

VARIATION IN SEPSIS SYMPTOMS OF HOSPITAL PATIENTS ADMITTED FROM
DIFFERENT POINTS OF ORIGIN

BY

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THESIS

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ABSTRACT

In 2011, the 11th leading cause of death in the U.S. was septicemia. Sepsis is a disease pathway that leads to death by infection of the blood and is a process that is highly time dependent.

The purpose of this study is to determine if there is a relationship between patients that come from different points of origin and their presentation of sepsis variables upon admittance to the hospital. The research questions were (1) is there a difference in the means of variables of importance to sepsis compared by point of origin? (2) Is there a relationship between patients from different points of origins and whether they present signs of sepsis within a normal or abnormal range at admission? These questions will be answered along with several sub-questions that will supplement the main research questions. Demographic data on sepsis patients as well as the symptomatic variables upon admission to Carle Foundation Hospital in Urbana, Illinois were obtained with permission from Carle Foundation Hospital.

The results show that, comprehensively, the symptomatic variables that are used to determine a diagnosis sepsis do not show a statistically significant relationship between the different points of origin. Upon study of the individual variables that indicate a sepsis diagnosis, many of the sepsis criteria variables showed no statistically significant relationship to patient point of origin. However, it was observed that oxygen saturation associated with breathing difficulty in septic patients was statistically significant at p -value 0.013 thus rejecting the null hypothesis for research question one but also rejecting the alternative hypothesis for research question two.

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CHAPTER 1

INTRODUCTION

1.1 SEPSIS: A HOSPITAL PRIORITY

Sepsis places a major burden on the health of our nation. With a trend of increasing incidence noted in a study by Martin et al in 2003, a recent estimate confirmed that the current annual number of total sepsis cases could be around 20 million cases a year (Daniels, 2011). Not only in the number of cases, but also in terms of the burden of life lost, sepsis has been estimated at a mortality rate of between 20-46%. The CDC estimates that last year alone, sepsis was the 11th leading cause of death with around 36,000 lives lost in 2010 (Rivers, E.P. & McIntyre & Morro & Rivers, K.K., 2005; National Vital Statistics Reports, 2011).

Taking into account the already high incidence of sepsis and a trend of increasing numbers; a high case fatality rate; the large health burden on specific populations; and the high costs to both society and healthcare facilities - sepsis remains an important health concern that is worthy of pursuing for further study (Martin et al, 2003; National Vital Statistics Reports, 2011; Angus, D.C. et al, 2001; Danai & Martin, 2005). In order for a study to begin, a proper definition of sepsis is required.

Chang, Lynm and Glass in 2010 offered a concise and colloquial definition of sepsis in the Journal of American Medical Association (JAMA) patient page “sepsis is a medical condition in which the immune system goes into overdrive, releasing chemicals into the blood to combat infection (microbes in the blood, urine, lungs, skin, or other tissues) that trigger widespread inflammation (cellular injury in body tissues). If the body is not able to regulate this immune response, it then overwhelms normal blood processes” (Chang, Lynm & Glass, 2010, p. 1856).

Even with a general definition of sepsis being around for years, there was much confusion of terminology used in lieu of sepsis with terms such as septicemia, sepsis, bacteremia, shock and other terms being used interchangeably (Hodgin & Moss ,2008). However, in 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine convened a consensus conference in which four levels of sepsis were established. In 1995, Rangel-Frausto et al adopted these definitions into a table that is helpful in understanding the clinical variables that go into a study of sepsis:

1. *Systemic inflammatory response syndrome (SIRS)*. Two or more of the following:
 - a. Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - b. Heart rate >90 beats/min
 - c. Respiratory rate >20 breaths/min
 - d. White blood cell count $>12.0 \times 10^9/\text{L}$, $<4.0 \times 10^9/\text{L}$
2. *Sepsis*. SIRS plus a documented infection (positive culture for organism).
3. *Severe sepsis*. Sepsis associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.
4. *Septic shock*. Sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities.

Even from looking at the SIRS criteria by which sepsis diagnoses are based on, the diagnosis of sepsis demands that there be a suspicion of infection but sometimes confirmation by microbiology is not available until much later (Heffner et al, 2010). Sepsis is not definitively diagnosed before treatment, the infection might be suspected because of signs of SIRS and treatment should begin. For this study, the patient base is already deceased and they have been

entered in the Carle Foundation Hospital medical records with diagnoses of sepsis.

Understanding this limitation that could lead to a diagnosis too late led many to study the prospects of early diagnostics and treatment of sepsis.

Studies have shown that the earlier you treat sepsis, the better the outcomes (Lundberg & Perl & Wiblin et al., 1998). With this in mind, Rivers et al applied early goal directed therapy (used in other conditions before), taking tested best practices as goals to best treat septic patients (2001). This was an early treatment system that studies confirmed as effective, reducing mortality by 33% in some cases (Jones et al, 2007).

However, along this same mentality of early treatment, it was still necessary to quickly diagnose and assess the risk of patients who might be showing signs of sepsis. There have been several variations of early detection and assessment systems but in 2003, Shapiro et al took the clinical signs previously defined to come up with a scoring system that could identify and assess the risk of patients presenting with sepsis. This method, called the Mortality in the Emergency Department due to Sepsis (MEDS) Score, was confirmed as effective, at the very least, and accurate for identifying SIRS patients in the Emergency Department, which was a step earlier than when patients were in the Intensive Care Unit where many times it is too late (Carpenter et al, 2009). This methodology of early identification and treatment is a similar base reasoning as the reason for investigating the current study.

This retrospective study allows for comparison of the conditions of sepsis cases at the time of arrival to the emergency department with knowledge that at some point they will develop sepsis. This is a preliminary study to see if there are differences in clinical symptoms of sepsis between patients coming from different points of origin. As mentioned, this study method of applying clinical symptoms as variables for assessment is similar to the MEDS score method

since it was a temporally mindful risk assessment in the Emergency Department (Shapiro et al, 2003). However, the current study differs in that it compares points of origin and not just assessing risk in the Emergency Department. For this study then, an important variable to measure is if patients present sepsis symptoms upon arrival to the hospital compare by different points of origin. The main study will be in taking points of origin and comparing them for each of the clinical symptoms and assessing if there are differences in these variables by point of origin.

1.2 RESEARCH QUESTION

The main question behind the study is to examine differences between these several points of origin while compared to individual clinical symptoms that are adapted from consensus definitions of sepsis. This study looks at the incidence of sepsis that has occurred over a defined time frame in the hospital and investigates if the cases that we see differ if they originate from the hospital or the non-hospital environment.

The hypothesis proposes that susceptibility to mortality may be impacted by the *origin* of the patient. Therefore, if a study is done to compare patients that have different points of origin, there will be perceivable differences in symptoms at the time of arrival of the patients to the Hospital.

(1) Points of origin show general variation in presentation of sepsis symptoms and are not equal

(2) Points of origin have varying populations coming from location types and are not equal.

Under these conditions, the questions at hand are:

1. Is there a difference in the variables relevant to a diagnosis of sepsis by point of origin?
 - a. Is there a difference in the mean number of patients that come from individual points of origin?
 - b. Is there a significant difference in the age and gender of people coming from different points of origin?
2. Is there a relationship between patients from different points of origins and whether they present signs of sepsis within a normal or abnormal range upon admission?

Significance

This study is a stepping-stone to a number of different intervention possibilities but is a necessary step along the way. This study could show that there are some points of origin that are different in terms of sepsis presentation and can open up the door to interventions that can be placed at earlier periods in the septic patient's time frame to mortality. The hope of this study is to be able to decide if time would be better spent on strategies and interventions in the hospital setting or in health care settings outside of the hospital. This could potentially improve levels and time to care and subsequently decrease mortality due to sepsis.

This study could serve as a preliminary inquiry for future study that could investigate whether 1) earlier detection and preventative interventions for patients susceptible to sepsis could lead to increased sepsis survival and 2) that a possibly more effective intervention approach might be to aim preventative measures at the earliest point of endangerment, namely the different points of origin a patient might come from before entering the hospital.

CHAPTER 2

LITERATURE REVIEW

2.1 CLARIFYING THE DEFINITION OF SEPSIS

Taking into account the recent high incidence of sepsis with the trend of increasing numbers; the high rate of attributed mortality; the large health burden on specific populations; and the high costs to both society and healthcare facilities – sepsis continues to remain an important health issue that is worth pursuing in further study (Martin et al, 2003; National Vital Statistics Reports, 2011; Angus, D.C. et al, 2001; Danai & Martin, 2005). For an appropriate study to take place, an appropriate definition of septicemia must be established.

Case definition:

According to Lever and Mackenzie, sepsis as a general term refers to:

systemic illness caused by microbial invasion of normally sterile parts of the body... a term that specifically serves to differentiate an illness of microbial origin from an identical clinical syndrome that can arise in several non-microbial conditions (2007)

This simplified definition can be helpful but is not comprehensive and leaves out an important progression of severity that other definitions include. Before the early 1990's, there was a lot of confusion and uncertainty surrounding the terms used to describe the systemic response to microbial infection. A number of terms including bacteremia, septicemia, sepsis, sepsis syndrome, and septic shock were often used interchangeably. This lack of set definitions was a problem for those who had to diagnose the disease process and also lead to confusion in the reported epidemiology of these disorders (Hodgin and Moss, 2008).

Some clarifications of these definitions come from a U.S. governmental manual on morbidity classification of coding and reporting that was taken from the World Health

Organization's International Classification of Disease (from the *ICD-9-CM Official Guidelines for Coding and Reporting*) and are paraphrased below:

Oftentimes, providers use the terms septicemia and sepsis interchangeably, but in reality they are not synonymous terms. The descriptions below generally explain the terminology used in clinical practice:

- i. Septicemia generally refers to a systemic disease associated with the presence of pathological microorganisms or toxins in the blood, which can include bacteria, viruses, fungi or other organisms.
- ii. Systemic inflammatory response syndrome (SIRS) generally refers to the systemic response to infection, trauma/burns, or other insult (such as cancer) with symptoms including fever, tachycardia, tachypnea, and leukocytosis.
- iii. Sepsis generally refers to SIRS due to infection.
- iv. Severe sepsis generally refers to sepsis with associated acute organ dysfunction

Still, this clarification leaves out many of the signs and symptoms that would make these definitions clinically useful and also lacks clarity on septic shock. In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine met at a Consensus Conference to come up with a common set of terminology and was put under review by Levy et al in 2001 who found that no new definitions were made or were necessary to be added to the ones established at the consensus conference in 1991. They suggested that, except for expanding the current list of symptoms of sepsis to “reflect clinical bedside experience,” there was no real evidence that called for a change in these definitions. This established set of consensus definitions was put into a clear and useful format by Rangel-Frausto et al (1995) as follows:

(1) *Systemic inflammatory response syndrome* (SIRS) refers to when two or more of the following are observed:

- a. Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- b. Heart rate >90 beats/min
- c. Respiratory rate >20 breaths/min
- d. White blood cell count $>12.0 \times 10^9/\text{L}$, $<4.0 \times 10^9/\text{L}$, or >0.10 immature forms (bands).

