized,
double-blind, confirmatory phase III trial published in July 1997 by Steven Opal. In this study, Opal and his colleagues designed a placebo-controlled, phase III clinical trial studying the association between sepsis mortality and use of anakinra as therapy. This study was modeled after an earlier phase III trial by Charles Fischer and Opal published four years earlier that tested two different doses of anakinra in septic patients versus placebo. The initial study did not show a significant reduction in mortality (28-day, all-cause mortality was 34% (102/302) in the placebo group, 31% (91/298) in the 1.0 mg/kg/hr rhIL-1ra group, and 29% (86/293) in the 2.0 mg/kg/hr rhIL-1ra treated group (p = .23)), however the researchers retrospectively discovered that the most critically ill patients enrolled in their study had slightly favorable survival benefit with anakinra.

In the confirmatory study performed in 1994, the researchers recruited 906 patients with sepsis and/or septic shock from across 91 ICUs in North America and Europe. The patients were randomized to either receive anakinra 100 mg bolus + 72-hr infusion at 2 mg/kg/hr in addition to standard therapy or standard therapy alone (placebo). The primary outcome assessed was all-cause 28-day mortality. Although the study was originally designed to recruit 1,300 patients, the researchers set an interim analysis to be performed when approximately half of the target population had been enrolled and had completed the trial. When this interim analysis was performed, the study had recruited 906 patients that met the inclusion criteria. Complete data was available for assessment of 696 patients. According to the interim analysis, the 28-day, all-cause mortality rate was 33.1% (116/350) in the anakinra treatment group, while the mortality rate in the placebo group was 36.4% (126/346), yielding a 9% reduction in mortality rate (p = .36). With these results, researchers concluded the intervention failed to
demonstrate a statistically significant reduction in mortality when compared with standard therapy.

Although the data failed to show marked reduction in mortality as predicted, the study was well designed in that it was performed in a large cohort from multiple medical centers in various countries. There were a total of 11 participating countries with no single center contributing more than 4% of the entire patient population in the study, strengthening the generalizability of the study. Nonetheless, a multi-national, multi-centered clinical trials also has its limitations such as the variability between centers in clinical practice, treatment protocol, prevalent pathogens and disease recognition and reporting patterns. The study was also double-blinded to reduce observer bias. However, the researchers reported they may have been susceptible to bias in favor of a good outcome due to the favorable results published in the earlier trials. Another confounding factor of the poor results may be due to the improvements in sepsis care mortality itself, due to advances in disease management. Continuous improvements have been made in managing critically ill patients with septic shock that may diminish the room to make improvements in the clinical care of this population.

In summary, Opal and his colleagues concluded the phase III trial of anakinra use in the treatment of septic patients to be unsuccessful in demonstrating a benefit to continue the trial. They suggested the need for additional studies to understand the activity of IL-1ra as well as more studies that target a well-controlled specific population within septic patients to observe a direct therapeutic benefit.

In the following years, anakinra stayed mainly as a therapy option for inflammatory states such as RA, gout, diabetes, chronic pericarditis, and autoinflammatory syndromes as well as MAS. Most clinical studies have been focused in these disease states as briefly outlined
below. Of note, all studies involving anakinra report little to no adverse side effects of anakinra. In one study, 31% of the anakinra-treated patients developed transient injection site reaction that responded to oral diphenhydramine and local hydrocortisone.\textsuperscript{10}

Among the more recent studies in the last decade, an article was published in Nature Reviews Rheumatology in 2008, of a 13-year-old girl with systemic juvenile idiopathic arthritis complicated by macrophage activation syndrome was successfully treated with anakinra.\textsuperscript{11} Also in 2011, Nigrovic, PA\textsuperscript{7} studied the efficacy of anakinra as first-line therapy for systemic juvenile idiopathic arthritis (JIA) and found rapid resolution of systemic symptoms and prevention of refractory arthritis in nearly 90% of their study subjects. This study helped transition the use of anakinra as first-line therapy in systemic JIA from a novel rescue. Later that year in August, Miettunen, PM et al\textsuperscript{12} reported a case series of 12 patients in which they reported resolution of severe pediatric rheumatic disease-associated macrophage activation syndrome with the added use of anakinra with conventional immunosuppressive therapy. Following the successful treatment, they concluded the early use of anakinra, used in conjunction with conventional immunosuppressive therapy, is effective in severe MAS. Additionally, in 2014, a retrospective review of eight patients with suspected secondary HLH (hemophagocytic lymphohistiocytosis), an inflammatory response with similar features to sepsis, in the PICU at Helen DeVos Children’s Hospital in Michigan which showed positive results in decreasing the systemic inflammation with anakinra use.\textsuperscript{13} Most recently in 2015, a retrospective review by Jain, S\textsuperscript{10} evaluated 13 cases of treatment-refractory recurrent pericarditis treated with anakinra and found that all 13 patients experienced partial to complete resolution of symptoms, suggesting anakinra as an effective alternative agent for the management of glucocorticoid-dependent recurrent pericarditis.
As such, while anakinra has shown to be effective in various inflammatory diseases through functional IL-1 receptor blockade as evidenced in the previously mentioned experimental trials and case reviews, its uses in sepsis has remained limited. To date, the most cited and valued clinical study investigating the value of rhIL-1RA as therapeutic option in patients with sepsis remains to be Opal’s study in the early 1990s, although the disappointing results failing to show a significant reduction in mortality had discouraged the utility of anakinra in sepsis management.

