ONE-YEAR SURVIVAL AND PERFORMANCE STATUS IN ADULT PATIENTS WITH SEPSIS, SEVERE SEPSIS, AND SEPTIC SHOCK

By

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TERUS HIDUP DAN STATUS PRESTASI SETAHUN DALAM PESAKIT DEWASA SEPSIS, SEPSIS TERUK, DAN KEJUTAN SEPSIS

oleh

Mustafa Salman M. Alkhalaf

Tesis yang dikemukakan sebagai memenuhi keperluan untuk ijazah

Doktor Falsafah

2013

DEDICATION

In the name of Allah, the beneficent, the merciful

And praise belong to God, lord of the universe.

I would like to dedicate my thesis for my beloved family and parents.

I dedicate this work to the gentlemen and leaders who have a special place in my heart and who taught me perseverance and access to the best and work sincerely, and who still followed them in my life.

Allah says in the holy Quran

[وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ} [التوبة:١٠٥}

Acts as you wish. God, his messenger and the believers will see your deeds.

Surat at-Tawbah (9), ayah 105

I believe "A thousand of miles journey begins with a step"

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Mustafa Salman M. Alkhalaf

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LIST OF ABBREVIATIONS

ACCP/SCCM	American college of chest physicians/society of critical care medicine consensus conference
Adj. HR	Adjusted hazards ratio
Adj. P	Adjusted probability value
AF	Atrial fibrillation
AIDS	Acquired immune deficiency syndrome
Alb.	Albumin
ALI	Acute lung injury
ANOVA	Analysis of variance
APACHE	Acute physiology and chronic health evaluation
APC	Activated protein C
aPTT	Activated prothrombine time
ARDS	Acute respiratory distress syndrome
AST/ALT	Aspartate aminotransferase (AST) / Alanine Aminotransferase (ALT)
BC	Blood culture
Bil.	Bilirubin
BP	Blood pressure
BUN	Blood urea nitrogen
C°	Celsius
C_{5a}	Complement component 5a
CAD	Coronary artery disease
CC	Continuity correction
CDC	Centre for disease control and prevention
CER	Comparative effective research
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease

CORTICUS	Corticosteroid therapy of septic shock
Cr	Creatinine
CrCl	Creatinine clearance
CRF	Chronic renal failure
CRP	C reactive protein
CRRT	Continuous renal replacement therapy
CVA	Cerebro-vascular accident
CVP	Central venous pressure
CVVH	Continuous veno-venous hemofiltration
CXC	CXC chemokines
CXCR2	Chemokines receptor.
Df	The degree of freedom used to obtain the observed significant level
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
Dop.	Dopamine
DVT	Deep vein thrombosis
EGDT	Early goal directed therapies
EQ-5D	EQ-5D™ is a standardised instrument for use as a measure of health outcome.
EPCR	Endothelial cell protein C receptor
F°	Fahrenheit
fMLP	formyl-methionyl-leucyl-phenylalanine, a chemotactic ligand
g/dl	Gram per decilitre
g/L	Gram per litter
GCS	Glasgow coma scale
G-CSF	Granulocyte colony stimulating factor
GH	General health
GIS	Geographic information system

GM-CSF	Granulocyte/macrophage colony stimulating factor
Golden Hours	First 6 hours.(sepsis resuscitation bundle)
GRADE	Grades of recommendation, assessment, development, and evaluation system
H	Hour
Hgb.	Haemoglobin
HR	Hazards ratio
HR-QOL	Health related quality of life
Htc.	Hematocrit
HTN	Hypertension
ICD9	International statistical classification of diseases, ninth revision
ICU	Intensive care unit
IHD	Ischemic heart disease
IL-1	Interleukin -1
IL-10	Interleukin -10
IL-12	Interleukin -12
IL-1_{β}	Interleukin -1_{β}
IL-2	Interleukin -2
IL-6	Interleukin -6
IL-8	Interleukin -8
INR	International normalized ratio (INR)
IT	Information technology
IV	Intravenous
LMWH	Low molecular weight heparin
LOS	Length of stay
LPS	Lipopolysaccharides
LTB4	Leukotriene B4
M	Mean
m mol/L	millimoles/liter

MAP	Mean arterial pressure
MDR	Multiple drug resistance
MET	Medical emergency team
Mg	Milligram
MI	Myocardial infarction
min.	Minute
mm Hg	Millimetre-mercury
mm3	Cubic millimetre
MOF	Multiple organ failure
MR No.	Medical record number
MV	Mechanical ventilation
N	Number
NE	Norepinephrine
NGH	National guard hospital, Riyadh, Saudi Arabia.
NHDS	National hospital discharge survey
NMBs	Neuromuscular blockers
NYHA	New York heart association
OR	Odds ratio
P	Probability
PaCo2	Pressure of arterial carbon-dioxide
PaO2	Partial pressure of arterial O_2
PaO2/FiO2	Ratio of partial pressure of arterial O_2 to the fraction of inspired O_2 (Hypoxemia Ratio)
PASW	Predictive analytics soft ware
PCT	Procalcitonone
PEEP	Positive end-expiratory pressure
Ph.E	Phenylephrine
PF	Physical function
Post Op.	Post operation

Pot.	Potassium
PRBC	Packed red blood cell
PS	Status performance
PS I	Able to work (on Karnofsky performance scale)
PS II	Unable to work (on Karnofsky performance scale)
PS III	Unable to care for self (on Karnofsky performance scale)
PT	Prothrombine time
QOL	Quality of life
r	Correlation coefficient
RBC	Red blood cell
RE	Emotional role
rhAPC	Recombinant human activated protein - c
RP	Physical role
RRS	Rapid response system
SBP	Systolic blood pressure
SBT	Spontaneous breathing trial
ScvO2	Central venous oxygen saturation
SD	Standard deviation
SE	Standard error
SF-36	Medical Outcomes Study Short-Form 36-Item Health Survey
Silver Day	First 24 hours. (sepsis management bundle)
SIRS	Systemic inflammatory response syndrome
SNK	Student-Newman Kenl`s test
Sod.	Sodium
SPSS	Statistical product and service solutions
SS & SK	Severe sepsis and septic shock
SSC	Surviving sepsis campaign
SvO2	Mixed venous oxygen saturation

SVR	Systemic vascular resistance
T. Bil.	Total bilirubin
TERM	Triggering receptor expressed on myeloid cells
TF	Tissue factor
TLR2	Toll-like receptor 2
TLR4	Toll-like receptor 4
TM	Thrombomodulin
TNF	Tumour necrotic factor
TNF-α	Tumour necrosis factor-alpha
UFH	Unfractionated heparin
Va	Clotting factor Va
Vasop.	Vasopressin
VIIa	Clotting factor viia
WBC	White blood cells
X^2	Chi-square test
Xa	Clotting factor Xa
μg	Microgram
μL	Micro-litter

LIST OF APPENDICES

Terus Hidup Dan Status Prestasi Setahun Dalam Pesakit Dewasa Sepsis, Sepsis, Sepsis Teruk Dan Kejutan Sepsis

ABSTRAK

Sepsis adalah punca utama morbiditi dan kematian. Pengiktirafan kesan jangka panjang dalam penyakit kritikal yang terselamat telah beralih nilai hasil daripada pengurangan kematian di hospital 'ke hasil berpusatkan pesakit' yang berkaitan kesihatan ia-itu kualiti penghidupan (HR-QOL). Data yang terhad berkaitan kesan susualan jangka panjang susulan pesakit sepsis teruk dan kejutan septik (SS & SK) yang terselamat. Oleh itu, objektif kajian ini adalah untuk mendapatkan siapa yang mampu untuk terus hidup berbanding bukan hidup dan untuk memastikan status prestasi mereka se tahun selepas keluar-hospital, bergikut melawan masa dan faktor-faktor ramalan.

