Sepsis Syndrome- Understanding and Evaluation

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What is Sepsis Syndrome?

Society of critical care medicine consensus conference: definitions of sepsis and organ failure and guideline for the innovative therapies in sepsis. Crit Care Med 1992;20:864

International sepsis definition conference. Crit Care Med 2003;31:1250

Definition

- Sepsis is defined as suspected or proven infection plus

  a systemic inflammatory response syndrome (e.g., fever/hypothermia, tachycardia, tachypnea, and leukocytosis/leukopenia).

Severe sepsis

- Severe sepsis is defined as sepsis with organ dysfunction
  - hypotension,
  - hypoxemia,
  - oliguria,
  - metabolic acidosis,
  - thrombocytopenia, or
  - obtundation).

Septic Shock

- Septic shock is defined as severe sepsis with hypotension, despite adequate fluid resuscitation.

  Septic shock and multiorgan dysfunction are the most common causes of death in patients with sepsis.

How Can One gets sepsis?

Breach of integrity of the natural barriers like skin and mucous membrane

may be very minor and inconspicuous

like, insect bites, thorn pricks or minor skin abrassions

Loss of integrity of internal barriers

GIT

Indwelling urinary catheters

Endotracheal tubes

Incidence

Not known in Bangladesh

>60% 0f ICU admission in Dhaka due to sepsis syndrome

Death rate is around 50% in these group of patients

Incidence

3 per 1000 population per year in the USA

But incidence is gradually increasing due to

- patients infected with treatment-resistant organisms,
- patients with compromised immune systems
- patients who undergo prolonged, high-risk surgery
- Increasing number of major accidents

Sepsis ranks in the top ten causes of death

Pathophysiology

Sepsis is the culmination of complex interactions between the

- Infecting microorganism and
- The host immune, inflammatory, and coagulation responses.

Pathophysiology

When host responses to infection are inadequate

Organ dysfunction occurs as a result

Pathophysiology

In addition, sepsis often progresses when the host cannot contain the primary infection

a problem most often related to characteristics of the microorganism, such as a high burden of infection and the presence of superantigens and other virulence factors, resistance to opsonization and phagocytosis and antibiotic resistance

