AN EVALUATION OF EARLY GOAL DIRECTED THERAPY IN THE MANAGEMENT OF
SEPSIS AND SEPTIC SHOCK

by

James P Gilligan, BSN, RN, CCRN

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SIGNED:  James P Gilligan

APPROVAL BY GRADUATE PROJECT COMMITTEE CHAIR
This Master's Project has been approved on the date shown below:

Leslie Ritter, PhD, RN                                      Date
Chair
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DEDICATION

This Masters Report is dedicated to my parents for their continual support and love. No matter what road my life may lead me down you have always been there to support and encourage me.
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ABSTRACT

Prior to the advent of early goal directed therapy (EGDT) in 2001, mortality rates for sepsis showed minimal if any improvement based on studies over the preceding 40 years. The introduction of EGDT has demonstrated significant improvements in mortality rates associated with sepsis when these bundled therapies are utilized for sepsis management; however there still remain healthcare practitioners that do not utilize these therapies when managing septic patients.

Sepsis is a common problem in medical intensive care units that Acute Care Nurse Practitioners (ACNP) will encounter during their tenure practice. It is the purpose of this paper to provide ACNPs with the required knowledge to effectively care for these critically ill patients based on current evidence-based research. Therefore, this paper will discuss the pathophysiology of sepsis, EGDT and the Surviving Sepsis Campaign as well as the barriers to implementation of sepsis and associated evidence-based research.
CHAPTER 1 – INTRODUCTION

Background

The effective management of sepsis has been an ongoing problem for healthcare practitioners for many years. While statistically the incidence of sepsis has been increasing, the mortality associated with the disease has remained relatively constant (Friedman, Silva & Vincent, 1998; Rivers, Nguyen, Havstad, Ressler, Muzzin, Knoblich, et al., 2001), validating that effective management strategies need to be elucidated. In recent years, sepsis has become the 10th leading cause of death in the United States and the number one killer in non-coronary intensive care units (ICU). Sepsis accounts for 20% of all ICU admissions and has mortality rates ranging from 20% to as high as 50% (Levy et al., 2010; LaRosa, n.d.; Rivers & Ahrens, 2008). It is estimated that nearly 750,000 people die each year due to sepsis and septic shock with trends placing the annual rate of increase at approximately 1.5% per year. Given that more than half of these patients are 65 years of age and older, and that the number of people in this cohort will continue to grow, there is great concern for the proper management of sepsis and septic shock in the coming years (El Sohl, Akinnusi, Alsawalha & Pineda, 2007). Persons greater than 65 years of age have a higher incidence of sepsis due to their comorbidities and alterations in immune function. Additionally, since persons 65 years and older account for approximately 50-60% of all ICU days and the costs associated with ICU care for all patients has been on the rise, resource consumption and utilization also plays a major role in finding effective management strategies for persons with sepsis and septic shock (Girard, Opal & Ely, 2005; Martin, Mannino & Moss, 2006).
While there has been tremendous progress in the guidelines for acute management of disease processes such as myocardial infarctions and cerebral vascular accidents, the use of guidelines for the management of sepsis and septic shock is still not well accepted. One explanation for this lack of progress comes from the lack of consensus in defining terms associated with sepsis. This lack of a consensus has resulted in numerous critical care societies jointly evaluating current practice definitions and issuing recommendations for standardizing practice (Rivers & Ahrens, 2008). Furthermore, until the sentinel research done by Rivers and colleagues in 2001 (Rivers et al., 2001), there was very limited research demonstrating that the use of guidelines resulted in significant improvements in mortality. As a result of the work by Rivers et al., the era of early goal directed therapy in the management of sepsis and septic shock began. Unfortunately, many practitioners still have not embraced this evidence-based approach and mortality rates associated with sepsis and septic shock remain high. Therefore, the purpose of this paper is to discuss this initial work done by Rivers and colleagues on early goal directed therapy (EGDT) for sepsis management, review the historical progression of sepsis management and conduct a literature review to assess the outcomes of studies that utilized the original EGDT framework presented by Rivers and colleagues. Literature reviews will also be performed in an effort to assess barriers of implementation of both emerging evidenced-based practice (EBP) and those of EGDT in sepsis management, with an attempt to identify any commonalities or differences that may be preventing its implementation.

Significance to the Acute Care Nurse Practitioner

The roots of the nurse practitioner (NP) movement can be traced back to the 1960s. The first NPs worked in primary care with a focus on wellness, patient education and prevention.
Since that point, the demands of a growing, more complex, healthcare system have played a part in the expansion of the NP role into the acute care setting. Initially, adult and family nurse practitioners expanded their practice through self-study and post-graduate occupational training in order to care for patients in these new healthcare settings. However, with the changing dynamics of medical training came mandatory reductions in medical house staff hours, which impacted the presence of medical residents in the hospital and created the need for improved coordination of care in an increasingly fragmented system. Thus, the acute care nurse practitioner (ACNP) role was officially created. The initial ACNP certification exam was given in 1995 (Hamric, Spross, & Hanson, 2009).

Acute care nurse practitioners are educated to care for patients with acute, chronic and critical conditions. They utilize EBP and provide comprehensive care in collaboration with an interdisciplinary team including physicians, nurses and allied health providers. In addition to their clinical skill sets, ACNPs also act as leaders in nursing and the delivery of healthcare. While acute care nurse practitioners maintain a focus on prevention and patient education, their primary goal is to provide “curative, rehabilitative, palliative and maintenance care” (Hamric et al., 2009, pg 407). Due to the complexity of their patients, ACNPs are educated and trained to have a different set of skills and knowledge relative to their community based NP counterparts. This different education and training includes advanced assessment skills, diagnosis of acute and chronic health conditions and the management of acute and chronic disease processes (Hamric et al., 2009).

Given the settings in which they work, and the increasing incidence of sepsis, ACNP’s require an in-depth knowledge of the pathophysiology of sepsis and septic shock. They must also
keep abreast of the latest research in the management of these complex patients in an effort to provide safe and effective care. Therefore, one focus of this paper is to provide a review of the pathophysiology of sepsis and discuss the current state of the research and outcomes associated with the implementation of EGDT in patients with sepsis and septic shock.
CHAPTER 2 – SEPSIS

Defining Sepsis

Adequately defining sepsis has been an ongoing problem for many years and continues to negatively impact clinical practice. To help resolve this issue the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) organized and held a consensus conference in 1991 with the goal of defining sepsis and its’ associated terminologies. It was the hope of this committee that if standardized definitions existed, earlier detection of sepsis would provide for earlier therapeutic intervention and improved outcomes. It was also felt that standardized definitions would allow for future comparative studies of sepsis diagnosis and management (Bone et al., 1992).

The ACCP/SCCM committee found that defining sepsis precisely was compounded by the use of different terms for the same condition, such as septic syndrome, septicemia and bacteremia, and by using the term to describe different pathological conditions, such as noninfectious inflammatory states (Bone et al., 1992). In response to the lack of consensus in the definitions, the committee created the new term systemic inflammatory response syndrome (SIRS). This acronym is intended to encompass the initial inflammatory process seen in sepsis as well as other non-infective processes; such as pancreatitis, major trauma and tissue injuries, hemorrhagic shock, and burn injuries. The relationship between non-infective and infective processes and SIRS is presented in Figure 1. As a result of the ACCP/SCCM committee's work, a set of four criteria and associated terms were developed to define SIRS and is presented in Table 1. The committee also attempted to reduce confusion by recommending and defining the
Figure 1. Relationship of Infective and Non-infective Processes and the Systemic Inflammatory Response Syndrome (SIRS).

terms: infection, sepsis, severe sepsis and septic shock; with the updated definitions presented in Table 2 (Definitions, 1992).

While this seminal work by the ACCP/SCCM Committee set the initial standard for the definitions of SIRS and sepsis, there remained problems in the understanding and acceptance of these criteria worldwide. An international survey of 1058 physicians, of which 307 practiced in the United States, was conducted in 2000 by Poeze, Ramsay, Gerlach, Rubulotta and Levy (2004). Of the 1058 physicians in the study, 528 of them practiced as ICU Intensivists. The results of this survey indicated that while 767 of the physicians agreed with the high mortality rate associated with sepsis, particularly with respect to other disease processes, 86% felt that the symptoms of sepsis could be mistaken for another disease process. Furthermore, 67% of the physicians felt that a lack of a common definition for sepsis still existed. Surprisingly, only 22% of the intensivists and 5% of the remaining physicians surveyed cited the ACCP/SCCM recommended definitions for sepsis and its associated terms.

