Updated Management of Refractory Shock

An Essay

Submitted for partial fulfillment of Master degree ***in General Intensive Care***

By

Sameh Mohamed Mohamed Yousof

M.B., B.Ch. (Cairo University)

Under supervision of

Dr. Ahmad Nagah El Shaer

Professor of Anesthesiology , Intensive Care and Pain Management

Faculty of Medicine- Ain Shams University

Dr. Heba Abdelazim Labib Ahmed

Assistant Professor of Anesthesiology, Intensive Care and Pain Management

Faculty of Medicine- Ain Shams University

Dr. Adel Alaa El-din Habib

Lecturer of Anesthesiology , Intensive Care and Pain Management

Faculty of Medicine- Ain Shams University

Faculty of Medicine

Ain Shams University

2018

﴿وَقُل رَّبِّ زِدْنِي عِلْماً﴾

سورة طـه الآيـــه رقم 114

Acknowledgement

First of all, all gratitude is due to ***Allah*** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to ***Dr. Ahmad Nagah El Shaer,*** *Professor of Anesthesiology, Intensive Care and Pain Management, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

I would like also to express my sincere appreciation and gratitude to ***Dr. Heba Abdelazim Labib Ahmed,*** *Assistant professor of Anesthesiology, Intensive Care and Pain Management, faculty of medicine, Ain Shams University, for her continuous directions and support throughout the whole work.*

Really I can hardly find the words to express my gratitude to ***Dr. Adel Alaa El-din Habib,*** *Lecturer of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University for his patience and support.*

Last but not least, I dedicate this work to my wife and my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Sameh Mohamed Mohamed Yousof

Contents

List of Abbreviations

ACE	:	Angiotensin converting Enzyme
ACS	:	American college of surgeons
ADH	:	Anti diuretic hormone
AIDS	:	Acquired immunodeficiency syndrome
AMI	:	Acute myocardial infarction
AMICS	:	Acute myocardial infarction with cardiogenic shock
ANG I	:	Angiotensin I
ANGII	:	Angiotensin II
AR	:	Aortic Regurge
ARDS	:	Adult respiratory distress syndrome
ASD	:	Atrial septal defect
ATHOS	:	Angiotensin II in treatment of high-output shock
ATLS	:	Advanced trauma life support
ATP	:	Adenosine triphosphate
CaO_2	:	Arterial oxygen content
CmVO2	:	Mixed venous oxygen content
CS	:	Cardiogenic shock
CT	:	Computed tomography
CVP	:	Central venous pressure
DNA	:	Deoxyribonucleic acid
DCR	:	Damage control resuscitation
dIVC	:	diameter of Inferior venae cava
DO2	:	Oxygen delivery
DVT	:	Deep venous thrombosis
dRV	:	Diameter of right ventricle
EBV	:	Estimated blood volume
ECMO	:	Extracorporeal Membrane Oxygenator
ESC	:	European society of cardiology
FWB	:	Fresh whole blood
GI	:	Gastrointestinal
GNI	:	Gross national income
HB	:	Hemoglobin
Hct	:	Hematocrit value
HLA	:	Human leucocyte antigen
HSD	:	Hypertonic saline dextran

List of Abbreviations (Cont.)

