SEPSIS

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ABSTRACT

Sepsis, which may be defined as the systemic illness caused by the suspected invasion of normally sterile parts of the body by microbial organisms, is a major healthcare problem, ranking among the top ten causes of death. This article reviews the evidence behind the general and specific measures in the management of sepsis, based on the Surviving Sepsis Campaign Guidelines.

WHAT IS SEPSIS, AND WHY IS IT IMPORTANT?

Sepsis is a major healthcare problem, affecting millions of people worldwide, occurring at all ages and in different patient groups, from healthy individuals in the community to ill hospitalized patients.[1] Sepsis may be defined as the systemic illness caused by the suspected invasion of normally sterile parts of the body by microbial organisms. Sepsis leading to acute organ dysfunction or tissue hypoperfusion is defined as severe sepsis, and severe sepsis resulting in hypotension not reversed with fluid resuscitation is septic shock. This definition of sepsis specifically distinguishes it from the similar clinical picture of systemic inflammatory response syndrome (SIRS) that arises without an underlying infection but secondary to, for example, pancreatitis and anaphylaxis. The similarity of these syndromes is due to the same underlying deleterious host response resulting in the same pathophysiological pathways and release of cytokines and other inflammatory peptides.[2]

THE PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF SEPSIS: FROM PATHOGEN ENTRY TO SEPTIC SHOCK

The first barrier to infection is the continuous membrane of the skin, and the internal mucous membranes of the respiratory, genitourinary and gastrointestinal tract. Loss of integrity may be obvious as in the case of severe burns, or an anastomotic leak following surgery, but it may also be subtle as in the case of an insect bite. In a hospital environment such loss of integrity is often due to the use of intravenous cannulas, catheters, drains and other devices. Once an organism has gained entry, it prompts a regional immune response mediated by various cellular, cytokine and other inflammatory peptide-controlled mechanisms. The release of these effector peptides such as TNF-α, interleukins and prostaglandins results in a cascade of regional, followed by a systemic, inflammatory response. Clinically, this inflammatory response results in the clinical features and presentation of sepsis. The features of this response are very variable as it is a combination of organism virulence and burden, together with the host response factors.

The diagnostic criteria for sepsis is therefore documented as suspected infection together with some of the following features which characterize a systemic inflammatory response.

A. GENERAL VARIABLES:

- Fever >38°C
- Hypothermia <36°C
- Heart rate >90/min
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance
- Hyperglycemia i.e. >7.7 mmol/L in the absence of pre-existing diabetes

B. INFLAMMATORY VARIABLES:

- Leukocytosis i.e. WBC count >12,000 μL^{-1}
- Leukopenia i.e. WBC count <4000 μL^{-1}
- Normal WBC count with greater than 10% immature forms
- Raised C-reactive protein
- Raised procalcitonin

C. TISSUE HYPOPERFUSION

- Raised lactate
- Decreased capillary refill time i.e. <2seconds

These criteria are based on the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Levy et al specifically point that rather than giving a specific number of criteria that must be reached, "The use of the word "some" reflects the clinical reality at the bedside, rather than an arbitrary list invented for the purpose of clinical trial entry criteria". Sepsis accompanied by evidence of acute organ dysfunction or tissue hypoperfusion is defined as severe sepsis. Examples of acute organ dysfunction include decreased urine output despite adequate fluid resuscitation, coagulopathy, raised bilirubin and acute lung injury. Sepsis accompanied by a systolic blood pressure (SBP) < 90 mm Hg, SBP decrease > 40mm Hg or the need for vasopressors in the absence of other causes of hypotension and despite adequate fluid resuscitation is known as septic shock.[3-5]

MANAGING SEPSIS – GENERAL & SPECIFIC MEASURES

A. GENERAL MEASURES

i. Fluids & monitoring

Initial resuscitation should be protocolized, quantitative, and started as soon as tissue hypoperfusion is recognized. Whether crystalloids or colloids are better for resuscitation remains a much debated, but unresolved question. The "Surviving Sepsis Campaign – Guidelines" (SSCG) recommend the use of crystalloids based on the absence of any clear benefit from colloids together with the expense associated with colloid solutions. Human albuminis now rarely used following a Cochrane meta-analysis showing an excess mortality associated with its use.[6]

During the first six hours of resuscitation the goals of therapy should be:

- Central Venous Pressure (CVP) 8-12mm Hg
- Mean Arterial Pressure (MAP) >65 mm Hg
- Urine output >0.5ml/kg/hr
- Superior vena cava oxygenation saturation 70%