However, a recent reanalysis published in 2016 by Bita Shakoory suggests otherwise. In this reanalysis study, the patients from Opal’s confirmatory phase III trial were regrouped based on the features of macrophage activation syndrome (MAS) – patients with hepatobiliary dysfunction (HBD) and disseminated intravascular coagulation (DIC) were grouped together while those without the two clinical signs of MAS comprised the control group. Patients were determined to have HBD if they showed presence of ≥2 of the following: prolonged prothrombin time (PT), elevated blood levels of aspartate or alanine aminotransferase and/or serum bilirubin levels above 2.5 mg/dL. DIC was defined as abnormal platelet counts with prolonged PT or partial thromboplastin time (PTT) in participants without anticoagulation or other pre-existing factors affecting anticoagulation. Following the regrouping of patients, the authors of the reanalysis discovered that while the 28-day survival rate remained statistically non-significant in the non-hepatobiliary dysfunction/disseminated intravascular coagulation patients (71.4% in anakinra treatment group vs. 70.8% in the control group), the 28-day survival rate in the hepatobiliary dysfunction/disseminated intravascular coagulation group was 65.4% (anakinra) vs. 35.5% (control). The significant improvement in the mortality rate in the reanalysis study revisited anakinra as a potential therapeutic agent in patients with septic shock.
and highlighted the need for a second evaluation of a specific subgroup of these patients for the advantages of IL-1Ra treatment.

Despite the promising results, this study was not without limitations. Since it was a reanalysis of a previous trial, the study had no control over assigning equal number of patients to each study arms. Although 763 patients from the original study were included in the reanalysis, the majority of the cases presented only with DIC or MBD and not both. Only 43 patients had both DIC and HBD, 26 of which were treated with anakinra, leaving 17 in the placebo arm and creating an underpowered study. Nevertheless, the study results suggested a targeted population, more specifically patients with septic shock, may benefit from interleukin-1 receptor blockade with anakinra.
<table>
<thead>
<tr>
<th>Date of Study</th>
<th>Author</th>
<th>Type of Study</th>
<th>Study Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Study Results</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Opal, SM</td>
<td>Phase III, Randomized Control Trial</td>
<td>893 patients with sepsis</td>
<td>anakinra 100mg bolus at 2mg/kg/hr, 1mg/kg/hr, placebo</td>
<td>28-day, all-cause mortality</td>
<td>28-day, all-cause mortality was 34% (102/302) in the placebo group, 31% (91/298) in the 1.0 mg/kg/hr rhIL-1ra group, and 29% (86/293) in the 2.0 mg/kg/hr rhIL-1ra treated group (p = .23)</td>
<td>Did not show significant reduction in mortality, but retrospective analysis showed favorable trend in critically ill subgroup</td>
</tr>
<tr>
<td>1997</td>
<td>Opal, SM</td>
<td>Phase III, Randomized Control Trial</td>
<td>91 ICUs in North America and Europe, 906 patients with sepsis/septic shock</td>
<td>anakinra 100mg bolus + 72-hr infusion at 2mg/kg/hr</td>
<td>28-day, all-cause mortality</td>
<td>33.1% (116/350) in the rhIL-1ra treatment group, while the mortality rate in the placebo group was 36.4% (126/346), yielding a 9% reduction in mortality rate (p = .36). Mortality rate 36% in placebo group vs. 33% in patients receiving IL-1ra</td>
<td>The study was terminated after an interim analysis found that it was unlikely that the primary efficacy end points would be met</td>
</tr>
<tr>
<td>2008</td>
<td>Kelly</td>
<td>Case Report</td>
<td>13 year-old female with systemic juvenile idiopathic arthritis(sJIA) and features of MAS</td>
<td>anakinra 1mg/kg SQ daily in addition to standard prednisolone and ciclosporin therapy</td>
<td>N/A</td>
<td>Significant improvement in symptoms</td>
<td>Showed potential for anakinra use in therapy for sJIA complicated by MAS</td>
</tr>
<tr>
<td>2011</td>
<td>Miettunen</td>
<td>Systematic Review</td>
<td>46 patients with systemic JIA from 4 countries</td>
<td>anakinra +/- corticosteroids or other DMARDs</td>
<td>N/A</td>
<td>Partial to full resolution of symptoms in &gt;95% of patients</td>
<td>Proposed anakinra as an effective first-line therapy for sJIA</td>
</tr>
<tr>
<td>2011</td>
<td>Rajasekaran</td>
<td>Retrospective Case Series</td>
<td>8 pediatric patients with secondary hemophagocytic lymphohistiocytosis(HLH)</td>
<td>anakinra at variable doses +/- IVIG or corticosteroids</td>
<td>N/A</td>
<td>Decline in inflammatory markers after anakinra use</td>
<td>Showed therapeutic potential for HLH, which has similar clinical features as sepsis</td>
</tr>
<tr>
<td>2015</td>
<td>Jain</td>
<td>Systematic Review</td>
<td>13 cases of treatment-refractory recurrent pericarditis</td>
<td>anakinra at various doses after refractory to NSAIDs, colchicine and prednisone for &gt;6mo.</td>
<td>N/A</td>
<td>all 13 patients experienced partial to complete resolution of symptoms</td>
<td>Proposed anakinra as an effective alternative agent for treatment refractory pericarditis</td>
</tr>
<tr>
<td>2016</td>
<td>Shakoory</td>
<td>Re-analysis of phase III trial by Opal</td>
<td>763 patients with sepsis/septic shock, grouped by hepatobiliary dysfunction and/or disseminated intravascular coagulation</td>
<td>anakinra 100mg bolus at 2mg/kg/hr, 1mg/kg/hr, placebo</td>
<td>28-day, all-cause mortality</td>
<td>28-day survival rate in the HBD + DIC group was 65.4%(anakinra) vs. 35.5%(control)</td>
<td>Revisited anakinra as a potential therapeutic agent in patients with septic shock</td>
</tr>
</tbody>
</table>

Table 5. Use of Anakinra in Literature
2.3 Confounding Variables in Literature

In Opal’s original study the 28-day all-cause mortality rate did not differ significantly between treatment groups by the site/source of infection, type of pathogen, presence of organ dysfunction at the time of study entry or the predicted mortality at the time of study entry, eliminating many of our confounding variables. However, given that the study was conducted decades earlier, we looked for additional literature on possible confounding variables.