(2) *Sepsis* refers to the SIRS criteria being met plus a documented infection (positive culture for organism or suspicion of a microbe).

(3) *Severe sepsis* refers to sepsis associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

(4) *Septic shock* refers to sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities.

These are the basic definitions that will be used in the rest of the proposal and in order to avoid confusion, the term sepsis will be applied with the understanding that it is a progression of severity unless specifically noted that it is either *severe sepsis* or *septic shock*.

2.2 EPIDEMIOLOGICAL BACKGROUND OF SEPSIS

Incidence of Sepsis

To say the least, sepsis is not an uncommon occurrence in the hospital setting. According to Esper and Martin, severe sepsis, which to reiterate is sepsis with severe organ dysfunction, is one of the most prevalent disease processes encountered in the intensive care unit (2007). Sepsis and severe sepsis occurs in approximately 2.9% of total hospitalizations and up to 75% of intensive care unit (ICU) patients, which makes up about 50% of ICU bed days. Fortunately, in

the last two decades there has been a decreasing rate of in-hospital mortality due to sepsis. However, even though the mortality rate has decreased, there has been a sharp increasing trend towards incidence of sepsis in the same time period seen in the 2003 study by Martin et al that spanned 23 years from the years 1977 to 2000. In this study of in-hospital incidence, it was found that the number of sepsis cases increased from 164,072 in 1979 to 659,935 in 2000. This was an increase of 13.7 percent per year. According to the Martin et al study these cases are still increasing rapidly and have doubled in incidence with expectation to increase from as little as 1.5% to as much as 10% per year.

There has not only been an increasing general trend of hospitalization due to sepsis, but also an incredible increase in the severity of those cases of sepsis that were observed. The Martin et al study found that the proportion of sepsis patients who had acute organ failure increased over time, going from 19.1 percent in the first 11 years, tripling to 30.2 percent in the final years (2003). This was again confirmed in a longitudinal study by Dombrovskiy and colleagues, who found that there was a doubling of hospitalization rates due to severe sepsis between 1993 and 2003 (2007). According to this study, the rate increase was five times faster than was previously predicted and the percentage of patients with severe sepsis, within the cohort of patients with sepsis, grew by 70%. Generally, the research literature agrees that there remains around 750,000 cases of sepsis each year in the U.S. with mortality ranging anywhere from around 20% to upwards of 50% (Wolk, D.M., 2010). Thus, sepsis is not only a problem in terms of increasing incidence but also in increasing severity that potentially increases likelihood of death.

Mortality due to Sepsis

Even if there is a trend of decreasing rates of mortality due to sepsis, within the cohort of those patients that are considered critically ill, sepsis remains the leading cause of death (Angus

et al, 2001). A number of smaller studies have found much higher mortality rates than Angus et al, especially when taking into consideration the cases of severe sepsis that occur outside the ICU. The given mortality rates due to sepsis may not be an accurate representation of the actual rates because there is much room for underreporting. Clinicians may not report a death as sepsis because they do not immediately recognize it and because comorbidities are shared between other high profile killers such as pneumonia (Nelson, 2009).

In a study that took 6 years of National Center for Health Statistics mortality data, Wang et al conducted descriptive analysis and found that the national age-adjusted sepsis mortality rate was 65.5 per 100,000 in 2010. From the CDC's fast stats website, it was seen that in 2007, sepsis was the 10th leading cause of death in the United States. In that year alone there was 34,828 deaths attributed to sepsis. In an update of the year 2008 to 2009, it was seen that sepsis was overtaken by intentional self-harm (suicide) and switched ranks to become the 11th leading cause of death. Even though the sepsis rank went down one spot over the last few years, it still remains to be in the top 15 leading causes of death declining only about 1% in numbers of deaths, going from 35,961 deaths in 2008 to 35, 587 deaths in 2009 (National Vital Statistics Reports, 2011).

There are various reasons why sepsis is such a prolific killer and will be discussed in greater detail later. However, one factor is simply the nature of a sudden multisystem wide inflammatory response. This immune response overwhelms the body and does not leave much time for normalization leading to death by shock. Beyond the nature of sepsis, is the human factor which includes delays in tests to determine the bacterial cause and then selecting for the appropriate antibiotic. When too much time has passed, there is an increase likelihood of death (Wolk and Fiorello, 2010). Angus et al summarized and listed several factors that contributed to incidence and mortality. This list included: a) an aging population with chronic morbidity; b)

ICU survivors who are predisposed to infections afterwards; c) an increased use of invasive procedures; d) more medical conditions treated with immunosuppressors; e) and increasing amounts of resistant bacteria (2006). The underlying mechanisms for these causes of death will be expanded on later in this review but it is plain to see that the issue of sepsis is quite multifaceted and must be approached by considering this complexity.

Effects on Populations

There have been quite a few studies that analyzed the demographics of sepsis development and there are subsets of the population that were found to be more at risk for developing sepsis than other groups within the U.S. populace. One such population at risk include infants and especially newly born infants, who were found to have an incidence of 5.3/1000 for those under the age of 1 (Angus, D.C. et al, 2001). This incidence decreases sharply for older children and as the age progresses to adulthood, remains to be a relatively low incidence when compared to other age groups. The incidence suddenly makes a large leap when it reaches the opposite end of the age spectrum, where there is a dramatic increase in the rate of sepsis found in the elderly.

Bacteremia, or generalized blood infection that leads to sepsis, has a high mortality rate in the elderly (Richardson and Hricz, 1995). Just being over 40 years old is a risk factor for sepsis. People over 65 years old account for only 1/8 of the U.S. population but account for 2/3 of all sepsis cases (Dellinger, R.P. et al, 2008). The worst outcomes are for those who are over the age 85. This age group has a mortality rate of over 38.4% (Angus, D.C. et al, 2001). The reasons why the elderly are so susceptible to blood infection are because of factors such as having decreased immune function due to cancer, organ failure, an increase in underlying

comorbidities, and increased hospitalizations along with living in extended care facilities like nursing homes (Khayr et al, 2004).

Over a 21 year period of study by Martin and colleagues in 2003, the average age of patients with sepsis continuously increased, going from 54.7 years ending up at 60.8 years. Among the elderly subpopulation, sepsis seemed to develop later in life for women as opposed to men, with both groups seeing an increase in the average age at which sepsis developed. According to Moss in 2005, men were 1.28 times more likely to develop sepsis than women. Within the population demographics, non-hispanic whites had the lowest rate of sepsis while Black and other nonwhite ethnicities were found to be twice as likely to develop sepsis. Black men have the highest rate of sepsis while also having the youngest onset and highest mortality (Martin et al, 2003). There were no studies that suggested the direct causes or reason for these findings but Moss suggested that comorbid conditions such as chronic alcohol consumption might be involved.

These slight differences between gender and race do not seem to play a significant role in the literature, nor have they spurred many interventional studies. However, the poignant differences between age groups have, as was previously stated, been shown to be a significant cofactor in sepsis outcomes. Overall, the sepsis rates “exceed the estimated rates for other disease that hold a heightened public awareness, including breast cancer and acquired immune deficiency syndrome,” and is a largely unpublicized disease process that dramatically affects the population as a whole (Moss, 2005).

Costs attributed to Sepsis

Not only is sepsis a common occurrence in our health care system with a high burden of lives lost, especially in the elderly, but it is also a high burden on our economy in terms of

dollars spent unnecessarily. In 2001, Angus et al estimated that the total national hospital cost associated with the care of patients with severe sepsis was \$16.7 billion a year. Even within this price tag, this given estimated cost does not include other indirect healthcare expenditures, post-hospitalization medical care, or loss of productivity due to sepsis (Danai & Martin, 2005).

The direct cost associated with those that were under the age of one year old was \$1.1 billion, representing 6.6% of the total national cost of care due to sepsis. The costs for care of those over the ages of 65 and over 75 were \$8.7 and \$5.1 billion respectively. This represented 52.3% and 30.8% of the total cost of care due to sepsis. The average adult admission for severe sepsis will directly cost a hospital about \$22,000 to take care of the patient. However, with increasing organ system dysfunctions, there are increased costs. Costs for those with one system dysfunction averaged \$19,500 but could increase to as much as \$32,800 for those with four or more organ systems in dysfunction (Angus et al, 2001). Bacteremia, the blood stream infection that precedes sepsis, is associated with a 25% increase in costs of hospital care, increasing from \$67,879 to \$85,137 (Laupland et al, 2006). This represents a huge burden on the hospital system in terms of the monetary investment being made on a patient. In turn, this affects the costs hospitals must charge in order to balance hospital budgets.

The people who feel the economic burden of sepsis most are those individuals who are personally affected by the disease process and subsequently have to pay for the hospital fees. In a very large and diverse retrospective study of long term mortality and medical care charges, Derek et al found that the average costs of simply being admitted to the hospital were \$44,600. The study also looked at the charges that accrued after admission for those who survived after release and found that the average medical care charges were \$78,500 after 1 year and at 5 years the charges totaled \$118,800 (2003).

Considering how much of an economic burden sepsis is to both patients and to the health care system, it is not hard to understand why studies would aim to try and implement interventions that would decrease the incidence and severity of sepsis. In a study of the cost effectiveness of an integrated sepsis protocol, Talmor et al found that investing in early interventions are in fact cost effective and do better than other common acute care interventions, having better survivorship at minimal implementation costs (2008). Thus, it is a worthwhile endeavor to invest in interventions aimed at identifying and treating sepsis as early as possible since studies have shown that doing so decreases the overall burden of cost, severity and mortality of sepsis incidents.

2.3 THE DISEASE PATHWAY OF SEPSIS

After examining the burden and impact sepsis has on the health system, it is apparent that further studies into interventional approaches are warranted. In order to create interventions adequately suited for the complexity of the sepsis disease process, it is necessary to understand in greater depth the nature of sepsis onset and the mechanisms that factor into its functioning.