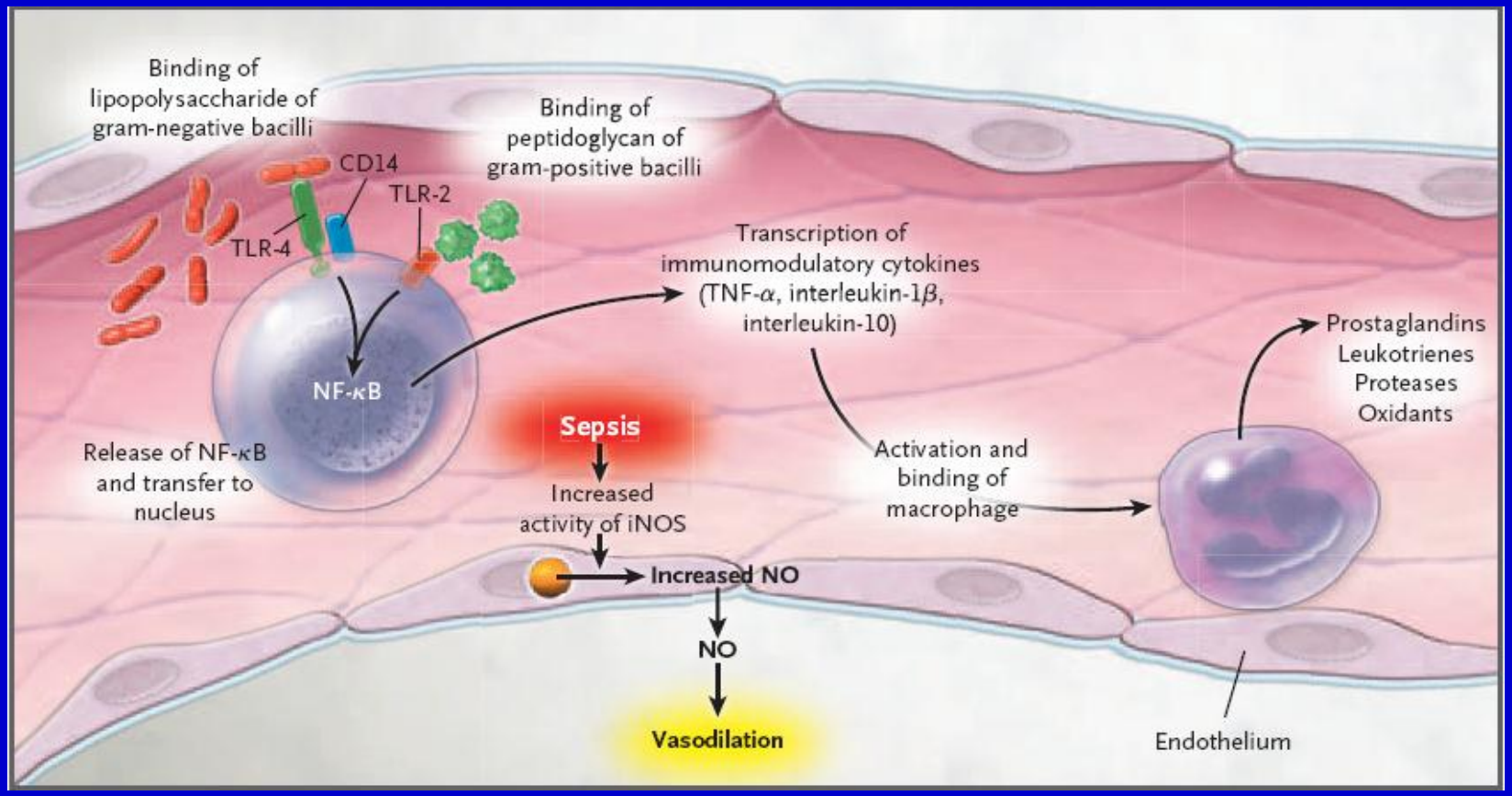
Host Defence

- Innate Immune system response
- Adaptive Immune system response

Innate Immunity in early sepsis

- The innate immune system responds rapidly by means of pattern-recognition receptors (e.g., toll-like receptors [TLRs]) that interact with highly conserved molecules present in microorganisms

Inflammatory response in sepsis



Pattern recognition receptor
Toll-like receptor
Activation of cytosolic NF
Inducible NO synthase

Endothelial Functions:
- Selective permeability
- Vasoregulation
- Anticoagulant surface

AMPLIFICATION OF THE IMMUNE RESPONSE BY ADAPTIVE IMMUNITY

Microorganisms stimulate specific

humoral and cell-mediated adaptive immune responses that amplify innate immunity.