Infection Control

Sepsis starts with an infection in the host and the variability of the infectious source or pathogen itself, may be a confounding factor in a study. One of the major concerns is the effect of infection source control (i.e. eradicating or hindering the infectious organism) on the outcome of sepsis. Current guidelines recommend intervention for source control within hours after diagnosis.

Most recently, in 2017, a Spanish multi-center, prospective observational study of 99 ICUs published by Martinez, M. et al attempted to determine the impact source control and its timing in the management of sepsis. The study enrolled 3,663 patients with severe sepsis or septic shock during three 4-month periods between 2011 and 2013. A total of 1,173 patients (32%) underwent source control and compared with patients who did not require source control, patients who underwent source control had greater prevalence of shock, major organ dysfunction, bacteremia, inflammatory markers, and lactic acidemia. Also, resuscitation compliance was worse. However, both hospital mortality and crude ICU mortality was lower in the source control group, leaving mixed conclusions on whether timely source control directly
affects sepsis mortality. One of the reasons of these mixed results can be attributed to the heterogeneity of the process of source control. Rather than a simple antibiotic therapy, proper source control is a multidisciplinary team effort that is linked to the management of a septic patient.\textsuperscript{16}

Another previous study reported comprehensive data on infection in sepsis. Gotts, et al\textsuperscript{17} published in 2016 an extensive review of 14,000 adult patients in 1265 ICUs from 75 countries on a single day in May 2007. The researchers included demographic, physiological, bacteriological, therapeutic and outcome data in their analysis to better understand sepsis. Of 7,000 patients identified with an infection, the most common site of infection was the lungs (64%). The most common isolated organism were Gram negative organisms such Pseudomonas spp. (20%) and Escherichia coli (16%). While the study does not specify the direct correlation between variables of infection and mortality, it can be supposed that the variables surrounding the infection itself can be a source of challenge in standardizing clinical trials.

\textit{Demographics}

Both Opal’s study and Shakoory’s reanalysis stratified their data by gender and age and both studies noted that there was no significant difference in mortality by these categories. However, a review article published recently by Gotts, J. et al\textsuperscript{17} invites some skepticism. Gotts and his colleagues report that while women have lower incidence of sepsis than men, the effect of gender on mortality rate was unclear. The researchers suggested the difference may be attributed to sex hormones and its effects on immunity as well as possible differences in cardiovascular physiology and response to infection.\textsuperscript{17,18} The study by Gotts also noted that patients are more susceptible to sepsis with increased age.\textsuperscript{17} The increased risk of sepsis can be
attributed to the elderly population having more comorbid conditions or generally less physiological capacity to fight off an infection. However, a multivariate analysis adjusting for comorbid conditions still showed that patients aged 65 or more with sepsis were 2.3 times more likely to die.\textsuperscript{17}

\textit{Immunosuppression}

Since the etiology of sepsis involves an initial infection, any causes of immunosuppression are risk factors for sepsis\textsuperscript{17,19,20}. A multi-centered, prospective observational study conducted between 1997-2011 in French ICUs that in patients with severe sepsis or septic shock concomitant with immunodeficiency had increased risk of mortality.\textsuperscript{21} In the analysis of 1,981 patients, the 28-day mortality was 31.3\% in the immunocompromised group compared to 28.8\% in the immunocompetent group(P=0.26). The conditions identified in the study to have association with increased mortality were AIDS, non-neutropenic solid tumor, nonneutropenic hematologic malignancies and all-cause neutropenia.\textsuperscript{21}

\textit{The Obesity Paradox}

While obesity is considered a risk factor of many chronic diseases, the association between obesity and mortality in sepsis has been mixed. While some studies show no association between obesity and mortality, other studies have shown either a positive or negative correlation with increased mortality.\textsuperscript{22} In a systematic review of the association between obesity and in-hospital mortality among septic patients, Trivedi, V et al identified three studies that reported no significant association between obesity and mortality as well as
one study that showed increased mortality. The analysis also identified three studies where mortality among obese patients were lower than other counterparts. While there are many factors that may contribute to variability in sepsis care in obese patients such as underlying comorbidities, fluid resuscitation, ventilation requirements or antibiotic administration, the paradoxical findings of decreased mortality in obese patients with sepsis may be associated with physiological differences in the capacity to respond to an acute inflammatory state.

*Inter-Intra-facility Transfer*

Studies have shown increased risk of mortality in septic patients that are subject to inter- or intra-facility transfers, most presumably attributed to the delay of early sepsis care. In a 1998 single-centered retrospective cohort study of 41 patients with septic shock, Lundberg, J and his colleagues compared the mortality between general ward and ICU setting care. The study found increased odds ratio of death for ward patients compared to ICU patients (3.57) and a delay of fluid administration and inotropic support in patients that developed septic shock in a ward setting. The delay in sepsis management for inter-facility transferred patients was confirmed in a more recent study published in 2015 by Faine, B et al. Also a single-center retrospective cohort study, this study reviewed 193 patients with severe sepsis and septic shock treated between 2009-2014. The patients were identified by whether they had been transferred from another local hospital or if they presented to the admitting facility directly through the emergency department. The results of the study showed that with similar illness severity, inter-hospital transferred patients were less likely to have received fluid resuscitation by 3 hours of care (54% vs 89%, p<0.001). However, the study did not find significant differences in the length of stay in the ICU or mortality.
2.4 Review of relevant methodology