Kajian kohort retrospektif dan keratan rentas yang dijalankan kepada pesakit dewasa (≥ 18 tahun) yang telah dimasukkan ke ICU perubatan- pembedahan dan trauma di hospital penjagaan tertiary sekurang-kurangnya 24 jam diantara April 2007 hingga Mac 2010. Hanya pesakit yang masih hidup pada masa pelepasan hospital telah dipilih. Pesakit yang masih hidup ditemuramah melalui telefon untuk menentukan status prestasi mereka setahun selepas keluar-hospital menggunakan "Karnofsky prestasi status skala".

Daripada 524 kes, hanya 195 kes memenuhi kriteria yang termasuk. Kira-kira satu pertiga daripada 195 pesakit-pesakit SS & SK telah meninggal. Satu pertiga menderita kemerosotan prestasi yang ketara (tidak dapat bekerja serta tidak mampu untuk menjaga diri-sendiri), dan hanya satu pertiga dapat bekerja semasa setahun selepas keluar-hospital.

Kematian meningkat berkadaran dengan masa dalam masa setahun keluar-hospital dan lebih daripada separuh kematian berlaku dalam masa tiga bulan selepas keluar-hospital. Status prestasi pra-sepsis dan berpenyakit CHF mempergaruhi hasil-hasil prestasi dan masih hidup yang ketara selepas keluar–hospital, terutamanya pesakit tua (≥ 65 tahun). Pesakit yang status prestasi terjejas semasa pra-sepsis, risiko kematian meningkat tiga kali ganda berbanding dengan mereka yang mampu bekerja semasa pra-sepsis. Selain itu, pesakit yang mampu untuk menjalankan aktiviti biasa dan bekerjasemasa pra-sepsis adalah lebih mampu untuk terus hudip dalam tempoh setahun selepas keluar-hospital.

Kesimpulannya, kematian telah meningkat dengan masa dalam tempoh setahun selepas keluar-hospital. Status prestasi dan berpenyakit CHF adalah faktor-faktor penting yang mempengaruhi hasil-hasil untuk mampu terus hidup dan prestasi dalam pesakit-pesakit SS & SK selepas keluar-hospital. Data ini menonjolkan kumpulan–kumpulan pesakit sepsis yang perlu diberikan lebih perhatian.

One-Year Survival and Performance status in Adult Patients with Sepsis, Severe Sepsis, and Septic Shock

ABSTRACT

Sepsis, based on a number of researches, is considered a significant cause of morbidity and mortality. Recognition of long-term sequelae in survivors from critical illnesses has shifted the outcome values from reduction in hospital mortality to 'patient centered outcomes', such as health related quality of life (HR-QOL). There is limited data available on long-term follow-up survivors with severe sepsis and septic shock (SS & SK). Therefore, the objectives of this study were to determine who were able to survive versus those unable to survive for one-year post-hospital discharge and to ascertain their performance status, survival versus time post discharge and prognostic factors.

A retrospective cohort and cross-sectional study was conducted in relation to adult patients (≥18 years) who were admitted to the medical-surgical and trauma ICU of a tertiary care hospital, at least 24 hours during the period between April 2007 and March 2010. The patients selected were the ones who were still alive at the time of hospital discharge. Survivors were interviewed on the telephone to determine their performance status after one-year of their hospital discharge using "Karnofsky performance status scale".

Among the 524 cases of patients assessed, only 195 cases were included based on inclusion criteria. Around one-third of the 195 SS & SK survivors died. Another one-third suffered significant impairment of performance status (unable to work plus or even care for self). It was also observed that only one third of these cases were able to work for one-year after being hospital discharged.

The mortality rate increased with time throughout the first year of patient's post-hospital discharge. However, more than half of the death cases occurred within the first three months of post hospital discharge. Pre-sepsis performance status and pre-existing CHF significantly affects the outcomes and duration of the survival of post-hospital discharged patients, particularly in elderly survivors (≥ 65 years). The risk of death for patients who had impaired pre-sepsis performance status increased three times more when compared to those who were able to work during their pre-sepsis status. Furthermore, the rate of survival among patients able to carry out normal activity and work during pre-sepsis was much higher during the one year post hospital discharge.

In conclusion, the mortality was increasing with time within one-year of post-hospital discharge. Pre-sepsis performance status and pre-existing CHF are important factors affecting the survival and performance outcomes in post hospital discharge SS & SK cases. This data highlights the need for more intensive attention for the groups of sepsis survivors.

CHAPTER 1

INTRODUCTION

1.1 Background and definitions

"Sepsis" as a word originally comes from the Greek word "sepo", which means decay or putrefaction, and the original usage of this word described the decomposition of organic matter in a manner that resulted in decay and death (Geroulanos *et al.,* 2006). In the Hippocratic model of health and disease, living tissues broke down by one of two processes. "Pepsis" was the process through which food was digested, leading to health. Sepsis, however, denoted tissue breakdown that resulted in disease. Hippocrates used this term to describe the process of abnormal tissue breakdown that resulted in a foul odour, pus-formation, and sometimes-dead tissue (Vincent *et al.,* 2006). This usage of the term sepsis persisted for almost 3 millennia, and subsequent work establishing a causal link between microbes and suppurative infections, or systemic symptoms from infection, did not change the use of the term as a description of a constellation of clinical findings, but rather established infection as the underlying cause (Schottmueller, 1914) The term "shock" comes from the French word "choquer meaning "to collide with," and aptly describes the body's response to invading microbes and, to a large extent, its disruptive effect on normal physiology. It was used in the medical literature initially in the 1700s; its earliest uses connoted a sudden jolt that often led to death (the initial physical injury). This definition evolved to describe widespread circulatory dysfunction following injury (Cannon, 1923; Nduka *et al.,* 2011)

Sepsis is the systemic maladaptive response of the body to the invasion of normally sterile tissue by pathogenic, or potentially pathogenic, microorganisms. Shock may be defined as a "state in which profound and widespread reduction of effective tissue

perfusion leads first to reversible, and then, if prolonged, to irreversible cellular injury." (Kumar & Parrillo, 2008). From a clinical standpoint, this progressive cellular dysfunction manifests as a continuum from sepsis, to severe sepsis, and finally to septic shock (Nduka *et al.,* 2011) as shown in (Figure 1.1 and Figure 1.2).