B cells release immunoglobulins

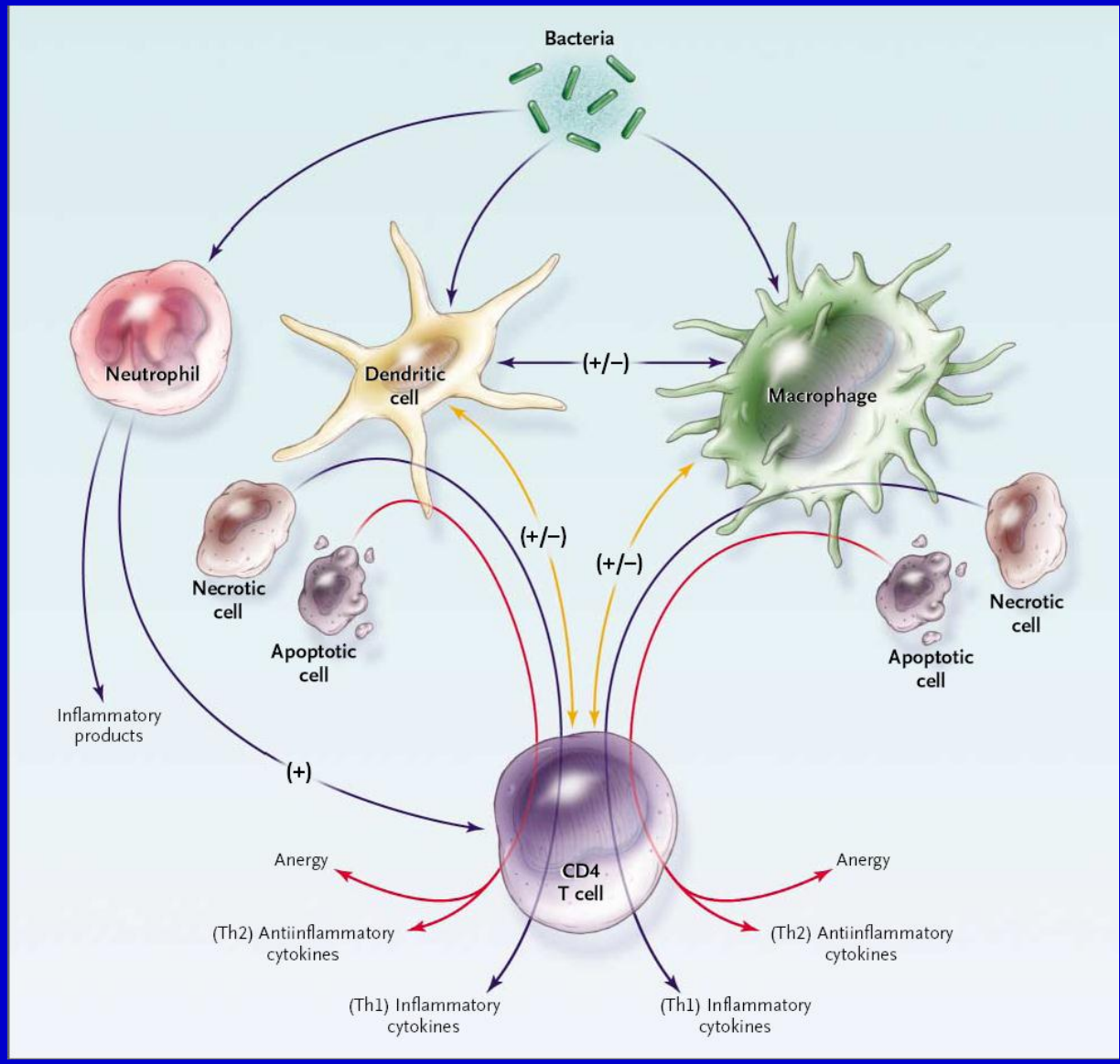
that bind to microorganisms,

facilitating their delivery by antigen-presenting cells to natural killer cells and neutrophils that can kill the microorganisms

Helper (CD4+) T cells
- type 1 helper (Th1)
- type 2 helper (Th2) cells.

Th1 cells secrete
- proinflammatory cytokines
- TNF-α and IL-1β

Th2 cells secrete
- antiinflammatory cytokines
- IL-4 and IL-10,



T-cell subgroups are modified in sepsis.

Helper (CD4+) T cells can be categorized as

type 1 helper (Th1)

type 2 helper (Th2) cells.

