A Fresh look

at

The Septic Response In Critically Ill I.C.U. Patients.

Essay

Submitted for partial fulfilment
of the master degree in Anaesthesia

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بسم الله الرحمن الرحيم

سبحانك

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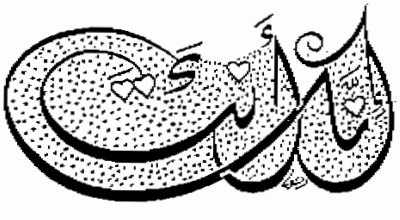

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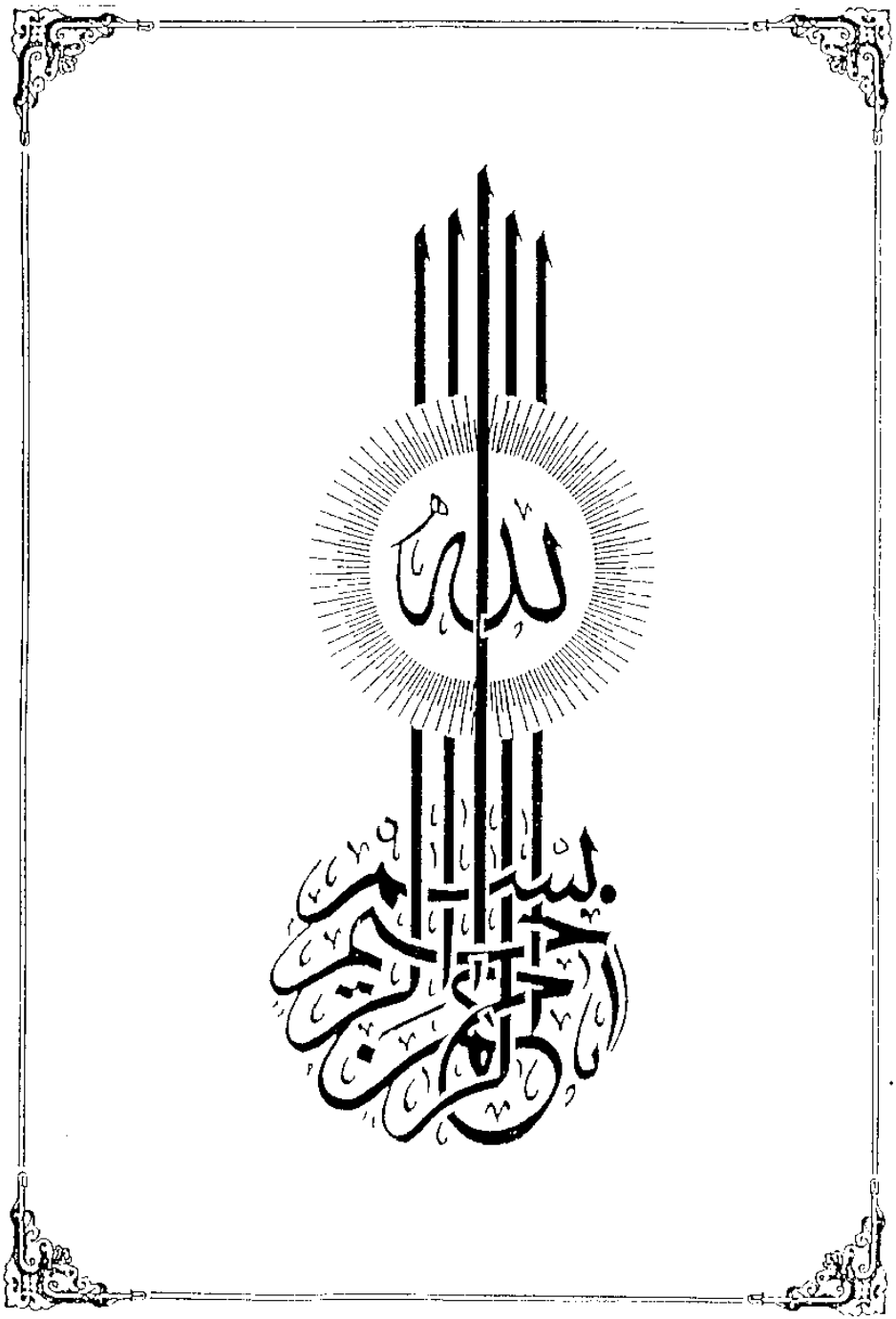