Sepsis syndrome results from a host reaction to infection, which includes a robust systemic inflammatory response, enhanced coagulation, and impaired fibrinolysis (Bone *et al.* 1992; Hotchkiss *et al*., 2003). The systemic inflammatory response syndrome (SIRS) is defined by the constellation of fever or hypothermia, tachycardia, tachypnea, and leukocytosis, leukopenia, or the presence of immature neutrophils. SIRS can result from numerous conditions but only becomes ‘‘sepsis’’ when infection is etiologic. When sepsis causes at least one organ dysfunction, the syndrome is termed ‘‘severe sepsis,’’ and sepsis-induced hypotension that is refractory to fluid challenge defines ‘‘septic shock’’ (Table 1.1). While the SIRS criteria are sensitive for septic patients, the investigators criticized it for lacking specificity. Many, if not most, of ICU patients have tachypnea and tachycardia, this raising doubt about the diagnostic utility of the SIRS criteria (Vincent, 1997). Although the specificity of SIRS is increased by requiring two or more of the criteria or by mandating that one of two required criteria is abnormal temperature or white blood cell count. (Bone *et al.,* 1992; Marshall *et al.,* 1995; Brun-Buisson, 2000; Levy *et al.,* 2003; Dellinger *et al.,* 2004; Lin SM *et al.,* 2004; Poze *et al.,* 2004; Emanuel *et al.,* 2005; Martin *et al.,* 2009)

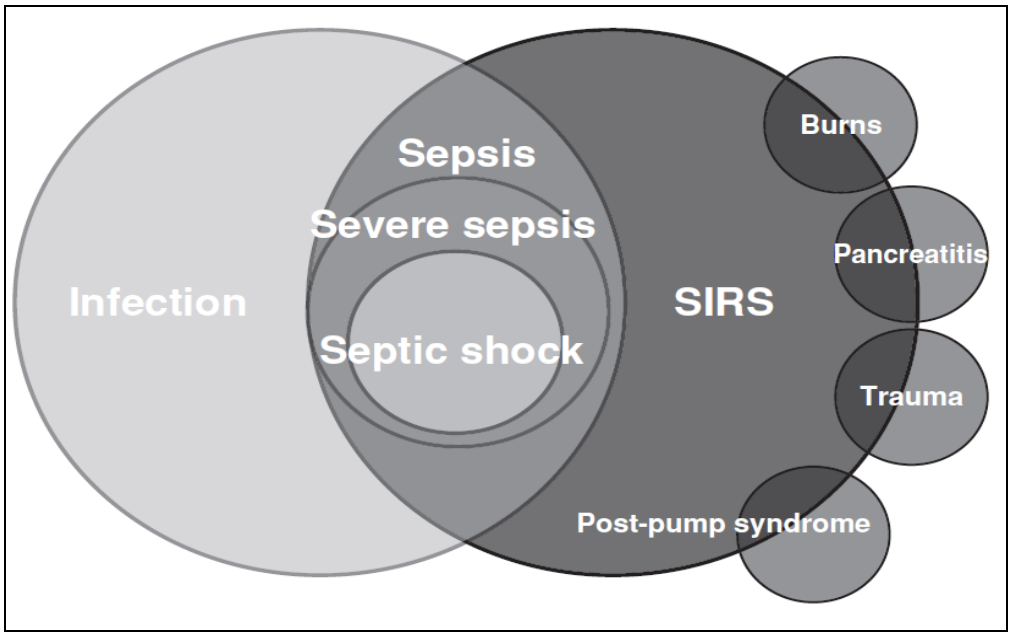

Figure 1.1: The relationship of infection, SIRS, severe sepsis, and sepsis. (Adapted from, Bone RC et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101:1644-55)

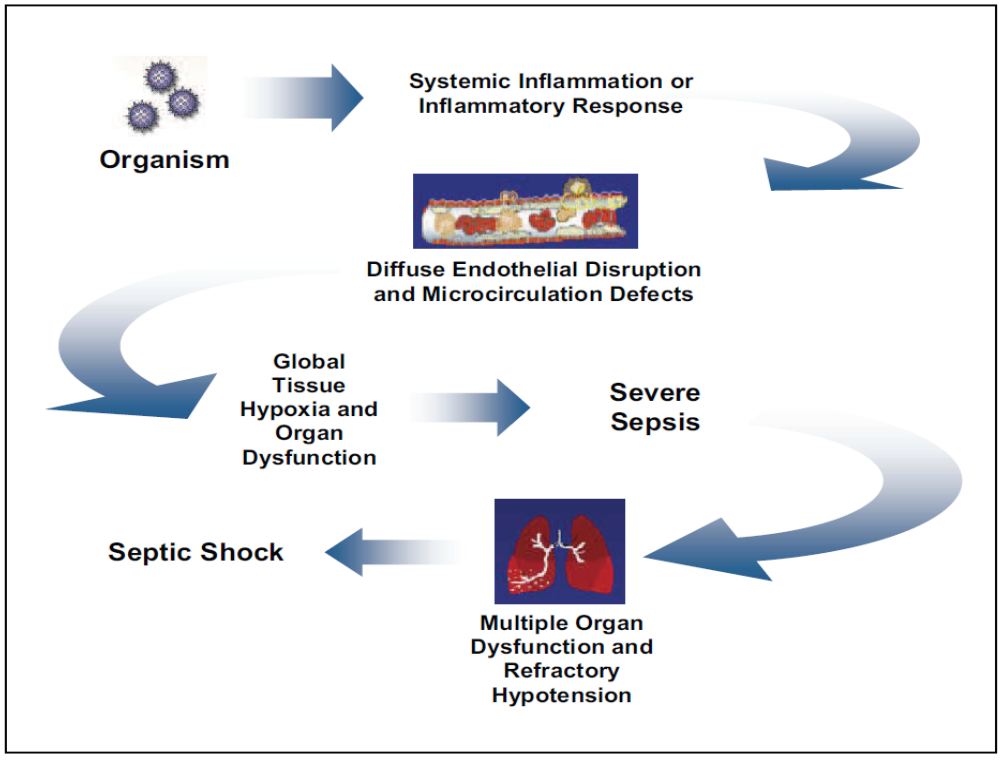

Figure 1.2: Pathogenic mechanisms from infection to septic shock. The initial response to an infecting organism is a systemic response, with release of inflammatory mediators and activation of the coagulation cascade. Microvascular injury, thrombosis, and diffuse endothelial disruption follow, resulting in imbalance between oxygen delivery and oxygen consumption. Global tissue hypoxia and cytopathic (cellular) hypoxia develop, leading to multiple organ dysfunction and irreversible shock (Adapted from, Nguyen, et al. (2006). Severe Sepsis and Septic Shock: Review of the Literature and Emergency Department Management Guidelines. *Ann Emerg Med, 48,* 28-54. With permission from corresponding author)

Table 1.1: Sepsis definitions (Astiz et al., 1987; Rivers, Nguyen et al., 2001; Emanuel et al., 2005)

Sepsis definitions

Systemic inflammatory response syndrome (SIRS)-includes two or more of:

- Temperature > 38º or < 36º C
- Heart rate > 90 beat/min. unless the patient is taking medications to reduce the rate (a beta-blocker or calcium-channel blocker) or the heart is paced.
- Respiratory rate > 20 breaths/min (or PaCo2 < 32 torr) or mechanically ventilated
- Leukocyte count > 12000/µL or < 4000/ µL or > 10% immature band forms.

Sepsis

- Presence or presumed presence of an infection accompanied by evidence of SIRS

Severe sepsis: presence of sepsis, plus organ hypoperfusion or dysfunction

- Organ hypoperfusion; for example:
  - Increased blood lactate levels
  - Oliguria
  - Abnormal peripheral circulation, such as poor capillary refill, mottled skin
  - Acute alteration in mental status
- Dysfunction* of one or more organs, such as abnormalities of:
  - The hematologic system; e.g. thrombocytopenia, disseminated intravascular coagulation
  - The pulmonary system; e.g., acute respiratory distress syndrome
  - The renal system; e.g., acute renal failure
  - The gastrointestinal system with hepatic dysfunction; e.g. hyperbilirubinemia
  - The central nervous system; e.g., delirium

Septic shock†

- Presence of sepsis
- Refractory hypotension:
  - Systolic blood pressure < 90 mm Hg
  - A mean arterial pressure < 65 mm Hg, or a 40 mm Hg drop in systolic blood pressure compared to baseline.
  - Unresponsive to a fluid challenge of 20-40 mL/kg
- Vasopressor dependency after adequate volume resuscitation

*Organs considered to have failed when the organ dysfunction becomes most severe.