Table 1

**Systemic Inflammatory Response Syndrome Defining Criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature $&lt; 36^\circ$C or $&gt; 38^\circ$C</td>
</tr>
<tr>
<td>Heart rate $&gt; 90$ beats per minute</td>
</tr>
<tr>
<td>Respiratory rate $&gt; 20$ breaths per minute OR PaCO2 $&lt; 32$ mmHg</td>
</tr>
<tr>
<td>White blood cell count $&gt; 12,000$ or $&lt; 4000$ cells/mm$^3$ or a bandemia of $&gt; 10%$</td>
</tr>
</tbody>
</table>

As a result of the work by Poeze et al. demonstrating that there was a lack of acceptance among healthcare providers of the ACCP/SCCM Committee’s recommendations internationally and that the science of sepsis and subsequent research into sepsis has continued to evolve, a second committee was formed to review and update the definitions of SIRS and sepsis. The original 1991 committee was expanded to include the American Thoracic Society (ATS), the Surgical Infection Society (SIS), and the European Society of Intensive Care Medicine (ESICM). Aside from revisiting the previous definitions and identifying their strengths and weaknesses, the second committee “sought to identify methodologies for increasing the accuracy, reliability, and/or clinical utility of the diagnosis of sepsis” (Levy et al., 2003, p. 1251).

Table 2

Definitions of Sepsis Terminology

<table>
<thead>
<tr>
<th>Infection</th>
<th>“a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms” (p.1252).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>“the clinical syndrome defined by the presence of both infection and a systemic inflammatory response” (p. 1251).</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>“sepsis complicated by organ dysfunction” (p. 1253)</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>“a state of acute circulatory failure [in adults] characterized by persistent arterial hypotension unexplained by other causes … despite adequate volume resuscitation” (p. 1253). (Hypotension is defined as a systolic blood pressure &lt;90 mmHg or &gt;40% decrease from baseline OR a mean arterial pressure &lt;60 mmHg)</td>
</tr>
</tbody>
</table>

*Note: mmHg = millimeters of mercury. Adapted from “2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference” by Levy et al., 2003 Critical Care Medicine, 31(4), 1251-1253.*

The consensus of the second committee reaffirmed the initial categories of sepsis, severe sepsis, and septic shock as recommended by the 1991 ACCP/SCCM Committee. After a review of the sepsis literature, the new committee found no evidence to support changing the SIRS- and sepsis-defining categories, although there were changes made to the wording of the 1991
definitions. Currently, the recommendations from the work of the 1991 and 2001 committees are accepted worldwide as the definition of sepsis/SIRS. The categories and associated terms defining sepsis can be found in Table 2 and will be the accepted definitions used throughout this paper. As demonstrated in Table 2, the onset of the sepsis differs from that of SIRS when a suspected or documented infection occurs. Sepsis also develops along a continuum, from infection to septic shock, as the severity of the disease worsens (Levy et al., 2003).

While minimal change was made to the definitions, the second committee did propose a new classification schema to stratify the severity of sepsis, based on the same design as the Tumor/Node/Metastasis (TNM) system which has been used for the staging of cancer since 1946. This new system was aptly named the PIRO system which is an acronym for its four domains: predisposition, infection, response, and organ dysfunction. The expectation of this new system will be the ability to discern morbidity associated with infection from that of the host’s response to infection. While the PIRO classification system is conceptually sound and based on the same framework as the TNM system, it is still a new concept and should serve as a template with the expectation that future research will help to further define and refine its criteria (Levy et al., 2003).

The second consensus committee considered the use of biomarkers as SIRS- or sepsis-defining criteria, rather than clinical signs; however, there was not enough data to support such a recommendation. They did, however, present a list of measurable signs that may be present with systemic infection in an attempt to ameliorate the generalization of the SIRS criteria with respect to sepsis. The lack of supporting evidence to make changes to the 1991 definitions supports the
assertion that further research is needed to more clearly define the future definition and
diagnostic criteria of sepsis (Levy et al., 2003).

The above section described the process of defining SIRS and sepsis. These definitions are
currently used worldwide. This paper will use “sepsis” when discussing the sepsis continuum
and its related definitions. In the next sections, the incidence, prevalence, and pathophysiology of
SIRS and sepsis will be discussed, as this information is the basis for the development of sepsis
management bundles.

At Risk Populations

While sepsis can affect anyone, there are certain populations at greater risk. Based on the
2001 SCCM/ESICM/ACCP/ATS/SIS definitions, the greatest susceptibility is seen in the very
young, specifically the neonate in which the incidence of sepsis is as high as 21% with mortality
rates ranging from 10% to 18% (Jones & Smith, 2009; Weil, 2006). The greatest risk factors
within this neonatal population are low birth weight, suboptimal pulmonary function at birth,
congenital abnormalities, obstetric complications such as placenta previa and abruption
placentae, and male sex (Caserta, 2006).

Conversely, persons 65 years of age and older are arguably becoming the greatest
population at risk of acquiring sepsis. They account for nearly half of the current ICU admissions
and 60% of all ICU days (Marik, 2006). They also account for approximately 60% of the
750,000 to 865,000 annual cases of sepsis (El Sohl et al. 2007). Furthermore, persons 85 and
older are the fastest growing age group (Marik, 2006). The incidence of sepsis in this age group
“is reported at 26.2 per 1000 population” (El Sohl et al., 2007, pg 272); the incidence will most
likely increase as the number of octogenarians is estimated to double as we approach the year 2030 (El Sohl et al. 2007).

It is postulated that advanced age is associated with increased immunosenescence, the term used to describe advanced age-related immune function decline. Aside from the immune function decline, there are also physical changes that occur in the elderly that increase the risk for sepsis, including alterations in skin integrity, inefficient urinary bladder emptying, immobility and obstructive processes such as neoplasm, uro- and cholestolithiasis; which further increase the risk of infection (Latto, 2008). Additionally, the study by Martin et al. (2006) demonstrated a higher incidence of gram negative sepsis in older adults 65 years of age and older when compared to adults younger than age 65. They also found that the highest incidence of sepsis was associated with respiratory infections (34.2%) when compared to other possible portals of entry; which are discussed in the next section. Considering the risk of nosocomial pneumonia due to the higher rate of resistant colonized oropharangeal gram-negative bacilli in institutionalized elders, which is confounded by a depressed cough and malnutrition (Girard et al., 2005), and that 88.3% of the 1.5 million institutionalized elders are 65 years and older, sepsis is a great concern in this population (Jones, Dwyer, Bercovitz & Strahan, 2009).

Aside from specific age groups, persons with compromised immunity, either secondary to illness in which the host defenses becomes weakened or chronic diseases that have negative effects on the immune system, are also categorically at risk for acquiring sepsis. Decreased immunity can be a result of immunologic diseases such as cancer, immunosuppressive therapy with steroids or chemotherapeutic drugs, alcohol or drug abuse; which indirectly lead to an inadequate support of the immune system (Sepsis, n. d.). Additional risk factors associated with
decreased immunity are diabetes mellitus, leukopenia, liver cirrhosis and chronic debilitating diseases. Part of the inpatient population of the hospital could also be considered within this population due to the use of invasive devices such as central venous catheters, Foley catheters, endotracheal tubes, and other drainage devices, as well as the use of steroids and antibiotics (Beers et al., 2006). It is also speculated that the number of cases of sepsis will rise as hospitals and other health-care facilities increase their utilization of invasive procedures and immunosuppressive therapies as a result of the improvements in healthcare technology (IHI, n.d.; Sepsis, n.d.).

Pathophysiology of Sepsis

*Initial Insult and Portals of Entry*

Infections that initiate the septic process can be a result of the introduction of either a bacterial, fungal, or viral pathogen. Bacterial pathogens remain the leading cause of infection, with gram-positive microbes becoming more prevalent than gram-negative microbes. Additionally, the rate of fungal infection has also been on the rise, which has been attributed to changes in host immunity (Balk, Ely, & Goyette, 2004) and changing dynamics of the healthcare system, with increased use of invasive procedures and immunosuppressive therapies (Beers et al., 2006).