Th1 cells generally secrete

proinflammatory cytokines

TNF-α and interleukin-1β

Th2 cells secrete

antiinflammatory cytokines

Interleukin-4 and interleukin-10,

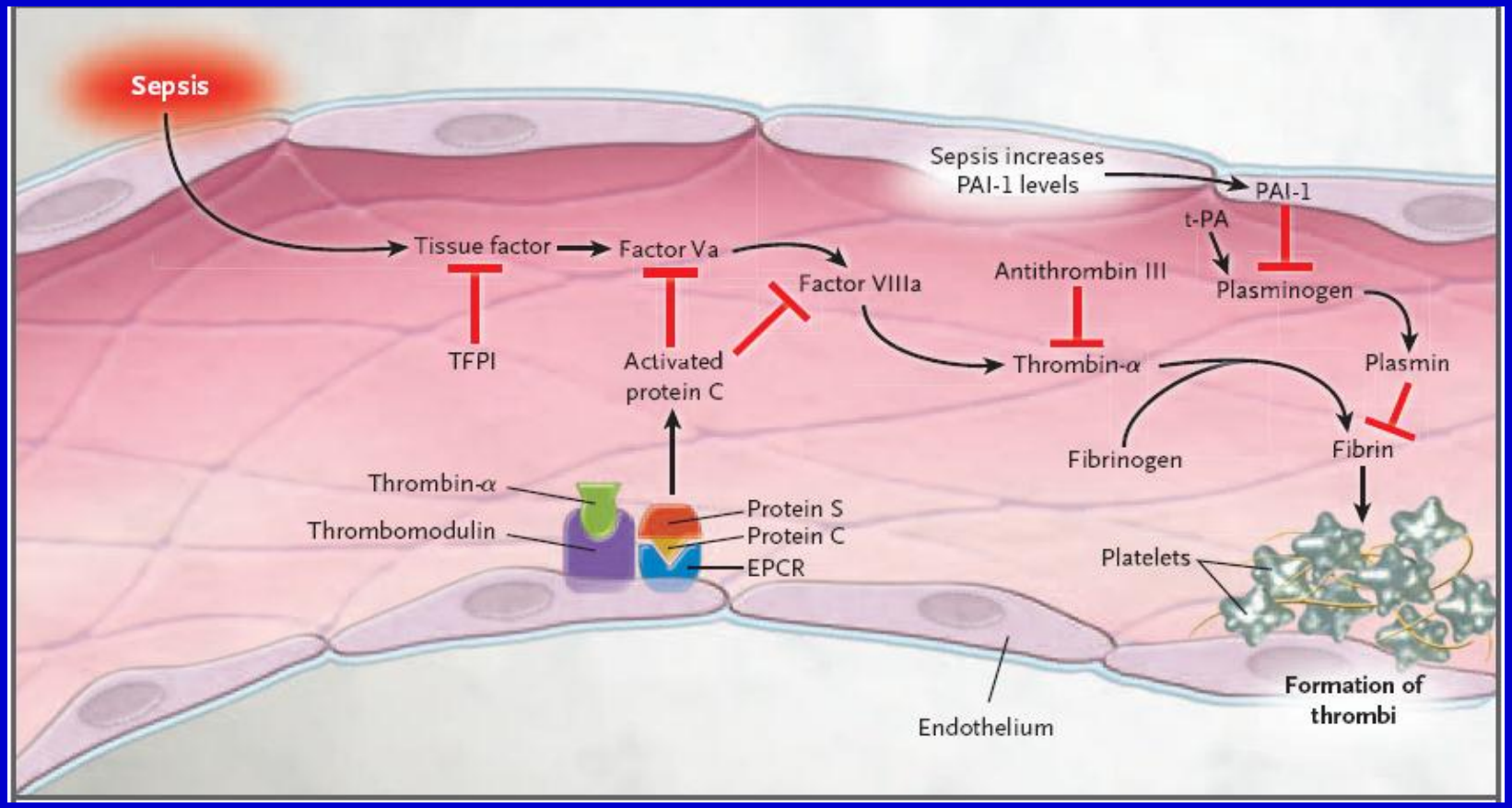
Disturbance Of Procoagulant–Anticoagulant Balance

Increase in procoagulant factors and a decrease in anticoagulant factors

Lipopolysaccharide stimulates endothelial cells to up-regulate tissue factor, activating coagulation.

Fibrinogen is then converted to fibrin, leading to the formation of microvascular thrombi and further amplifying injury.

Procoagulant Response in Sepsis



TFPI – Tissue factor pathway inhibitor
EPCR – Endothelial prot C receptor
PAI 1 – Plasminogen activator inhibitor 1

What happens ?

Clinical consequences of changes in coagulation caused by sepsis are:

- increased levels of markers of DIC
- wide spread organ dysfunction

Immunosuppression in Late Sepsis

Late death in patients with sepsis

the sequelae of anergy, lymphopenia, hypothermia, and nosocomial infection

Apoptosis

Responsible for the multiple organ dysfunction in sepsis

apoptosis of key immune, epithelial, and endothelial cells

apoptosis of circulating and tissue lymphocytes (B cells and CD4+ T cells) contributes to immunosuppression.

Apoptosis

Apoptosis is initiated by

- Proinflammatory cytokines,
- Activated B and T cells, and
- Circulating glucocorticoid levels, all of which are increased in sepsis.

Increased levels of TNF-α and

- Lipopolysaccharide during sepsis may also induce apoptosis of lung and intestinal epithelial cells

Organ Dysfunction in Sepsis

The altered signaling pathways in sepsis ultimately lead to tissue injury and multiorgan dysfunction.

For example, cardiovascular dysfunction is characterized by circulatory shock and the redistribution of blood flow, with decreased vascular resistance, hypovolemia, and decreased myocardial contractility associated with increased levels of nitric oxide, TNF-α, interleukin-6, and other mediators

Organ Dysfunction in Sepsis

Respiratory dysfunction is characterized by

Increased microvascular permeability, leading to acute lung injury.