Pathogenesis: Causative Agents

The actual disease process begins with a microbe. Sepsis is differentiated from SIRS by the confirmation or suspicion of infection; however, positively tested blood cultures are present in only one-third of the cases of severe sepsis (Hodgin and Moss, 2008). In a lot of cases of sepsis, the actual microbial agent that is causing sepsis is never identified. This might be attributed to a number of reasons. One reason is that some patients do not survive the infection long enough for cultures to be of use and are thus never documented in patient records. Heffner and colleagues stated that many times trying to confirm the suspicion of infection is not possible for several days after a patient presents sepsis symptoms (2010). Another issue is that many

times, patients that come in with sepsis are not actually suspected of blood infection at first diagnosis because the symptoms are very similar to other comorbidities such as pneumonia (Nelson et al, 2009). Only 17% of cases of sepsis, 25% of cases of severe sepsis and 69% of cases of septic shock were actually identified by microbiological cultures (Rangel-Frausto, 1995).

Of the cases of sepsis that were identified by culture, gram-negative bacteria were the major causative agent of sepsis prior to 1987. However, in a 2003 study by Martin et al, the group found that gram-positive overtook gram-negative bacteria to become the more prevalent causative agent. In 2000, between the organisms that were reported to cause sepsis, gram-positive bacteria made up 52.1% of cases, gram-negative bacteria 37.6%, polymicrobial infections 4.7%, and anaerobes 1.0%. The prevalence of gram-positive bacteria was confirmed by Alberti et al who found that these bacteria accounted for 48% of all cases of severe sepsis with the most common organisms being methicillin-sensitive *Staphylococcus aureus* (2002). It was observed that gram-negative bacteria, still the second leading causative organism, accounted for 30-40% of cases with the most commonly cultured being *E. coli* and *Pseudomonas spp* (Hodgin and Moss, 2008). Other than gram-positive bacteria becoming the more common causative agent, another change that calls for concern is the change in fungal sources that saw a change from 5231 cases in 1979 to 16,042 cases in 2000 (Martin et al, 2003).

Sites of Infection

After a person is identified as having been infected with a microbe, the next question to ask is where the microbe attacked. Sepsis originates from a breach of integrity of the host barrier, either physical or immunological, and direct penetration of the pathogen into the bloodstream (Lever and Mackenzie, 2007). There aren't many pathogens that like to multiply in the blood therefore it is the usual case with sepsis that infection begins at an initial site and then makes a

way into the bloodstream. Finding these sites of infection helps understand the sepsis process pathway.

In 1995, Rackow and Astiz asserted in a study of sepsis pathophysiology that the site most commonly infected was the genitourinary tract with the respiratory and gastrointestinal tracts coming in as the next most frequent sites. Also, some other major sites of infection included skin and wounds. This study was consistent for the most part with Alberti et al in 2002 when they claimed that most epidemiological studies find that pulmonary, gastrointestinal, urinary tract, and primary bloodstream infections make up about 80% of the total sites of infection among patients who develop sepsis or severe sepsis. The leading site is the lung, which can be held accountable for almost half of the cases sepsis or severe sepsis. The rest of the cases of sepsis or severe sepsis can be attributed to infections of the skin/soft tissue, bone, or central nervous system (Esper et al, 2006).

Risk Factors for Sepsis

After understanding that sepsis begins with a microbial infection that breaks into the bloodstream, it is helpful to understand the factors beyond mere physiology, and move into the processes at work in and around the patient host that play into the pathogen being exposed to the blood supply. Some of the external factors influencing the patient risk include genitourinary issues such as chronic urinary tract catheterization or urinary tract infection which has been found to leave patients at high risk of infection. Other factors include health processes at work in the patient including Alzheimer's disease, reduced serum albumin and cholesterol levels, anemia, and elevated blood glucose levels, which all have been associated with patients found with blood infection. Furthermore, a study that looked at specific at risk groups found that pressure ulcers,

tube feeding and urinary incontinence are significant risk factors for sepsis in the nursing home (Khayr et al, 2004).

2.4 PATHOPHYSIOLOGY OF SEPSIS

Bloodstream infections lead to sepsis because the causative agent, whether it is a gram-positive or gram-negative bacterium, triggers an inflammatory response in the host patient because of the toxins found on the microbes. This inflammatory response engages the patient's natural immunological responses which are supposed to be protective; however, this function that is meant to heal us actually, in the case of sepsis, goes astray and ends up out of control. (Wolk et al, 2010).

The human immune response to microbial invasion begins with white blood cells and proinflammatory mediators that are released in the blood stream to fight the infection. These mediators cause vasodilation and a movement of fluids that create a drop in blood pressures. In order to raise the blood pressure, the body naturally increases the cardiac output. What normally happens when the body begins to normalize is that anti-proinflammatory cytokines are released to maintain balance. With sepsis however, the balance between mediators and between the process of clotting and lysis, is disturbed. Circulation to the periphery is reduced because of clotting that blocks the blood vessels and blood pressure continues to fall. In order to restore vitals, the heart rate and cardiac output increases. The brain tries to help restore circulation so it signals the adrenal glands to release vasoconstricting epinephrine and norepinephrine. As the heart works against vessels constricted by clots and signals, it becomes overworked and output falls. As the body starts to lack oxygen, anaerobic metabolism and lactic acidosis (a key indicator of septic shock) begins to set in (Mower-Wade and Kang, 2004; Rackow and Astiz, 1991; Wolk and Fiorello, 2010).

The Diagnosis

Because the inflammatory response is so severe and so widespread in the body, the symptoms are highly variable and according to a JAMA article by Rangel-Frausto et al in a 1995 study of SIRS, these can include: fever, chills, hypotension, neutrophilic leukocytosis or neutropenia, hypothermia (especially in the elderly), diaphoresis, apprehension, change in mental status, tachypnea, tachycardia, hyperventilation and respiratory alkalosis, reduced vascular tone, and ultimately organ dysfunction. Hematologic (which means that it pertains to the blood) findings are also extremely important because the septic patient can present with thrombocytopenia, toxic granulations of neutrophils, or disseminated intravascular coagulation. Renal and gastrointestinal (GI) signs include acute tubular necrosis, oliguria, anuria, upper GI bleeding, cholestatic jaundice, increased transaminase levels, and hypoglycemia (1995).

To reiterate, patients are defined as having SIRS if they meet two or more of the following criteria: heart rate >90 beats per minute, body temperature <36 (96.8 oF) or >38 oC (100.4 oF), respiratory rate >20 breaths per minute or a PaCO₂ less than 32mmHg on a blood gas, and a white blood cell count $<4 \times 10^9$ cells/L or $>12 \times 10^9$ cells/L or greater than 10% band forms. SIRS is usually used to label acute illness that comes from a microbial source but patients can also develop SIRS in response to a variety of stimuli including but not limited to trauma, ischemia, burns, and pancreatitis (Hodgin and Moss, 2008).

For a diagnosis of sepsis to be made, there has to be some suspicion of an infectious agent and only if time allows will there be a confirmation by microbiological culture (Heffner, Horton, Marchick and Jones, 2010). Despite the large financial and human costs, the diagnosis for sepsis is mainly a clinical one because there are not presently any rapid laboratory tests that are sensitive and specific enough to identify the causative agents (Wolk et al, 2010). However, in

our case, since the patient records that we have are all coded as septicemia, we can apply the case that SIRS is due to infection and call it sepsis. The progression along the disease pathway that is sepsis can be considered a “continuum of a disease process that progresses from *sepsis* - infection with an inflammatory response - to *severe sepsis* - sepsis with organ dysfunction - to *septic shock* - sepsis with tissue hypoperfusion” (Heffner, Horton, Marchick and Jones, 2010).

It is helpful to put this disease continuum into a practical and easily identifiable set of clinical signs. This was done by Neviere in 2011 for an online medical reference database:

1. SIRS is, as the definition before stated, having two or more symptoms in abnormal ranges for temperature, heart rate, respiratory rate and white blood cell count.
2. Sepsis is considered SIRS with suspicion or identified infection
3. Severe sepsis is considered sepsis with the following signs of organ perfusion or dysfunction:
 - a. Areas of mottled skin
 - b. Capillary refilling requires three seconds or longer
 - c. Urine output less than .5 mL/kg for at least on hour, or renal replacement therapy
 - d. Lactate greater than 2 mmol/L
 - e. Abrupt change in mental status
 - f. Abnormal electroencephalographic (EEG) findings
 - g. Platelet count below 100,000 platelets/mL
 - h. Disseminated intravascular coagulation
 - i. Acute lung injury or acute respiratory distress syndrome
 - j. Cardiac dysfunction, as defined by echocardiography or direct measurement of the cardiac index
4. Septic shock is severe sepsis plus one or both of the following:
 - a. Systemic mean systolic blood pressure below 60 mmHg (of below 80 if patient has baseline hypertension) despite adequate fluid resuscitation
 - b. Maintaining the systemic mean blood pressure greater than 60 mmHg requires dopamine greater than 5 mcg/kg per min, norepinephrine less than 0.25 mcg/kg

per min, or epinephrine less than 0.25 mcg/kg per min despite adequate fluid resuscitation (Neviere, 2011)

2.5 TREATING SEPSIS

After understanding the physiological response to the systemic blood infection, it is possible to understand the reasoning behind different treatment approaches. There are many different treatments that have been developed to try and deal with the sepsis disease process. However, the literature has shown that because sepsis is so complex, when looking for a treatment for sepsis, there is not a single protocol or prescribed course of action that can comprehensively address the issue. There are however, several sets of clear clinical practices that can and should be applied to septic patients in conjunction to one another. In a very broad and generic treatment guideline, several studies agree that treatment of sepsis requires at the minimum (1) Early Antibiotic Administration, (2) Fluid Resuscitation/Loading which is hemodynamic management and (3) Vasoactive Drugs or vasopressors (Daniels, 2011; Claessens & Dhainaut, 2007).

Early antibiotic administration gets to the root of the issue and suggests that physicians apply antibiotics intravenously to eliminate the microbial invaders that are causing the inflammatory response since rapid antimicrobial intervention has been shown to be critical to survival. It was shown in a prospective study that the factor most strongly associated with death was an ineffective antimicrobial treatment against the microbe identified (Weinstein et al, 2007). One of the issues with this treatment though, is that the pathogen takes time to identify and therefore researchers suggest applying a broad spectrum of antibiotics until the pathogen is identified at which point broad-spectrum therapy should be discontinued (Wolk, 2010).

