ROLE OF BIOMARKERS IN THE MANAGEMENT OF ANTIBIOTIC THERAPY DURING SEPSIS

Essay

Submitted for Partial Fulfillment of the Master degree in
Intensive Care Medicine

Presented By

Dr. Rokia Darwish Ayad

M.B., B.Ch. Mansoura University

Under Supervision of

Prof. Dr.Magdy Mohammed Hussin Nafie

Professor of Anesthesia and Intensive care

Faculty of Medicine, Ain Shams University

Dr. Sherif Sameer Wahba

Assistant Professor of Anesthesia and Intensive Care

Faculty of Medicine, Ain Shams University

Dr.Mai Mohsen Abd El Aziz

Lecturer of Anesthesia and Intensive Care

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2014

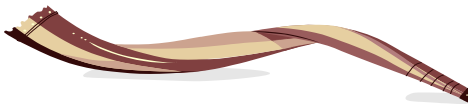
Acknowledgment

First thanks to **Allah** *whose magnificent help was the main theme in accomplishing this work.*

It is a great pleasure to express my sincere thanks and gratitude to **Prof. Dr. Magdy Mohammed Hussin Nafie,** *Professor of Anesthesia and Intensive care, Faculty of Medicine, Ain Shams University for his vast knowledge, skillful scientific comments, wide experience, constructive advices that added much to this work and made this work executed. Any attempt to express my indebtedness to him, will be far from being complete.*

I am also very grateful and appreciative to **Dr.Sherif Sameer Wahba,** *Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his contributive comments and sincere efforts that served much in the construction of this work.*

I find no words by which I can express my deepest gratitude and sincere thanks to **Dr. Mai Mohsen Abd El Aziz,** *Lecturer of Anesthesia and Intensive Care, Faculty of medicine, Ain Shams University, for her kind care, honest help and guidance throughout the performance of this work.*



Rokia Ayad

Contents

Title	Page
Introduction	1
Definition of sepsis and septic shock.....	6
Causes and Pathophysiology of septic shock	**8**
Sources of infection	8
People at risk	10
Pathophysiology of sepsis	12
Diagnosis of sepsis.....	**15**
History and physical examination	15
Differential diagnosis	18
Laboratory studies	25
Imaging studies	27
Role of biomarkers in diagnosis of sepsis	**28**
PCT and CRP as biomarkers of sepsis.....	32
Biomarkers of complement proteins in sepsis	36
Biomarkers of activated neutrophils and monocytes in sepsis	37
Bomarkers of the immunosuppressive phase of sepsis	44
Biomarkers of organ dysfunction in sepsis	47
Multi-marker approach to the diagnosis of sepsis	51
Role of biomarkers in antibiotic strategy during sepsis	**56**
Antimicrobial Therapy	57
Biomarkers currently available for optimizing antibiotic therapy	64
C-reactive Protein	65
Procalcitonin	67
limitations of procalcitonin	71
Procalcitonin versus C-reactive protein	72
Lower respiratory tract infection.....	75
Algorithm 1: LRTI Initial PCT Value	76
Algorithm 2: LRTI PCT Value Follow Up	76
Sepsis	77
Algorithm 3: Sepsis Initial PCT Value	79
Algorithm 4: Sepsis PCT Follow Up	80
Summary	**83**
References	**85**
Arabic Summary	**1**

List of abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
APTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome.
ATP	Adenosine triphosphate
CARS	Compensatory anti-inflammatory response syndrome’
CBC	Complete blood count
cGMP	Cyclic guanosine monophosphate
CHF	Congestive Heart Failure.
CK-MB	Creatine kinase MB
CLP	Cecal ligation and puncture
CNS	Central nervous system
CO	Cardiac output
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein.
CT	Computed tomography
CTLA-4	CTLA-4: cytotoxic T lymphocyte-associated antigen-4
CVP	Central venous pressure.
CVs	Cutoff values
DA	Diagnostic accuracy
DAMPs	Damage-associated molecular patterns
DIC	Disseminated Intravascular Coagulation.
ECG	Electrocardiography
ED	Emergency Department
ED	Emergency department
ER	Emergency room
FDA	US Food and Drug Administration
FiO2	Fraction of inspired oxygen
FSP	Fibrin split products
GI	Gastro Intestinal .
Gu	Genito-urinary
HBP	Heparin-binding protein
HMGB1	High-mobility group box 1
ICU	Intensive care unit
IL-1ra	IL-1 receptor antagonist
ILs	Interleukins.
INR	International normalized ratio
IV	Intravenous
LPS	Lipopolysaccharide.
LPS	Lipoproteins
LRTI	Lower respiratory tract infection.
MAP	Mean arterial blood pressure.
MCP-1	Monocyte chemoattractant protein-1
MHC	Major histocompatability complex.
MI	Myocardial Infarction.