Study Design

Our goal was to design a study largely based on the phase III trial of anakinra in sepsis by Opal et al. However, as suggested in Shakoory’s reanalysis, we decided to target patients in a more critical stage of sepsis – septic shock, to evaluate the efficacy of anakinra in this targeted population. Opal and his colleagues designed a multicentered, double-blind, randomized control trial of reviewing all-cause 28-day mortality in sepsis upon which we modeled our study. While a multicentered trial would provide better generalizability as well as better chance of recruiting a large sample size, we decided to design a single-center trial to eliminate center-specific variability in practices. Also, we deemed that based on the estimated incidence of septic shock at YNHH, we were confident we would be able to reach our sample size goal of 394 patients within the two-year timeframe of this study.

To achieve the goal of assessing the efficacy of an intervention (anakinra) in a clinical trial, we determined a prospective experimental design would be necessary as in Opal’s study. Thus, we propose a randomized, placebo-controlled clinical trial that allows for evaluation of the cause and effect of our intervention.

Inclusion and Exclusion Criteria (Sepsis-3 definition, SOFA, qSOFA)

The inclusion and exclusion criteria for our proposed study is similar to the criteria used in Opal’s confirmatory phase III trial (See Appendices I & III). However, we revised the inclusion criteria to include the most recent definition for sepsis and septic shock to better match our target population. The entry criteria for our study utilizes the SOFA scoring system
as well as the current revised definition of septic shock according to the Sepsis-3 consensus discussed in Chapter 1.\(^{25}\)

In our proposed study, we will be following the new Sepsis-3 Guidelines recommendation to use the SOFA scoring system to define the organ dysfunction of a potentially septic patient. Based on these guidelines, the authors recommended use of SOFA scoring to define sepsis, where organ dysfunction is recognized as an increase in the SOFA score of 2 points or more, which we will use in our study. While we will not be using qSOFA scores in our screening of patients, the following figure (Figure 3) depicts a proposed clinical decision-making algorithm for evaluating patients for sepsis or septic shock.

Figure 4. Operationalization of Clinical Criteria Identifying Patients with Sepsis and Septic Shock\(^{25}\)

Additionally, according to the consensus, the clinical criteria for septic shock is defined as sepsis requiring vasopressor therapy to elevate MAP $\geq 65\text{mmHg}$ AND lactate $>2\text{mmol/L}$.\(^{18}\)
mg/dL) despite adequate fluid resuscitation. This was based on the finding that the risk-adjusted hospital mortality was significantly higher in patients with fluid-resistant hypotension requiring vasopressors and hyperlactatemia (42.3% for serum lactate level of >2 mmol/L) compared with either hyperlactatemia or hypertension alone.25

Randomization/Sampling/Blinding Techniques

In Opal’s study, randomization was performed by a computer-generated process. All principal investigators involved in the study were blinded to the results of the study.8 The intervention was kept blinded by keeping anakinra and placebo in identical packages prepared by the manufacturer.8

Also, in another placebo-controlled, randomized, double-blind, parallel-group trial by Annane, D et al, randomization was performed through a concealed, computer-generated random number table. To blind the investigators of the assignment, pharmacists utilized sequentially numbered boxes containing the randomized treatment according to the generated list, which was confidentially delivered to the investigators.26

In our study, all patients, family members, medical/pharmacy staff and related investigators will remain blinded throughout the study period utilizing similar randomization and blinding techniques as the two studies mentioned above.

Primary Outcome Measures and End Points

Opal’s study used 28-day mortality as well as the reanalysis by Shakoory.8,14 While some other studies have looked at overall mortality, studies such as Annane, D et al.26 studying
the effects of anakinra used the 28-day survival or mortality as their end point. Also, we based the mortality of our control group on the mortality rate reported by Stevenson et al.\textsuperscript{2} which used 28-day mortality as well.\textsuperscript{2}

To decrease variability in length of stay and thus an overestimate or underestimate of mortality, we propose a 28-day mortality to observe a direct effect of anakinra therapy.

\textit{Sample Size}

Opal and Fischer’s first phase III trial calculated the sample size needed to be 300 patients per treatment group to detect a 35% reduction in 28-day all-cause mortality with 91% power at P=0.05. The calculation assumed the placebo mortality rate would be 40%.\textsuperscript{9}

The study was designed to enroll 1,300 patients but the study was terminated after an interim analysis at which point approximately half of the target population had completed the trial. Thus, their study power calculation was limited (power 1%).\textsuperscript{8}

The proposed study will aim to have an effect size similar to the original phase III trial by Fischer and Opal. However, given our study limitations of shorter time to conduct the study and smaller sample size, we will use a power of 80% with an alpha of 5% to calculate the sample size of this study. The assumed 28-day mortality for the intervention (anakinra) group is 33.1% as reported by the confirmatory analysis by Opal.\textsuperscript{8} As for the control group, we determined the reported by Stevenson et al better reflected the target control group than Opal’s study.\textsuperscript{2} According to the study, the worldwide 28-day mortality rate of septic shock patients was reported to be 46.9% during years 1991-1995, which is the same time frame Opal’s confirmatory trial was conducted.\textsuperscript{2} Based on the data, we expect approximately 13% difference to be statistically significant. Although Shakoory’s reanalysis was underpowered, the 28-day
mortality in the intervention group was 34.6% compared to 64.7% in the placebo group, corresponding to a 47% reduction in mortality which further supports are estimation.\textsuperscript{14}