†Note that this is a standard definition. It is important to recognize that a patient may be in septic shock with a normal blood pressure if the baseline blood pressure is elevated (e.g., someone with a history of hypertension, diabetes or vascular disease) or there is concomitant myocardial dysfunction.

Adapted from, Emanuel, P. R., Lauralyn, M., David, C. M., & Kandis, K. R. (2005). Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. *CMAJ, 173*(9), 1054-65. (Reprinted with permission from, the corresponding author and publisher "Access Copyright, the Canadian copyright licensing agency").

1.1.1 Previous and current definitions of sepsis

The previous history of sepsis word is derived from ‘‘sepo’’ “σηψις” which originally a Greek word used for the decomposition of animal or vegetable organic matter (Geroulanos *et al.,* 2006). Homer was the first one who used the word “Sepsis” since more than 2700 years ago, and the link between bacteria and systemic signs of disease was made around 100 years ago (Schottmueller, 1914). Later "sepsis” became almost synonymous with severe infection. More recently, as the role of the immune response has become clearer, we have realized that what we had called sepsis is in fact a host response to the invading microorganism rather than any specific feature of the microorganism itself. Indeed, sepsis can be initiated by any microorganism, whether it is bacterial, fungal, viral, parasitic, or by microbial products and toxins, and is then propagated by a complex network of inflammatory mediators and cellular dysfunction. Sepsis is a syndrome and one of the first attempts to establish a set of clinical parameters to define patients who have severe sepsis came in 1989 when Roger Bone and colleagues (Bone *et al.,* 1992) proposed the term ‘‘sepsis syndrome’’. Sepsis syndrome was defined as hypothermia (less than 96 F [35.5 C]) or hyperthermia (greater than 101 F [38.3 C]); tachycardia (greater than 90 beat/min); tachypnea (greater than 20 breath/min); clinical evidence of an infection site; and the presence of at least one end-organ demonstrating inadequate perfusion or dysfunction expressed as poor or altered cerebral function, hypoxemia (PaO2 less than 75 torr on room air), elevated plasma lactate, or oliguria (urine output less than 30 mL/h or 0.5 mL/kg body weight/h without corrective therapy). However, although it has been used as an entry criterion for clinical trials (Bone *et al.,* 1992; Panacek *et al.,* 2004) sepsis syndrome does not successfully define a homogeneous group of patients.

Therefore, the American college of chest physicians (ACCP) and the society of critical care medicine (SCCM) convened a consensus conference in 1991 in an attempt to create a set of standardized definitions (ACCP-SCCM consensus conference, 1992).

Thirty-five experts in the field of sepsis were gathered together to provide a framework to define the systemic inflammatory response to infection (i.e., sepsis). The result of this conference was the introduction of the term ‘‘systemic inflammatory response syndrome’’ (SIRS). It had been recognized for some time that the same inflammatory response to infection could also occur in response to other conditions, including acute pancreatitis, trauma, ischemia/reperfusion injury, and burns. SIRS was an attempt to differentiate sepsis from these non-infectious causes. According to the ACCP-SCCM consensus conference, infection defined as a microbial phenomenon characterized by the invasion of microorganisms or microbial toxins into normally sterile tissues. SIRS is defined, by consensus, as the presence of at least two of four clinical criteria:

1. Body temperature >38 C or <36 C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min or hyperventilation with a PaCO2 <32 mmHg
4. White blood cell count WBC >12,000/mm3, <4000/mm3, or with >10% immature neutrophils

SIRS represent a systemic inflammatory response of any etiology, including sepsis, which is therefore defined by the presence of SIRS in association with a confirmed infection. Sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension is called severe sepsis, and septic shock is defined as severe sepsis with sepsis-induced hypotension persisting despite adequate fluid resuscitation.

The SIRS approach has been rapidly adopted and widely used to define populations of patients in interventional clinical trials. Trzeciak and colleagues (Trzeciak *et al.,* 2005) reported that 69% of clinical trials in sepsis published between 1993 and 2001 used the consensus conference definitions. Similarly, Veloso and colleagues (Veloso *et al.,* 2009) reported that 10 of the 11 multicenter, randomized controlled trials of new therapeutic interventions in adult patients who had severe sepsis published between January 2000 and December 2007, used SIRS as part of the entrance criteria. Nevertheless, in the survey of 1058 physicians, including 529 intensives, conducted by Poeze and colleagues in 2000, only 5% (22% of the intensivists) gave the ACCP/SCCM definition when asked to define sepsis. Although the SIRS criteria do have the prognostic value of defining a group of patients who are at an increased risk of developing complications and with increased mortality (Napolitano *et al.,* 2000; Malone *et al.,* 2001; Sprung *et al.,* 2006) they have been criticized for being too sensitive and nonspecific to be of much clinical use (Vincent, 1997). Most ICU patients and many general ward patients meet the SIRS criteria (Pittet *et al.,* 1995; Rangel *et al.,* 1995). In the sepsis occurrence in acutely ill patients study, 93% of ICU admissions had at least two SIRS criteria at some point during their ICU stay.

Moreover, each of the SIRS criteria can be present in many different conditions, so that a label of SIRS provides little or no information about the underlying disease process. For example, fever can be present in sepsis, but also after myocardial infarction, pulmonary embolism, or postoperatively; tachycardia and tachypnea may be present in heart failure, anemia, respiratory failure, hypovolemia, sepsis, and so forth; a raised white blood cell count can be present in many diseases encountered in ICU patients, including trauma, heart failure, pancreatitis, hemorrhage, and pulmonary edema. The use of the SIRS criteria to define septic shock was also unrealistic. Any type of shock is

associated with hyperventilation (to compensate for the lactic acidosis), tachycardia (either to compensate for a decreased stroke volume or to achieve a supranormal cardiac output), and an increased white blood cell count (as part of the stress response). The body temperature is often within the normal range in septic shock. Accordingly, the SIRS criteria cannot separate septic from other types of shock. Furthermore, patients who meet the SIRS criteria have a wide range of disease severity, and hence, likely mortality. Use of the SIRS criteria to identify patients for enrolment in clinical trials has been disappointing, and has likely contributed to the negativity of almost all these trials. Indeed, use of SIRS for entrance into clinical trials generates a very heterogeneous group of patients with multiple underlying pathologies and disease severity; while some patients in such a mixed population may well benefit from the intervention, it is likely that others will not, thus diluting out any beneficial effect (Vincent *et al.*, 2009).

In 2001 Sepsis definitions conference with advances in our understanding of sepsis pathogenesis and pathophysiology and with continued dissatisfaction with available definitions of sepsis, a consensus sepsis definitions conference of 29 international experts in the field of sepsis was convened under the auspices of SCCM, the European Society of Intensive Care Medicine, ACCP, and the surgical infection societies (Levy *et al.*, 2003). The conference participants concluded that the definitions of sepsis, severe sepsis, and septic shock, as defined in the 1991 North American consensus conference, might still be useful in clinical practice and for research purposes. The key change was in the use of the SIRS criteria, which considered too sensitive and nonspecific. The participants suggested that other signs and symptoms added to better reflect the clinical response to infection (Table 1.2). Sepsis is now defined as the presence of infection plus some of the listed signs and symptoms of sepsis. Severe sepsis is now defined as sepsis complicated by organ dysfunction and septic shock is defined as severe sepsis with

acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Importantly, the list of signs of sepsis is meant as a guide, not all patients who have sepsis will have all the signs and symptoms listed, and many patients who do not have sepsis will have several of them. In addition, the list will change as new biomarkers are identified. These signs of sepsis should be considered as alarm signals that suggest the possibility of an infection and when combined with microbiological results and other evidence of organ involvement, can help in decisions regarding the need for antibiotics. (Klein Klouwenberg *et al.*, 2012).

