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Review Article

Sepsis: Epidemiology, Pathophysiology, Classification, Biomarkers and Management

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Abstract

Every physician has been trained early in their careers on how to recognize and manage sepsis. Although sepsis has been one of the most researched ailments in medicine, it also remains one of the deadliest diseases in the face of recent advances. In this current article, we review the diagnostic and management criteria for Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis, septic shock, and Multi Organ Dysfunction Syndrome (MODS). We then examine the implications of the "surviving sepsis" campaign as well as explore the philosophy of Early Goal Directed Therapy (EGDT) and its role in the modern day management of sepsis. In addition, we sought to highlight potential new biomarkers and current available therapies in sepsis.

Introduction

Sepsis continues to be a critical problem in regards to morbidity and mortality in the clinical setting. Ranked as a top cause of morbidity and mortality, sepsis can be the result of a number of pathologies and can greatly complicate the care of patients in and out of the hospital setting [1]. Despite advances in the treatment of sepsis, 28 day in hospital mortality rates still range from 15 to 45% [2].

Epidemiology

Inpatient expenses related to the treatment of sepsis infections are on the rise with annual costs estimated to be in excess of $20 billion [3]. This places sepsis as one of the most costly burdens on the health care system. Sepsis rates are on the rise (Table 1) [4]. The elderly population is at a greater risk for the development of sepsis and sepsis related complications. As a result this population makes up a significant amount of the total number of sepsis patients [1]. Similar to the general population, the elderly also have experienced dramatic increases in sepsis hospitalizations as shown in table 2 [3]. A more recent study has shown that sepsis likely contributed between 30 and 50% of mortality and had a large impact on healthcare costs in the US between 2010 and 2012 [4]. With the growing burden of sepsis on the healthcare system, there is a strong drive to develop more efficient mechanisms to detect and manage sepsis patients.

	2000 Hospitalization Rate (per 10,000)	2008 Hospitalization Rate (per 10,000)
Sepsis as a Primary Dx	11.6	24
Sepsis as any Dx	22.1	37.7

Table 1: Sepsis Hospitalization Trends 2000-2008: Hospitalizations for sepsis have more than doubled from 2000 to 2008 demonstrating the increasing burden of sepsis on the US healthcare system [5].

Age Group	2003 Sepsis Hospitalization Rate (per 10,000)	2007 Sepsis Hospitalization Rate (per 10,000)
18-64	8.3	13
65-84	64.7	99.8
85+	177.1	219.7

Table 2: Age specific Sepsis Hospitalization Rates in USA. Hospitalization rates increased dramatically in the 5 year span. The rates increased dramatically in all age groups over the short 5 year period [3].

Mortality

Mortality rates for sepsis in recent years have ranged from 18 to 40%. The identification of the correct microbial strain and initiation of the proper antibiotic treatment could significantly affect the incidence of mortality in these patients. The highest incidences of mortality are associated with sepsis arising from nosocomial infections by organisms such as methicillin resistant and sensitive *staphylococcus* species, *pseudomonas* and both *candida* and non-candidal fungal infections. Polymicrobial infections are also associated with increased mortality rates [6].

Biomarkers currently used in the identification and management of septic patients can provide insight into the response to therapy and prognosis. Although using biomarkers to rule in sepsis have not been identified with strong support, Lactate level measurements have been the greatest focus in recent years and have been shown to correlate well with mortality [7]. Lactate levels greater than 4.0 mmol/L have been shown to correlate with an increase in mortality. In addition, this correlation is even stronger if there is a coexistence of elevated lactate with observed hypotension [7]. Other sources have found correlations with 48 hour resolution of elevated lactate levels and sepsis prognosis [8].