Fluid resuscitation or loading takes into account the physiological response of the human inflammatory system to the microbial invaders. This hemodynamic management essentially aims at restoring the blood circulation by the use of various therapies that are applied intravenously to raise fluid levels. Several treatments have been attempted including albumin and transfusion of red blood cells; however, research supports the preferential use of crystalloids – which are aqueous solutions of water-soluble molecules that expand volume (normal saline for example) - in these cases (Daniels, 2011).

Vasoactive drugs or vasopressors are administered to deal with the hypotension that arises from decreased circulation and cardiac output. These vasopressor agents increase arterial pressure and include dopamine, norepinephrine, phenylephrine and vasopressin. Studies show that the first course of action should be to use either dopamine or norepinephrine but this may vary depending on the patient, the situation and the persistence of hypotension (Rivers et al, 2005; Claessens and Dhainut, 2007).

Therapies working together

These are baseline, generic therapies that should be engaged to directly respond to the immediate physical needs of a patient with inflammatory patterns. Other therapies and treatment interventions have come up with a more comprehensive group of tasks that should be used in concert to tackle sepsis. One example of taking these basic tasks is the “Sepsis Six” and was adapted from the Survive Sepsis organization which asserted that there are 6 tasks that should be accomplished together within the first hour. These included: (1) deliver high-flow oxygen, (2) take blood cultures and other cultures, consider source control, (3) administer empirical intravenous (IV) antibiotics, (4) measure serum lactate or alternative, (5) start IV fluid resuscitation, and (6) commence accurate urine output measurement (Daniels, 2011).

Essentially, these tasks work together and accomplish together what one task alone would not have been able to. These are called “bundles” which are defined as “a group of ‘therapies’ built around the best evidence-based guidelines, which, when implemented together, produce greater benefit in terms of outcome than the individual therapeutic interventions” (Khan & Divatia, 2010). This term was coined by the Surviving Sepsis Campaign (SSC), in conjunction with the Institute for Healthcare Improvement (IHI), when the SSC got together a group of experts to develop these practice bundles. From this collaboration, two severe sepsis bundles were created by Marshall, Dellinger, and Levy in 2010 which are presented in a modified summary below:

1. The 6-hour resuscitation bundle

- Measure serum lactate concentration
- Obtain blood cultures prior to antibiotic administration
- Administer broad-spectrum antibiotic within 3 hours of emergency department (ED) admission and within 1 hour of non-ED admission
- In the event of hypotension and/or serum lactate >4 mmol/L:
 - Deliver an initial minimum of 20mL/kg of crystalloid or equivalent
 - Administer vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65 mm Hg
- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L:
 - Achieve a central venous pressure (CVP) of ≥ 8 mm Hg
 - Achieve a central venous oxygen saturation (ScvO₂) $\geq 70\%$ or mixed venous oxygen saturation (SvO₂) $\geq 65\%$

2. The 24-hour management bundle

- Administer low-dose steroids for septic shock in accordance with a standardized intensive care unit policy. If not administered, document why the patient did not qualify for low-dose steroids based on the standardized protocol.
- Administer recombinant human activated protein C (rhAPC) in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for rhAPC.
- Maintain glucose control ≥ 70 , but ≤ 150 mg/dL
- Maintain a median inspiratory plateau pressure (IPP) <30 cm H₂O for mechanically ventilated patients

These bundles play a very useful role in standardizing the treatment protocol. Usually, there are constraints created because of deviations and variations of treatment from patient to

patient and practitioner to practitioner. This bundling allows a certain level uniformity and consistency. However, it is one issue to treat the patient symptoms but it is to no avail unless these treatments are done in time. It is vital to be aware of the time constraint placed on the interventions within these bundles.

2.6 TIME DEPENDENCY OF SEPSIS SEVERITY

Time Dependent

Many conditions are time sensitive, and the earlier one comprehensively addresses the issues, the better the outcome (Rivers et al, 2005). Time has been considered a key factor in treatment of septic patients and there is a direct relationship between negative outcomes of septic patients and delays of diagnosis and treatment (Lundberg & Perl & Wiblin et al., 1998). The Surviving Sepsis Campaign recommends a 24-hour sepsis pathway for treatment and the first 6 hours are most critical (Dellinger et al, 2004). In other conditions, the term “golden hour” refers to the correlation of improved outcomes with early diagnosis and treatment while here this time dependence is applicable to sepsis as well (Rivers et al, 2005).

Early Goal Directed Therapy

With this sensitivity to time in mind, Rivers et al published a landmark study in which they applied Early Goal Directed Therapy (EGDT) to patients with signs of sepsis (2001). First, in clarification, EGDT was applied to other conditions and is basically engaging in early diagnosis and time-sensitive therapies as soon as the patient shows presentation of the condition, in this case sepsis (Otero et al, 2006). The novelty of EGDT lies in the fact that it is applied as soon as the patient starts to show symptoms of sepsis rather than waiting until they are admitted at the ICU (Rivers, 2006). Basically, EGDT strives to provide patients with sepsis the best care possible as soon as possible and is a broad strategy for evaluating septic patients. In their 2006

study, Otero et al stated that this includes: (1) assessment of the sepsis prevalence and mortality at the hospital, (2) identification of high-risk patients based on early pathogenesis, (3) mobilization of resources for intervention, (4) performance of a consensus-derived protocol to, (5) reverse early hemodynamic perturbations, (5) appraisal of the quality indicators to assess compliance, (6) quantification of health-care resource consumption, and (7) assessment of outcomes.

EGDT not only benefits the burden of mortality and morbidity, but EGDT has positive financial implications as well. EGDT was estimated to reduce net hospital costs by about 23%, mainly by decreasing length of stay (Dremsizov, 2007). Dremsizov et al concluded that even though there are high start-up costs, in the end, EGDT saves the hospital money by decreasing length of stay and could possibly result in increased overall savings when mortality decreases because of EGDT (2007). In general, studies have revealed that this method is very effective. A report on the external validity of EGDT by Jones et al showed that EGDT was clinically effective, with a 33% reduction of in-hospital mortality from severe sepsis and septic shock in an emergency department (Jones et al, 2007).

Rapid Risk Assessment

Along with the importance of time necessitating rapid identification and treatment, it is also important to quickly ascertain those patients who are most at risk. If the patient is already presenting with sepsis, then it could be too late to apply EGDT. It is a worthwhile venture to assess patient conditions in a timely manner. Shapiro et al attempted to make this sort of rapid classification system in 2003 by taking the consensus definitions of Sepsis and using the clinical symptoms of sepsis to form a prediction rule that would allow providers to assess patient conditions. This prediction rule is called the Mortality in Emergency Department Sepsis (MEDS)

score. This simple scoring system takes the clinical symptoms that a patient shows to allow for a calculated mortality risk. Other scoring systems have been used in the ICU to score severity of illness and predict risk of mortality, but Shapiro et al felt that none of these scoring systems (like APACHE, APACHE II, Simplified Acute Physiology Score, etc.) were clinically practical since they require information and diagnostic tests that are not immediately available in the ED (2003).

This method was later validated by Carpenter et al in 2009 and concluded that the MEDS score was an accurate and reliable tool for ED SIRS patients. The limitation of this study, as Carpenter et al suggested, is that the score may not be accurate against undifferentiated SIRS. However, for this study, the patient base is already deceased and has been confirmed as septicemia. This retrospective study allows for a comparison of the conditions at the time of arrival with a clear knowledge that at some point they will develop sepsis.

2.7 NEW THERAPIES

There has been a general decrease in the rates of mortality in the past two decades and many researchers attribute this to the increased number of sepsis initiatives. Other than the therapies just mentioned, there are several treatments that have emerged recently that makes use of the advances in scientific medical technology. In an analysis of mortality data from ten years of new therapy trials, van Ruler and colleagues narrowed down the list of new therapies and found through comparative analysis that early appropriate antibiotics, early goal-directed therapy, activated protein C and intensive insulin therapy were, in order, the most effective new therapies (2009).

Of the top four most effective therapies, the first two – early appropriate antibiotics and early goal-directed therapies – have already been discussed. The latter two therapies and one more honorable mention, corticosteroids, have been of high interest in the literature in the past

decade but still remain underutilized because they are still considered controversial in terms of their effectiveness and implementability. These three controversial therapies were put under review by Sandrock and Albertson in 2010 and are worth examining for the sake of thoroughness in the investigation of sepsis treatment.

Activated protein C (or APC) is the most promising of the three controversial new therapies and makes use of a recombinant human activated protein C that has been tested on a wide, multi-centered scale. APC functions by compensating for the deficit of naturally produced anticoagulant protein C that occurs in patients with sepsis. It was shown in some studies to decrease the numbers of organ failures and increase survival while also rapidly improving hypotension and vasopressor withdrawal. It also seemed to have added benefits on positively effecting complex interaction with inflammation, innate immunity and apoptosis (Claessens and Dhainut, 2007). Yet, APC still remains controversial because it is so new that there have not been many comprehensive studies on it and the results of available studies have not yet completely agreed. Some studies show that APC is effective in the more severe cases of sepsis but it leaves risk of bleeding, while other studies show that the statistics are not robust enough to warrant use (Sandrock and Albertson, 2010).

Corticosteroids given at low doses were found to decrease the requirements for vasopressors in patients with septic shock and also have lowered the mortality rate compared to a placebo (Rivers et al, 2005). It has been proposed that the effects steroids have on adrenergic receptor cycling and sodium to water balance are the reasons for its benefits to vasopressor withdrawal. Also, steroids seem to have an anti-inflammatory and anticoagulant role (Claessens and Dhainut, 2007). However, they are still considered controversial because there have been some studies that have shown there is not a significant survival benefit. Moreover, meta-analyses

results are inconsistent and inconclusive, some even showing that there was no effect on mortality due to steroids (Sandrock & Albertson, 2010).

One of the physiological responses to sepsis is hyperglycemia and intensive insulin therapy is aimed at maintaining the blood glucose that goes out of control during the bodily reactions of a septic patient. Intensive Insulin Therapy intravenously introduces insulin to hyperglycemic sepsis patients and maintains a normalized blood sugar level. There were moderate results that showed a decrease in mortality due to this tight glycemic control (von Ruler et al, 2009). Again, the reason why this therapy is still considered controversial is that there is no substantial body of evidence that supports the fact that this therapy actually universally reduces mortality of sepsis or that it has any other significant health benefits (Sandrock & Albertson, 2010).

Overall, these adjunctive therapies have been shown on small scale studies to have marginal benefits but professional opinion in the literature seems to convene on the idea that there is not enough supporting evidence in the available research studies to properly qualify the immediate use of any of these therapies. Whether it is the fear of side effects or inconsistent and inconclusive evidence, there is much room to grow in the treatment of sepsis. However, it is not out of reach to positively affect mortality outcomes with the current suggested therapies. Early appropriate antibiotic treatment as well as early goal directed therapies remain a well-tested and supported therapy recommendation. Keeping this in mind, the current study moves forward with the underlying principle of these two therapies: early action.