MODS	Multiple organ dysfunction syndrome
MODS	Multi Organ Dysfunction Syndrome.
MOF	Multi Organ Failure.
MRI	Magnetic resonance imaging
MRP:	Myeloid related protein
MRSA	Methicillin-resistant S. aureus.
MSSA	Methicillin-sensitive S aureus
NGAL	Neutrophil gelatinase-associated lipocalin
NO	Nitric oxide
NOD	Nucleotide-oligomerization domain
NPV	Negative predictive value
PAMP	Pathogen-associated molecular pattern
PASS	Procalcitonin and Survival Study
PCR	Polymerase chain reaction
PD	Programmed death
PMNs	Polymorph-nuclear neutrophils
PPV	Positive predictive value
PRRs	Pattern recognition receptors
PT	Prothrombin time
PCT	Procalcitonin.
PTX3	Pentraxin
PVR	Peripheral vascular resistance;
RAGE	Receptor for advanced glycation end-products
RCTs	Randomized, controlled trials
RIG-I	Retinoic-acid-inducible gene I
RNA	Ribonucleic acid
SIRS	Systemic inflammatory response syndrome
SOFA	Sepsis-related Organ Failure Assessment
STREM	Soluble Triggering Receptor Expressed on Myloid cells.
TGF	Transforming growth factor
Th2	Type 2 helper lymphocytes.
TLRs	Toll-like receptors.
TNF- α	Tumor Necrosis Factor-alpha.
VRE	Vancomycin-resistant enterococi
Vs	Versus.
WBC	White blood cell.

List of Tables

Table	*Title*	*Page*
1	Definitions of sepsis	7
2	Clinical conditions associated with sepsis.	19
3	Non infectious conditions mimicking clinical and hemodynamic parameters of sepsis.	21
4	Characteristics of pseudosepsis and sepsis.	22
5	LRTI Initial PCT value.	76
6	LRTI P PCT value follow up.	76
8	Sepsis Initial PCT value	79
9	Sepsis PCT value follow up	80

List of figures

Figure	***Title***	***Page***
1	A right lower quadrant abdominal wall abscess	10
2	Phases of sepsis	14
3	Cytokines are essentially responsible for the features of SIRS	30
4	Activated inflammatory cells up-regulate a number of proteins which may be detected as biomarkers of sepsis	39
5	Biomarkers of the immune-suppressive phase of sepsis	44
6	An alternative model for the progression of sepsis to severe sepsis	54

Introduction

Sepsis is a growing problem worldwide associated with mortality rates as high as 60%.***(Wang andYang , 2010)***

Sepsis is not a true disease, rather an innate response by the immune system to bacterial, viral or fungal infection. ***(Hunter , 2006).***

Sepsis is a leading cause of mortality in critically ill patient . Delay in diagnosis and treatment have been shown to increase mortality in this cohort ,however, differentiating sepsis from non infectious triggers of the systemic inflammatory response syndrome(SIRS) is difficult especially in critically ill patients who may have SIRS for other reasons.

It is the conundrum that drives broad spectrum antimicrobial use and associated evolution of antibiotic resistance in the critical care environment .It is perhaps un surprising ,therefore that the search for a highly accurate biomarker of sepsis has become one of the holy grails of medicine ***(Savitri Kibe1 et al.,2011)***

Current researches focus on: Improving earlier diagnosis, Improving understanding of the inflammatory response**,** how best to treat the syndrome and what points of treatment are most effective.

Pathophysiology of sepsis is complex and results from the effects of the circulating bacterial products mediated by cytokine release caused by sustained bacteremia. Cytokines are responsible for the clinically observable effects of bacteremia in the host. ***(Ipec., 2010).***

Impaired pulmonary, hepatic, or renal function may result from excessive release of cytokines during septic process. Increasing understanding of the inflammatory host response to bacterial pathogens has led to discovery of multiple potential biomarkers that may aid in diagnosing serious bacterial infections quickly and accurately.