For these pathogens to cause infection, they must elude host defense systems and enter the bloodstream. The most common portals of entry are the lungs, abdomen, urinary tract, soft tissue, and invasive intravenous catheters with occurrence rates of approximately 46%, 36%, 33%, 9%, and 5%, respectively (Munford & Suffredini, 2010). After host defenses are breached and a pathogen gains access to the systemic circulation, the host response to infection is no
longer contained at the original site of injury/entry. This initiates a systemic innate immune response, triggering a cascade of immunologic events that ultimately defines the clinical sequelae associated with sepsis and septic shock.

**Cellular Alterations in Sepsis**

Recent research into the pathogenesis of sepsis reveals that the activation of the immune system is initiated by pattern recognition receptors (PRRs) in response to the invading pathogen. Toll-like receptors (TLRs), one of the three families of PRRs, are located on the surface of immune cells and are activated by binding to “unique cell-wall molecules known as pathogen-associated molecular patterns (PAMPs)” (Cinel & Dellinger, 2007, pg 346). An example of this interaction is the binding of the TLR-4 receptor of the CD14 complex to the lipopolysaccharide (LPS) of invading gram-negative bacilli. It is the interaction of these PAMP-TLR complexes that initiates the inflammatory and pro-coagulation processes of sepsis (Cinel & Dellinger, 2007).

The innate immune system is responsible for the initial host response to invading pathogens. The release of pro-inflammatory mediators, mainly interleukin (IL) -1 and tumor necrosis factor-alpha (TNF-α), by macrophages and neutrophils induce fever and increase the thermogenic set point in the hypothalamus. These mediators also initiate the clotting cascade, which further promotes immune activity. Aside from their initial pyrogenic affect, IL-1 and TNF-α initiate up-regulation of tissue factor expression. There is also a subsequent down-regulation and destruction of thrombomodulin which results in hypercoagulation, increased cytotoxicity, induction of nitric oxide synthase, and neutrophil activation. Finally, there is endothelial cell adhesion molecule up-regulation that results in the activation of acute phase proteins and further cytokine production such as IL-6 and IL-8, interferon gamma and high...
The combined effect of the initial immune response is to increase inflammation and blood clotting, promote immune cell chemotaxis and function, and release cytotoxic agents that are harmful to the invading organisms (Balk et al., 2004). Current research also suggests that reactive nitrogen species (RNS) and reactive oxygen species (ROS), both of which are free radicals, play a major role in the development of sepsis. While the normal physiologic effects of both RNS and ROS play a beneficial role and aid in the defense against invading pathogens via regulation of reduction/oxidation reactions and intercellular signaling, they can become highly destructive to the host. When the magnitude of RNS and ROS exceeds the ability of antioxidant defenses, unchecked destruction of deoxyribonucleic acid and cell membranes occurs, leading to further cellular dysfunction (Cinel & Dellinger, 2007).

This pro-inflammatory response does not go unchallenged. Even as the pro-inflammatory response is proliferating, there are anti-inflammatory cytokines already at work. Among the many cytokines promoting anti-inflammatory effects, the majority of the work is done by IL-4 and IL-10. Interleukin-4’s main role is to decrease T-cell function as well as decrease the secretion of TNF-α, IL-1 and the immunoglobulin’s E and G; which trigger histamine release from mast cells and basophils and induce complement activation, respectively (Parslow, Stites, Imboden, Terr, STAT!Ref, & Teton Data Systems., 2001). Interleukin-10 works to inhibit inflammation and decrease coagulation as well as decrease monocyte and macrophage activity. Interleukin-6, while playing a major role in the proinflammatory response also has an inhibitory effect on the release of IL-1 and TNF-α by endotoxins. If the host’s immune response becomes
overwhelmed, an imbalance occurs and there is unopposed pro-inflammatory mediator activity manifesting a generalized systemic response defined by the SIRS criteria (Balk et al., 2004).

Endothelial cells (EC) play an integral role in the homeostasis of cell function. Of their many regulatory functions those specific to sepsis include their impact on both the pro- and anti-thrombotic pathways and their ability to either induce or protect against apoptosis, release substances that affect the vessel’s vasoactivity, and influence the expression of cell adhesion molecules (CAM). However, the massive release of cytokines during the inflammatory process cause a disruption of the homeostatic properties of EC. These cytokines promote a procoagulopathic state in the EC that promotes thrombi formation within the microvasculature. This process is exacerbated by the fact that the EC disruption also increases the expression of CAMs which increases the local number of active immune cells releasing these toxic cytokines. As the cytokine release increases there is worsening EC dysfunction with microvascular leakage and increased microvascular thrombi formation that results in cellular ischemia and further EC dysfunction (Balk et al., 2004).

The continued dysfunction and cellular ischemia results in a profound dysregulation of the ECs ability to maintain homeostatic vasoactivity. A major contributing chemical involved in the regulation of vascular tone is nitric oxide (NO). It is important to realize that NO is synthesized through three different pathways. The two pathways pertinent to this discussion are that of the endothelial nitric oxide synthase (eNOS), which provides for a low producing, transient response, and inducible nitric oxide synthase (iNOS), which generates a larger NO pool and has a sustained response that can last for days. Under normal conditions, the EC is able to maintain vascular tone, maintain blood viscosity though inhibition of platelet aggregation and regulate
CAM expression by the controlled release of NO via the eNOS pathway. As EC dysfunction continues, there is a decrease in the expression of eNOS with a subsequent decrease in NO production. Therefore, the lack of normal NO production, via the eNOS pathway, further exacerbates the EC dysfunction that was originally initiated by the increased cytokine release (Kirkeboen & Strand, 1999).

Unfortunately, even with the profound EC dysfunction and resulting decrease in NO production via the eNOS pathway there is persistent vasodilation that worsens the cellular ischemia. This continued hypoperfusion can be attributed to NO production via the iNOS pathway. In contrast to eNOS, iNOS takes substantially longer to express and is contained in the cytosol of many different cells including macrophages, leukocytes and vascular smooth muscle cells. Furthermore, iNOS expression is induced by cytokines, endotoxins such as LPS and the inflammatory response (Kirkeboen & Strand, 1999). These characteristics of iNOS expression can explain why the negative effects associated with EC dysfunction are not inhibited and why there is a continued profound hypoperfusion and associated ischemia at the microcellular and macrocellular levels.

Research suggests that mitochondrial dysfunction also contributes to end organ dysfunction. On the cellular level, hypoperfusion greatly impacts oxygen delivery and utilization. The decreased availability of oxygen to the mitochondria hampers many of its key roles within the cell, thus increasing overall cellular and organ dysfunction (Cinel & Dellinger, 2007).

While most of the discussion has focused on the innate immune system, it is important to note that sepsis also has a profound effect on the adaptive immune system; specifically the T and B cells. Sepsis induces an increased rate of apoptosis of these cells. Given the interdependence of
the adaptive and innate immune systems on each of their respective optimal function, this increased apoptosis contributes to the overall dysfunction of the immune system and proliferation of the pathogen (Cinel & Dellinger, 2007).

This discussion has presented many cellular alterations seen with inflammation and sepsis. The remainder of the pathological discussion will focus on the importance of these cellular alterations and how they are manifested into an observable systemic response.

Systemic Effects of Sepsis

Given that the definitions for sepsis occur on a continuum, so will the signs and symptoms a patient presents with. The following discussion will review the macroscopic changes seen in septic patients; beginning with inflammation and culminating with the cardiovascular derangements associated with septic shock.

After pathogenic invasion and infection, the initial host response is a normal inflammatory process, characterized by increased capillary permeability, and a localized increase in blood flow. These normal physiologic changes occur in an effort to improve the host immune response and stave off infection. When the host is unable to contain the microbe at the initial site of injury and the pathogen enters the bloodstream systemic signs and symptoms begin to occur such as fever, tachycardia, and tachypnea; these symptoms are reflected in the SIRS criteria (Balk et al., 2004; Steen, 2009). As previously discussed, these systemic manifestations of inflammation are due to the host’s inability to contain the infection, and the inflammatory response and cytokine release now occur on a systemic level. Thus, given the suspicion of an underlying infection and the presence of the SIRS criteria a diagnosis of sepsis can be made (Bone et al., 2009).
As the systemic infection worsens, the host immune response accelerates out of control in an attempt to contain the infection. Thus we see a progression from sepsis to septic shock. There is onset of systemic hypotension due to the effects of cytokine release, NO via iNOS production and EC dysfunction. At this point there may be an increase in tachypnea, which can progress to acute respiratory failure as a result of the lactic acidosis caused by decreased oxygen delivery and utilization. The microvascular clotting secondary to EC dysfunction contributes to this problem. Without intervention there is progression from tissue hypoxemia to end organ dysfunction and failure (Marik & Varon, 1998). Some clinical signs that may be present at this stage include altered mental status, oliguria due to renal dysfunction, a decrease in gastrointestinal motility, and a decrease in capillary refill time (Levy et al., 2003).