Table: 1.2: 2001-Sepsis definitions (Vincent, Martinez & Silva, 2009)

Move from 1991 systemic inflammatory response syndrome criteria to expanded list of signs and symptoms in 2001-sepsis definitions conference

SIRS criteria:

- Fever/hypothermia
- Tachycardia
- Tachypnea
- Altered white blood cell count

Sepsis definitions conference 2001:

General signs and symptoms

- Fever/hypothermia
- Tachypnea/respiratory alkalosis
- Positive fluid balance/edema

General inflammatory reaction

- Altered white blood cell count
- Increased biomarker (C-reactive protein (CRP), IL-6, PCT) concentrations

Hemodynamic alterations

- Arterial hypotension
- Tachycardia
- Increased cardiac output/low systemic vascular resistance (SVR)/high SvO2.
- Altered skin perfusion
- Decreased urine output
- Hyperlactatemia (increased base deficit).

Signs of organ dysfunction

- Hypoxemia
- Coagulation abnormalities
- Altered mental status
- Hyperglycemia
- Thrombocytopenia, disseminated intravascular coagulation
- Altered liver function (hyperbiblirubinemia)
- Intolerance to feeding (altered gastrointestinal motility)

Abbreviation; PCT, procalcitonin; CRP C-reactive protein; IL-6 interleukine -6; SVR systemic vascular resistance; SvO2 Mixed venous oxygen saturation

(Reprinted with permission from, corresponding author Prof. Jean-Louis Vincent). Adapted from, Vincent, J. L., Martinez, E. O., & Silva, E. (2009). Evolving Concepts in Sepsis Definitions. *Crit Care Clin, 25,* 665–675.

1.2 Pathophysiology of sepsis

Historically, mediators such as cytokines e.g. tumor necrosis factor [TNF], interleukin [IL]-1 were considered most important in the pathophysiology of sepsis. This view was derived from experiments indicating that when such mediators were injected into animals or healthy volunteers a syndrome with many features of septic shock developed (Beutler, 1993). However, in the mid 1990s it became evident that this view of the pathophysiological alterations in sepsis was clearly too narrow and in reality there is a very complex interaction between microbial pathogen, immunocompetent cells, their mediators, endothelial cells and the coagulation system.

Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management. Multiple derangements exist in sepsis involving several different organs and systems, although controversies exist over their individual contribution to the disease process. Septic patients have substantial, life-threatening alterations in their coagulation system. Previously, it was believed that sepsis merely represented an exaggerated, hyperinflammatory response with patients dying from inflammation induced organ injury. Data that are more recent indicate that substantial heterogeneity exists in septic patients' inflammatory response, with some appearing immuno-stimulated, whereas others appear suppressed.

Cellular changes continue the theme of heterogeneity. Some cells work too well such as neutrophils that remain activated for an extended time. Other cellular changes become accelerated in a detrimental fashion including lymphocyte apoptosis.

Metabolic changes are clearly present, requiring close and individualized monitoring. At this point in time, the literature richly illustrates that no single mediator/system/ pathway/pathogen drives the pathophysiology of sepsis (Daniel *et al.*, 2007).

Progress in the molecular mechanisms of sepsis has provided a new level of understanding into the complex clinical course of human sepsis. Appropriate design of clinical trials in patients with sepsis needs to account for genetic and environmental variations found in patients and potential microbial pathogens. It has become evident that patients with sepsis are a very heterogeneous population. Certainly not every patient who meets the clinical criteria for severe sepsis is an ideal candidate for a clinical trial with a new therapeutic agent. It is now clear that there is no 'magic bullet' for sepsis, and it is likely there will never be one because most patients with sepsis have some form of underlying morbidity that predisposes them to develop sepsis.

One of the major conclusions derived from the 'first generation' of sepsis trials was the insight that patients with a high risk of dying during their septic episode because of their underlying illness should not have been enrolled into clinical trials. Such patients are unlikely to have any benefit from any therapy. In clinical trials, these patients introduce statistical 'noise', making it more difficult to detect a beneficial 'signal' of the compound under investigation, especially if this signal (effect) is weak (Eidelman *et al.*, 1994).

The application of these new insights into the pathophysiology of sepsis together with optimized patient selection and conduct of clinical trials eventually yielded the long-sought-after progress in sepsis therapy (Glück & Opal *et al.*, 2004).

1.2.1 Dysregulated coagulation

Normal hemostasis exists as a finely tuned balance where the blood typically remains liquid to allow free flow within the vessels yet clots appropriately to control bleeding. Under normal conditions, the clotting cascade is extremely complex (Esmon, 2006).

During inflammatory situations such as sepsis, significant alterations occur at multiple levels within both the coagulation system and the cells that regulate this system (Esmon, 2005). Septic patients frequently manifest disseminated intravascular coagulation (DIC) with consumption of platelets and prolongation of clotting times. In addition, the altered hemostasis allows blood to clot when it should not be clogging blood vessels and reducing blood flow. Because the liver produces fixed quantities of procoagulant factors, and the bone marrow releases a defined number of white blood cells into the circulation, local effects modulate the systemic coagulopathy. In other words, although the coagulopathy is systemic, the bleeding typically occurs in select sites, where dysfunctional vasculature provides the necessary environment for bleeding to occur at that site. The interaction between the clotting system, circulating white blood cells and platelets, and the endothelium adds another layer to an already multifaceted picture. Although several of these abnormalities have been documented in septic patients, the underlying cause of the coagulopathy almost certainly remains multifactorial. Abnormalities in the coagulation system resulting from systemic illnesses, which cause local disturbances in hemostasis and the thrombotic potential of cancer patients, have been described since the time of Virchow (Fink, 2001). Virchow's classic triad consists of changes in coagulability, endothelial cell injury, and abnormal blood flow. In septic patients, all three of these classic alterations are present and culminate in reduced blood flow to vital organs. Septic patients frequently have poor tissue perfusion in addition to inappropriate use of oxygen with resulting cytopathic hypoxia (Fink, 2001). The coagulation abnormalities in septic patients are profound and have led to a successful, food and drug administration-approved therapeutic intervention: activated protein c (APC, marketed under the name Xigris; Eli Lilly & Co., Indianapolis, IN). (Fink *et al.*,

2001). The approval of APC was controversial, with half of the food and drug administration panel voting to require a confirmatory trial (Eichacker *et al.,* 2006).

The successful clinical trials with APC for the treatment of sepsis were initiated following studies in the baboon model of *Escherichia coli* sepsis (Esmon *et al.,* 1987). There are very few compounds that have successfully made the transition from preclinical sepsis trials to a viable therapeutic option. Approval of APC for the treatment of septic patients clearly demonstrates that alterations in the coagulation system are important in sepsis mortality. Despite the success, the mechanism of action, beyond the coagulation system, has not been fully defined. It has been postulated that APC has anti-inflammatory properties that help to explain the beneficial effects. However, the question of whether excessive inflammation plays a critical role in sepsis mortality has yet to be definitively answered. Although APC improves survival in patients with severe sepsis, it is clearly not a panacea for all patients. Analysis of the initial data showed that the most beneficial effects were observed in patients with the worst prognosis. Follow- up studies demonstrated that patients at low risk for death had no improvement in survival and had a significantly increased risk of bleeding if treated with activated protein C (Jimenez *et al.,* 2002; Segal, 2002; Abraham *et al.,* 2005; Gullo *et al.,* 2005; Heper *et al.,* 2006).