2.8 NOVEL STUDIES OUTSIDE THE ICU

Looking at the various treatment studies and the reviews of those most effective therapies, it is plain to see that those interventions that take into consideration the temporal component of

treating sepsis are the most beneficial to health outcomes. Identifying and treating sepsis as quickly as possible has been proven to reduce case fatality. Treating sepsis as soon as possible means that perhaps the hospital is not the only place that needs to be considered since patients are coming from other places before arriving at the hospital and might either already have sepsis or are predisposed to sepsis.

According to Nelson et al, there is not a single health care site that can consider themselves exempt from feeling the effects of some level of septicemia, claiming that “patients in every health care setting are at risk for systemic inflammatory response syndrome, sepsis, severe sepsis and even septic shock” (2009). Even though severe sepsis requires treatment in the ICU, the assessment of sepsis doesn’t have to be limited to those practitioners that are in the ICU. There could be potential improvements to patient outcomes if providers in health care settings prior to the ICU take premeditated early action.

One study that actually began to look outside of the hospital was similar to the current study in the initial methods used; however, the study by Wang, Weaver, Shapiro and Yealy was applied only towards Emergency Medical Services (EMS). The group believed that EMS systems might be a good opportunity for early sepsis diagnosis and care. The proposed plan was to take action before the patient arrived to the ICU and try to assess the patients during the transfer process. The idea came from the fact that EMS was seen to play a pivotal role in the rapid identification and treatment of several other critical illnesses such as trauma, myocardial infection and stroke. EMS plays an important role in providing the initial care to over one third of the patients that come in to the hospital with infection and thus includes a solid majority of the patients with severe sepsis and septic shock (2010). This continues on with the logic that getting to sepsis early is important and with that mindset it might be a logical thought to attempt the

identification and prevention of sepsis at the point of origin which would allow assessment at the earliest time point possible.

One novel idea was proposed by Nelson et al in 2009 to approach the sepsis problem even earlier than the time of transfer by EMS. It was proposed that the patient should be assessed as early as the patient place of origin. Taking into account the fact that a highly at risk population is the elderly combined with the fact that many older people reside in nursing homes, it was suggested that therapies and interventions be aimed at nursing homes. In support of this claim, Richardson and Hricz stated that more than 1.5 million people live in nursing homes and estimated that more than 40% of the elderly will live in a nursing home for at least part of their lives (1995). This growing elderly population living in nursing homes serves as a highly at risk subpopulation of those who acquire sepsis and yet seems to lack any substantial or comprehensive studies.

The idea to study nursing homes is validated in one of the few substantial works in the nursing home and sepsis field performed by a 2002 study in which admissions of elderly people from several long term facilities to a single hospital were examined and found that 69% of the episodes of blood infection were nursing home acquired. This means that the early identification of sepsis in the nursing home is a vital factor to seeing better health outcomes, since infection is acquired at such a rate in the nursing home (Mylotte, Tayara & Goodnough, 2002). Since sepsis has been seen to have an association with nursing home residence, finding this correlation between nursing homes and sepsis acquisition could prove to be a potentially key factor in the attempt to prevent and rapidly diagnose sepsis.

2.9 APPLYING RECENT STUDIES

The methodology of assessing patients' conditions in connection to sepsis presentation before admission or immediately upon admission to the hospital is the concept we have used. This study extends the concept further by taking the clinical symptoms and comparing these against several different points of origin.

Using early recognition and risk assessment models, the current study applied the commonly held clinical symptoms of sepsis, severe sepsis and septic shock to a comparison between several different patient points of origin. A literature search was applied for the effect of portal of entry, also referred to as points of origin, and the relation these points of origin have to sepsis. Individual places such as nursing homes, care-homes, extended stay facilities, and other such health care facilities were searched for in relation to sepsis and no substantial materials were found other than the ones presented already.

The application of risk assessment for patients of variable points of origin could be a novel study in which further application of treatment and prevention may be applicable. The study thus applies assessment of clinical symptoms in the patients of the study to examine if there is a difference between points of origin and risk for sepsis. Sweet et al confirmed that implementing a sepsis protocol before arrival at the ICU improves care for patients with severe sepsis and septic shock (2010). This supports the study rationale that if preventative measures were placed at an earlier time, there will be better outcomes. This study may show it is worthwhile to implement such interventions and protocols, not just at the hospital, but also at various points of origin such as nursing homes. This will be validated by using hospital data to see if there is a statistically significant relationship between the various clinical symptoms and these different points of origins.

CHAPTER 3

RESEARCH METHODS

3.1 PURPOSE OF THE STUDY

The purpose of this study was to determine if there is any relationship between the clinical symptoms of sepsis shown by patients that came into Carle Hospital and the several different points of origin patients were coming from immediately prior to arrival at the hospital. Cases of sepsis that occurred over a defined time frame in the hospital and that were categorized based on whether they originated in the hospital or in the non-hospital environment were compared by the clinical signs of sepsis in each individual case. The findings of the following chapter are based on one main research question that has several sub-questions.

Research Questions

1. Is there a difference in the variables relevant to a diagnosis of sepsis by point of origin?
 - a. Is there a difference in the mean number of patients that come from individual points of origin?
 - b. Is there a significant difference in the age and gender of people coming from different points of origin?
2. Is there a relationship between patients from different points of origins and whether they present signs of sepsis within a normal or abnormal range upon admission?

3.2 RESEARCH METHODOLOGY

Data Collection

The data for this project were collected at Carle Foundation Hospital (Carle) under the supervision of the Director of Medical Affairs and Quality, Dr. Napoleon Knight under IRB approval to study the data. Data were collected using the Carle electronic medical record (EMR)

which Carle uses to organize and maintain all records and documentation of patient visits to the hospital. The database collected contained the data of 197 patients that passed away within a three year period defined as the time from August 2007 to August 2009. Patient charts and records were examined in detail and assessed for each of the clinical variables of sepsis at the time of first treatment of the patient. The variables used are described below and are based on consensus criteria for sepsis symptomatic variables that are also in use at Carle.

The primary variables are the clinical symptoms associated with a diagnosis of septicemia (sepsis = SIRS + infection, severe sepsis and septic shock). The variables needed to make an initial assessment of patients with septicemia are adapted from a large list of patient presentation symptoms that were defined at the 1991 ACCP/SCCM Consensus Conference and later clarified and confirmed in the 2001 International Consensus Conference (Levy et al, 2001). The database was made with assumptions that variables should not be time or diagnosis dependent. Instead, clinical symptoms were assessed at the initial prognosis to ensure that patients presented sepsis or susceptibility to sepsis at admission to the hospital. Specific variables/symptoms that are readily available in patient charts or nursing notes are applied as a modified version of conference definitions and come from the MEDS score assessment by Shapiro et al in 2003. These include:

Temperature - abnormal temperature was defined as hyperthermia which is a core temperature of $>100.4^{\circ}\text{F}$ (38°C) or hypothermia which is a core temperature of $<96^{\circ}\text{F}$ (35.5°C).

Blood Pressure - hypotension as systolic blood pressure <90 . Septic shock was defined as severe sepsis plus hypotension (systolic blood pressure <90) that persisted after an initial fluid challenge of 20–30mL of crystalloid per kilogram of body weight

Heart Rate - tachycardia as >90 beats per minute

Respiratory Rate - respiratory difficulty can be defined as tachypnea (respiratory rate >20)

Oxygen Saturation - respiratory difficulty can also be defined as hypoxia (oxygen saturation/pulse oximetry <90%) or the need for oxygen supplementation to maintain adequate saturation or the need for oxygen supplementation by either face mask or 100% non-re-breather to maintain adequate oxygenation

Leukocyte Count - leukocytosis is an important sign of systemic inflammatory response syndrome (SIRS) and is defined as white blood cell count >12 x 10⁹ cells/L, <4 x 10⁹ cells/L or bands >10%

Additionally to the six main criteria for sepsis diagnosis, the database also includes data useful for the analysis of the septic patient's situation and includes:

Neutrophil Count - abnormal neutrophil count >90% (left shift)

Platelets - low platelets is <150,000 cells/mm³

Organ dysfunction – is a sign of severe sepsis if in conjunction with at least two of the preceding variables. Organ dysfunction includes lactic acidosis with an anion gap >16, neurologic issues seen in altered mental status and/or pulmonary issues measured by oxygen saturation <90%.

Diagnosis – initial diagnosis and location of the diagnosis. This is important because patients are not always admitted to the ICU after a diagnosis of sepsis but may end up dying because of it. Understanding where the diagnosis was made and when it was made allows for a comparison of those patients that did not initially show signs but were susceptible to becoming septic, to those who were already showing signs of sepsis, and those who were not susceptible but still died from Sepsis.

Age & Sex – demographic data taken from patient records in the electronic medical record at Carle for age and gender

The patients are grouped by point of origin and the clinical symptoms were taken from the earliest moment when documentation occurs upon patient admission to the hospital as they came from various points of origin. Usually, these patients will have moved to the ICU and in this study, passed away due to coded septicemia which is sepsis. These “points of origin,” as they will be called, are based on the designations made by the Carle EMR and the way patient points of origins are coded into the database. These classifications include: (1) skilled nursing facilities (SNF), (2) Non-Healthcare Facility Point of Origin (NHF), and (3) transfers from other hospitals (TRAN)

SNF include places that have a nurse on staff and include organizations like nursing homes, assisted-living facilities and other long - term care facilities. NHF include places such as personal homes, apartments, residential buildings, etc. TRAN designates transfers from various local hospitals that cannot support the patient due to lack of resources (Knight, 2011).

Data Analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0. A 95% confidence interval was calculated, and statistical analyses were performed using two-sided tests of significance at the 0.05 level. Cross tabs and a Pearson Chi-Square were performed to test whether there was a significant difference between clinical sepsis variables and points of origin. Chi-square analyses were taken for the clinical variables of sepsis and were categorized as either normal or abnormal based on criteria from the consensus definitions.

One-way ANOVA was used to study the differences in mean between the several clinical signs of sepsis. Each variable was analyzed for variance and compared between the different points of origin. Furthermore, Microsoft Excel 2010 was used to visualize and compare the means of several key variables by point of origin using graphs, tables and charts.