**Hemodynamic Derangements**

There are a number of cardiovascular and hemodynamic changes that occur. A prominent change is a decrease in systemic vascular resistance (SVR). In the case of septic shock, SVR is minimally responsive to aggressive fluid and vasopressor therapies due to the host’s inability to control the systemic immune response. Additionally, there is increased venous capacitance coupled with increased venous pooling, as well as a drop in both systolic and diastolic function of the heart. All of these factors, combined with the cellular response to sepsis, contribute to a decreased intravascular volume and represents the associated decrease in SVR. Furthermore, there is an inter-dependant and inverse relationship between SVR and cardiac output (CO). Systemic vascular resistance represents the pressure that must be overcome for the heart to eject blood into the systemic circulation. Therefore, if fluid resuscitation has been successful in stabilizing blood pressure, the severe reduction in SVR is accompanied by a rapid heart rate and
high CO suggesting a greater intravascular volume or hyperdynamic state. The high CO is relative and secondary to the reduced SVR. However, if there is insufficient fluid resuscitation then there is a low CO and greater relative intravascular volume depletion (Marik & Varon, 1998).

Regardless of a high CO or a low CO, the relative intravascular volume depletion seen in septic shock is worsened by the shifting of fluid and essential electrolytes into the intravascular space. As capillary leakage worsens with cytokine release and EC dysfunction, sodium as well as water is allowed to shift into the interstitial space. The movement of both water and sodium shifts the normal osmotic and electrical gradients in favor of the interstitial space, worsening the already deplete intravascular space. The end result of all these alterations is an exacerbation of the ongoing end organ dysfunction that eventually results in multi-system organ failure (Marik & Varon, 1998; Sherwood, L., 2004). The treatment of these alterations and the associated organ failure is the primary goal in the management of sepsis.

Evidence Based Guidelines for the Management of Sepsis

*Early Goal Directed Therapy*

Early goal-directed therapy (EGDT) was introduced in 2001 by Rivers and colleagues for the management of sepsis and septic shock. It is based on the hypothesis that early recognition and intervention can improve patient outcomes and reduce mortality associated with sepsis and septic shock (Rivers et al., 2001). The theory of using protocols for early intervention to improve patient outcomes is not a new concept and has been used successfully in the management of other disease states, such as myocardial infarction and stroke (Huang, Clermont, Dremsizov & Angus, 2007).
The concept of EGDT is based on interventions to improve oxygen delivery and demand through the manipulation of cardiac contractility, preload and afterload. The interventions used to improve oxygen delivery and demand includes fluid and blood resuscitation, SVR support via vasopressors, and inotropic agents to support CO. The initial work done by Rivers et al. found that grouping these interventions into an algorithm, commonly referred to as a bundle or protocol, yielded better outcomes than when they were instituted individually (Rivers et al., 2001).

The interventions within the algorithm include targeting specific values for central venous pressure, mean arterial pressure (MAP) and central venous oxygen saturation (ScvO₂). Initial resuscitation begins with the evaluation of CVP and requires the patient to be within a specific threshold to advance to the next stage of the bundle. If the initial CVP is not within the targeted parameter, administration of either colloids or crystalloids is recommended until the target value for the parameter is reached. This allows for adequate fluid resuscitation, which is required to achieve an appropriate response with vasoactive medications in the target values of the second resuscitation measure, which is MAP. The final resuscitation end point is ScvO₂ values and is achieved through the use of inotropic agents and red cell transfusion. These interventions encompass the original six-hour emergency department (ED) based resuscitation bundle developed by Rivers and colleagues (Rivers et al., 2001). A graphical representation can be found in Figure 2. It should be noted that while early antibiotic therapy was not a focus of the original work by Rivers and colleagues it has become a cornerstone therapy in the recommendations by the SSC (Dellinger et al., 2008).
Initiate targeted antibiotic therapy based on suspected/documented source

Insert CVC w/ ScvO2 and arterial line

CVP
Goal 8-12 mmHg

If CVP ≤ 8 mmHg
Infusion of crystalloids & colloids

MAP
Goal ≥ 65 and ≤ 90 mmHg

If MAP < 65 or > 90
Infusion of vasoactive agents

ScvO2
Goal ≥ 70%

If ScvO2 less than 70%
Infusion of PRBCs until Hct ≥ 30%. If ScvO2 still less than 70% then:

All Goals Achieved
Admit to Intensive Care Unit

Infusion of inotropic agents until ScvO2 ≥ 70%

Figure 2 Early Goal Directed Therapy

Since the initial implementation of EGDT by Rivers and colleagues was so successful, additional protocols based on this initial work have been developed. Additionally, the 2004 and 2008 SSC Guidelines advocate for this early six-hour ED-based bundled therapy. Many of the current bundles of EGDT have been expanded to 24-hour management bundles. The management bundles are designed to include the six-hour ED resuscitation bundle with continued management upon admission to the intensive care unit (ICU). These expanded management bundles allowed for additional therapies to be added to the management of septic shock. These additional therapies, which are discussed in the SSC guidelines, include recombinant human activated protein C, corticosteroids, and aggressive glucose control with continuous infusion insulin therapy (Dellinger et al., 2008).

Analysis of Outcomes Associated with Implementation of EGDT.

The initial work by Rivers and colleagues with EGDT for the management of sepsis resulted in a 16% decrease in overall mortality between the EGDT group and traditional therapy group (Rivers et al., 2001). Given the increasing incidence of sepsis and the sepsis-specific barriers to bundle implementation, a literature review was done to ascertain if the reductions in mortality reported by Rivers and colleagues in 2001 had been duplicated.

A literature review was done via Evidence Based Medicine Search, which utilizes the PubMed search engine, and The Cumulative Index of Nursing and Allied Health Literature Databases (CINAHL). A series of three searches was performed on each engine, all utilizing the keywords “sepsis” and “outcome” and then each of the three searches were done with the keywords of “bundle,” “protocol” and “implementation.” The only inclusion restrictions for this literature review was that the studies be done within the United States to correlate with the
literature reviews done to assess the barriers to implementation. This was done to limit any extraneous circumstances that could affect outcomes in studies outside the United States that may not be reproducible in other countries. It also eliminates any bias that a particular barrier would not apply due to the country in which the study occurred; such as limited access to state of the art medical devices or limited access to healthcare services. A total of eight studies were reviewed, including the 2001 study by Rivers and colleagues, and have been presented in the Appendix. While the study by Rivers and colleagues was included on the table presented in the Appendix, it was not included into the analysis of the remaining eight studies.

The findings from the eight studies reviewed are similar to the Rivers et al. 2001 study. The studies demonstrated a 16 to 28% reduction in 28 day mortality, a 9 to 25.6% reduction in in-hospital mortality, and the study by Puskarich, Marchick, Kline, Steuerwald and Jones (2009) demonstrated a 12% reduction in one year mortality rates. This decrease in mortality rates, associated with early intervention, is further supported by a meta-analysis done by Jones and colleagues. The investigators reported benefit of EGDT as evidenced by a mortality odds ratio of 0.5 (95% confidence interval 0.37-0.69) with early intervention and 1.16 (95% confidence interval 0.6-2.22) with late intervention (Jones et al., 2008).

While these results are encouraging, there is still limited research investigating long-term outcomes given the increasing prevalence of sepsis in persons 65 and older (El Sohl et al., 2007). One study was found that addressed one-year mortality rates and demonstrated a 12% reduction. The mean ages of the participants in the pre-and post implementation groups were 56 ± 16 years and 58 ± 18 years, respectively (Puskarich et al., 2009). While these results are the product of a
single study, they show promise and support long-term outcomes with early intervention. However, further research is required to validate these results.