1.2.2 Aberrant mediator production

The inflammatory response represents an important, central component of sepsis because elements of the response drive the physiological alterations that become manifest as the systemic inflammatory response syndrome. An appropriate

inflammatory response eliminates the invading microorganisms without causing damage to tissues, organs, or other systems, (Figure 1.3).

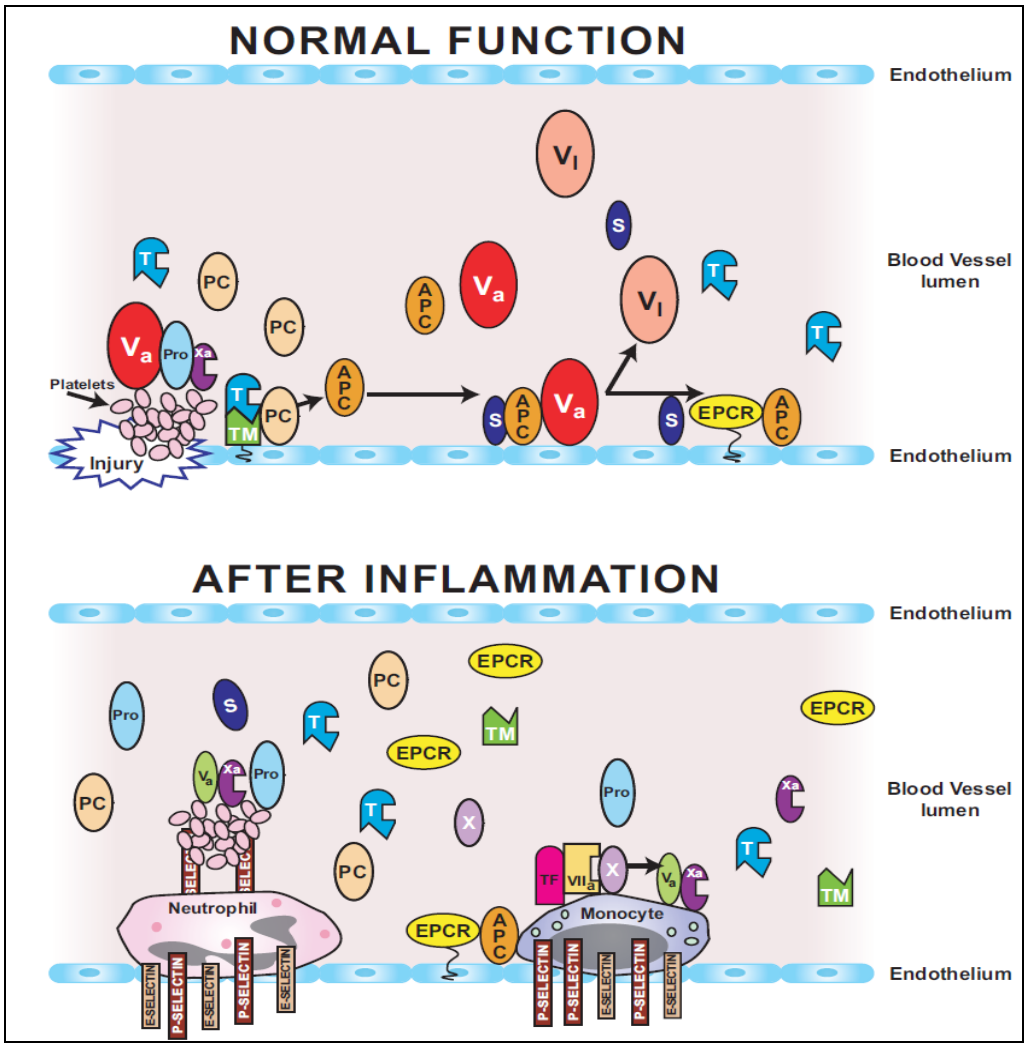

Figure 1.3: Control of coagulation in normal and inflamed vasculature. Top panel: normal function. Vascular injury, indicated on the lower portion of the blood vessel wall, initiates prothrombin (Pro) activation, which subsequently induces thrombin (T) formation. Prothrombin activation involves the formation of complexes between factor V_a and factor X_a. Thrombin then binds to thrombomodulin (TM) on the luminal side of the endothelial cell wall, and the thrombin-TM complex converts protein C to APC. APC then binds to protein S (S) on endothelial cell surfaces. The complex composed of protein S and APC then converts factor V_a into an inactive complex (V_I). Protein S and APC also interact with the endothelial cell protein C receptor (EPCR). Bottom panel: after inflammation. During inflammation, specific mediators cause the disappearance of thrombomodulin from the endothelial cell surface. The endothelial cell leukocyte adhesion molecules P-selectin and E-selectin are synthesized and expressed on the surfaces of endothelial cells or platelets. Tissue factor (TF) is expressed on monocytes where it binds to factor VII_a. The TF-VII_a complex converts factor X to factor X_a, which then complexes with factor V_a to generate thrombin from prothrombin. Very little APC is formed, and that which is formed does not function well because of low levels of protein S. Consequently, factor V_a is not activated, and the prothrombin activation complexes are stabilized. Modified from Br J Haematol, 131, Esmon CT, The interactions between inflammation and coagulation, 417–430, Copyright (2005), (Reprinted with permission from corresponding author. Daniel, G. R. (2007). Biological Perspectives Pathophysiology of Sepsis. *BAm J Pathol, 170,* 1435–1444)

1.2.2.1 Hyperinflammatory response

Several years ago, many basic science investigators and clinicians believed that the problem of sepsis was directly related to the exuberant production of proinflammatory molecules. The problem seemed rather simple: inflammation was excessive. The solution was easy: blunt inflammation, and save lives. This concept was driven by four pieces of information. First, septic patients with increased levels of specific mediators such as tumor necrosis factor (TNF) are at increased risk for death (Waage *et al.,* 1987). Second, injection of TNF molecules into experimental animals results in widespread inflammatory alterations (Remick *et al.,* 1987) and tissue injury (Tracey *et al.,* 1986) similar to that observed in septic patients. Third, experimental animals injected with lethal doses of endotoxin display elevated levels of the same mediators. Finally, inhibition of these specific mediators improves survival in endotoxin shock models (Beutler *et al.,* 1985; Abraham, Glauser *et al.,* 1997; Abraham, Laterre *et al.,* 2001; Cohen, 1999; Gordon *et al.,* 2004). Together, these observations launched a series of clinical trials aimed at blocking TNF or interleukin (IL)-1.

Although these individual trials did not show significant or dramatic improvements in survival, a meta-analysis of all TNF inhibitors did demonstrate overall improvement (Marshall, 2003). Despite these failed endeavors', exploration of new mediators of organ injury should still be explored. Among the potential candidates is high mobility group (Wang *et al.,* 1999; Baron, 2006) triggering receptor expressed on myeloid cells (TREM), (Gibot *et al.,* 2006) and vascular endothelial growth factor (Rodrick *et al.,* 1986). Another work mentioned the role of the complement system in sepsis, undoubtedly providing another fruitful area for investigation (Niederbichler *et al.,* 2006).