Pathophysiology

Sepsis and disease severity depend on various factors, ranging from the properties of the invading pathogen to the current immune status of the host [9]. Severe sepsis can develop following local infection and can stem from a number of sites including the abdomen, skin, soft tissue, urinary tract, lungs and is usually due to a primary

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bloodstream infection. The pathophysiology of sepsis can be initiated by the host response to a pathogen insult, particularly the outer membrane component of gram negative organisms such as Lipid A component of LPS (Lipopolysaccharide), also known as endotoxin or components of gram positive organisms such as lipoteichoic acid and peptidoglycan. Sepsis can also be triggered by viral, fungal, and parasitic components. The innate immune system is the first line of defense, which includes the monocytes and dendritic cells, which recognize various pathogens based on their pathogen recognition receptors. Through interaction of pathogenic components via signaling of Toll like Receptors on monocytes, the transcription factor NF-κB is activated and important pro-inflammatory cytokines are generated such as TNF-alpha and IL-1. These inflammatory cytokines then lead to production of mediators such as prostaglandins, leukotrienes, platelet-activating factor and phospholipase A2 which leads to increased vascular permeability and vasodilation. TNF-alpha and IL-1 also lead to the production of adhesion molecules such as E and P selectin that eventually leads to neutrophil recruitment and further endothelial injury through neutrophil components, particularly nitric oxide, which is a potent vasodilator which leads to septic shock [9]. Activated neutrophils also promote clearance of the bacteria. While beneficial, this process in turn can do more damage by contributing to more inflammation via respiratory burst, cytotoxicity, degranulation, vascular permeability and organ injury. Many sources of literature cite this massive trigger of inflammation as the "cytokine storm" [9].

The adaptive immune system as well, plays an active role. The adaptive immune systems also attempt to attenuate the harmful effects of the proinflammatory state. For example, regulatory T cells produce various mediators such as IL-10 and TGF-beta to reduce inflammation. The complement cascade is also activated by microbial components leading to production of anaphylatoxins, chemotactic fragments and opsonins all of which lead to a proinflammatory state. Microbial components can also activate coagulation by activating factor XII of the coagulation cascade or indirectly through changing the endothelium function. The continual pro-inflammatory state also activates immunosuppressive mechanisms, leading to oscillations between hyper-inflammatory and immunosuppressive states during the clinical course of the disease. Some mechanisms propose that there is a shift towards a Th2 (anti-inflammatory) response from a Th1 (pro-inflammatory) response [9]. With complement activation and coagulation cascade, micro-vascular blood flow may be compromised which will result in local ischemia, ultimately leading to global tissue hypoxia and insufficient oxygen delivery to meet oxygen demands of the body. This can lead to metabolic acidosis, hypotension, impaired myocardial contractility, multi-organ dysfunction syndrome and death [9].

Classification

Sepsis is defined as a systemic illness where bacteria enter a normally sterile place in the body. The definition takes evidence of Systemic Inflammatory Response Syndrome (SIRS) and incorporates it with suspicion of a microbial origin. When this criteria includes acute organ dysfunction of at least one organ, this becomes severe sepsis. Further dysfunction accompanied with refractory hypotension or hypoperfusion, while fluid resuscitation is being attempted, classifies as septic shock. Finally, when organ dysfunction progresses to the point where the patient is unable to maintain homeostasis without intervention it's called Multi-organ Dysfunction Syndrome (MODS). The creation of a staging system for sepsis has allowed for a goal driven therapy to improve out comes [6].

Classification	Parameter
Systemic Inflammatory Response Syndrome	Core body temperature >38°C or <36°C HR ≥90 bpm Respirations ≥20/min (or $PaCO_2$ <32 mmHg) WBC ≥12,000/µl or≤4000/µl or >10% immature forms
Sepsis	At least two SIRS criteria caused by known or suspected infection
Severe Sepsis	Sepsis with acute organ dysfunction
Septic Shock	Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation
Multi-Organ Dysfunction Syndrome	The presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Table 3: Classification of Sepsis [6].

Sepsis can be caused by a variety of pathogens. The classification of sepsis is typically described as either community-acquired or nosocomial in origin. They can be bacterial or fungal in etiology. In addition, infections are not mutually exclusive and polymicrobial infections can and do occur. Within the bacterial causes of severe sepsis, there is some controversy as to the primary causative agents. Different epidemiological studies have found both gram negative and gram positive organisms to be of the greatest cause. Historically the gram negative organisms were of the greatest prevalence, however; data has shown an increase in incidence of gram positive infections in recent years [6]. Of the gram positive organisms, *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common organisms found. Of the gram negative organisms, *Escherichia coli*, *Klebsiella* and *Pseudomonas aeruginosa* are found in the greatest numbers [10].