CHAPTER 4

RESULTS

Demographic Data

As displayed in Table 1 below, the total number (N) of patients in the database is 197. Divided into the points of origin (POI), skilled nursing facilities (SNF) accounted for 35% of this at 69 patients, transfer from other hospitals (TRAN) another 35% and non-healthcare facilities (NHF) made up 30% of the total with 59 patients. In order to see if there was a significant difference between the number of patients and point of origin a chi-square was run and found that, although NHF had fewer numbers than should be expected if there is no difference between these points of origin, there was not a statistically significant difference with a *p*-value of 0.602 and 2 degrees of freedom.

Table 1

Distribution of Patients by POI

POI	Frequency		Chi-Square Test	
	<i>n</i>	<i>Percent</i>	<i>df</i>	<i>p-value</i>
SNF	69	35%		
TRAN	69	35%		
NHF	59	30%		
Total	197	100%	2	0.602

Between the 197 patients total, there was not much variation between the genders with 95 males making 48.2% of the total and 102 females contributing the rest of the 51.8% as seen in Table 2. However, there seemed to be some variation between the points of origin. SNF had higher numbers of female than the 28.45 that would be expected if all points of origin were equal. Of the 69 patients that came from a SNF, 38 were female and 31 were male. From TRAN, 36

were male and 3 fewer at 33 were female. NHF had 31 females and 28 males. To see if these variations were significant, a chi-square was used and found a *p*-value of .689 with 2 degrees of freedom, confirming that any differences between point of origin and gender were not statistically significant.

Table 2

Distribution of Genders by POI

Point of Origin	Sex		Total	Chi-Square Test	
	<i>Male</i>	<i>Female</i>		<i>df</i>	<i>p-value</i>
SNF	31	38	69		
TRAN	36	33	69		
NHF	28	31	59		
Total	95	102	197	2	0.689

Between each of the points of origin, there also seemed to be some slight differences in the age breakdown of the patients. Displayed in Table 3, the minimum age for SNF was at least 31 years higher than either TRAN or NHF. The way that the ages were entered into the database put a maximum value of 89 and above and all three origins had at least one patient that met that maximum cap. Looking at the means of the different points of origin SNF had a higher overall mean of 77.52 with an SD of 10.82 while TRAN and NHF had similarly lower means of 65.67 with an SD of 19.41 and 67.75 with an SD of 19.75 respectively. To test whether the differences in these mean ages between the points of origin were of statistical significance, an ANOVA was run and confirmed that there was a significant difference with a *p*-value <.001 with 2 degrees of freedom between the groups.

Table 3

Age Distribution by POI

POI	Frequency					Anova		
	<i>N</i>	<i>Min</i>	<i>Max</i>	<i>Mean</i>	<i>SD</i>	<i>df</i>	<i>F</i>	<i>p-value</i>
SNF	69	34	89	77.52	10.82			
TRAN	69	2	89	65.67	19.41			
NHF	59	3	89	67.75	19.75			
Total	197	2	89	70.31	16.66	2	9.427	0.000***

Note. *** $p < .001$

Sepsis Criteria Variables

The means for each clinical sign of sepsis by individual points of origin can be found in Table 4 below. The total mean systolic blood pressure (SBP) for all of the points of origin was 112.52 with an SD of 32.1. The mean SBP for the SNF point of origin was 114.6 with an SD of 34.6. The mean SBP for the TRAN point of origin was 106.7 with an SD of 26.2.

Table 4

Mean and SD of Sepsis Criteria Variables by POI

Variable	SNF			TRAN			NHF		
	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>
SBP	69	114.6	34.6	69	106.7	26.2	57	117.1	35.0
Heart Rate	68	111.0	26.9	68	105.0	25.0	58	114.0	26.7
Temperature	65	99.2	2.7	63	98.7	2.7	54	98.8	2.60
Respirations	69	26.9	10.0	69	23.9	7.3	58	23.7	6.30
O2SAT	67	0.899	0.094	69	0.938	0.075	57	0.931	0.063
WBC	68	16.5	9.5	69	17.70	11.8	59	14.5	11.60

Table 5

Results of ANOVA for Sepsis Criteria Variables and POI

	Sum of Squares	df	Mean Square	F	p-value
SBP					
Between Groups	3880.22	2	1940.11	1.897	0.153
Within Groups	196384.43	192	1022.84		
Total	200264.65	194			
Heart Rate					
Between Groups	2685.45	2	1342.72	1.957	0.144
Within Groups	131017.87	191	685.96		
Total	133703.32	193			
Temperature					
Between Groups	8.77	2	4.39	0.618	0.540
Within Groups	1270.95	179	7.10		
Total	1279.72	181			
Respiratory Rate					
Between Groups	432.63	2	216.32	3.303	0.039
Within Groups	12638.37	193	65.48		
Total	13071.00	195			
Oxygen Saturation					
Between Groups	0.06	2	0.03	4.587	0.011*
Within Groups	1.19	190	0.01		
Total	1.25	192			
White Blood Cell					
Between Groups	330.22	2	165.11	1.368	0.257
Within Groups	23291.21	193	120.68		
Total	23621.43	195			

Note. *p < .05

The mean SBP for NHF was 117.1 with an SD of 35.0. The means seem to show a slight variation between the points of origin. However, study by ANOVA (shown in Table 5) did not show a significant difference in the SBP means between the three points of origin pressure with a p -value of 0.153 with 2 degrees of freedom.

The total mean heart rate for all of the points of origin was 109.8 with an SD of 32.1. The mean heart rate for the SNF point of origin was 111.0 with an SD of 26.9. The mean heart rate for the TRAN point of origin was 105.0 with an SD of 25.0. The mean heart rate for NHF was 114.0 with an SD of 26.7. The means for heart rate seem to show only a very slight variation between the points of origin. A study by ANOVA confirms that there was not a significant difference in the means between the three points of origin with a p -value of 0.144 with 2 degrees of freedom.

The total mean temperature for all of the points of origin was 98.9°F with an SD of 2.7°F. The mean temperature for the SNF point of origin was 99.2°F with an SD of 2.7°F. The mean temperature for the TRAN point of origin was 98.7°F with an SD of 2.7°F. The mean temperature for NHF was 98.8°F with an SD of 2.6°F. The means for temperature also do not seem to show much difference between points of origin. ANOVA shows that there was not a significant difference in the temperature means between points of origin with a p -value of 0.540 with 2 degrees of freedom.

The total mean respiratory rate for all of the points of origin was 24.9 respirations with an SD of 8.2. The mean respiratory rate for the SNF point of origin was 26.9 with an SD of 10.0. The mean respiratory rate for the TRAN point of origin was 23.9 with an SD of 7.3. The mean respiratory rate for NHF was 23.7 with an SD of 6.3. The means for respiratory rate seem to

show a slight elevation in respirations in the SNF point of origin compared to the lower number of respirations found in the TRAN and NHF points of origin. ANOVA showed that there was a significant difference in the means between the three points of origin and respiratory rate with a p -value of 0.039 with 2 degrees of freedom.

The total mean oxygen saturation was 92.26% with an SD of 8.06%. The mean oxygen saturation for the SNF point of origin was 89.94% with an SD of 9.44%. The mean oxygen saturation for the TRAN point of origin was 93.78% with an SD of 7.48%. The mean oxygen saturation for NHF was 93.05% with an SD of 6.31%. The means for oxygen saturation also seem to show a noticeable difference in the means between SNF compared to the higher saturations of TRAN and NHF points of origin. ANOVA again reinforces this contrast and shows that there was indeed a significant difference in the means between the three points of origin with a p -value of 0.011 with 2 degrees of freedom.

The total mean white blood cell count for all of the points of origin was 16.3 with an SD of 11.0. The mean white blood cell count for the SNF point of origin was 16.5 with an SD of 9.5. The mean white blood cell count for the TRAN point of origin was 17.7 with an SD of 11.8. The mean white blood cell count for NHF was 14.5 with an SD of 11.6. The means for white blood cell count seem to show only a very slight variation between the points of origin. A study by ANOVA confirms that there was not a significant difference in the means between the three points of origin with a p -value of 0.257 with 2 degrees of freedom between the three points of origin and white blood cell count.