A frequent explanation put forth for the previous inhibitor trial failures was that the anti-inflammatory agents were not administered quickly enough. The classic endotoxin model of "sepsis" drove much of this thinking. In this model, lethal doses of endotoxin are injected intraperitoneally or intravenously into an experimental animal. Endotoxin induces a massive, rapid release of several proinflammatory molecules, including cytokines in both humans and experimental animals (Copeland *et al.*, 2005). However, subsequent work has shown that models of sepsis that more closely reproduce the clinical situation, such as caused by cecal ligation and puncture, induce a proinflammatory response that is substantially lower in magnitude and longer in duration than that observed after acute exposure to endotoxin (Remick *et al.*, 2000; Osuchowski *et al.*, 2006). In addition, human clinical trials aimed at giving global immunosuppression with high-dose glucocorticoids failed to yield any improvement in survival. Although the cecal ligation and puncture model of sepsis has become widely used, it may not represent the best preclinical model because most septic patients have a pulmonary source of infection (pneumonia) rather than peritoneal. Controversy remains about the best animal model for the study of sepsis (Buras *et al.*, 2005).

In traditional thinking, a mediator must be elevated and detectable to be implicated in the pathogenesis of disease. In septic patients with poor survival, TNF was elevated, and this provided a portion of the rationale on why it should be blocked. However, it must be borne in mind that cytokines may have significant effects at the local level such that detectable plasma levels may not be necessary for the cytokine blockade to be effective. This was shown dramatically in a recent clinical trial of neonatal-onset multisystem inflammatory disease where children treated with the IL-1 receptor antagonist demonstrated a remarkable improvement in both objective and subjective criteria (Goldbach-Mansky *et al.*, 2006). This dramatic improvement occurred even though IL-1

was not detectable in the plasma. As one index of improvement, IL-6 levels were significantly decreased with IL-1 receptor antagonist treatment.

1.2.2.2 Blunted inflammatory response

Another viewpoint would argue that septic patients failed to control the bacterial infection and died as a result of immunosuppression rather than immunostimulation. Recent work has shown that intensive care unit patients have reduced production of both TNF and IL-6 in response to endotoxin stimulation (Heagy *et al.,* 2000; Heagy *et al.,* 2003). Another study demonstrated that although TNF was reduced, IL-10 production was not impaired in patients with sepsis (Rigato *et al.,* 2003). These studies would indicate that the proinflammatory response could not be initiated, whereas the anti-inflammatory response continued unabated, producing the equivalent of a blunted inflammatory response. Patients with severe burns and sepsis exhibit defects in their T lymphocytes because the cells fail to proliferate in response to mitogenic stimuli and also fail to produce IL-2 or -12 (Rodrick *et al.,* 1986; O'Sullivan *et al.,* 1995). Because blocking the inflammatory response with specific inhibitors was not tremendously effective, the possibility was raised that the patients required immunostimulation. However, in the clinical trial using granulocyte colony-stimulating factor (G-CSF) to treat 701 patients with pneumonia and severe sepsis, there was no improvement in survival (Root *et al.,* 2003). In a smaller study with 58 patients, granulocyte macrophage colony-stimulating factor (GM-CSF) also did not improve survival but did decrease length of hospitalization and improve other clinical parameters (Orozco *et al.,* 2006; Carr *et al.,* 2009). The blunted monocyte response observed in septic patients has been reversed with interferon, and systemic therapy successfully cleared sepsis in eight

of nine patients (Do¨cke *et al.,* 1997). A larger clinical trial with 416 trauma patients indicated that interferon therapy did not reduce infections or overall mortality but did reduce deaths due to infections (Dries *et al.,* 1994).

1.2.2.3 Unknown inflammatory response

The previous data would indicate that the inflammatory response in septic patients is complex and not as neatly defined as enhanced or decreased. Because of this heterogeneous response, some patients will benefit from blunting their inflammation, whereas others would be better served by augmenting their inflammatory response. Tailoring the therapy to the individual patient occurs with many diseases, and sepsis should not be an exception. Work with the preclinical model of sepsis has indicated that blunting inflammation only improves survival in those animals at a high risk of dying (Remick *et al.,* 2003). Clinical evidence favoring a tailored response comes from sepsis trials demonstrating that low-dose glucocorticoid therapy is most effective in those patients with an impaired adrenal response (Annane *et al.,* 2002). Roger Bone observed, "We should spend more time learning how to achieve an accurate diagnosis and less time searching for a magic bullet." (Bone *et al.,* 1996). In this context, different plasma markers have been proposed as diagnostic markers for the presence of sepsis as well as the severity of sepsis. These molecules may not actually participate in the cell or organ injury but may serve as markers for the presence and severity of sepsis. It must be acknowledged that controversy exists in this area. Some investigators believe that IL-6 serves as a marker of injury (Remick *et al.,* 2002); whereas others believe, that IL-6 may be responsible for the altered pathophysiology. Measuring plasma levels of cytokines is probably not sufficient to determine whether a patient or experimental

animal is hyperinflammatory or hypoinflammatory. If only the proinflammatory mediators are measured, then the patient will appear hyperinflammatory. Conversely, if only cytokine antagonists or anti-inflammatory mediators are measured, a person appears to be hypoinflammatory. In fact, both proinflammatory and anti-inflammatory mediators may be circulating at the same time in the plasma. Better methods for determining the precise immunological status may be achieved via either a multiplex format for cytokine measurements (Marti *et al.,* 2003; Knight *et al.,* 2004; Kumar, Sudhir *et al.,* 2009) or an evaluation of cellular function.

1.2.3 Cellular dysfunction

Many cellular aspects become dysfunctional in sepsis and may be characterized as either excessive activation or depressed function. Excessive activation refers to cells that are primed such that they respond in a very vigorous manner to a second stimulus. An example of excessive activation would be neutrophils generating excess toxic products that cause damage to nearby cells (Weiss, 1989). An example of depressed function would be neutrophil failure to phagocytize and clear invading pathogens. One of the current areas of active investigation concerning cellular function is the induction of cellular apoptosis or necrosis. The signaling mechanisms and molecules that induce apoptosis are currently being described in great detail by a number of investigators. One must carefully evaluate the literature with regard to apoptosis because some detection methodologies suffer from a high rate of false-positive reactions with subsequent controversy concerning the findings (Grassme *et al.,* 2001; Hotchkiss *et al.,* 2001). Apoptosis and necrosis in the field of sepsis have been reviewed quite nicely in the recent past (Oberholzer *et al.,* 2001; Wesche *et al.,* 2005). Apoptosis may contribute to

the pathogenesis of sepsis by delayed removal of those cells that should be removed (i.e. neutrophils) and early removal of those cells that should not be removed (i.e. lymphocytes).

1.2.3.1 Lymphocyte apoptosis

Lymphocytes are critical cells in the response to sepsis, and the interactions between the innate and adaptive immune system are becoming increasingly important. Pioneering studies by Hotchkiss *et al.,* (1999) have defined that septic patients have significant apoptosis of lymphocytes.

These apoptotic lymphocytes were observed in virtually all lymphoid organs including the obvious locations, such as the spleen and thymus, but also in the gastric associated lymphatic tissue and essentially, wherever collections of lymphocytes exist. These murine experiments were extended in a very interesting study when these investigators performed rapid autopsies in the intensive care unit on patients who died from sepsis (Hotchkiss *et al.,* 1999). It was necessary to perform the autopsies rapidly to collect tissue that did not display substantial post-mortem autolysis. Lymphocyte apoptosis may be the cause of the reduced lymphocyte function in septic patients previously described (failure to produce cytokines). In septic patients, there is a combination of apoptotic and necrotic cell death. The importance of apoptosis in the pathophysiology of sepsis has been demonstrated in multiple studies (Wesche *et al.,* 2005). It has been shown transfer of apoptotic splenocytes will worsen survival in a mouse model of sepsis, whereas transfer of necrotic splenocytes improves survival (Hotchkiss *et al.,* 2003).