Risk factors

There are many risk factors associated with sepsis and severe sepsis. Most of these factors relate to a patient's ability to fight infection and the probability that acute organ failure develops in response to infection. In general, greater risk is associated with male gender, black race, age, and chronic health conditions. Age arguably might be the most important risk factor to consider. As patients age the incidence of severe sepsis increases disproportionately to the point where patients over the age of 65 years old account for more than 50% of severe sepsis cases [11]. On the other end of the age spectrum neonates have a high incidence of severe sepsis and septic shock as well compared to the total population. Estimates attribute over 36% of all neonatal deaths to cases of neonatal sepsis worldwide [6]. Immature immune systems and early exposure to various microbial agents, including those stemming from maternal sources, have made neonatal sepsis potentially dangerous complication in this population with case fatality rates ranging from 7% to 25% [12]. Group B *Streptococcal*, and to a lesser degree *E coli*, infections appear to comprise the majority of cases with early onset. In later onset cases the causative agent is more likely to be coagulase negative *Staphylococcus* species and *Staphylococcus aureus* are the most common causative agents [12]. More than half of patients who present with severe sepsis have at least one chronic health condition concurrently. The most common chronic conditions are immune insufficiency (primary or secondary), cancer, chronic obstructive pulmonary disease, chronic renal disease, diabetes, and chronic liver disease. Situational risk factors include immunosuppressive drugs, malnutrition, prosthetic devices, and residence in long term care facilities. Of note, environmental factors such as cold weather coincide with greater occurrence of severe sepsis and increased mortality despite a similar severity of illness [11].

Diagnosis

Sepsis is a disease that is classified by a wide variety of clinical presentations. It is important to mention the proper screening with a goal of early detection for better patient outcomes. Early detection is key for better patient outcomes which have been accomplished by the creation of screening tools. Patients who are already admitted for severe infections should be screened routinely for sepsis using the diagnostic criteria mentioned. It is imperative that these patients are diagnosed early to allow for the early implementation of therapy. There has been Sepsis screening tools developed for ICU care that assist in this process. It should be of the utmost importance to reduce the time to diagnosis in all patients.

If there is clinical suspicion of an infection being the etiology of septic shock, there should be no delay in the prompt treatment with antimicrobials. Two or more blood cultures should be drawn once there is access to initiate treatment and more directed antimicrobial therapy for later on. Blood cultures should be drawn from peripheral sites, not from existing IV access and care should be taken that they are filled properly (>10ml of blood). If cultures prove to be positive from vascular access site, earlier than peripheral blood site this would suggest vascular access as the point of entry [6]. Ideally, Cultures of IV and catheters should also be taken with peripheral blood smears to help determine the source of infection [6].

Gram stain is also a useful tool, most commonly for respiratory tract specimens, with positive cultures for lower respiratory tract infections. Simultaneously, tests such as Rapid influenza antigen should be used during proper seasons for additional information. As with most diagnoses a focused history is a crucial source of information. Use of the 1,3 Beta, D-glucan assay, mannan and anti mannan assay has proven useful for the early diagnosis of systemic fungal infections of which the usual culprit is invasive candidiasis [6]. However, it should be noted that false positives are possible with colonization alone, and more study is needed. Thorough analysis of specimens is required. It has been shown that a delay in treatment has adverse outcome for patients with sepsis. Therefore, it is imperative that clinical suspicion should be taken seriously as patients fall into parameters associated with sepsis. The clues involved can be put into 5 different categories. Each of these categories should be considered when an infection is documented or suspected [6].

a. General variables

- Fever > 38 degrees C
- Hypothermia core temperature <36 degrees C
- Heart rate >90/min or more than two SD above the normal value range
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance > 20 mL/kg over/24hr
- Hyperglycemia plasma glucose >140 mg/dL or 7.7 mmol/L in the absence of diabetes

b. Inflammatory variables

- Leukocytosis WBC >12,000/microL
- leukopenia WBC count < 4000/uL
- Normal WBC count with greater than 10% immature forms (shift to left)
- Plasma C reactive protein more than 2 above normal value
- Plasma procalcitonin more than 2 above normal value

c. Hemodynamic

- Arterial hypotension Systolic Blood Pressure <90 mmHg, Mean Arterial Pressure <70 mmHg or a decrease in systolic blood pressure >40 mmHg in adults or less than two SD below normal for age.
- Organ dysfunction
- Arterial hypoxemia Pao_2/Fio_2 <300
- Acute Oliguria urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation
- Creatinine increase > 0.5 mg/dL or 44.2 micromol/L
- Coagulation abnormalities INR >1.5 or aPTT > 60s
- Thrombocytopenia platelet count < 100,000/microL
- Hyperbilirubinemia plasma total bilirubin > 4 mg/dL or 70 micromol/L

d. Tissue perfusion variables

- Hyperlactatemia >1mmol/L
- Decreased capillary refill or mottling

In some institutions these variables and also specifically the criteria as associated with the classification of sepsis are used in electronic medical records to trigger alerts and help with a timely diagnosis.