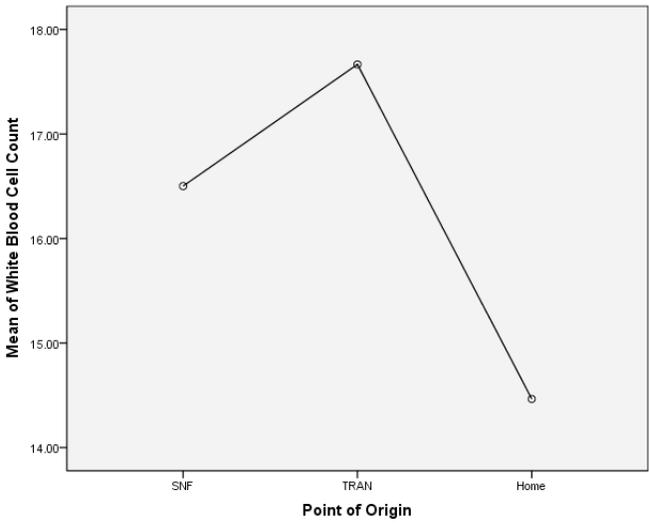
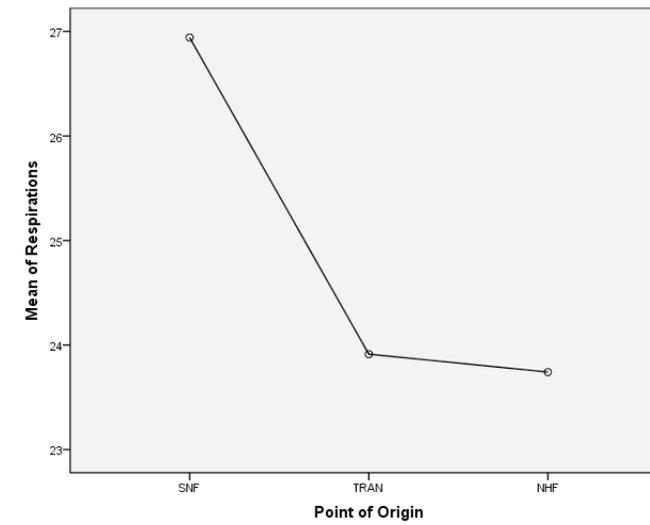
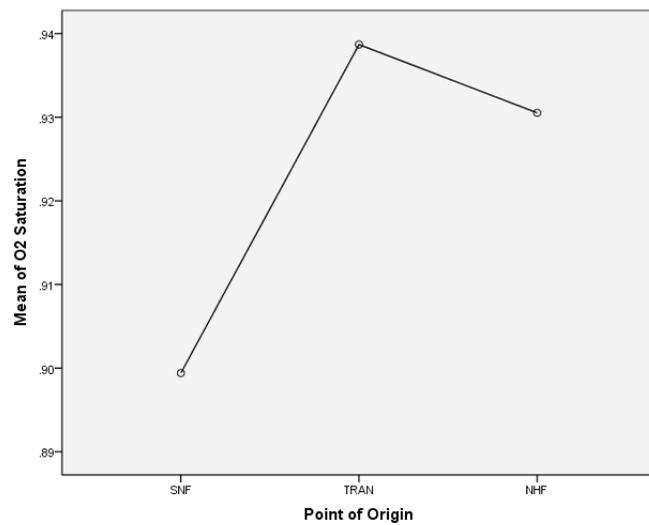
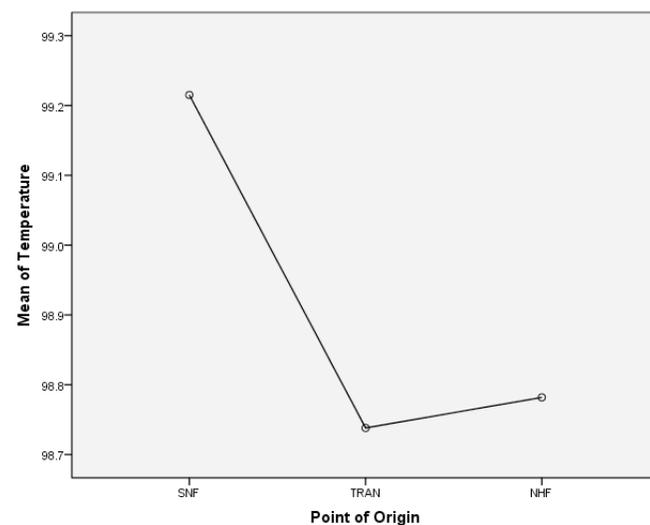
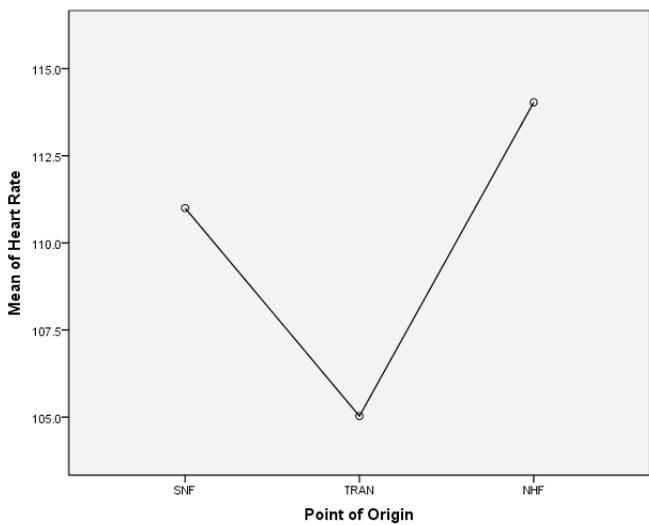
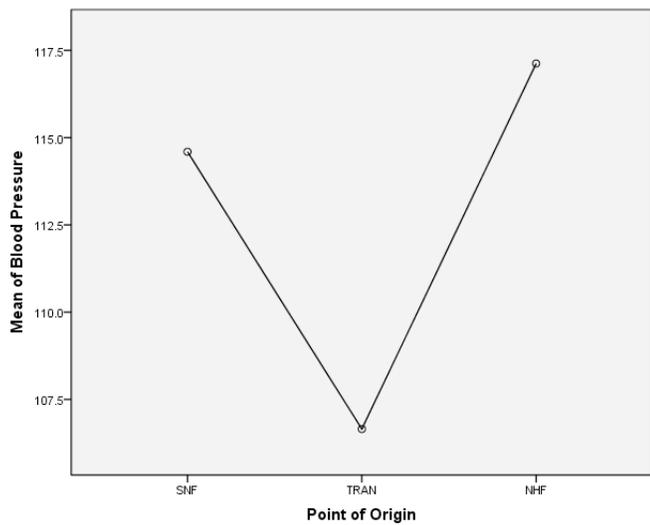


Figure 1. Graphical comparison of sepsis criteria variables by point of origin

Chi-Square Analysis

The tables that follow in this next section show the chi-square analysis done via cross tables between the three nominal categories of individual points of origin and the categorization of normal versus abnormal ranges for each of the clinical sign of sepsis.

Table 6

Results of a Chi-Square Test of Blood Pressure and POI

POI	Blood Pressure		Total	Chi-Square Test		
	<i>Normal</i>	<i>Abnormal</i>		<i>Value</i>	<i>Df</i>	<i>p-value</i>
SNF						
Actual	47.0	22.0	69			
Expected	50.2	18.8	69			
TRAN						
Actual	54.0	15.0	69			
Expected	50.2	18.8	69			
NHF						
Actual	41.0	16.0	57			
Expected	41.5	15.5	57			
Total				1.826	2	0.401
Actual	142.0	53.0	195			
Expected	142.0	53.0	195			

Between the three points of origin, SNF had 22 counts of abnormal ranges for blood pressure and 47 normal ranges while TRAN and NHF had lower counts of abnormal ranges, 15 and 16 respectively, which might suggest that there would be a difference between the points of origin and abnormality in blood pressure when a count of 18.8 or 15.5 would be expected if there was no difference. However, chi-square analysis did not find any significant relationship between the three points of origin and a categorization of abnormal and normal range for the systolic blood pressure (SBP) variable with a *p*-value of 0.401 with 2 degrees of freedom.

For heart rate, all three points of origin had more counts of abnormal ranges for heart rate than normal. SNF had 52 counts of abnormal of 68 total counts, TRAN similarly had 51 of 68 total counts and NHF had 49 of 59 total counts abnormal when a count of 53.3 or 45.4 would be expected if there was no difference. Chi-square analysis did not find any significant relationship between the three points of origin and a categorization of abnormal and normal range in heart rate with a *p*-value of 0.391 with 2 degrees of freedom.

Table 7

Results of a Chi-Square Test of Heart Rate and POI

POI	Heart Rate		Total	Chi-Square Test		
	<i>Normal</i>	<i>Abnormal</i>		<i>Value</i>	<i>Df</i>	<i>p-value</i>
SNF						
Actual	16.0	52.0	68			
Expected	14.7	53.3	68			
TRAN						
Actual	17.0	51.0	68			
Expected	14.7	53.3	68			
NHF						
Actual	9.0	49.0	58			
Expected	12.6	45.4	58			
Total				1.878	2	0.391
Actual	42.0	152.0	194			
Expected	42.0	152.0	194			

Temperature seemed to have a higher number of patients who were in the abnormal range with a count of 29 in SNF where 22.5 was expected and this when compared to the 17 abnormal counts in the TRAN where 21.8 would be expected and NHF points of origin when a count of

18.7 would be expected if there was no difference. However, chi-square analysis did not find a statistically significant relationship between the three points of origin and a categorization of abnormal and normal range of temperature with a *p*-value of 0.094 with 2 degrees of freedom.

Table 8

Results of a Chi-Square Test of Temperature and POI

POI	Temperature		Total	Chi-Square Test		
	<i>Normal</i>	<i>Abnormal</i>		<i>Value</i>	<i>df</i>	<i>p-value</i>
SNF						
Actual	36.0	29.0	65			
Expected	42.5	22.5	65			
TRAN						
Actual	46.0	17.0	63			
Expected	41.2	21.8	63			
NHF						
Actual	37.0	17.0	54			
Expected	35.3	18.7	54			
Total				4.727	2	0.094
Actual	119.0	63.0	182			
Expected	119.0	63.0	182			

There seemed to be more variation in the respiratory rate variable between the 3 points of origin. SNF had 48 counts of abnormal ranges out 69, TRAN had 43 counts of 69 total counts, and NHF had 34 out of 58 when a count of 44 and 37, respectively, would be expected if there was no difference. To confirm this seeming relationship, a chi-square analysis was run but even though there seemed to be a difference based on the means, the chi-square analysis found that there does not exist a statistically significant relationship between the three points of origin and a

categorization of abnormal and normal range in respiratory rate with a p -value of 0.421 with 2 degrees of freedom.

Table 9

Results of a Chi-Square Test of Respiratory Rate and POI

POI	Respiratory Rate		Total	Chi-Square Test		
	<i>Normal</i>	<i>Abnormal</i>		<i>Value</i>	<i>df</i>	<i>p-value</i>
SNF						
Actual	21.0	48.0	69			
Expected	25.0	44.0	69			
TRAN						
Actual	26.0	43.0	69			
Expected	25.0	44.0	69			
NHF						
Actual	24.0	34.0	58			
Expected	21.0	37.0	58			
Total				1.732	2	0.421
Actual	71.0	125.0	196			
Expected	71.0	125.0	196			

Again, like respiratory rate, oxygen saturation seemed to have a noticeable elevation of abnormal counts in SNF compared to TRAN and NHF. SNF had 29 counts abnormal where 20.5 were expected while TRAN had 14 of an expected 21.1 and NHF 16 of 17.4. This made it appear that oxygen saturation was different by point of origin and unlike respiratory rate the significance of this difference was confirmed by chi-square analysis which found a statistically significant relationship between the three points of origin and a categorization of abnormal and normal range in oxygen saturation with a p -value of 0.013 with 2 degrees of freedom.

Table 10

Results of a Chi-Square Test of Oxygen Saturation and POI

POI	Oxygen Saturation		Total	Chi-Square Test		
	<i>Normal</i>	<i>Abnormal</i>		<i>Value</i>	<i>df</i>	<i>p-value</i>
SNF						
Actual	38.0	29.0	67			
Expected	46.5	20.5	67			
TRAN						
Actual	55.0	14.0	69			
Expected	47.9	21.1	69			
NHF						
Actual	41.0	16.0	57			
Expected	39.6	17.4	57			
Total				8.706	2	0.013*
Actual	134.0	59.0	193			
Expected	134.0	59.0	193			

Note. * $p < .05$

For white blood cell count (WBC), the chi-square analysis did not find any significant relationship between the three points of origin and a categorization of abnormal and normal range and WBC with a p -value of 0.513 with 2 degrees of freedom. SNF had a count of 44 abnormal ranges in WBC from 47.5 expected counts, TRAN had 50 abnormal counts where 48.2 were expected and NHF had 43 abnormal counts when 41.2 were expected.