IABP	:	Intra Aortic Balloon Pump
ICU	:	Intensive care unit
IVC	:	Inferior venae cava
LOS	:	Length of stay
LV	:	Left ventricle
LVADs	:	Left ventricle assist devices
LVEF	:	Lef ventricle ejection fraction
MAP	:	Mean arterial pressure
MCS	:	Mechanical circulatory support
MCT	:	Multislice computed tomography
MDR	:	Multi drug resistance
MI	:	Myocardial infarction
MODS	:	Multi organ dysfunction syndrome
MTP	:	Massive transfusion protocol
NO	:	Nitric oxide
NSTACS	:	Non ST segment elevation acute coronary syndrome
OHCA	:	Out of hospital cardiac arrest
PBW	:	Predicted body weight
PCWP	:	pulmonary capillary wedge pressure
PE	:	Pulmonary embolism
PRBC	:	Packed red blood cell
RA	:	Right atrium
RAAS	:	Renin angiotensin aldosterone system
RBBB	:	Right bundle branch block
RCTs	:	Randomized control trials
RNA	:	Ribonucleic acid
RUSH	:	Rapid ultrasound for shock and hypotension
SIRS	:	Systemic inflammatory response syndrome
SPECTV/Q	:	Single positron emission computed tomography ventilation perfusion
StO_2	:	Tissue oxygen saturation
TNF	:	Tumor necrosis factor
TSS	:	toxic shock syndrome
ULMCA	:	unprotected left main coronary artery

List of Tables

List of figures

Introduction

Shock is defined as a state of cellular and tissue hypoxia due to reduced oxygen delivery and/or increased oxygen consumption or inadequate oxygen utilization. This most commonly occurs when there is circulatory failure manifested as hypotension (ie.,reduced tissue perfusion). Shock is initially reversible, but must be recognized and treated immediately to prevent progression to irreversible organ dysfunction ***(Vincent and De Backer , 2013).***

Four types of shock are recognized: distributive, cardiogenic, hypovolemic, and obstructive. However, these are not exclusive, and many patients with circulatory failure have a combination of more than one form of shock. There are many etiologies within each class ***(Vincent and De Backer , 2013).***

Septic shock, a form of distributive shock, is the most common form of shock among patients admitted to the intensive care unit, as reported by Randomized clinical trial between December 2003 and octobre 2007 in Belgium ,Spain and Austria, followed by cardiogenic and hypovolemic shock; obstructive shock is rare ***(De Backer et al., 2010).***

The term refractory shock is applied when, in spite of apparently adequate therapy, the shock state continues. Commonly, the treatment later proves to have been inadequate, in which case the shock was not true refractory shock. This often occurs following a major injury in which there is internal bleeding, leading to underestimation of true blood loss and therefore to inadequate transfusion. In certain cases, however, even if the therapy actually is

appropriate, the shock state persists; if patients in such cases respond to further special treatment, then this is true physiological refractory shock **(Prout, 2016).**

The microcirculation in refractory shock is characterized by heterogeneous alterations in both flow and vessel density **(Ince,2005).** Because these microcirculatory alterations are associated with increased morbidity and mortality, the microcirculation appears to be an appealing target in resuscitation **(Trzeciak et al., 2008).**

Despite significant improvement in the treatment of cardiogenic shock, including early revascularization, supportive treatment with intra aortic balloon pump (IABP), mechanical ventilation and diverse pharmacological treatments, the outcome of patients with cardiogenic shock remains dismal**.** Nitric oxide NO synthase inhibitors may be beneficial in the treatment of patients with refractory cardiogenic shock (**Hochman et al.,2006).**

Terlipressin (TP) is an effective vasopressor agent that could be an alternative or complementary therapy in refractory vasodilatory septic shock **(Masarwa et al.,2017).**

Aim of the Essay

The aim of this essay is to clarify the recent updates in diagnosis and management of refractory shock in the intensive care unit.

Pathophysiology of Shock

Shock is a clinical state of acute circulatory failure that can result from one, or a combination, of four mechanisms, The first of these is a decrease in venous return due to a loss of circulating volume (i.e. due to internal or external loss of fluids). The second is a failure of the pump function of the heart that results from a loss of contractility**,** The third is an obstruction due to pulmonary embolism, tension pneumothorax or cardiac tamponade. The fourth is loss of vascular tone that results in maldistribution of blood flow (due to sepsis, anaphylaxis or spinal injury)**(Cecconi et al.,2014).**

The features of each of these four types of shock often overlap, and patients admitted with one type of shock can develop other types of shock. For example, patients hospitalized with hemorrhagic shock due to trauma or with cardiogenic shock occasionally develop septic shock (**Vincent and De Backer,2013**).