Biomarkers

Biomarkers, although important in many other clinical diagnoses, have not been thoroughly studied and if used have the greatest efficacy in ruling out sepsis diagnoses. Further studies must be made into biomarkers for the early detection of sepsis as well as their use prognostically. Two biomarkers have been studied in adults for the early diagnosis of sepsis with a sensitivity and specificity greater than 90% with a high positive predictive value. Group II phospholipase 2 (PLA2-II) has been studied in brief with a high sensitivity and specificity for bacteremia in adults within 24 hours of admission. Although there was a high sensitivity and specificity for early diagnosis with CD64 it was unable to distinguish local from systemic infection and bacterial from viral infections [13]. It seems the CD64 also know as Fc gamma RI which is displayed on neutrophils and monocytes, is more indicative of febrile infection.

As stated before, currently biomarkers have the greatest use clinically as means to rule out sepsis. Both CD64 and PLA-II are research phase markers that may or may not show clinical application in the future [13]. Although there is data supporting the use of PCT to differentiate infectious from noninfectious forms of SIRS, it should be noted, as with most diagnoses, that biomarkers should only aid in the diagnosis. All of the aforementioned biomarkers were studied in only culture positive sepsis, further showing a weakness in the diagnostic value due to the possibility of culture negative sepsis [14].

C-Reactive Protein

C-Reactive Protein (CRP) is an acute phase reactant and biomarker used for tracking inflammation in response to infection and tissue injury. Although it is possible to aid in the diagnosis of severe sepsis, CRP is also elevated in the following conditions: late pregnancy, active inflammation, bacterial infections, viral infections, and elderly age. The specificity of CRP testing in severe sepsis and the use of CRP to track sepsis progression has never been proven. However, since severe sepsis is an inflammatory state, it follows that it should be used to create a picture in septic patients [15].

Procalcitonin

Procalcitonin has been intensely studied in recent years and has had some positive feedback clinically. Studies have been done showing PCT to be of use in tracking the severity of sepsis in general (without any guidelines as of yet) with evidence of peak PCT levels immediately before death due to MODS [16-18]. Although it should be said that, most studies that showed this result were associated with severe sepsis secondary to burn injury. The most recent edition of Surviving Sepsis Campaign states that using PCT to differentiate acute inflammation from severe sepsis has not been demonstrated to be useful as of yet [6]. There is also a role for PCT to help guide antimicrobial therapy which has not been demonstrated to reduce mortality or morbidity but does offer less exposure of ICU patients to antimicrobials. Low PCT levels, along with other clinical factors, may aid in early discontinuation of antimicrobials [6,19]. Procalcitonin (PCT) level is currently the most reliable biomarkers due to its strong negative predictive value

Management

The “Surviving Sepsis Campaign” is an international coalition of experts that developed categorical recommendations and suggestions on the resuscitation of patients experiencing septic shock. From this was created two “bundles” of care; one to be instituted within 3 hours and another within 6 hours.

The first bundle is to be achieved within 3 hours of the identification of severe sepsis. At initiation of the protocol, baseline lactate levels should be obtained for later comparison and to get a sense of the patient’s current perfusion status. Blood cultures should also be drawn at this time for a more directed antimicrobial treatment plan, if possible, once resulted. To start treating the underlying cause broad spectrum antimicrobials will lay the framework for long term treatment. Finally, if the patient has a lactate greater than or equal to 4 mmol/L or hypotension at the time of presentation, they should be administered 30 ml/kg of crystalloid solution, where the time of presentation is defined as the time of triage in the emergency department or the earliest record of all the elements consistent with severe sepsis or septic shock [6].