Table 11

Results of a Chi-Square Test of White Blood Cell Count and POI

POI	WBC Count		Total	Chi-Square Test		
	<i>Normal</i>	<i>Abnormal</i>		<i>Value</i>	<i>df</i>	<i>p-value</i>
SNF						
Actual	24.0	44.0	68			
Expected	20.5	47.5	68			
TRAN						
Actual	19.0	50.0	69			
Expected	20.8	48.2	69			
NHF						
Actual	16.0	43.0	59			
Expected	17.8	41.2	59			
Total				1.337	2	0.513
Actual	59.0	137.0	196			
Expected	59.0	137.0	196			

The final analysis done was a comparison of the three points of origin and whether a patient met the criteria for being sepsis positive upon arrival at the hospital. To be a sepsis positive patient, at least 2 of the 4 criteria for sepsis categorization had to be met. This criteria included either a (1) abnormal heart rate, (2) abnormal temperature, (3) abnormal breathing which could either be respiratory rate or oxygen saturation, and/or (4) abnormal white blood cell count. SNF had a higher sepsis positive count than the other two categories with 27 of 22.5 expected counts being positive for the criteria compared to only 15 of 21.8 in TRAN and 21 of 18.7 in NHF. However, chi-square analysis revealed that this difference was not statistically with a *p*-value of 0.077 and 2 degrees of freedom.

Table 12

Results of a Chi-Square Test of Sepsis Upon Arrival and POI

POI	Sepsis Upon Arrival		Total	Chi-Square Test		
	<i>Negative</i>	<i>Positive</i>		<i>Value</i>	<i>df</i>	<i>p-value</i>
SNF						
Actual	37.0	27.0	64			
Expected	41.5	22.5	64			
TRAN						
Actual	47.0	15.0	62			
Expected	40.2	21.8	62			
NHF						
Actual	32.0	21.0	53			
Expected	34.3	18.7	53			
Total				5.118	2	0.077
Actual	116.0	63.0	179			
Expected	116.0	63.0	179			

CHAPTER 5

DISCUSSION

The purpose of this study was to determine if there is a relationship between patients that come from different points of origin and their presentation of sepsis variables upon admittance to the hospital. Data on each variable was compared by point of origin and then analyzed together to see if there was a relationship between the variables and point of origin. The findings of this chapter were based on two main research questions and supplemental sub-questions.

Research Questions

1. Is there any difference in the variables relevant to a diagnosis of sepsis when compared by point of origin?
 - a. Is there a difference in the mean number of patients that come from individual points of origin?
 - b. Is there a significant difference in the age and gender of people coming from different points of origin?
2. Is there a relationship between patients from different points of origins and whether they present signs of sepsis within a normal or abnormal range upon admission?

5.1 FINDINGS

Research question one asked if there is a difference in the variables relevant to a diagnosis of sepsis when compared by point of origin. There was no real difference comprehensively in the variables important to a clinical diagnosis of sepsis. However, when looking at individual symptoms, there were some variables specifically that were statistically significant. For example, not all of the clinical variables associated with sepsis were found to be statistically significant but the means associated with respiratory rate and oxygen saturation were

shown through ANOVA to have means that were significantly different between the points of origin being at a p -value of 0.039 and 0.011 respectively.

Research sub-question 1a asked if there is a difference in the mean number of patients that come from individual points of origin. Statistically analysis showed that there was not a significant difference between points of origin with a p -value of 0.602 for the chi-square test but although there was not a statistically significant difference in the number of patients coming from different points of origin, it was noticed that there was a higher tendency for patients to be coming from outside of NHF origins.

Research sub-question 1b asked if there is a significant difference in the demographic data of age and gender for people coming into the hospital from different points of origin. It was observed that gender did not make a statistical difference between of origin with a chi-square p -value of 0.689 but as confirmed by the research study by Dellinger et al in (2003), it was seen in this study that age was a statistically significant variable with a p -value of < 0.001 . In this study specifically, age was seen to be on average much higher for those patients coming from the SNF point of origin.

Research question two asked if there is a relationship between patients from different points of origins and whether they present signs of sepsis within a normal or abnormal range upon admission. The results show that comprehensively, the symptomatic variables that are used as a criterion to determine if patients came into the hospital presenting sepsis do not show a statistically significant relationship between the different points of origin. Upon study of the individual variables, many of the sepsis criteria variables showed no statistically significant relationship by chi-square similarly to the ANOVA analysis of means for research question 1. However, it was observed that those variables associated with breathing difficulty in septic

patients (namely respiratory rate and oxygen saturation) seemed to be different based on pre-statistical analysis observation of the means. After statistical analysis was done, only one of these variables was observed to be statistically significant for the chi-square test: oxygen saturation at p -value 0.013. Having only one of these variables proven to be statistically significant does not take away the significance of the fact that respiratory difficulty is the issue at hand. After a dialogue with the project coordinator that collected the dataset, Dr. Napoleon Knight, it was assessed that the statistical support of one of the variables that show respiratory difficulty would suffice in proving that there is an issue of respiratory difficulty. The fact that respiratory difficulty is defined by either abnormal respirations or abnormal oxygen saturation was further discussed and supported above in the methods section.

Overall, patients that came from SNF were seen to have higher counts of abnormal breathing difficulty when compared to the other points of origins. When looking at the rest of the sepsis criteria symptoms, almost all of the variables were elevated above expected counts in SNF when compared to TRAN and NHF. When looking at the comprehensive chi-square analysis performed for sepsis upon arrival, it was noticed that although the statistics were not significant, the SNF point of origin had a higher count for being sepsis positive at admission to the hospital.

5.2 LIMITATIONS

This study had several limitations. One limitation was that the data collected from Carle Foundation Hospital were not absolutely complete; there were several patient cases where certain variables had to be omitted for uncontrollable circumstances. However, the amount of missing data, as confirmed by SPSS statistical analysis, was not significant enough to affect results and was always less than 4% or never greater than a rate of 5 missing persons.

Another limitation was the small sample size. The data collected amounted to 197 cases of patients that passed away due to sepsis. Although the sample size was small, in order to maintain the integrity of consistent data and allow a manageable number of cases for collection, the supervisor limited the collection of patient data to a three year timespan which allowed enough of a sample size to perform a meaningful statistical analysis.

Another limitation was that there was no comparison control group. Although the study was looking specifically at patients who passed away from sepsis between specified points of origin, it might have been a more comprehensive study if analysis could have been completed between a randomized control group and the groups already studied.

Another limitation was the consistency of the time at which variables were collected. The data were collected at the earliest point at which a provider assessed the values of clinical signs of sepsis. However, in order to control completely the comparison of variables, it would have been ideal if all variables were collected at a standardized time between all 197 variables. However, given the clinical nature of the study and the fact that it was a retrospective study, it was impossible to control for this.

Finally, another limitation was the scope of the study. This study was limited to one regional hospital and may not be applicable to all hospitals. If possible, a more complete study could be made if the study was done between multiple hospitals on a larger, more randomized scale.

Conclusion

In this study, when looking at research question one comprehensively, it may seem as though there was not a complete difference between each of the variables for each of the points of origin. However, because there was at least one variable, namely those associated with

respiratory distress discussed below, that was significantly different between each of the points of origin the null hypothesis for research question was rejected. The alternative hypothesis for research question two, however, was rejected since there was not a statistically significant difference in the relationship between those patients that came in presenting signs of symptoms versus those who did not compared between points of origin. Therefore, the study cannot confirm that any point of origin is more likely to present sepsis upon arrival, there were findings that may allude to and be of use in further study for preventative measures against symptoms that are known to be involved in the sepsis disease pathway.

This study found that clinical symptoms associated with respiratory distress, both respiratory rate and oxygen saturation at p -value 0.039 and 0.011 respectively for ANOVA and oxygen saturation being specifically statistically significant at p -value 0.013 for the chi-square analysis, were found to be significantly different for both research question one and partially for research question two. This was consistent with studies previously done that have shown that sepsis is highly associated with respiratory injury. In a study by Ozturk et al in 2008, sepsis was the highest cause of acute respiratory distress (ARD) and also had the highest association with mortality for those cases of ARD. This explains the pathophysiology of sepsis as a condition highly associated with lung function.

Furthermore, in a study by Slutsky (2002) it was found that the lungs may have a more prominent role in the development of sepsis than is actually believed. It was hypothesized that the lung could actually play a pivotal role as a source for the development of many of the inflammatory responses that contribute to the onset and clinical signs of sepsis. This idea that the lungs play a primary role in the development of sepsis serves as a helpful foundation to understand the significance of the findings. The statistical significance of the variables associated

with respiratory distress serve to prove that there was a meaningful difference between the points of origin in at least relation to respiratory distress and only serve to confirm that the findings of this study are consistent with past research.

In this study it was observed that there was a significant variation in the means for age with a p -value of < 0.001 . This finding is consistent with studies previously administered. In an overview research paper of sepsis by Latta in 2008, the researcher reiterates that being elderly is a risk factor for sepsis as well as the fact that the elderly have higher rates of mortality due to sepsis because increased age is associated with decreased immune function. Latta further elaborates that the elderly have a high risk for developing infection community-acquired infection which may lead to the development of sepsis. In this study, it was seen that the skilled nursing facilities (SNF) point of origin had higher numbers of elderly patients with a mean age of 77.52 when compared to transfer from other hospitals (TRAN) at 65.67 and non-healthcare facilities (NHF) at a mean of 67 and so the study seemed to remain consistent with literature research. Furthermore, when looking at the data for the SNF point of origin, it was observed that 100% of these patients came from a nursing home. These findings bare many practical implications as well as implications for future study.

This study has shown that there is a statistically significant variation between the different points of origin that people are coming from into Carle Foundation Hospital and certain tell-tale clinical variables for sepsis (in this case those variables associated with respiratory distress and age by POI). In showing that there is a difference in important and specific variables, it serves as a starting point for isolating and targeting specific locations for interventional programs that could aim at an earlier diagnosis and more prompt treatment of patients showing signs of sepsis.

For example, since nursing homes make up all of the SNF point of origin, the hospital can take pre-emptive measures to assess and treat patients at Nursing Homes before they get to the hospital and in doing so, decrease treatment costs in hospital and simultaneously lower the overall mortality rates in the hospital and the mortality due specifically to sepsis. This is consistent with our findings since, although it was not statistically significant, in conjunction with the significant findings of research question one, there were more patients coming in from the SNF point of origin who were already presenting signs of sepsis at the time of admission and so would serve as an appropriate point of origin to begin an early targeting of sepsis.

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