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Index

List of tables

List of Figures

Table 1 . The clinical "sepsis" Syndromes
(Cruzen & Evans 1996)

Sepsis : The systemic response to infection .
Includes two or more of the following :
- Temperature >38° C or <36° C
- Heart rate > 90/min
- Respiratory rate > 20/min or Pa CO_2 < 4.3 kilo pascal (k Pa)
- White cell count > 12 000/mm^3 <4000/mm^3 or >10% band (immature) forms .

Sepsis Syndrome : Sepsis with evidence of altered organ perfusion.
Altered organ perfusion includes one or more of the following :
- $PaO_2/FiO_2 \leq 280$ (without other cardio-pulmonary disease)
- Elevated lactate level (> upper limit of normal for the lab)
- Oliguria <0.5 ml/kg body weight.

Systemic Inflammatory Response Syndrome (SIRS) : The response to a variety of severe clinical insults (not necessary infective) which is indistinguishable from sepsis .
Septic shock : sepsis with hypotension (sustained decrease in systolic blood pressure <90 mm Hg, or drop>40mm Hg , for at least 1h) despite adequate fluid resuscitation in the presence of perfusion abnormalities that may include , but are not limited to lactic acidosis , oliguria or an acute alteration in mental status . Patients who are on inotropic or vaso-pressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

A number of non-infections clinical processes including pancreatitis , multiple trauma, autoimmune disorders , and drug reactions can elicit the clinical manifestations of sepsis- the so - called systemic inflammatory response syndrome (SIRS) - in the absence of infection . Infection is a common cause of SIRS in the ICU, however because of inherent difficulties in the diagnosis of common intensive care unit (ICU) acquired infections such as pneumonia , it has been difficult to ascertain how frequently SIRS in the critically ill patient results from

non-infectious causes . It is clear , however , that conventional clinical criteria for sepsis are neither sensitive nor specific for the presence of infection in the critically ill . (Marshall 1994).

Criteria for sepsis syndrome , originally developed for a multicenter trial to assess the efficacy of steroids in the management of severe sepsis and septic shock, have been widely employed in studies of mediator antagonism (Table 2) . (Bone et al (1987) . Bacteremia , the classical manifestation of overwhelming sepsis, was present in only 45% of placebo-treated patients meeting these criteria in the original study of Bone and associates (Bone et al (1989a)) ; the distribution of other infections, or the percentage of patients with documented infection , was not described . Sepsis syndrome criteria are clearly not diagnostic of bacteremic infection , although there is an increasing consensus that bacteremia per se is not a necessary feature of the clinical process to be recognized as sepsis (Marshall & Sweeney (1990)) . The criteria , however , are also not specific for the presence of infection or for the activation of a particular pattern of cytokine release .(Marshall 1994) .

Table 2 . Diagnostic criteria for sepsis syndrome (Bone et al (1987))

Clinical evidence of infection
Rectal temperature > 38.3° C or < 35.6° C
Tachycardia (> 90 beats/min.)
Tachypnea (20 breaths/min. while breathing spontaneously) At least one of the following manifestations of inadequate organ function/perfusion :
- Alteration in mental status
- Hypoxemia (PaO_2> 72 torr. breathing room air)(overt pulmonary disease not direct cause of hypoxemia)
- Elevated plasma lactate
- Oliguria (urine output < 30 ml or 0.5 ml/kg for at least 1 h)