The second phase, to be completed within 6 hours, is to place a monitor and possibly adjust the previously started treatment. To start, fluid responsiveness should be assessed by methods noted in the hemodynamic resuscitation section. Patients, who cannot maintain a Mean Arterial Pressure (MAP) greater than 65 mmHg after an attempt at hemodynamic resuscitation, should be treated with vasopressors to prevent further hypotension. If hypotension persists (MAP less than 65 mm Hg) or if the baseline level of the drawn lactate was greater than 4 mmol/L volume status and tissue perfusion should be assessed again and the findings documented in accordance with table 1 diagnostic criteria. After this the lactate should be measured again if the initial lactate was elevated [6].

Antimicrobials

Studies have shown that delay in the administration of intravenous antibiotics increased mortality. Antimicrobial therapy should be administered within the first hour of the recognition of severe sepsis or septic shock. This initial treatment should consist of one or more drugs that have activity against all likely pathogens (bacterial and/or viral) and at concentrations that have the ability to penetrate the tissues of the supposed point of entry or source of the sepsis. Anti fungals should only be used in those at risk of invasive fungal species. Treatment should also be directed based off of the setting in which the infection was developed and medical history [6].

Reassessment of the patient after 6 hours should focus on monitoring and supporting organ function, treatment of complications, and careful de-escalation of care. This is in conjunction with the monitoring of lactate and other pertinent biomarkers to guide therapy. Empiric broad spectrum antibiotic therapy should not be continued for more than 3-5 days to prevent the emergence of resistant microbial species, minimize drug toxicity, and to reduce costs. Once cultures have returned their susceptibility profiles, targeted therapy should be initiated. The duration of therapy should normally not take more than 7-10 days barring a slow clinical response to therapy, immunodeficiency and infection with *S. aureus*, fungal infections and some viral infections [10].

Corticosteroid therapy

The use of corticosteroids in the treatment of septic patients has proven to be quite controversial. The presence of glucocorticoids whether endogenous or exogenous is essential for control of the host inflammatory response. Almost unanimously, studies have shown high dose steroid regimen increases morbidity and mortality in patients with severe sepsis and in septic shock [20]. The question remaining is the efficacy of low dose treatment on sepsis outcomes. Low dose corticosteroid therapy is generally considered to be below 300 mg/day [20]. Mortality rate has been shown to improve with the use of low dose corticosteroid therapy [21]. A number of studies showed 28 day mortality rates ranging from 10% to 30% below those of control groups [20]. In addition multiple studies have found that low dose corticosteroid treatment of septic patients significantly improved hemodynamic status through an increase in blood pressure and decreased duration of pressor usage [20,22]. Other studies have found no efficacy toward corticosteroid administration or found increased mortality [23,24]. Those observed to have the most benefit from therapy also were found to have adrenal insufficiency. The Surviving Sepsis campaign recommends use of corticosteroid therapy only in the presence of septic shock and only following a failure of blood pressure response to pressor and fluid therapies. The Surviving Sepsis campaign recommends hydrocortisone administration at 200 mg/day in these patients and gradual tapering off once pressor therapy is no longer needed to maintain adequate blood pressure [6].

Hyperglycemia management

Septic shock has a tendency to raise blood glucose level. This effect is also present in various other illness and/or stressors and is collectively called “stress hyperglycemia”. It was thought initially that intensive management of glucose was the best route to take and the surviving sepsis guidelines in 2008 recommended that glucose be kept between 80-100 mg/dl [25]. However, it was noted by many medical institutions that this aggressive insulin management was leading to marked hypoglycemia [26]. Researchers began to question whether the hypoglycemia induced by aggressive insulin therapy was more detrimental than maintaining the patient at a more normal physiologic glucose level. This is where the NICE-SUGAR study comes to our attention. This trial is the largest randomized control trial to date and looks at 2 populations of patients: those with aggressive insulin management and those with conventional management [27]. The investigators found that ICU patients in the aggressive insulin therapy group showed an increased in 90 day mortality in comparison to their conventional counterparts [27]. The investigators consequently recommended that keeping glucose levels below 180 mg/dl lowered mortality in comparison to tight management of the patient at a glucose level of 81 to 108 mg/dl [27]. Surviving sepsis was consequently updated and its 2012 publication recommended keeping patients below 180 mg/dl but no lower limit was set except for the avoidance of hypoglycemia and the avoidance of wide swings in glucose levels [6].