Renal dysfunction in sepsis, as discussed recently by Schrier and Wang, may be profound, contributing to morbidity and mortality

Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med 2004;351:159-69.

Diagnosis & Evaluation

- Early diagnosis and evaluation is critical because of the efficacy of early, goal-directed therapy in the first 6 hours.

Evaluation

- Assessment of airway
- Assessment of breathing
  - Respiratory rate
  - Signs of respiratory distress
  - Pulse oximetry
- Circulation
  - Heart rate, blood pressure
  - Skin
  - Jugular venous pressure

Identify SIRS

Two or more of the following:

- Increased heart rate (>90/min)
- Increased respiratory rate (>20/min) or $PaCO_2$ <32 mm Hg or use of mechanical ventilation
- Increased temperature (>38°C) or decreased temperature (<36°C)
- Increased white-cell count (>12,000/mm3) or decreased white-cell count (<4000/mm3)

Identify source of infection

Respiratory (pneumonia, empyema)

Abdominal (peritonitis, abscess, cholangitis)

Skin (cellulitis, fasciitis)

Pyelonephritis

CNS (meningitis, brain abscess)

Assessment of organ function

CNS

- LOC, focal signs and GCS

Renal function

- Urinary output

Laboratory Evaluation

- Identify SIRS
  - Complete blood count with White-cell differential
- Blood Gas Analysis

Identify source & type of infection

Culture and sensitivity of blood, sputum, urine; perhaps other fluids and CSF

Chest radiography

Ultrasonography,

CT

Assessment of organ function

Renal function

- Electrolytes, BUN, creatinine

Hepatic function

- Bilirubin, AST, alkaline phosphatase

Coagulation

- INR, PTT, platelets and BT CT

Assessment of organ dysfunction

should be based on few important principles:

organ failure should not be seen as an all-or-none phenomenon, but rather as a continuum of alterations. The introduction of "acute lung injury" as a lesser degree of acute respiratory failure than full-blown acute respiratory distress syndrome is in accordance with this concept.

organ failure as being either present or absent, ignoring the presence of degrees of severity between the two extremes.

Assessment of organ dysfunction

The time course must be taken into account.

Organ failure is a dynamic process and the degree of dysfunction may vary with time.

People who die early may not even have time to develop organ failure. Regular assessment of organ function is therefore required to enable the physician to follow the evolving disease process.

Assessment of organ dysfunction

The description of organ dysfunction/failure should be based on simple variables, specific to the organ in question, and routinely available everywhere.

The ideal descriptors should be derived from simple, independent clinical and laboratory data measuring physiologic dysfunction.

SOFA Score

With these principles in mind, a group of critical care physicians developed, by consensus, the so-called "Sepsis-Related Organ Failure Assessment" (SOFA) score in December 1994.

Since the score is not specific for sepsis, it was later called "Sequential Organ Failure Assessment”.