The systemic septic response is an adaptive process that serves to optimize systemic homeostasis to eradicate an invading pathogen, and limit its systemic spread . However that process is not without biologic cost , and it is now apparent that a significant , though undefined , component of the injury resulting from invasive infection is attributable to the host response , rather than to the direct effects of the invading pathogen , Moreover it is apparent from animal studies that removing the stimulus that initiated the systemic response does not necessarily result in the immediate cessation of the response (Demling et al (1986)) . Improvements in diagnostic imaging techniques and systemic antibiotic therapy have resulted in the earlier diagnosis and definitive management of occult foci of infection , without convincingly altering the course of overwhelming infection . Thus it can be Hypothesized that the septic response itself may represent the unsolved problem in the critically ill patient. (Marshall 1994).

Marshall and Sweeney 1990 studied the differential roles of invasive infection and the host response in critically ill surgical patients. Infections were diagnosed by microbiologic, operative , radiographic criteria alone without reference to the accompanying clinical response . That response was characterized by means of a sepsis score that evaluated abnormalities in five cardinal manifestations of a septic response-fever, leukocytosis , alterations in mental status , insulin resistance , and the presence of a hyperdynamic circulatory response (Table 3) . The worst value for each of these components was scored daily and summed to produce a sepsis score (maximum score of 15) that reflected the magnitude of the clinical response , independent of the process that evoked it. Patients with infection had a significantly higher mortality than patients without infection (20.7 vs. 3.3% , $p< 0.001$) . Similarly , mortality rose linearly as the maximum sepsis score rose ; no patient with a score of 0 died , whereas the mortality for patients with a score ≥ 10 was 100% .

Table 3. The sepsis score (Marshall & Sweeney (1990)

variable	0	1	2	3
Maximum daily temperature (C°)	<38.0	38.0-38.9	39.0-39.9	40.0–
White blood cell count (ML)	<12000	12-18000	18-25000	25000+
Decrease in Glasgow Coma Score (from baseline)[a]	0	1	2	3+
Insulin requirements (units/h)[b]	0	1-2	3	4+
Cardiac output (L/min.)or	<7.0	7.0-8.9	9.0-10.9	11.0–
Systemic vascular resistance (dynes.sec.cm-5)	>800	600-800	400-600	<400

a. The baseline Glasgow Coma Score is that obtained 24 to 48 h following ICU admission (after recovery from anesthesia) : decreasing levels of consciousness are calculated relative to this score .
b. Units of exogenous insulin required to achieve a serum glucose level of 10 m.M/L or lower (200 mg/ml).

Missing data are recorded as 0 : the Sepsis Score is the sum of the worst scores for each variable on a particular day (maximum 15) .

To determine the relative importance of infection and response , Marshall & Sweeney 1990 first compared maximum sepsis scores in survivors and non-survivors with infection . As shown in figure 1 , non-survivors had significantly higher maximum scores than survivors , both for infections present at the time of ICU admission , and for those occurring over the course of the ICU stay . However , when infection-related variables were analyzed in those patients manifesting a septic response , no variable could be identified that discriminated survivors , except the magnitude of the host response. When non-survivors were analyzed, no difference in maximum sepsis score , or in sepsis score on the day of death could be detected when patients dying with infection were compared to those who had no evidence of infection (Fig. 2). These studies suggested that the host response , independent of its cause , has a

significant impact on outcome , and that for the patient in whom infection has been controlled , the major threat to survival is the ongoing response . (Marshall & Sweeney (1990))