Given that the studies in this review were evaluating EGDT and the bundling of therapies, a further analysis was done to assess the change in utilization of the interventions. The literature review revealed that when the individual interventions were bundled there was: earlier use of antibiotics (El Sohl et al. 2007; Jones, Focht, Horton & Kline, 2007; Micek et al., 2006; Shapiro et al. 2006), greater amounts of fluid resuscitation (Jones, Focht, et al., 2007; Micek et al., 2006; Shapiro et al. 2006; Trzeciak et al., 2006), increased, and earlier, packed-red blood cell transfusions (Kortgen, Niederprum & Bauer, 2006; Micek et al., 2006; Trzeciak et al., 2006), earlier intervention with inotropic agents, greater use of vasopressors when indicated (Jones, Focht, et al., 2007; Shapiro et al., 2006), shorter duration of vasopressor treatment and less need for vasopressor use when larger amounts of fluid resuscitation was used (El Sohl et al., 2007; Micek et al., 2006). The researchers demonstrated that the use of bundled interventions resulted in profound reductions in mortality.

Another key point that emerged during this review is the cost-effectiveness associated with the implementation of EGDT. While cost of implementation did not emerge from the literature review of sepsis specific barriers, it was listed among the general barriers to EBP implementation. This suggests that it may also affect the implementation of EGDT in the management and treatment of sepsis and septic shock, given that the cost effectiveness of a medical intervention may dictate whether it is implemented within an institution (Talmor et al., 2008).
In an effort to assess the cost-effectiveness of implementing a sepsis bundle, Talmor et al. (2008) used the Multiple Urgent Sepsis Therapies (MUST) protocol developed by Shapiro et al. (2006); a 24-hour resuscitation and management bundle. The implementation of the MUST protocol yielded a 9.1% reduction in mortality but did have a higher associated cost of implementation, estimated at approximately $8800 per patient, when compared to standard therapy. The study authors felt that this increase was attributed to the additional costs of an extended ICU length of stay (LOS). Overall, they were able to demonstrate incremental cost-effectiveness ratio’s of $11,264 per life year gained and $16,309 per quality-adjusted life years gained. While it is difficult to place a value on what an individual will pay for healthcare services, the currently accepted cost-effectiveness of healthcare interventions in the United States is approximately $50,000 to $100,000 per life year gained. When compared to these higher accepted values, Talmor et al. felt that implementation of EGDT was cost-effective and well below the costs of other healthcare interventions in ICUs (Talmor et al., 2008; Talmor, Shapiro, Greenberg, Stone & Neumann, 2006).

Huang and colleagues (2007) demonstrated similar cost-effectiveness as that found by Talmor and colleagues (2008) in their comparison of implementation costs between initiation in the ED, the ICU or via a team approach in either setting. The main difference between the two studies is that survivors in the Huang et al. study had lower ICU LOS and attributed their reduction of 22.9% in per patient hospital costs to protocol implementation; which resulted in lower ICU LOS and decreased resource allocation. They found that in comparing implementation costs of EGDT to a standard, non-EGDT intervention, can not only be potentially cost-effective, but provide cost-savings as well (Huang et al., 2007).
While the study done by Trzeciak et al. (2006) was primarily focused on the feasibility of EGDT implementation, a secondary goal of the study was to assess resource allocation and utilization. They did not notice any significant reduction in ICU, ED or total in-patient LOS, but implementation did significantly improve mortality rates – 25.6% reduction in hospital mortality, as well as an estimated $50,000 savings. This estimate in savings resulted from a comparison of the median facilities charges pre- and post- EGDT implementation of $135,199 and $82,233, respectively (Trzeciak et al., 2006). While these estimates seem much higher than those found in the two previous studies, it validates that there are associated cost savings with EGDT implementation; both in the life years saved as well as the cost-savings to the institution.

The Surviving Sepsis Campaign

Given the high rates of mortality associated with sepsis, a consortium of three international organizations was formed with the hopes that standardizing the treatment of sepsis, and ultimately improving its recognition, management, and improving overall outcomes. In 2002 the SCCM, the European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum (ISF) began the Surviving Sepsis Campaign (SSC or “the Campaign”) (Levy et al., 2010; Sepsis, n.d.). In an effort to reduce confusion and follow current research, this group based the campaign on the 2001 SCCM/ESICM/ACCP/ATS/SIS committee’s definitions. The Campaign consisted of three phases, with the goal of a 25% reduction in global mortality by 2009, with the following action plan (Rivers & Ahrens, 2008, p. S2):

- Build awareness of sepsis.
- Improve early and accurate diagnosis.
- Increase the use of appropriate treatments and interventions.
– Educate [health care professionals] about sepsis diagnosis, treatment, and management.
– Improve access to post-ICU care for sepsis patients.
– Develop global standards of care.

Phase 1 was focused on introducing the Campaign and its mortality reduction goals. Phase 2 was focused on developing a set of guidelines that clinicians could use in the recognition, management, and treatment of sepsis and septic shock. To accomplish phase 2, 11 international critical care and infectious disease organizations came together and developed guidelines in 2003. The “Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock,” was originally published in 2004 (Dellinger et al. 2004) and the current guidelines are the revised edition which was published in 2008 (Dellinger et al., 2008). The third and final phase consisted of an evaluation on the implementation of the guidelines (Dellinger & Vincent, 2005; Levy et al., 2010).

The 2008 SSC Guidelines are a set of recommendations for the management of sepsis and septic shock. Each of the recommendations underwent review and grading based on available literature and the expert opinion of committee members. The guidelines cover management of sepsis (diagnosis, source control and fluid and medication management), supportive therapies (ventilator management for lung injury, sedation and analgesia, glucose control, renal replacement therapy, and prophylaxis), and care of the pediatric septic patient (Dellinger et al., 2008).

After a three year international analysis of sepsis bundle implementation, from January 2005 until March 2008, the SSC was concluded. Any hospital was allowed to enter into the campaign. For entry into the database, patients were required to present with at least two of the
SIRS criteria, have either a confirmed or suspected site of infection and have at least one organ in failure. The main aims of the analysis were to assess bundle compliance as the primary outcome measure with the secondary outcome of assessing both overall hospital mortality and hospital and ICU LOS. Over the 2 year study period, data from the 165 hospitals that submitted patients into the data pool showed an unadjusted 6.2% reduction in hospital mortality with compliance rates increasing from 18.4% to 36.1%. Regretfully, the study did not report any results for the secondary aim of changes in hospital or ICU LOS. This study included the largest cohort of patients of any of the studies done on sepsis to date (Levy et al., 2010).

While the data collected for the SSC was on a voluntary basis, and there was a lack of a control group, results demonstrate a positive outcome with respect to the previously stated action plan from Phase 1 of the campaign (Levy et al., 2010). Since the Campaign can be considered an imperfect study given its lack of a control group, there still remains skeptics with regards to the efficacy of EGDT (Finfer, 2010). The barriers to implementation of EBP and that of EGDT for sepsis management will be discussed next.

Barriers to Implementation

Common Barriers of Protocol Implementation

Since disease management and healthcare practices have traditionally been based on usual practice, personal experience, colleagues’ anecdotes, and expert opinion, the implementation of evidence-based practice has struggled regardless of documented improved outcomes (Kingston, Krumberger & Peruzzi, 2000; Weinert & Mann, 2008). Barriers to implementation exist, not only in the practice and management of sepsis, but for many other protocols and bundle-based
EBP. A two-part literature review was done to uncover barriers to implementation with respect to any EBP and sepsis bundles.

The first part of the literature review was focused on barriers of implementation for any form of EBP. The focus was on studies looking at barriers rather than individual barriers of implementation for specific interventions or EBP. An English-language review was done using PubMed and CINAHL. The search terms used were barriers, implementation, protocols and bundles. To remain consistent with the literature review of EGDT implementation studies, only articles that applied to practice within the United States were included. The combination of terms through five separate searches returned 141 articles of which four were applicable; one of which was used in part two of this literature review because of its focus on sepsis protocols. Two articles were obtained via the reference lists of the three included articles while one additional article was found on Google scholar with similar search criteria. In total, six articles were included in this section of the review.