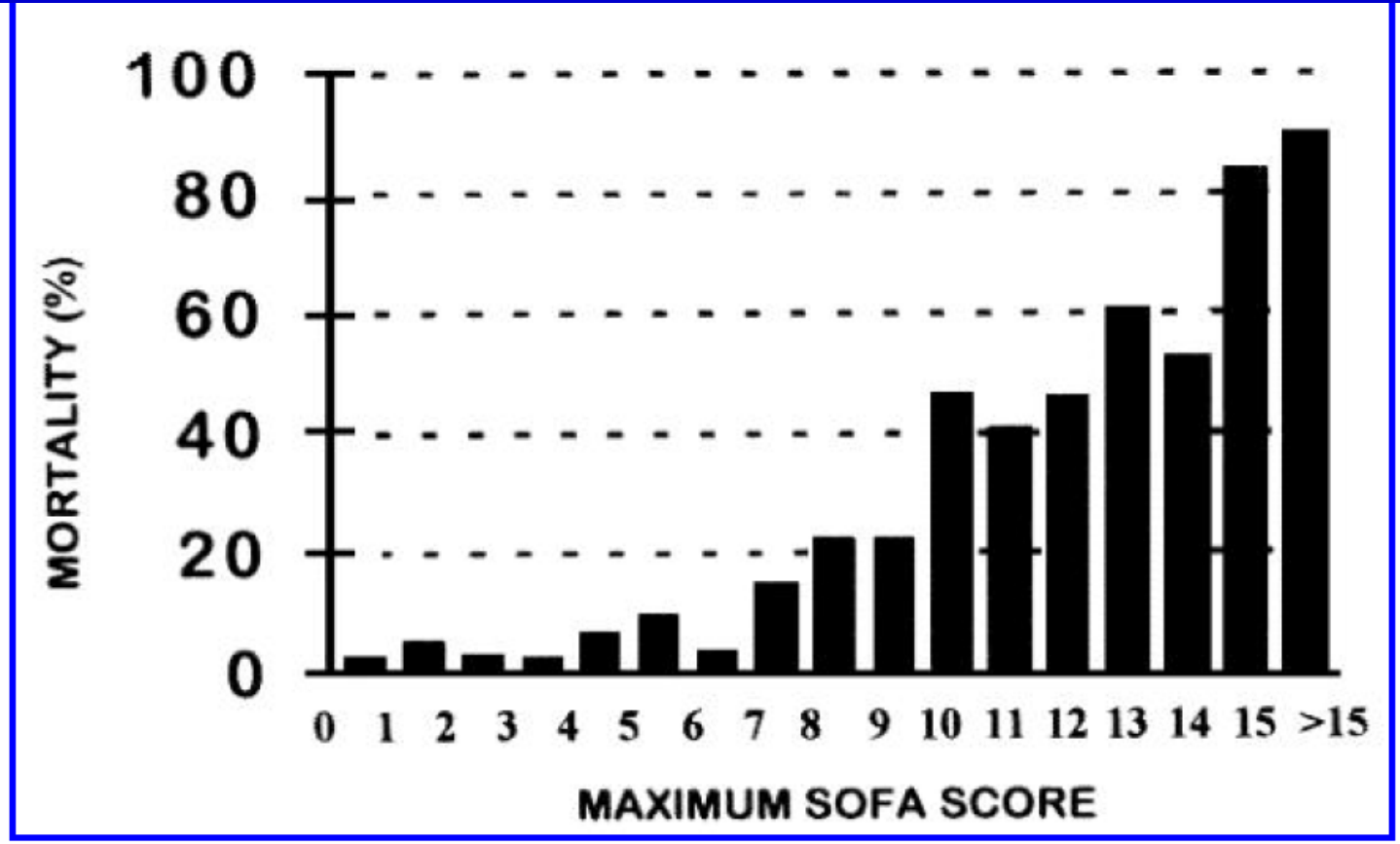
SOFA Score

The SOFA score is composed of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction/failure

SOFA score

	0	1	2	3	4
Respiration Pao2/Fio2	>400	≤400	≤300	≤200 With respiratory Support	≤100 With respiratory Support
Coagulation Platelets $\times 10^3$ $\times mm^3$	>160	≤150	≤100	≤50	≤20
Liver Bilirubin (mg/dl)	< 1.2	1.2 – 1.9	2 – 5.6	6 – 11.9	> 12
Cardiovascular Hypotension	No Hypo	MAP < 70 mmHg	Dopamine≤ 6 or Dobutamine Any dose	Dopa >6 or epi <0.1 or norepi <0.1	Dopa >15 or epi > 0.1 or norepi > 0.1
CNS GCS	15	13-14	10-12	6-9	<6
Renal Function Creatinine (mg/dl) Or urine output	< 1.2	1.2-1.9	2-3.4	3.5-4.9 or <500ml/day	>5 or <200ml/day

Correlation of SOFA score with mortality



Crit Care Med 1998; 26:1793-1800

SUMMARY POINTS

Sepsis encompasses a spectrum of illness that ranges from minor signs and symptoms through to organ dysfunction and shock

Sepsis ranks in the top 10 causes of death

The pathophysiology of sepsis arises largely from the response of the host's innate immune system, under the influence of genetic factors

SUMMARY POINTS

The signs and symptoms of sepsis are influenced by the virulence of the pathogen, the portal of entry, the susceptibility and response of the host, and the temporal evolution of the condition

Sepsis is a clinical diagnosis; microbiological investigations are commonly negative

Powerful molecular biological techniques are likely to make a substantial contribution to the diagnosis of sepsis in the next five to 10 years

Thank You