We also propose our study to be a 1-sided test as the study is designed to test the hypothesis of reduction in mortality with intervention versus placebo, and we will not be testing the opposite hypothesis (increase in mortality rate with intervention). This is similar to the 1-sided test design conducted by Annane et al in determining the effect of corticosteroids in patients with septic shock.\textsuperscript{26} 90\% power with 0.05 type I error was used to calculate the sample size in this study.\textsuperscript{26}

\textit{Data Analysis}

Fischer and Opal’s first trial used a generalized Wilcoxon statistic to evaluate the survival times for the three groups studied. They also used Pearson’s $X^2$ analysis, one-way analysis of variance, or nonparametric rank comparisons using the Kruskal-Wallis Test to stratify the three groups according to demographic and pretreatment variables.\textsuperscript{9}

Opal and his colleagues used analysis of variance to test for treatment comparability of continuous baseline measurements in the second study. 28-day mortality rates and other categorical measurements were analyzed using Chi-square tests.\textsuperscript{8}

Both prospective trials followed the intent-to-treat principle to the primary end point.

In the confirmatory study by Opal, an independent Safety and Efficacy Monitoring Board was tasked to perform an interim analysis approximately half of the target population had been enrolled and had completed the trial. The interim analysis was to evaluate major safety issues or statistically significant difference in outcome as well as to evaluate the
probability of study end points to be met. Our study will utilize a similar interim analysis by an independent review board at 1 year of study.

2.5 Conclusion

The meta-analysis by Friedman, Stevenson and Fleischmann highlighted the burden of sepsis and sepsis mortality remains high. As we make progress in understanding the complex physiology behind sepsis as well as the challenges in accurately staging and defining sepsis, there is a need to make equal progress in discovering effective, targeted therapies. Although Opal and his colleagues introduced interleukin-1 blockade in treatment of sepsis in his highly cited study over two decades ago, anakinra wasn’t recognized as potential therapy for patients with sepsis until the reanalysis of the original trial just recently by Shakoory et al.

As part of an effort to tackle the widespread challenge of sepsis, we propose a targeted double blind, randomized control trial evaluating the efficacy of anakinra verses placebo to reducing all-cause 28-day mortality in patients with septic shock, using the Sepsis-3 definition to specifically target patients with higher mortality.
References:


CHAPTER 3 – STUDY METHODS

3.1 Study Design

This is a placebo-controlled, randomized, double-blind study to be performed at the adult medicine intensive care unit at Yale-New Haven Hospital (YNHH). Randomization will be obtained using a computer-generated random number sequence that will maintain concealed and blinded to all participants of the study including but not limited to study subjects, pharmacists, medical providers and research analysts. We plan to randomize patients into either the intervention (anakinra) group or the placebo group in 1:1 ratio.

The primary objective of the study will be to evaluate the efficacy of anakinra in reduction of 28-day mortality in comparison with a placebo.

3.2 Study Population and Sampling

The study will screen all adult patients (≥18 years old) admitted to the YNHH Medical Intensive Care Unit during the study period to determine if the patient meets the criteria for septic shock according to the Sepsis-3 definition. The clinical criteria we will use to identify patients in septic shock an increase of two or more points of the SOFA score with vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

The evaluation of eligible participants will be conducted through the electronic medical record system, EPIC by a registered nurse research analyst hired by the investigators using flyers (Appendix F). The analyst will review patient’s medical records daily to identify patients that meet the eligibility criteria.
Exclusion criteria includes advanced directives, pregnancy, scheduled operations within 28-days, and conditions that cause immunocompromise (i.e. HIV, hematologic malignancies).

### 3.3 Recruitment Timeline

We propose the following timeline for our study:

**Figure 5. Timeline of Planned Study**

This study will be conducted over a total of 2 years, including recruitment, data collection and analysis. Patients will be enrolled as identified for the first 22 months of study. All recruitment of subject will end by no later than 2 months prior to the completion of the study. Data will be collected throughout the study as patients are enrolled and the outcome observed. Data analysis will be performed at 12 months (interim analysis) and at 22 months,
allowing two months for data analysis at each point. (See Appendix C for proposed study flow chart)

3.4 Subject Protection and Confidentiality

We plan to seek approval by the Human Investigation Committee (HIC) at Yale before August 2017 as specified above. Written informed consent will be obtained from eligible patients or their family members if patients are not able to provide consent (Appendix C). Special considerations for special patient populations, issues regarding breach of confidentiality and methods to ensure HIPAA compliance are all outlined in the consent form. To ensure safety of our participants, we plan an interim analysis at the 12-month mark. An independent safety monitoring board shall meet after at the interim analysis end point to decide whether the study shall continue or be terminated.

All study investigators will be required to sign a Confidentiality and Non-Disclosure Agreement Form to ensure the confidentiality of data obtained throughout the study, in compliance with current HIPAA regulations (Appendix D).

3.5 Study variables and measures

The independent variable of this study will be the administration of anakinra. The intervention group will receive an initial 100mg bolus of anakinra at enrollment of trial followed by a 72-hr intravenous infusion at 2mg/kg/hr. The control group will receive normal saline as placebo in the same manner of administration (100mg bolus + 72-hr IV infusion of anakinra equivalent volume*). *anakinra is commonly manufactured in 100mg/0.67mL form.
The primary dependent variable observed in this study will be 28-day, all-cause mortality. All eligible patients will be followed over the 28-day study period after study entry or until death, whichever occurs first.

Baseline data of the study participants will be collected at the time of enrollment by our research coordinator. The data set will include age, sex, race, BMI, comorbidities, pathogen of infection (if identified), SOFA score, lactate level, vital signs, and vasopressors administered. The research analyst will require access to EPIC, the Medical Intensive Care Unit of YNHH and workspace with computer access.

3.6 Blinding of Intervention and Outcome

The computer-generated list to randomize patients into the two arms of the study will be concealed to all participants and investigators of the study. The pharmacy will provide unlabeled vials of either the placebo or anakinra following the sequence of the randomization list. A confidentiality form will be signed by all pharmacists and medical staff involved in the study to ensure blinding (Appendix C). Data analysis by the independent review board will be kept blinded to all study participants and investigators until termination of the study.

3.7 Adherence

There are no foreseen major concerns with adherence in our study population. However, a patient may withdraw from the study at any time for any reason as specified in the consent form. The data from patients that withdraw from the study will be censored at the time of withdrawal and included in the analysis.
To ensure adherence to intervention, the research analyst will confirm the administration of anakinra or placebo each day during the intervention period.

3.8 Monitoring of adverse events

Safety of Anakinra in human use is well documented in previous studies. We will continuously monitor for adverse reactions including but not limited to: headache, nausea/vomiting/diarrhea, opportunistic infection, arthralgia, fever, and cytopenia. Given that anakinra is an immune suppressing agent and it is being administered to patients with severe bacterial infections, care to monitor for worsening infection or a high rate of new, hospital-acquired infection will be taken.

3.9 Sample Size Calculation

To calculate our sample size, we used severe sepsis 28-day mortality of 46.9% reported by Stevenson et al. in their 2014 study of severe sepsis (including septic shock) worldwide. The expected 28-day mortality in the intervention group we used in our sample size study was 33.1% as calculated in the reanalysis of the anakinra vs. placebo phase III trial. To detect a 13.8% difference with 80% power and 0.05 alpha our predicted sample size needed was a total of 394 patients (Appendix G).
3.9 Analysis

The primary outcome of the study (28-day, all-cause mortality rate) will be analyzed using Chi-square tests, which we determined to be the best method to analyze a binomial outcome. All analyses will be conducted on an intention-to-treat basis. Patient baseline characteristics and study variables will be stratified using multiple logistic regression to adjust for differences that may affect outcome.
References:


CHAPTER 4 – CONCLUSION

The primary limitation of the proposed study may lie in its design as a single-center trial, which complicates the generalizability of the results. The advantage of a single-centered trial is that it helps lessen the variability that exists between individual clinician practice and sepsis treatment protocol on from institutional level. The more controlled setting of a single-center, fixed care setting of the adult Medical Intensive Care Unit may provide a more uniform standard of care compared to a multi-centered study.

Another possible limitation of the study is in its time restriction of a two-year timeframe, potentially making it difficult for the study to reach its target sample size based on the current incidence of septic shock. This may result in an underpowered study or the early termination of the study during the interim analysis if the target sample size is deemed not to be achievable.

Determining the precise timing of anakinra administration for maximum efficacy has been a question that has been challenging to clinicians. The complexity of the inflammatory process makes it difficult to assess when the IL-1Ra blockade will be most beneficial to the patient. Finding the right balance between controlling a dysregulated host inflammation while allowing the body to respond appropriately to an infection remains a challenge and may work as an invisible confounding factor of outcome. However, we are reassured that by standardizing the timing of the intervention, we can reduce the confounding to a lesser degree. Although each patient may undergo a different physiological timeline of responding to sepsis and recovery time from septic shock may vary, the prospective design of the study allows for maximum correlation between cause and effect of the intervention planned.
The variability between entry criteria for sepsis has been a confounding factor in many previous studies due to the inconsistent definition of sepsis and septic shock. Following the recommendations set by the Sepsis-3 Consensus, we were able to standardize the entry criteria for septic shock thereby reducing the variability between patients in terms of baseline illness severity.

Also, using a drug with an established safety profile minimizes the risk of adverse side effects, increasing the safety for our subjects. While unforeseen side effects are difficult to eliminate, we are hopeful there will be minimal risk of harm to our study population with the intervention planned.

Despite novel efforts to treat sepsis and septic shock, mortality remains high and we are still in search of a definitive therapy. Positive results from this study can lead clinical practice in a new therapeutic approach to septic patients. Through immune modulation, our understanding the pathophysiology of sepsis in the past years may be translated into more effective therapy.

While the mortality rate from sepsis has been slowly declining over the years, incidence is rising, possibly due to the aging population. Also, both the mortality rate and incidence remain much higher in lower income countries. Devising an easily reproducible, novel therapy may serve as a much-needed answer to the difficult question posed by septic shock, which affects all populations worldwide.
APPENDICES

APPENDIX A – Inclusion Criteria Reported by Opal et al. in the 1997 Phase III Trial

1. Clinical evidence of infection, as suggested by, but not limited to, the presence of one or more of the following signs within the previous 72 hrs
   a. Presence of polymorphonuclear cells in a normally sterile body fluid
   b. Culture or Gram stain of blood, sputum, urine, or normally sterile body fluid is positive for a pathogenic microorganism
   c. Chest radiograph is consistent with a diagnosis of pneumonia
   d. Focus of infection is identified by visual inspection (e.g., ruptured bowel with the presence of free air or bowel contents in the abdomen found at the time of surgery; wound with purulent drainage; radiographic or computed tomography evidence of an abscess or osteomyelitis, etc.)
   e. Patient has an underlying disease or condition that is likely to be associated with infection (e.g., ascending cholangitis, ischemic bowel, etc.)