1.2.3.2 Neutrophil hyperactivity

Neutrophils are critical components of the innate immune response to infectious challenges. Neutropenic patients, regardless of the cause of the neutropenia, and patients with neutrophil dysfunction are at increased risk for the development of infectious complications (Lekstrom-Himes *et al.*, 2000). The appropriate neutrophil response will help the patient to eradicate an infectious focus. The difficulty lies in attempting to define an appropriate response versus a hyperactive response (Brown *et al.*, 2006; Koch & Zacharowski, 2009), as illustrated in Figure 1.4. Patients who have suffered traumatic injury are at increased risk for the development of multisystem organ failure, and neutrophils recovered from such patients demonstrate increased chemotactic responses to CXC chemokines (Bhatia *et al.,* 2005). However, neutrophils isolated from septic patients demonstrate decreased chemotaxis toward IL-8 and depressed expression of CXCR2 (Chishti *et al.,* 2004). These results were further explored in an article showing that high CXCR2 function correlates with the development of organ injury, i.e., acute respiratory distress syndrome, whereas low function predisposes to pneumonia and sepsis (Adams *et al.*, 2001). These studies aptly demonstrate the heterogeneity of the septic response in that some patients have an excessive response, whereas others have a blunted response. Modulating the recruitment of neutrophils to the site of inflammation has potential benefits, but this should be via specific modulation rather than global inhibition of neutrophil function. Recently, classes of immunomodulatory compounds termed pepducins, which are cell-penetrating lipopeptides, have been used to target CXC chemokine receptors (Kaneider *et al.,* 2005). These compounds were able to block neutrophil chemotaxis to CXC chemokines without affecting neutrophil responses to other stimulants such as the formyl peptides. These compounds were used in the murine model of cecal ligation and puncture-induced sepsis, where they were able to

significantly improve survival. Another significant issue concerns inappropriate apoptosis of neutrophils in the septic patients. Neutrophils in the circulation typically have a very short lifespan of approximately 24 hours. However, patients with sepsis have a delay in their neutrophil apoptosis, causing them to persist longer in the bloodstream. This is due to prolonged activation of nuclear factor B and reduced caspase 3 levels (Taneja *et al.,* 2004). As a result, the septic patient has increased numbers of activated cells with the potential to cause organ injury. However, it must be borne in mind that these activated neutrophils are also the precise defenders that are critical in the innate immune response to clear an infection (Smith, 1994; Brunialti *et al.,* 2006; Zhu & Qu, 2007; Salomao *et al.,* 2009).

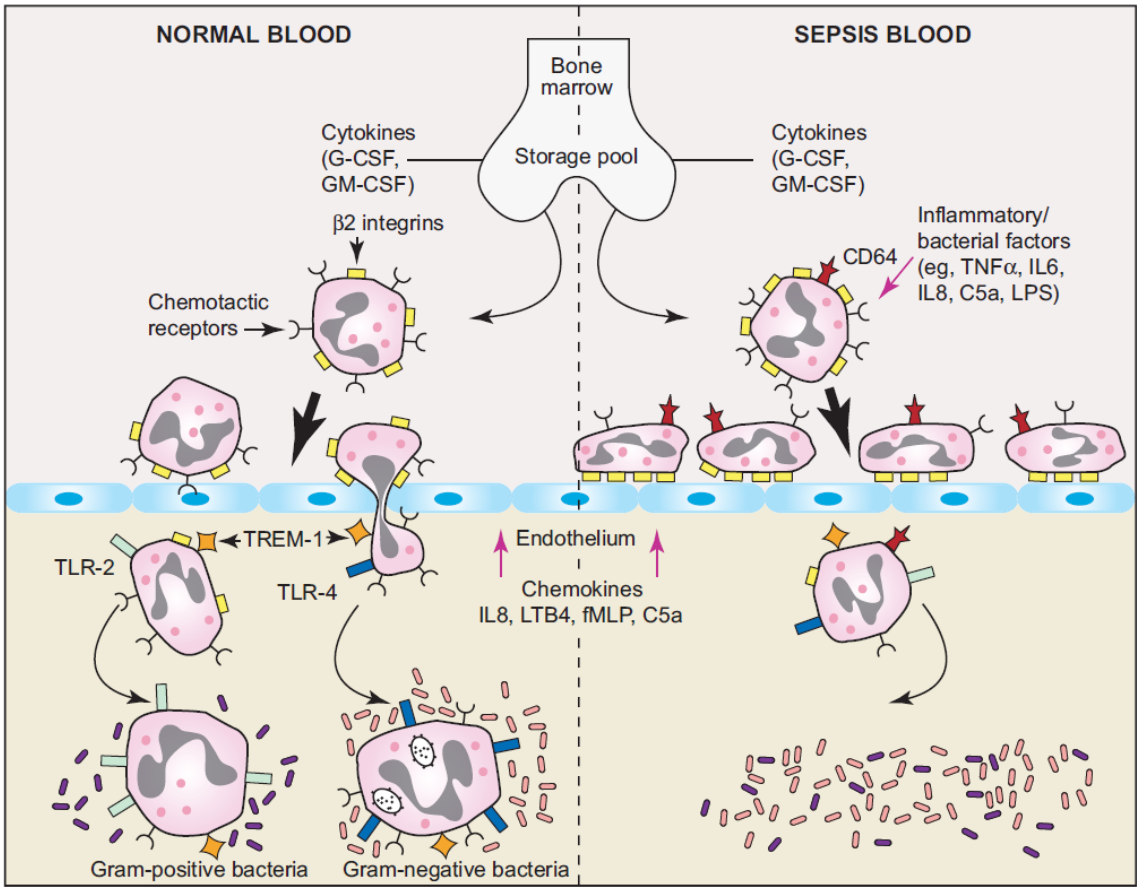

Figure 1.4: Proposed model for dysregulation of neutrophil recruitment to bacterial infection in non-pulmonary tissue under normal conditions (left) and in sepsis (right). Colony stimulating factors [granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF)] induce the release of neutrophils from the bone marrow. Under normal conditions, large numbers of the peripheral blood neutrophils enter sites of bacterial infection by first adhering to activated endothelial cells and then migrating along a gradient of chemotactic factors. These chemotactic factors are produced at the local site of infection. Neutrophils use Toll-like receptors (TLR-2 or TLR-4) to interact with pathogen-associated molecular patterns on bacteria to phagocytize and eliminate the pathogens. In contrast, neutrophils from septic patients have increased expression of surface integrins, which promote firm adhesion to endothelial cells. As a consequence, the neutrophils remain bound more tightly to the endothelial cells and fail to migrate appropriately into the site of the bacterial infection. (Reprinted with permission from corresponding author. Daniel, G. R. (2007). Biological Perspectives Pathophysiology of Sepsis. *BAm J Pathol, 170,* 1435–1444)

1.2.3.3 Endothelial cell failure and apoptosis in other cells

Endothelial cells reside at the critical interface between the blood and tissue. Intact endothelial cells exhibit anticoagulant properties through elaboration of anticoagulant molecules such as protein C. These cells also serve as a barrier between blood products and procoagulant molecules, such as heparin, residing in the extracellular matrix. Endothelial disruption comes about because of increased expression of adhesion