In review of the selected articles, a large number of barriers to implementation were found to exist (Table 3). Some common themes were a lack of knowledge, lack of desire to change current practice and a lack of agreement or mistrust in the efficacy of the guidelines. When discussing barriers, a majority of the time a generic term such as clinician or healthcare provider was used; with a majority of the focus on physicians and nurses. At the time of this literature review, there were no articles that discussed the behaviors of Advance Practice Nurses (APN) or offered a comparison between physicians and APNs with respect to barriers to implementation. A further analysis of these selected barriers follows.
### Table 3

**Perceived Barriers to Implementation of Evidence Based Practice**

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Article(s)</th>
<th>Article(s)</th>
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<tbody>
<tr>
<td>Lack of Knowledge</td>
<td>Berenholtz &amp; Pronovost, 2003</td>
<td>Kingston et al., 2000</td>
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<td></td>
<td>Cabana et al., 1999</td>
<td>Thomson et al., 2000</td>
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<td>Kalassian et al., 2002</td>
<td>Weinert &amp; Mann, 2008</td>
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<td>Kalassian et al., 2002</td>
<td>Thomson et al., 2000</td>
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<td></td>
<td>Kingston et al., 2000</td>
<td>Weinert &amp; Mann, 2008</td>
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<td></td>
<td>Kalassian et al., 2002</td>
<td>Cabana et al., 1999</td>
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<tr>
<td>Difficult to implement, burdensome, time consuming or</td>
<td>Berenholtz &amp; Pronovost, 2003</td>
<td>Kingston et al., 2000</td>
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<td></td>
<td>Kalassian et al., 2002</td>
<td>Weinert &amp; Mann, 2008</td>
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<tr>
<td>Lack of feedback on outcomes or insignificant effect</td>
<td>Berenholtz &amp; Pronovost, 2003</td>
<td>Cabana et al., 1999</td>
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<td></td>
<td>Kalassian et al., 2002</td>
<td>Weinert &amp; Mann, 2008</td>
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<tr>
<td>Lack of supporting research</td>
<td>Berenholtz &amp; Pronovost, 2003</td>
<td>Kingston et al., 2000</td>
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<td></td>
<td>Kalassian et al., 2002</td>
<td>Weinert &amp; Mann, 2008</td>
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<tr>
<td>Guidelines challenge practitioner autonomy/inhibit</td>
<td>Kingston et al., 2000</td>
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<td>analytical thought</td>
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<tr>
<td>Rate of knowledge generation surpasses dissemination</td>
<td>Kingston et al., 2000</td>
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<td>of newer data</td>
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<tr>
<td>Lack of resources/equipment to implement protocol</td>
<td>Weinert &amp; Mann, 2008</td>
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<tr>
<td>No perceived “imminent” need to institute protocol-</td>
<td>Weinert &amp; Mann, 2008</td>
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<td>based care</td>
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<tr>
<td>Perceived third party financial gains with protocol</td>
<td>Weinert &amp; Mann, 2008</td>
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<tr>
<td>implementation</td>
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<tr>
<td>Increased cost of implementation (system level barrier)</td>
<td>Kalassian et al., 2002</td>
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*Note: Priority listing based on frequency of occurrence within literature review.*
In all the articles some form of knowledge deficit was reported. In the review by Kingston et al, the knowledge deficit was related to a lack of awareness or familiarity of the protocols (2000). These two points seem to encompass the majority of the knowledge deficits found within the review of the additional articles. In support of these findings, Berenholtz and Pronovost (2003) found that a providers’ knowledge to the existence of a protocol or their lack of ability to implement a given protocol remains a significant barrier to the implementation of evidence-based practice. Some of the reasons why this lack of knowledge exists can be attributed to poor knowledge dissemination (Thomson, Angus & Scott, 2000) and a lack of training and education (Kalassian, Dremsizov & Angus, 2002). These deficits have manifested in providers as demonstrated by their lack of comfort (Kalassian et al., 2002) and familiarity of protocols (Cabana et al., 1999; Kingston, 2000). Weinert and Mann (2008) further identified a knowledge deficit as recognized by providers’ difficulty in selecting appropriate patients for protocol implementation.

The second major barrier found was the lack of desire of providers to change their current practice. Personal opinion and comfort in current practice seems to fuel the barrier; even in the light of evidence-based practice. In their review of clinicians’ practice with mechanically ventilated patients, Thompson, Angus and Scott (2000) found that instillation of normal saline into endotracheal tubes to assist thick secretion removal and the daily changing of ventilator circuits to prevent bacterial colonization still occurs in spite of demonstrated evidence against these practices. An additional behavior that fits into this barrier is practitioner experience. Implementation failure can also be a result of practitioners’ unwillingness to accept new
information based on their own anecdotal experiences (Weinert & Mann, 2008) or those of their peers (Kingston et al., 2000).

The third most mentioned barrier encompasses many different views of lack of agreement and mistrusts in protocols. In a survey conducted by Cabana et al. (1999), they found that some of the top reasons were: differences in interpretation of supporting evidence between providers, oversimplification of patient management and risk to the patient population with respect to patient comfort, costs, applicability to the selected population and overall risk versus benefit with respect to positive outcomes. Additionally, some of the respondents questioned the credibility of the guideline authors. Not only was the authors’ credibility questioned, so were the validity and reliability of their selected quality measures (Barenholtz & Pronovost, 2003). Furthermore, some clinicians see protocols as a measure of cost containment, benefiting hospitals and insurance companies rather than supporting patient outcomes. This belief that the protocol only favored financial outcomes and not patient outcomes worsened the perception and increased some clinician mistrust for protocol implementation (Kingston et al., 2000).

While the presented data appears to imply that providers’ attitudes, practices and beliefs are the reason barriers to implementation exists, it would do them an injustice not to discuss system barriers. Cost containment is the number one barrier from a systems approach. It encompasses barriers such as best practices for educating providers and eliminating confusion of protocols, monitoring costs of compliance to protocols, and cost of implementation of the protocols themselves (Kalassian et al., 2002).
Barriers to Implementation of Sepsis Protocols

A second literature review was done to assess if the barriers to the implementation of EBP protocols for the management of sepsis and septic shock were similar or different to those identified for other EBP protocol implementation. Again, an English-language search of CINAHL and Medline was done with the parent term of sepsis, and included the terms barrier, implementation, protocol, and bundle. The restriction to United States based studies was followed to keep with the same criteria for the previous literature reviews. Of the eight different combinations of search terms, “sepsis and bundle” and “sepsis and protocol,” did not yield any contributing articles. The best results were seen with a general term search of “sepsis protocol” utilizing Medline.

As with the EBP literature review, a majority of the clinicians questioned regarding barriers to implementation of EGDT were mainly physicians followed by registered nurses. At the time of this literature review there have not been any studies that focused on APN practice with respect to EGDT implementation.

Results of the second literature review demonstrated both similarities and differences with respect to implementation of sepsis EBP bundles. In this literature review, we see that lack of knowledge and lack of resources are the two dominating barriers. These two dominating factors were followed by clinician perception that the bundles can be too time-consuming, as well as to resource intensive; especially in the ED (Carlbom & Rubenfeld, 2007). The complete list of the perceived barriers can be seen in Table 4.
Table 4