2. Evidence of a systemic response to infection, as defined by the presence of all of the following signs within the previous 24 hrs
   a. Fever or hypothermia (core temperature of \(\geq 38.0^\circ\text{C} [\geq 100.4^\circ\text{F}]\) or \(\leq 36.0^\circ\text{C} [\leq 96.8^\circ\text{F}]\))
   b. Tachycardia (HR of \(\geq 90\) beats/min), except in patients receiving a \(\beta\)-adrenergic receptor blocking agent or with a rate control pacemaker
   c. Tachypnea (RR of \(\geq 20\) breaths/min while spontaneously breathing) or patient requires mechanical ventilation

And either

Sustained hypotension or use of vasopressors (except dopamine of \(< 5.0\ \mu\text{g/kg/min}\)) for a minimum of 1 hr in the presence of adequate fluid resuscitation and in the absence of antihypertensive agents. Sustained hypotension was defined as two or more blood pressure measurements a minimum of 1 hr apart with a systolic blood pressure of \(< 90\) mm Hg or mean arterial pressure of \(< 65\) mm Hg

Or

Evidence of end-organ dysfunction or hypeperfusion, as defined by the presence of two or more of the following signs, which are not the results of underlying disease but are attributable to sepsis
   a. Arterial hypoxemia (\(\text{Pa}_2\) of \(\leq 75\) torr \([\leq 10\ \text{kPa}]\) or \(\text{Pa}_2/\text{Fi}_2\) of \(\leq 250\) [corrected for altitude])
   b. Metabolic acidosis (pH of \(< 7.30\); or base deficit of \(\geq 5.0\) mmol/L, or an increased plasma lactic acid concentration)
   c. Sustained oliguria (urine output of \(< 0.5\) mL/kg/hr for a minimum of 2 hrs in the presence of adequate fluid resuscitation)
   d. Recent (within 24 hrs) coagulation abnormality (prothrombin time of \(\geq 1.2\) [\(\geq 50\%\) activity] or partial thromboplastin time of \(\geq 1.2\) times the upper limit of normal)
   e. Thrombocytopenia (platelet count of \(< 100,000\) cells/mm\(^3\) \([\leq 100,000 \times 10^6\) cells/L\])
   f. Cardiac index of \(> 4.0\) L/min/m\(^2\) with systemic vascular resistance of \(< 800\) dyne-sec/cm\(^5\) in the presence of adequate fluid resuscitation

3. Patient or authorized representative provided informed consent or assent, respectively

HR, heart rate; RR, respiratory rate.
Patients meeting any of the following criteria were not eligible to participate:

1. Pregnancy
2. Weight of >130 kg
3. Cardiopulmonary resuscitation within 72 hrs before study entry
4. Evidence of nonseptic cardiogenic shock or source of uncontrolled acute blood loss
5. Presence of severe, preexisting, parenchymal liver disease
6. Anuria (~50 mL of urine output per day)
7. Status post solid organ (i.e., heart, kidney, and/or liver) or bone marrow transplant
8. Evidence of neutropenia
9. Administration of high doses of corticosteroids (i.e., doses of >1.5 mg/kg/day of prednisone or equivalent) within 72 hrs before study entry
10. Immunosuppression secondary to immunomodulatory medications (e.g., cyclosporine, azathioprine, OKT3), chemotherapy, or radiation therapy within 3 wks before study entry
11. Known HIV seropositivity
12. Any disease sufficiently advanced to suppress resistance to infection

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OKT3, murine anti-T lymphocyte monoclonal antibody; HIV, human immunodeficiency virus.
Enrollment

- (#) Patients assessed for eligibility
- excluded
  - pregnancy
  - immunocompromised
  - scheduled surgery

Randomization

- (#) Randomized

Allocation

- placebo + standard of care
- anakinra + standard of care

Follow-up

- lost to follow-up
- discontinued treatment

Analysis

- () included in analysis
- () included in analysis
APPENDIX D – Consent Form for Study Participants

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

200 FR. 1 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Reducing Mortality with Anakinra in Septic Shock

Principal Investigator: Geoffrey Connors, MD

Co-Principal Investigator: Juyeon Chung

Funding Source: (To be determined)

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the efficacy of using anakinra, an interleukin-1 inhibitor in reducing mortality in patients with septic shock. You have been asked to participate because you meet the clinical criteria defined by the Sepsis-3 definition as “septic shock”. This study will aim to recruit approximately 400 participants admitted to the Medical Intensive Care Unit and Step-Down Unit of Yale-New Haven Hospital between August 2017 and June 2019.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.
Description of Procedures

- As a participant of this study, you will be randomized to one of two groups:
  - The “placebo” group. This is the study “control” group.
  - The “anakinra” group. This is the study “intervention” group.
- Randomization will be obtained by a computer-generated algorithm.
- The clinicians, researchers and participants will all be blinded to the group assignments. This means all parties will not know which group a participant is assigned to.
- The “placebo” group WILL NOT receive anakinra, an anti-inflammatory agent in addition to standard of treatment for septic shock.
- The “anakinra” group WILL receive anakinra in addition to standard of treatment for septic shock.
- For the anakinra group, 100 mg bolus of anakinra will be administered intravenously (IV) initially, followed by a 2mg/kg/hr IV infusion for 24hrs. For the placebo group, the same amount of normal saline will be administered. Normal saline is a non-harmful solution that is optimized to the concentration of your blood. The amount administered will be a negligible amount to have any significant physiological effects. It is also a part of standard of therapy for patients in septic shock.
- The administration of anakinra or placebo should not require additional intravenous access than needed for standard treatment for septic shock.
- The total length of participation in this study is 28 days.
- Treatment related to this study will last 72 hours (3 days) from point of enrollment and initiation of treatment.
- You will receive standard of care during the remainder of the hospitalization.
- This study requires reviewing of participants’ medical record for demographic information as well as other information relevant to the study. For example, researchers of this study may collect information that may include but not limited to: your age, gender, race, height, weight, past medical history and medication history. This information will help researchers evaluate potential confounders in the results of this study. For research involving review of subject’s medical record, the consent form should explain what types of information will be collected, and why.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.
**Risks and Inconveniences**