Hemodynamic resuscitation

In the landmark 2001 paper by Rivers et al., the authors recognize several factors which are paramount to EGDT. These factors include physical findings, vital signs, central venous pressure, and urinary output [28]. Having these values are key to early detection and the start of rapid management to decrease mortality, but individually they do little to address and determine the level of global tissue hypoxia. A far better indicator of the patient's hypoxia and condition is the observation and response of cardiac output to medical intervention [29]. By manipulating preload, arfterload, and contractility, the medical team can better perfuse vital organs and prevent the degradation of sepsis to septic shock and/or MODS [30]. The gold standard for such intervention revolves around fluid resuscitation and pressor therapy. Given the pharmacologic side effects of vasopressors, fluid therapy is usually considered first line. However, if a patient is not fluid responsive, then pressors are preferred as further fluid infusions will present its own set of issues such as edema, pleural effusions, high blood pressure, and acute renal failure [31]. Following surviving sepsis guidelines, Nor-epinephrine should be considered first line at a dose of 0.01-3 mcg/kg/min IV infusion [6]. Adjunctive therapy can include the use of 0.03 units/minute of Vasopressin to help improve perfusion. Epinephrine is considered a second line vasopressor but can also be added to Nor-epinephrine therapy, if Nor-epinephrine alone cannot maintain a MAP of 65 mm Hg [6].

Fluid responsiveness is a large part of sepsis management and currently also one of the most researched topics in regards to reducing mortality. Patients are considered "fluid responsive" if fluid resuscitation alone improves the blood pressure [32]. After adequate replacement of intravascular volume, further infusion of fluid can adversely affect their hemodynamics. With fluid therapy used initially to improve tissue perfusion, it becomes imperative to identify whether patients are fluid responsive or unresponsive. Those that are not responsive to fluid therapy would then be candidates for pressor therapy. The desired effect of fluid therapy revolves around improving stroke volume and cardiac output. By increasing pre-load, there can be more filling of the ventricles and consequently greater contractility via the Frank-Starling mechanism. Patients are defined as "Fluid-responsive" and "Non-responsive" depending on the degree of hemodynamic improvement in response to initial fluid bolus defined as an increase in stroke volume of 10-15% [32]. It has been proposed that heart-lung interactions can also be used to determine fluid responsiveness and in 2000 Michard, Pinsky, and Teboul published the caval index to be used on patients as a marker of fluid responsiveness [22]. The Caval Index is defined as;

Caval Index = (IVC-exp diameter - IVC insp diameter) / (IVC-exp diameter) * 100

A normal IVC diameter is 1.5-2.5 cm and if there is a less than 50% collapse of the IVC, this suggests fluid overload [33]. This type of patient would not benefit from fluid therapy and in fact can be harmed from hyperperfusion. By using ultrasonography to measure IVC diameter, we can determine a patient's response to fluids without invasive methods such as swan ganz catheter or CVC.

Another non-invasive tool used to assess fluid responsiveness is the passive leg raise test. Due to the large compliance of the venous system, the human body has a tendency to pool extra blood volume in the legs where the effects of gravity and compliance are felt the most. Physicians can utilize this physiological occurrence to guide their route of management. The technique is best done with the patient flat on their back with their feet propped up to 45 degrees. 30-90 seconds in this position is enough to replicate the effects of a 250cc bolus of fluids as blood is being returned to the effective circulation and causing an increase in preload [34]. There are many methods to measure the effects of this pseudo-bolus including stroke volume index via a cardiac output monitor or through a surrogate measurement such as pulse pressure via arterial line. Another way to measure this response to fluids would be to utilize the same ultrasonography techniques as used to measure the IVC and calculate the caval index as mentioned above.

Each method has a set of advantages and disadvantages and it is up to the physician to determine which method is most likely to aid in their initial management of the patient. Invasive measures are best reserved for patients who already have a CVC and/or are being managed in the ICU under constant monitoring. Patients however who present acutely to the ED stand little benefit in going directly to invasive cardiac monitoring to assess fluid response. The major caveat here of course would be if the physician in unable to attain peripheral IV access and a CVC needs to be placed to gain circulatory access. However, in most cases, patients arriving to the ED would be better candidates for non-invasive measurements of fluid responsiveness via ultrasonography of the IVC before and after an initial trial fluid bolus or a passive leg raise test.

Recent Advances

EGDT in clinical trials

Trials in recent years have looked to assess the effect of early goal directed therapies and standardized treatment bundles on sepsis outcomes. These various studies have yielded mixed results. The Surviving Sepsis Campaign treatment bundles were largely based off of the 2001 Rivers paper [28]. This study was one of many that found improved health outcomes with the implementation of a set protocol aimed at achieving a few key goals. These studies, demonstrating efficacy of treatment bundles and early goal directed therapies, all showed their value through observed reductions in mortality [24,35-37].

Other studies, primarily the United States' ProCESS, United Kingdom's ProMISe and the Austrailasian ARISE studies, failed to find significant reductions in mortality following implementation of EGDT modalities and treatment bundles. These studies, following study protocols based on the 2001 Rivers paper, found potential benefits of EGDT not directly associated with mortality. Not surprisingly these three studies found that following implementation of set protocols patients were more likely to receive therapies included in the treatment bundles [38-40]. The ProCESS trial found an increase in length of hospital stay while the ProMISe trial found patients were more likely to receive higher levels care for sepsis [38,39]. The ARISE Trial interestingly found a decrease in the average time for sepsis patients spent in the Emergency Room offering another potential benefit [40]. The mix in results of these studies makes it difficult to definitively determine the benefits of EGDT and bundle set treatment modalities in sepsis. At this point it appears more research is needed to make definitive conclusions.

NICOM

As sepsis therapy progresses, there is a push to continue to find non-invasive alternatives rather than relying on highly invasive methods of management such as PICC lines, CVC, and/or Swan Ganz catheter. Of specific interest to recent advances is the Non-invasive Cardiac Output Monitoring (NICOM) machine. The NICOM machine works by measuring the phase shift between superior thoracic leads and inferior abdominal leads. The machine elicits an alternating current in the upper thoracic leads where it then travels down through the vasculature and tissue to the lower leads, a process called "bioreactance" [41]. The phase shift is dependent largely on the volume of fluid in the large thoracic vasculature. By measuring the phase shift of the electrical impulses the machine calculates the stroke volume. The electrodes of the machine are also capable of monitoring heart rate. By taking the heart rate and stroke volume into the account, the machine provides real time feedback about cardiac output.

There is still more research required to determine whether this method of monitoring is as reliable as inspiratory IVC diameter ultrasonography as well as the IVC diameter measurements before and after passive leg raise test. A few preliminary research studies have shown promise in the sensitivity of NICOM related to other currently accepted, yet invasive therapies [42-45]. Until further trials can prove the efficacy of this device in contrast to time tested gold standards like those mentioned previously, the NICOM machine will need to remain in a trial only phase before it can be rolled out to hospitals worldwide. There is certainly no harm in using it on patients as an added modality while still maintaining other methods to assess fluid response. This is exactly what is occurring at medical centers currently conducting clinical trials with the NICOM, but at this point the device should not be used as an end all for patient cardiac output monitoring.

Yet, the machine holds much promise in the future management of sepsis patients, particularly in the realm of fluid management. While using Ultrasonography requires testing before and after a therapy is given (i.e., fluid bolus), NICOM can be left on the patient and give medical teams real time feedback on the patient's cardiac output and fluid responsiveness. To the patient's advantage particularly is the ability of this device to do all this in a non-invasive method and without cumbersome devices and modalities such as repeated ultrasounds and there is also reduced risk of nosocomial infections.

Conclusion

Severe sepsis and septic shock while heavily researched; still impose a huge burden on patients and the healthcare system. While mortality rates have dropped in recent years, overall hospitalizations for sepsis have increased. Studies have been split on whether the establishment of protocols, like the EGDT series introduced in the Rivers 2001 paper and those outlined by the Surviving Sepsis Campaign, should be credited with the observed drop in mortality. More research is needed to fully understand the efficacy of treatment bundles and identify the important components that should be included in them. We the authors feel the greatest potential in future management of sepsis patients is in the development of new biomarkers and improved methods in the assessment of fluid responsiveness. Additionally, there should be a continued push towards mastering non-invasive monitoring techniques and matching the sensitivity and accuracy of these techniques to those of current more invasive practices.

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