The field of infection associated biomarkers has grown within the past few years, and still expanding. Routinly available biomarkers which might be useful for antibiotic management of acute infection are currently limited to C-Reactive Protein (CRP) and Pro calcitonin (PCT). Other promising biomarkers that may prove useful in the near future but need to undergo clinical testing includes:

- **The soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1).**
- **Soluble urokinase-type Plasminogen receptor (suPAR).**
- **proadrenomedullin (ProADM).**
- **Prespepsin.**

A biomarker is a biological characteristic ,objectively measured and used as indicator for a physiological or pathological process or the activity of a medicine.
According to The National Institute of Health (NIH) panel, biomarkers can be stratified into: Prognostic markers and Predictive markers. Prognostic markers allow stratifying patients according to their individual risk of having specified outcome independently of therapy (or of the lack of therapy) .Predictive markers allow predicting the potential benefit (efficacy) and/or the risk .(Toxicity) of a therapy according to the biomarker status. ***(Dupuy et al. , 2013)***

Early diagnosis of sepsis is helpful in initiating effective antibiotics which is useful to de-escalate antibiotic therapy for sepsis whenever possible. Empirical antimicrobials should be chosen that cover all likely causative pathogens,Nearly always including bacteria but ,sometimes also fungi and /or viruses.***(surviving sepsis guidelines 2013).***

In 2004 and again in 2008, an international group of experts representing 11organisation published the first and the second internationally accepted guidelines to improve outcomes in severe sepsis and septic shock ***(Delinger ,crit .care .med 2004 ,2008)*** and now ,the third edition were published in Feb.2013.Surviving sepsis guidelines recommendations for treating severe sepsis are:

- Give appropriate and effective antibiotics as early as possible for patients known or suspected to be in severe sepsis or septic shock.
- Early Goal-Directed Therapy for severe sepsis/septic shock . For patients with tissue hypo perfusion from sepsis. Surviving Sepsis Guidelines advise volume resuscitation should start immediately and follow an institutional protocol.
- Transfusion of blood products for severe sepsis and septic shock.
- Erythropoietin : not advised as treatment for anemia from sepsis/septic shock.
- No Anti thrombin III for severe sepsis / septic shock.
- Vasopressors are provided for septic shock that does not respond to fluid resuscitation. Nor epinephrine (Levophed), epinephrine, vasopressin, phenylephrine (Neo-Synephrine), and dopamine are the most commonly used vasopressors for septic shock.

Prognosis of sepsis depends on the health and host defenses, early and empiric antimicrobial therapy and surgical interventions**. *(Sarikonda et al.,2010).***

Aim of the study

To discuss the role of biomarkers in early diagnosis and management of sepsis, and the potential role of biomarkers in improving antimicrobial prescription.

Contents:

1. Definition of sepsis and septic shock.
2. Causes and Pathophysiology of sepsis.
3. Diagnosis of sepsis.
4. Role of biomarkers in diagnosis of sepsis.
5. Role of biomarkers in antibiotic strategy during sepsis.
6. Summary.
7. References.
8. Arabic summary.

References

- ***Cardelli P, Ferraironi M, Amode R*** . Evaluation of neutrophil CD64 expression and procalcitonin as useful markers in early diagnosis of sepsis. *Int. J. Immunopathol. Pharmacol.* 21(1), 43–49 (2008).
- ***Cheng BL, Xie GH, Yao SLl.*** Epidemiology of severe sepsis in critically ill surgical patients in ten university hospitals in China. *Crit. Care Med.* 35, 2538–2546 (2007).
- ***Dellinger***, crit care med(2004)-(2008).
- ***Dupuy*** . Annals of intensive care(2013).
- ***Hunter P.*** Sepsis under siege – a new understanding of sepsis might lead to the development of therapies to treat septic shock. *EMBO Rep.* 7, 667–669 (2006).
- ***Ipek IO, Saracoglu M, Bozaykut A***. α(1)-acid glycoprotein for the early diagnosis of neonatal sepsis. *J. Matern. Fetal Neonatal Med.* 23(7), 617–621 (2010).
- ***Kauss IAM, Grion CMC, Cardoso LTQ*** . The epidemiology of sepsis in a Brazilian teaching hospital. *Brazilian J. Infect. Dis.* 14(3), 264–270 (2010).
- ***Rego MAC, Martinez FE, Elias J, Mussi-Pinhata MM***. Diagnostic value of interleukin-6 and C-reactive protein on early onset bacterial infection in preterm neonates with respiratory distress. *J. Perinat. Med.* 38(5), 527–533 (2010).
- ***Sankar MJ, Agarwal R, Deorari AK, Paul VK***. Sepsis in the newborn. *Indian J. Pediatr.* 75(3), 261–266 (2008).
- ***Savitri Kibe1, Kate Adams1 and Gavin Barlow***. J Antimicrob Chemother 2011; 66 Suppl 2: ii33–ii40--doi:10.1093/jac/dkq523.
- ***Surviving Sepsis Guidelines*** 2013 – Review & Update.

- ***Wang P, Yang Z, He Y, Shu C.*** Pitfalls in the rapid diagnosis of positive blood culture. *Rev. Med. Microbiol.* 21(3), 39–43 (2010).
- ***Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC.*** The epidemiology of severe sepsis in children in the United States. *Am. J. Respir. Crit. Care Med.* 167(5), 695–701 (2003).
- ***Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE.*** Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. May 2010;38(5):1276-83.