- There are no significant foreseeable risks, discomforts or inconveniences associated with the study.
- Anakinra has been proven to be safe for use in multiple clinical trials.
- The most common reported side effect of anakinra is skin irritation at the injection site. Our study will utilize intravenous administration of anakinra, therefore eliminating the side effects of skin/tissue injection.
- Other possible side effects of anakinra may include but not limited to: headaches, nausea, vomiting, diarrhea, joint pain, changes in blood cell count, or increased risk of infections.
- There are no documented studies showing risk of using anakinra during pregnancy. However, as there are limited research on anakinra use in your population, please discuss with your clinician of if you are pregnant or could be pregnant.
- Participation in this study may involve risks that are currently not known.
- There will be no genetic testing or related testing involved with this research.

**Benefits**

- The goal of this study is to identify whether the use of anakinra can risk of death in septic shock patients. Thus, if you receive the assigned treatment, we hope it may improve your survival and outcome.
- Any findings derived from this study will also serve to advance scientific knowledge for medical experts at large.

**Economic Considerations**

- There are no additional medical care costs you will be subject to in association with this research.
- You will still be responsible for any co-pays required by your insurance company for standard treatment.
- If you are assigned to receive the intervention(anakinra), it will be offered at no charge to you.
- Subjects may be offered an estimate of the charges they will be expected to cover.
Treatment Alternatives/Alternatives

- The use of anakinra is a new approach to sepsis care and therefore no parallel alternative treatment exists. There may be other experimental treatment to sepsis outside of this study. Please consult your physician if you are interested in knowing what other clinical trials may be available.
- You may choose to not participate in this study.
- Please note that alternatives are not limited to curative procedures. For chronic or terminally ill subjects, alternatives may include procedures for symptom management, improving the ability to function, or palliative care.

Confidentiality

- Study subjects’ data will be kept for a maximum of 3 years before it is destroyed or de-identified.
- Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)
- Authorized representatives of the Food and Drug Administration (FDA) [or a funding agency, such as the National Institutes of Health] and the manufacturer of anakinra may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.
- Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. [Describe the methods used to safeguard the confidentiality of subjects’ data (e.g., coding data or samples with numbers, storing research materials in locked cabinets, password-protecting data stored on a computer, etc.)] When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.
- Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.
In Case of Injury

- If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.
- If you become ill or are physically injured due to the study [drug/device] [provide name of agent] or any investigational procedure specifically required by the plan for this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study [drug/device] or properly performed non-standard of care investigational procedure required by the study will be covered by the Sponsor as long as you have followed the directions of the study doctor.
- If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the study doctor.
- You will not receive any other kind of payment. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study. You do not give up any of your legal rights by signing this consent form.
- Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.
Withdrawing from the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. This included during or after treatment with anakinra or placebo.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments (if applicable).

The researchers may withdraw you from participating in the research if necessary. Involuntary withdrawal may be due to development of serious side effects or early termination of the study.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.
Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:___________________________

Signature:___________________________________

Relationship:_____________________________

Date:______________________________________

___________________________________________
Signature of Principal Investigator        Date

or

___________________________________________
Signature of Person Obtaining Consent     Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator: Juyeon Chung, (xxx) xxx-xxxx

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
APPENDIX E – Non-Disclosure and Confidentiality Agreement

NON-DISCLOSURE AND CONFIDENTIALITY AGREEMENT

Research Title: Reducing Septic Shock Mortality with Anakinra

As a participant of this research I understand that I may have access to confidential information about the study intervention and participants. By signing this statement, I am demonstrating my understanding of my responsibilities to maintain confidentiality and agree to the following:

- I understand that any identifying information about study sites and participants are completely confidential.

- I agree not to divulge, publish, or otherwise make known to unauthorized persons or to the public any information obtained in the course of this research project that could identify the persons who participated in the study.

- I understand that all information about study sites or participants obtained or accessed by me in the course of my work is confidential. I agree not to divulge or otherwise make known to unauthorized persons any of this information, unless specifically authorized to do so by approved protocol or by the local principal investigator acting in response to applicable law or court order, or public health or clinical need.

- I understand that I am not to read information about study sites or participants, or any other confidential documents, nor ask questions of study participants for my own personal information but only to the extent and for the purpose of performing my assigned duties on this research project.

- I agree to notify the local principal investigator immediately should I become aware of an actual breach of confidentiality or a situation which could potentially result in a breach, whether this be on my part or on the part of another person.

__________________________________________  __________________________  __________________________
Signature                                      Date                                      Printed name

__________________________________________  __________________________  __________________________
Signature of local principal investigator       Date                                      Printed name
RESEARCH STUDY

Would you like to participate in clinical research?

We are looking for part-time or full-time research assistants to aid in the study of evaluating the efficacy of a new therapy for patients with septic shock. This is a paid position. Please contact the number below for information on compensation.

**Eligibility:** Registered Nurse or equivalent level medical-degree.

**Responsibilities:**
- Dedicate 8-40hr/wk depending on full- or part-time participation
- Review patient records on EPIC while complying to HIPAA (training is required)
- Screen and interview potential study subjects in the Medical Intensive Care Unit at YNHH

For questions or if you are interested in participating in this study, please contact the primary investigator:

Juyeon Chung at (xxx)xxx-xxxx or email at juyeon.chung@yale.edu
APPENDIX G – Sample Size Calculation

*28-day, all-cause mortality

BIBLIOGRAPHY