*Perceived Barriers to Implementation of Early Goal Directed Therapy*

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Article(s)</th>
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<tr>
<td>Lack of Resources (includes staff, equipment &amp; space/beds)</td>
<td>Carlbom et al., 2007</td>
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<td>Huang et al., 2007</td>
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<td></td>
<td>Jones, Focht, et al., 2007</td>
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<td></td>
<td>Nguyen, et al., 2010</td>
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<td></td>
<td>Otero et al., 2006</td>
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<td></td>
<td>Rivers &amp; Ahrens, 2008</td>
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<td></td>
<td>Schorr, 2009</td>
</tr>
<tr>
<td>Lack of Knowledge (insufficient education, training or procedural</td>
<td>Carlbom et al., 2007</td>
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<td>competency)</td>
<td>Fong et al., 2007</td>
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<td>Huang et al., 2007</td>
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<td>Jones, Focht, et al., 2007</td>
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<td>Nguyen et al., 2009</td>
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<td></td>
<td>Otero et al., 2006</td>
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<tr>
<td></td>
<td>Rivers &amp; Ahrens, 2008</td>
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<tr>
<td>Protocols/Procedures too time consuming and/or resource intensive</td>
<td>Carlbom et al., 2007</td>
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<td>Fong et al., 2007</td>
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<td></td>
<td>Otero et al., 2006</td>
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<tr>
<td>Failed recognition of patients with sepsis</td>
<td>Carlbom et al., 2007</td>
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<td>Moore et al., 2009,</td>
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<td></td>
<td>Nguyen et al., 2010</td>
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<tr>
<td>Lack of agreement with the protocol/or perceived need for protocol use</td>
<td>Carlbom et al., 2007</td>
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<td></td>
<td>Jones, Focht, et al., 2007</td>
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<tr>
<td></td>
<td>Fong et al., 2007</td>
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<tr>
<td>Emergency Department overcrowding</td>
<td>Huang et al., 2007,</td>
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<td></td>
<td>Otero et al., 2006</td>
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<tr>
<td></td>
<td>Schorr, 2009</td>
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<tr>
<td>Poor Knowledge Transition (Bench to Bedside)</td>
<td>Carlbom et al., 2007</td>
</tr>
<tr>
<td>Resistance to Change (clinician and organization)</td>
<td>Huang et al., 2007</td>
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<td>Rivers &amp; Ahrens, 2008</td>
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*Note: Priority listing based on frequency of occurrence within literature review.*
In assessing the similarities between the barriers identified in the two literature reviews, the greatest commonality existed with a lack of knowledge. The knowledge deficit with the sepsis bundles seem to coincide with data reported by Kinston et al. (2000) of a lack of familiarity or awareness of the protocols. Given that on an annual basis over 600,000 patients initially present to the ED (Rivers, Coba & Whitmill, 2008), the lack of knowledge regarding the sepsis bundles and their implementation (Huang et al., 2007) is a problem requiring further study. Furthermore, a lack of training on central line placement and hemodynamic monitoring must be addressed, if it is to be included in EGDT bundles initiated in the ED, given the reported knowledge deficit associated with their use (Carl bom et al., 2007; Jones, Focht, et al., 2007).

While lack of resources did not rank high on the list of perceived barriers with the general implementation of EBP, it was one of the most commonly mentioned barriers with respect to sepsis bundles. This was most notably appreciated in the articles that discussed implementation in the ED, where overcrowding and long patient wait times are a frequent problem (Huang et al., 2007). Additionally, this overcrowding of the ED was cited as a barrier to implementation. Ortero et al. report that overcrowding occurs not only from the inflow of patients to the ED, but also from the lack of availability of inpatient beds, which further burdens the already strained ED resources (2006).

Of the remaining barriers, the inability to identify septic patients is of great concern as delayed diagnosis can result in poorer outcomes (Rivers et al., 2001). As previously mentioned, the study by Poeze et al. (2004) recognized there was a problem with identification given that the earlier signs of sepsis can resemble other disease processes. Aside from the similarity on presentation, it could be stipulated that the overcrowding of the ED and burden on its finite
resources may be a contributing factor. Furthermore, given that knowledge deficit was cited as the second highest barrier could this also be a contributing factor as to why these patients remain undiagnosed? While the reason for this barrier could not be determined, Moore et al. (2009) felt that the multiple tasks and priorities of the clinician, at any given time, was a major contributing factor in not identifying these patients.

It is estimated that the translation of knowledge into practice is causing delays in care in up to 50% of patients requiring acute medical care (Jones, Shapiro & Roshon, 2007). Given this estimate, it is worthwhile to mention that of the ten articles from the EGDT barriers literature review, both Carlbom and Rubenfeld (2007) and Jones, Focht, et al. (2007) mentioned poor knowledge transition as a barrier to implementation. Additionally, there remain a fair number of practitioners who fail to support the current evidence and bundles, regardless of the supporting outcomes. In the barrier assessment study done by Carlbom and Rubenfeld (2007) of ED physician directors and ED nursing directors, they found that 16% of the interviewed physicians disagreed with the EGDT protocols, whereas none of the nursing directors listed this as a barrier. Some of the rational provided by the physician directors was that they felt their physicians followed an “unwritten protocol” (pg. 2528) or that they provided adequate resuscitation without the need of a protocol. The fact that there are many different EGDT bundles currently being utilized further confounds the problems associated with acceptance of EGDT (Fong et al., 2007). Unfortunately, in the interviews done by Carlbom and Rubenfeld (2007), they also found that sepsis is also not well “advertised” and therefore not seen as an emergent illness when compared to other disease processes such as myocardial infarction.
Thus far, a presentation of the severity of illness related to sepsis has been discussed, as well as the need to come up with acceptable management options. The seminal work by Rivers and colleagues, as well as the SSC initiative, has led to demonstrated improvements in both the delivery of care as well as reductions in the mortality associated with bundle implementation. However, there still exist barriers to sepsis bundle implementation and acceptance within the healthcare practitioner community. The next chapter will provide a brief discussion of the initial EGDT presented by Rivers et al. and the results of the SSC, discuss the need for future study, and how the future of advanced practice nursing can impact the changes needed in the delivery of care with respect to the management of sepsis.
CHAPTER 3 – SUMMARY & RECOMMENDATIONS

Summary of the Benefits Associated with EGDT and the SSC Recommendations

A literature review done by Friedman et al. (1998) showed that mortality associated with sepsis had been relatively unchanged over the preceding 40 years. These authors looked at mortality rates from 1958 to 1997 and found that while the overall mortality rate due to sepsis was 49.7%, this slight improvement in mortality rates should not be seen as a true improvement in care. The authors felt that little research existed that demonstrated improved mortality rates from newer therapies.

In 2001, Rivers et al. presented a new concept in the management of sepsis known as EGDT. In their study they were able to demonstrate a 16% reduction in mortality. Since this seminal study, further research has been done in an attempt to duplicate these outcomes. The results of the literature review from this paper concur with that of Rivers et al. and demonstrated mortality reductions of 16 to 28% in 28 day mortality, 9 to 25.6% in in-hospital mortality, and one study demonstrating a 12% reduction in one year mortality.

In 2002 the SSC was assembled to help combat the continued high rates of mortality due to sepsis. The results of Phase 3 demonstrated an unadjusted 6.2% reduction in mortality; with continued improvement in mortality reduction that correlated with increasing bundle compliance. Therefore, the latest SSC recommendations support the concept of bundling interventions in the management of sepsis and septic shock (Levy et al., 2010).

Regardless of the studies demonstrating decreasing mortality associated with the implementation of EGDT and the recommendations by the SSC, there are still healthcare providers that disagree with this method of management. As this paper’s literature review
demonstrates, there are many different reasons why EGDT has not been widely welcomed and accepted as the primary treatment modality in managing patients with sepsis and septic shock. Given that EGDT was the first modality to have such a substantial reduction in mortality rates while still not receiving widespread acceptance leads us to our next point of how to increase compliance with bundled care.

The Need for Future Study

One of the aims of this paper was to assess the barriers in implementation of both EBP (Table 3) and EGDT (Table 4). There is little research with regards to interventions that assist in the transition of research into practice. Education has been suggested as a primary measure to overcome these issues, but requires other measures to be effective. It is suggested that well respected leaders are required to help champion the cause and promote the need for implementation and education (Kingston, Krumberger, & Peruzzi, 2000; Thomson, Angus & Scott, 2000).

Education is not the only obstacle to overcome. Some investigators are looking at cost analysis (Huang et al., 2007; Talmor et al., 2008) as a way to justify the use of EGDT from a system prospective. Given that the leading barrier observed through this paper’s literature review is that of a lack of resources (Table 4), it would be helpful to have future studies that can not only focus on overall cost savings but also look at how best to utilize already scarce resources. The current political climate surrounding the healthcare debate suggests that the results of such research would be invaluable.

While additional research focused on the barriers to implementation would provide a wealth of knowledge, it still would not answer the question of how to assist in the transition of
research into bedside practice. A strategic plan is required, one that would incorporate such research, to approach both institutions and healthcare practitioners alike. Such a plan would require ways to tackle resource utilization and education. The consideration for resource allocation needs to include physical resources such as healthcare providers, monitoring equipment, hospital space in which to treat the patient and the associated costs to provide these resources. Education needs to address the importance of early identification and treatment of sepsis, recognition of high risk populations, the pathophysiology of the disease process, proper use of the EGDT bundles and associated procedures such as ScvO₂ monitoring, and current research in the management of sepsis and septic shock.

Potential Impact of Advanced Practice Nursing on EGDT Implementation Outcomes

As discussed in Chapter 1 of this report, the ACNP must have an understanding of the pathophysiology of sepsis as well as the current EBP with respect to sepsis management in order to provide appropriate and high quality care to patients with sepsis and septic shock. As advanced practice nursing pushes forward towards the educational utility of doctoral preparation to the Doctor of Nursing Practice (DNP) there exist further opportunities for the ACNP. Given the poor progression of research into practice many patients are not receiving the latest EBP to optimize their outcomes (Weinert & Mann, 2008). Based on the American Association of Colleges of Nursing’s Position Statement and The Essentials of Doctoral Education for Advanced Nursing Practice (DNP Essentials), the DNP is focused on implementing and evaluating current and emerging research (AACN Position, 2004; AACN Essentials, 2006). In addition to implementation and evaluation, the expectation of the DNP is to further benchmark research with respect to clinical practice. To prepare the DNP for these roles the educational
preparation and scholarly study includes didactic studies regarding dissemination of research and best practice strategies in an effort to improve care or care processes (AACN, 2004). Given the AACNs Position Statement and the DNP Essentials, the DNP can play an integral role in improving the outcomes of patients with sepsis and septic shock.
APPENDIX

Analysis of Outcomes Associated with Implementation of Early Goal Directed Therapy
Appendix: Analysis of Outcomes Associated with Implementation of Early Goal Directed Therapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Purpose</th>
<th>Sample</th>
<th>Concepts</th>
<th>Protocol Design</th>
<th>Measurement</th>
<th>Results</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Sohl, et al. (2008)</td>
<td>To evaluate if a sepsis protocol could improve management and decrease mortality in older people with septic shock</td>
<td>Control (n=87) Study group (n=87) Location: Tertiary Care Facility</td>
<td>EGDT protocol, plus, insulin gtt, SDS &amp; hAPC.</td>
<td>Observational prospective study with historical control group</td>
<td>APACHE II score</td>
<td>16% reduction in 28-day mortality rate vs control group, less time on VP, increased appropriate EABX use</td>
<td>Use of a protocol incorporates new therapeutic strategies and improves standard of care</td>
</tr>
<tr>
<td>Jones, Focht, et al. (2007)</td>
<td>To evaluate the clinical effectiveness of EGDT as standard protocol</td>
<td>Before group (n=79) After group (n=77) Location: Urban, 800 bed teaching hospital</td>
<td>EGDT protocol</td>
<td>Prospective interventional study</td>
<td>SOFA and MEDS scores</td>
<td>9% reduction of In-hospital mortality rates. Significant decrease in initiation time of EABX, increase use of VP and larger fluid resuscitation volumes.</td>
<td>EGDT is clinically effective as a standard of care for sepsis management</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Intervention</td>
<td>Control</td>
<td>Comparison</td>
<td>Results</td>
<td>Conclusion</td>
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<td>Kortgen, et al. (2006)</td>
<td>To assess if a sepsis protocol can improve the standard of care in septic shock</td>
<td>Retrospective cohort study</td>
<td>EGDT protocol, plus insulin gtt, SDS &amp; hAPC.</td>
<td>Control (n=30) Study (n=30) Location: 10-bed ICU of a university hospital</td>
<td>SOFA score and comparison of lab work and interventions</td>
<td>Study group showed a 26% reduction in 28-day mortality, increased early utilization of PRBC &amp; inotropes</td>
<td>EGDT improves time to intervention and is effective as a standard of care</td>
</tr>
<tr>
<td>Micek, et al. (2006)</td>
<td>To determine if a standardized order set focused on EABX and fluid resuscitation could improve management of septic shock in the ED</td>
<td>Prospective before and after implementation study design</td>
<td>EGDT protocol</td>
<td>Before (n=60) After (n=60) Location: ED of a 1200-bed urban academic medical center</td>
<td>APACHE II score</td>
<td>18.3% reduction in 28-day mortality rate vs control group. Earlier initiation of EABX, greater fluid resuscitation, increased PRBC transfusion and less need for VP seen in EGDT group.</td>
<td>Indicated that EGDT would provide for earlier EABX and goal oriented fluid resuscitation in septic patients</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Objective</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Outcome Measures</td>
<td>Result</td>
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<tr>
<td>Nguyen, et al. (2007)</td>
<td>To examine outcome implications with initiation of a sepsis bundle to completion in the ED</td>
<td>n=330 Location: 47-bed academic tertiary ED w/ 65,000 visits/yr</td>
<td>EGDT protocol, plus, insulin gtt, SDS &amp; hAPC.</td>
<td>APACHE II score, ER &amp; hospital LOS</td>
<td>Bundle completion demonstrated a 18.7% reduction in In-Hospital mortality compared with patients in incomplete bundle group</td>
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<tr>
<td>Puskarich, et al. (2009)</td>
<td>To evaluate 1-yr mortality outcomes after implementation of EGDT in the ED</td>
<td>Pre (n=79), Post (n=206) Location: ED of 800-bed urban teaching hospital w/ 100,000+ visits/yr</td>
<td>EGDT protocol</td>
<td>SOFA, organizational wide medical records and the SSDI</td>
<td>12% decrease in mortality at one year after initial treatment in EGDT group.</td>
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</table>

Implementation of a sepsis bundle in the ED was feasible and demonstrated a decrease in patient mortality.
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Purpose</th>
<th>Group Information</th>
<th>Study Characteristics</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers, et al. (2001)</td>
<td>To evaluate the efficacy of EGDT in the ED</td>
<td>EGDT (n=130), Standard Therapy (n=133) Location: 850-bed academic medical center</td>
<td>3 year prospective, randomized study</td>
<td>APACHE II, SAPS II, MODS</td>
<td>EGDT use yielded an overall inpatient mortality reduction of 16% as well as lower lactate base deficit levels, higher pH and ScvO2 values and shorter hospital LOS. EGDT has many short &amp; long term benefits with respect to morbidity and mortality associated with end-organ dysfunction and cardiovascular collapse.</td>
</tr>
<tr>
<td>Shapiro, et al. (2006)</td>
<td>To describe the effectiveness of a comprehensive sepsis protocol and its associated outcomes when compared to similar historical patient profiles for septic shock</td>
<td>Historic control (n=51), Septic Study group: (n=79) Location: ED &amp; ICU of 490-bed urban, teaching hospital w/ approx 46,000 ED visits/yr</td>
<td>Prospective, interventional cohort study with historical comparison</td>
<td>APACHE II and MEDS scores</td>
<td>When compared to historical data, protocol patients received more fluids, more VP, earlier &amp; more appropriate EABX use plus a 9.1% reduction in 28-day mortality. Demonstrated that EGDT in the ED is feasible and showed more aggressive treatment of sepsis.</td>
</tr>
<tr>
<td>Trzeciak, et al (2006)</td>
<td>To determine if reliable EGDT end points could be achieved in real world practice and compare EGDT to historical pre-EGDT for resource analysis.</td>
<td>Pre-EGDT (n=16) EGDT (n=22) Location: ED of an urban, academic medical center w/ 48,000 visits/yr</td>
<td>EGDT protocol, plus, insulin gtt, SDS &amp; hAPC.</td>
<td>Retrospective cohort study</td>
<td>APACHE II and MEDS scores</td>
</tr>
</tbody>
</table>

APACHE II – Acute Physiology and Chronic Health Evaluation; CVP – Central Venous Pressure; EABX – Empirical Antibiotic; EGDT – Early goal directed therapy (includes CVP, ScvO2, and arterial line monitoring. Administration of fluids, PRBCs, EABX, Vasopressors & Inotropes); hAPC – human activated protein C; P MEDS – Mortality in Emergency Department Sepsis; MODS – Multiple Organ Dysfunction Score; QALY – quality-adjusted life expectancy; RBCs – Packed red blood cells; ScvO2 – Central venous oxygen saturation; SAPS II – Simplified Acute Physiology Score II; SDS – Stress dose steroids; SOFA – Sequential Organ Failure Assessment score; SSDI – Social Security Death Index; VP – vasopressors (includes: dopamine & norepinephrine)
REFERENCES


