Updates in management of septic shock & role of Statins in sepsis

An Essay Submitted for Partial Fulfillment of Master Degree in Anesthesiology
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List of abbreviations:

ARDS	Acute respiratory distress syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation II
APC	Activated Protein C
ALI	Acute lung injury
AVP	Arginine vasopressin
BG	Blood glucose
CYP	Cytochrome P450 isoenzymes
DIC	Disseminated intravascular coagulation
DO2	Oxygen delivery
ECM	Extracellular matrix
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Ganulocyte macrophage colony-stimulating factor
GTPases	Guanosine triphosphatase
KATP	Adenosine triphosphate–sensitive potassium
HDL-C%	High Density Lipoproteins-Cholesterol%
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
ICU	Intensive care unit
IgG	Immunoglobulin G
IL-1	Interleukin-1
LDL-C%	Low Density Lipoproteins-Cholesterol%

LOS	Length of stay
MBP	Mean blood pressure
MHC	Major histocompatibility complex
MIF	Macrophage inhibitory factor
MRSA	Methicillin resistant Staphylococcus aureus
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NE	Norepinephrine
NMBA	Neuromuscular blocking agents
NO	Nitric oxide
ORSA	Oxacillin-resistant Staphylococcus aureus
PAF	Platelet activating factor
PaO2/FIO2	Partial arterial oxygen pressure/fraction of inspired oxygen
PaCO2	Partial arterial carbon dioxide pressure
PBW	Predicted body weight
PEEP	Positive End Expiratory Pressure
rhAPC	Recombinant Human Activated Protein C
SBP	Systolic blood pressure
SBT	Spontaneous breathing trial
ScvO2	Central venous oxygen saturation
SSC	Surviving Sepsis Campaign
SVO2	Mixed venous oxygen saturation
TFPI	Tissue factor pathway inhibitor
TG	Triglycerides

TNF	Tumor necrosis factor
t-PA	Tissue plasminogen activator
VAP	Ventilator-associated pneumonia
WBC	White blood cells count

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INTRODUCTION

Sepsis reflects the delicate balance between defense mechanisms against invading micro-organisms and both direct and indirect effects of these micro-organisms and their products. Severe sepsis is accompanied by the inability to regulate the inflammatory response. The cause of that is unknown ***(Riedemann et al, 2003).*** Except in few occasions, patients appear to die from the body's response to infection rather than from infection itself ***(Novack et al, 2006).***

Numerous trials have failed to demonstrate that blocking specific inflammatory mediators is beneficial in sepsis. Despite this frustration, new strategies are being explored ***(Riedemann et al, 2003***). However, in complex situations such as severe sepsis, multiple cellular activation processes are involved, so blocking a single component may be insufficient to arrest the inflammatory process ***(Almog, 2003)***.

Severe sepsis and septic shock are major healthcare problems, affecting millions of individuals around the world each year, killing one in four and often more, and increasing in incidence. The speed and appropriateness of therapy administered in the initial hours after severe sepsis influence outcome ***(Linde-Zwirble & Angus, 2004)***.

Statins have a variety of properties that are independent of their lipid lowering ability. These anti-inflammatory,

antioxidant, immunomodulatory, and antiapoptotic properities have been collectively referred to as pleiotropic effects ***(Blanco-Colio et al, 2003)*.**

Definition &Diagnosis

Severe sepsis is an infection-induced inflammatory syndrome that ultimately leads to organ dysfunction. It is estimated that more than 500,000 episodes of sepsis occur each year in the USA alone, and that 20–50% of these patients will die ***(Martin et al, 2003)***.The incidence of sepsis and number of sepsis-related deaths appear to be increasing. Important progress has been made in recent years, and interventions such as activated protein C, early goal-directed therapy, and possibly low-dose corticosteroids have been shown to improve survival in patients with severe sepsis ***(Riedemann et al, 2003)*** . Despite these advances, mortality remains unacceptably high and care for patients with sepsis costs as much as $50,000 per patient, resulting in an economic burden of nearly $17 billion annually in the USA alone ***(Martin et al, 2003)***.

Sepsis is defined as infection plus systemic manifestations of infection (Scheme 1). Sepsis is an inflammatory injury to the body resulting from the host immune response to an infectious stimulus. Uncomplicated sepsis, such as that caused by 'flu and other viral infections, gastroenteritis, or dental abscesses, is very common and is experienced by millions of people each year. Death is common among sepsis patients, with around 28–50%. The majority of these people will not need hospital treatment (**Levy et al, 2003**)**.**

Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Threshold for this dysfunction has varied somewhat from one severe sepsis research study to another. An example of typical thresholds identification of severe sepsis is shown in Scheme (2). Sepsis induced hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure <70 mm Hg or a SBP decrease >40 mm Hg in the absence of other causes of hypotension.Severe sepsis is a complex and often life-threatening condition. It can affect anyone but often develops in patients with pneumonia, trauma, surgery, burns or cancer. Severe sepsis results in the hospitalization of more than 750,000 people each year in the United States and similar in Europe. These patients have a mortality rate of approximately 30-35 % ***(Levy et al, 2003).***

Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis induced tissue hypoperfusion is defined as septic shock, an elevated lactate or oliguria ***(Sepsis Definitions Conference, 2003)***. Septic shock refers to sepsis patients with arterial hypotension that is refractory to adequate fluid resuscitation and leads to problems in one or more of the vital organs, the body does not receive enough oxygen to properly function, thus requiring vasopressor administration. Septic shock patients are very ill and need rapid emergency admission to the hospital intensive care unit ("ICU"). Despite active treatment in the ICU, the death rate is around 50%.Sepsis has risen to the 10th leading cause of death in United States ***(Levy et al, 2003).***

Diagnosis can be difficult as some of the symptoms of sepsis, such as fever, rapid pulse and respiratory difficulty, are very general and can be found in many other disorders. The symptoms of sepsis can easily be attributed to other conditions, creating problems of late or misdiagnosis

Scheme (1): *(Levy et al, 2001)*

Diagnostic criteria for sepsis

1-General variables

- Fever (>38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min or >2 SD(Standered Deviation) above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
- Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

2-Inflammatory variables

- Leukocytosis (WBC count >12,000/μL-1)
- Leukopenia (WBC count <4000 /μL -1)
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SDabove the normal value
- Plasma procalcitonin >2 SD above the normal value

3-Hemodynamic variables

Arterial hypotension (SBP <90 mm Hg; MAP <70 mm Hg; or an SBP decrease >40 mm Hg in adults or >2 SD below normal for age)

4-Organ dysfunction variables

- Arterial hypoxemia (PaO2/FIO2 <300)
- Acute oliguria (urine output <0.5 mL/Kg/ hr or 45 mmol/L for at least 2 hrs, despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL or 44.2 μmol/L
- Coagulation abnormalities (INR >1.5 or a PTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count<100,000 μL-1)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL)

5-Tissue perfusion variables

- Hyperlactatemia
- Decreased capillary refill or mottling

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation

Plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following