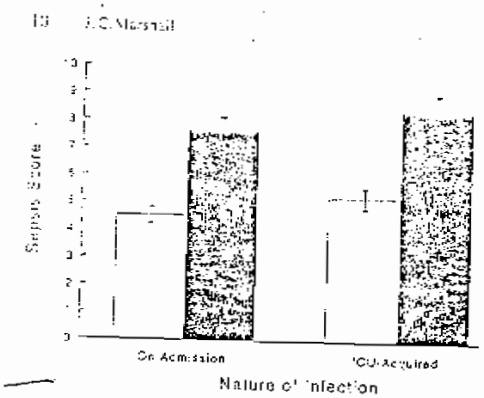

Fig.1 Maximum sepsis scores (mean ± standard error of the mean) In ICU survivors (clear bars) and non-survivors (solid bars) admitted with infection (n=56) or developing ICU-acquired infection (n=51), Non-survivors had significantly higher scores than survivors ($p<0.001$. Student's t test) , indicating a more pronounced host response . (From (Marshall & Sweeney (1990))

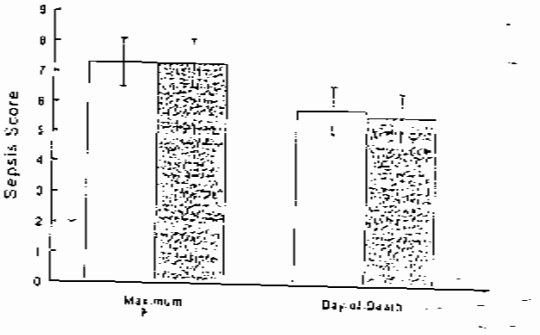

Fig. 2 Non-surviving patients were characterized as having no infection (clear bars) or uncontrolled infection defined as autopsy evidence or documented infection within one week of death (hatched bars) Neither maximum sepsis scores nor scores on the day of death differed between patients dying with or without infection , indicating that the clinical response correlates poorly with the presence of infection . Data are mean ± standard error (From (Marshall & Sweeney (1990))

The pathophysilogy of septic shock involves an extremely complex interplay between tissue hypoxia and the host's immune response . In the first few days following the onset of illness , death from septic shock is frequently caused by refractory hypotension with a low systemic vascular resistance . The-most frequent cause of death in later stages of the disease is sepsis-induced multiple organ failure (MOF), typical examples being pulmonary failure from adult (or acute) respiratory

distress syndrome (ARDS)and renal failure. Therefore , even in those patients for whom resuscitation succeeds in restoring blood pressure , septic shock may still present the risk of subsequent MOF . (Vincent 1991a)

Clearly , the successful treatment of septic shock depends on effective responses to both the hypoxic and immunological alterations . The immediate aim must be to sustain organ function through haemodynamic stabilization thus facilitating the definitive treatment , based on the removal of the source of sepsis and the administration of medications directed against the infectious organisms . Advances have been made in two major areas . First , resuscitation regimens have been improved with the aim of augmenting oxygen supply to the cells and thereby preventing tissue hypoxia . Second , new therapeutic options have been offered through a deeper understanding of the immunological alterations provoked by infection .(Vincent 1995)

The list of putative endogenous mediators of the septic response whose presence or absence may contribute to injury of the host is constantly growing . some of the more important cytokines contributing to the morbidity of the septic response are outlined in Table 4.(Marshall 1994)

Table 4 . The effects of cytokine manipulation on mortality in experimental sepsis (Marshall 1994)

mediator	Model
Blockade Improves Outcome	
IL-1	Endotoxemia , gram-positive bacteremia
IL-6	Endotoxemia
TNF	Endotoxemia , gram-positive bacteremia
LIF(Leukemia Inhibitory Factor)	Endotoxemia
MIF (Macrophage migration Inhibitory Factor)	Endotoxemia
Administration Improves Outcome	
IL-1	E.coli peritonitis
TNF	Cecal ligation and puncture : pretreatment for endotoxemia
IL-10	Endotoxemia
TGFβ	Knockout of gene results in early death from generalized inflammation

Interleukin-1 (IL-1)
Interleukin-6 (IL-6)
Interleukin-10 (IL-10)
Tumor necrosis factor (TNF)

CHAPTER 2