These end points are based on a randomized single-centre

study, which showed improved survival with targeting of these goals.[7] This "early goal-directed therapy" strategy also showed improved survival in a multicentre trial in China.[8] New methods for measuring the adequacy of fluid resuscitation such as esophageal Doppler, pulse contour analysis, and stroke volume variation in ventilated patients are used in some centers, but clinical endpoints remain useful: blood pressure, heart rate, lactate, base deficit, urine output, mixed venous saturation and central venous pressure. Pulmonary artery catheters have been shown to result in neither harm, nor benefit.[9]

ii. **Vasopressors**

Vasopressor therapy is required to maintain tissue perfusion and should be started even when hypovolemia has not yet been resolved. SSCG recommend that vasopressor therapy should target a mean arterial pressure (MAP) of 65mmHg; they also recommend norepinephrine as the first choice of vasopressor, with epinephrine being added if an additional agent is required. The use of Dopamine as a vasopressor was previously widespread, however modern advice is that Dopamine should be used only in highly selected patients i.e. those with a relative bradycardia and at low risk fortachyarrhythmias.[4,10]

iii. **Inotropes**

A trial of dobutamine infusion should be carried out in the presence of (a) myocardial dysfunction and low cardiac output, (b) tissue hypoperfusion despite adequate intravascular volume and arterial pressures. However large prospective trials have shown that using dobutamine to increase oxygen delivery to supranormal levels does not result in any benefit.[11]

iv. **Blood products**

In 1999 the results of the "Transfusion Requirements in Critical Care Trial" published in the New England Journal of Medicine, suggested that there is no increased mortality with a hemoglobin level of 7 to 9 g/dL, when compared with 10 to 12 g/dL. Thus, in the absence of specific circumstances such as ischemic heart disease or acute hemorrhage, the target range for red cell transfusion should be 7 to 9g/dL.[12]

B. SPECIFIC MEASURES

i. **Antimicrobials and diagnosis**

Although antimicrobial therapy should never be delayed to obtain samples, obtaining samples prior to therapy is essential in obtaining useful cultures. Two or more blood cultures should be taken. If present at least one culture should be taken through each lumen of indwelling devices. If cultures from a vascular device are positive much earlier than the peripheral cultures this suggests that the device may be the source of infection.[13] Prompt, appropriate antimicrobial therapy is the backbone of the management of sepsis. A treatment delay in hypotensive patients increases mortality by 7.6% per hour.[14] Even without shock there is a lot of evidence supporting giving early antibiotics.[15] The SSCG identify starting intravenous antimicrobials within the first hour of recognition of or severe sepsis or septic shock as one of the goals of therapy.

ii. **Corticosteroids**

A French multicenter randomized controlled trial showed that hydrocortisone therapy in vasopressor-unresponsive septic shock resulted in significant shock reversal and reduction in mortality in patients with relative adrenal insufficiency.[16] The CORTICUS trial enrolled patients without sustained shock, and in these patients hydrocortisone did not result in decreased mortality.[17] On this basis the SSCG recommend intravenous hydrocortisone only in patients where fluid and vasopressor therapy fail to restore hemodynamic stability. However there is no empirical evidence to guide the cessation and duration of therapy.

PREVENTION AND EARLY RECOGNITION OF SEPSIS

Sepsis-related mortality has decreased and outcomes of sepsis have also improved with earlier identification. Reducing the time of diagnosis appears to be the key step in preventing the progression of sepsis. Screening for sepsis in Intensive Care Unit environments has been shown to decrease mortality.[18] Careful infection control practices should be instituted and include hand washing, catheter care, barrier precautions, airway management, head-of-bed elevation and subglottic suctioning.[19] The role of selective oral decontamination (SOD) and selective digestive decontamination (SDD) remain somewhat controversial. Overall, the data relating to the latter techniques show a slight reduction in ventilator-associated pneumonia, but no change to overall mortality.[20]

FUTURE THERAPIES IN SEPSIS

The high mortality in sepsis means that new therapies are always being looked at, as even small decreases in mortality will result in many lives saved. Statins are well-recognized to have anti-inflammatory properties and in murine models they have shown to prolong survival, however as yet this has not undergone any human RCT.[21] Human immunoglobulin has also been investigated as a therapy in sepsis. The concept is that anti-endotoxin antibody cross reactivity will reduce the inflammatory response. However one meta-analysis concluded that, as yet, there is insufficient evidence for intravenous immunoglobulin to be used outside trials.[22] Other inflammatory response mediators include the high-mobility group box protein 1 (HMGB-1) protein that acts as a transcriptional cofactor and has a potent inflammatory cascade effect in sepsis. In rodent models, antagonism of HMGB-1 improves mortality. Ethyl pyruvate has been shown to suppress these abnormal biochemical markers including HMGB-1, and may therefore have a role in the treatment of sepsis. Ethyl pyruvate has undergone phase 2 clinical trials in patients undergoing cardiopulmonary bypass, but no results have yet been published.[23]

CONCLUSION

While exciting new therapies are being developed, sepsis care bundles, such as those introduced by the Surviving Sepsis Campaign Guidelines, remind us that the key to reducing mortality remains good clinical judgment with early diagnosis, taking appropriate samples preceding broad-spectrum antibiotic treatment tailored by local protocols, and aggressive circulatory support.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET