Interleukin 17-A as a marker of severity of sepsis in polytrauma patients: A prospective observational study

Thesis

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Abstract

Rationale and Background: Trauma is the fourth leading cause of death worldwide. One of the major complications of trauma is sepsis. Sepsis is a critical problem with significant morbidity and mortalityand is one of the most frequent indications of ICU admission. Interleukin 17A has a central role in the pathogenesis of systemic response to injury.

Objective: The current study investigates Interleukin 17A as a predictor of sepsis in polytrauma patients and as a marker of its severity.

Patients and methods: One hundred polytraumatized patients were enrolled in our study. Each patient was tested for interleukin 17A within the first 24 hours of ICU admission.

Results: There was a significant correlation between serum level of Interleukin 17A and sepsis and septic shock development and with 28 day mortality.

Conclusion : Interleukin 17A could be regarded as a good predictor of sepsis in poly trauma patients

Keywords:Sepsis- ICU – Interleukin-17A – polytrauma

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LIST OF ABBREVIATIONS

AIS	Abbreviated Injury Severity
ALI	Acute lung injury
APACHE	Acute physiological and chronic health evaluation
ARDS	Acquired respiratory distress syndrome
BBB	Blood Brain Barrier
CBC	Complete blood count
CNS	Central nervous system
CVP	Central venous pressure
CXC	Chemotaxis
CRP	C-Reactive Protein
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
DO2	Oxygen delivery
ECG	Electrocardiogram
FiO_2	Fractional inspired oxygen concentration
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte monocyte colony stimulating factor
GI	Gastrointestinal
HDL	High density lipoproteins
HPA	Hypothalamo –pituitary- axis
HR	Heart rate
ICU	Intensive care unit
IHD	Ischemic heart disease

INR	International normalized ratio
IL	Interleukin
LDL	Low density lipoprotein
LPS	Lipopolysaccharide
LMWH	Low molecular weight heparin
MAP	Mean arterial pressure
MHC	Major histocompatibility complex
MIF	Macrophage inhibitory factor
MODS	Multiple Organ Dysfunction Syndrome
MRSA	Methicillin resistant staph aureus
NMBA	Neuromuscular blocking agent
NO	Nitric oxide
PAF	Platelet activating factor
PMNs	Polymorphnuclear leucocytes
PCT	Procalcitonin
RBC	Red blood corpuscles
RCT	Randomized controlled trial
ROC	Receiver Operating Characteristic Curve
rhAPC	Recombinant human activated protein C
RR	Respiratory rate
SDD	Selective digestive tract decontamination
SBP	Systolic blood pressure
SIRS	Systemic inflammatory response syndrome
SVO_2	Saturated venous oxygen tension

TNF	Tumor necrosis factor
TH17 cells	T- Helper 17 cells
VAP	Ventilator associated pneuomonia
WBC	White blood cells

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Background and Rationale

Trauma is the fourth leading cause of death worldwide.[1] One of the most serious complications of major trauma is the sequential dysfunction of vital organs, which is associated with posttraumatic sepsis in most cases.[2, 3]

In adults, major trauma initiates a two-fold compromise of the immune system with hyper-inflammation in response to injury and subsequent immunosuppression. [4, 5]

Posttraumatic hyper-inflammation is characterized by local and systemic release of proinflammatory cytokines, metabolites and acute phase proteins [6] leading to a systemic inflammatory response syndrome (SIRS)[6,7]. Later, anti-inflammatory mediators are released inducing immunosupression with susceptibility to infection and septic complications during the further clinical course [8]. The imbalance of this dual immune response seems to be responsible for organ dysfunction and multiple organ failure in adults. [6]

Sepsis develops in around 750,000 people annually and accounts for more than 210,000 deaths per year. Evolving definitions of sepsis including predisposing factors, host response, and end-organ damage emerged in recent years leading to our improved understanding of the pathophysiology of the disorder and the targeted treatments. [9]

Systemic inflammatory response syndrome (SIRS) is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, killing one in four (and often more), and are increasing in incidence.[10-14]

IL-17 has been linked to the severity of inflammation in tissues. IL-17 initiates production of other proinflammatory mediators such as IL-1, TNFα, IL-6, IL-8, CCL20 and G-CSF, collectively resulting in an influx of neutrophils. [58]
IL-17 synergizes with other mediators such as IL-1, IL-6 and TNFα to activate tissue-infiltrating neutrophils to facilitate the effective elimination of invading bacteria or fungi.

There is growing evidence that genetic variation in the IL-17A gene rs1974226 single nucleotide polymorphism (SNP) is intimately associated with responsiveness to gram-positive bacteria and susceptibility to infectious and noninfectious diseases. [59]
Goals of early resuscitation in patients with sepsis include restoration of tissue perfusion and normalization of cellular metabolism. When appropriate fluid administration fails to restore adequate tissue perfusion and arterial pressure, vasopressors are usually necessary to increase mean systemic pressure, cardiac output and oxygen delivery.[15]

Anesthetists are frequently involved in the care of severely septic patients in the emergency department, operating theatre & intensive care unit. Infection source control, involving surgical drainage of an abscess or debridement of necrotic tissue coupled with early effective antimicrobial therapy, is crucial to the successful treatment of a patient with severe sepsis. In high-risk surgical or trauma patients with sepsis, early hemodynamic optimization before the development of organ failure reduced mortality by 23% in comparison with those who were optimized after the development of organ failure.[16]

Objective

In the view of the central role of IL-17A in the pathogenesis of systemic inflammatory response to injury, this study will further investigate whether there is a correlation between the level of IL17A and the degree of severity of sepsis in polytrauma patients.

Hypothesis

Our hypothesis was that IL-17A level would be higher in those patients who will develop sepsis.

Systemic Inflammatory Response Syndrome (SIRS):

The idea behind defining SIRS was to define a clinical response to a nonspecific insult of either infectious or noninfectious origin. Two or more of the following are present in systemic inflammatory response syndrome:

• Temperature > 38 OR <36 degrees Celsius

• Heart rate > 90 beats/minute

• Respiratory rate > 20 breaths/minute OR $PaCO_2$< 32 mm Hg

• White blood cell count > 12,000/mm^3 OR < 4,000/mm^3 OR > 10% immature (band) forms.[14]

Sepsis:

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Tables 1 and 2).[14]

Sepsis- induced hypotension is defined as a systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg or a SBP decrease > 40 mm Hg or less than two standard deviations below normal for age in the absence of other causes of hypotension.[14]

Septic shock:

Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypo-perfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.[14]

Table (1)Diagnostic Criteria for Sepsis[15]

Infection, documented or suspected, and some of the following:

General variables
Fever (> 38.3°C).
Hypothermia (core temperature < 36°C) .
Heart rate > 90/min^{-1} or more than two SDabove the normal value for age .
Tachypnea .
Altered mental status .
Significant edema or positive fluid balance (> 20 mL/kg over 24 hours) .
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes.
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1}) .
Leukopenia (WBC count < 4000 μL^{-1}) .
Normal WBC count with greater than 10% immature forms .
Plasma C-reactive protein more than two standard deviations above the normal value.
Plasma procalcitonin more than two SD above the normal value .
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age).
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2< 300) .
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hours despite adequate fluid resuscitation) .
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L.
Coagulation abnormalities (INR > 1.5 or aPTT> 60 s).
Ileus (absent bowel sounds) .
Thrombocytopenia (platelet count < 100,000 μL^{-1}).
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L).
Tissue perfusion variables .
Hyperlactatemia (> 1 mmol/L).
Decreased capillary refill or mottling.

WBC; white blood cell, SBP; systolic blood pressure, MAP; mean arterial pressure, INR; international normalized ratio, aPTT; activated partial thromboplastic time,PaO_2;arterial oxygen tension,FiO_2; fraction of inspired oxygen.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature> 38.5° or < 35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mentalstatus, hypoxemia, increased serum lactate level, or bounding pulses.[7]

Table (2) Diagnostic criteria for Severe Sepsis[15]

Severe sepsis definition is sepsis induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection):
Sepsis-induced hypotension.
Lactate above upper limits laboratory normal.
Urine output < 0.5 mL/kg/hour for more than 2 hours despite adequate fluidresuscitation.
Acute lung injury with PaO_2/FiO_2< 250 in the absence of pneumonia as infection source.
Acute lung injury with PaO_2/FiO_2< 200 in the presence of pneumonia as infection source.
Creatinine> 2.0 mg/dL(176.8 μmol/L).
Bilirubin > 2 mg/dL(34.2 μmol/L).
Platelet count < 100,000 μl.
Coagulopathy (INR> 1.5).

PaO_2;arterial oxygen tension,FiO_2; fraction of inspired oxygen, INR; international normalized ratio.

Causative organisms

Gram-negative organisms account for most adult cases of septic shock. In the hospitalized patient, the most common gram-negative organisms are E. Coli, Klebsiella,Enterobacter and Pseudomonas aeruginosa.Gram-positive organisms are becoming increasingly associated with sepsis due to the use of intravenous catheters and invasive devices. The most common gram-positive organisms seen are the Staphylococcus and Streptococcus species as well as Pneumococcus and Enterococcus faecalis. Viruses, protozoa, parasites, fungi (i.e. Candida albicans) and anaerobic organisms (i.e. Clostridium, Bacteroidesfragilis) are also known to be associated with sepsis. [16]