Shock state

Irrespective of the etiology, shock is described as a syndrome initiated by acute systemic hypoperfusion that leads to tissue hypoxia and vital organ dysfunction. All forms of shock are characterized by inadequate perfusion to meet the metabolic demands of the tissues. A maldistribution of blood flow to end organs begets cellular hypoxia and end organ damage, the well-described multisystem organ dysfunction syndrome. The organs of vital importance are the brain, heart, and kidneys (**Schulman et al.,2004).**

A decline in higher cortical function may indicate diminished perfusion of the brain, which leads to an altered mental status ranging from confusion and agitation to flaccid coma. The heart plays a central role in propagating shock. Depressed coronary perfusion leads to worsening cardiac dysfunction and a cycle of self-perpetuating progression of global hypoperfusion. Renal compensation for reduced perfusion results in diminished glomerular filtration, causing oliguria and subsequent renal failure(**Schulman et al.,2004).**

Up to one-third of patients admitted to the ICU are in circulatory shock and early recognition of the condition is vital if subsequent tissue injuries are to be avoided**.** Shock can be categorized according to the underlying cause, including septic shock, cardiogenic shock, anaphylactic shock and shock associated with burns, trauma and hemorrhage. In the 1,679 ICU patients in the European Sepsis Occurrence in Acutely Ill Patients II **(SOAP II) trial,,2010** , septic shock was the most frequent cause of shock, accounting for 62 % of cases, followed by cardiogenic shock (17 %) and hypovolemia (16 %) **(De Backer et al.,2010**).

Septic shock is the most severe manifestation of sepsis, with reported case-fatality rates in the range of 40-50 %, reaching as high as 80 % , Limited data are available on the epidemiology of septic shock, particularly in low-income countries, but the literature suggests that its incidence is increasing, according to the medline database of citations and abstracts between 1980 and 2008(**Jawad et al.,2012),** The reported incidence of septic shock in patients admitted to the French intensive care units varies between 6.3 and 14.7 % **(Quenot et al.,2013)**.

Types of Shock

1-Distributive Shock

Distributive shock results from excessive vasodilation and the impaired distribution of blood flow. Septic shock is the most common form of distributive shock and is characterized by considerable mortality (treated, around 30%; untreated, probably >80%). In the United States, this is the leading cause of noncardiac death in intensive care units (ICUs) **(Garden et al.,2012).**

Other causes of distributive shock include systemic inflammatory response syndrome (SIRS) due to noninfectious inflammatory conditions such as burns and pancreatitis; toxic shock syndrome (TSS); anaphylaxis; reactions to drugs or toxins, including insect bites, transfusion reaction, and heavy metal poisoning; addisonian crisis; hepatic insufficiency; and neurogenic shock due to brain or spinal cord injury, The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee defined SIRS as the presence of at least 2 of the following 4 criteria :

- Core temperature of higher than 38°C (100.0°F) or lower than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) less than 32mm Hg
- White blood cell (WBC) count of more than 12,000/µL, less than 4,000/µL, or more than 10% immature (band) form

(Levy et al., 2003)

The most common sites of infection, in decreasing order of frequency, include the chest, abdomen, and genitourinary tract. Septic shock is commonly caused by bacteria, although viruses, fungi, and parasites are also implicated. Gram-positive bacteria are being isolated more, with their numbers almost similar to those of gram-negative bacteria, which in the past were considered to be the predominant organisms. Multidrug-resistant organisms are increasingly common **(Crum-Cianflone ,2008).**

Adrenal insufficiency

Adrenal insufficiency can result from the following:

- Destruction of adrenal glands due to autoimmune disease, infection (tuberculosis, fungal infection, acquired immunodeficiency syndrome (AIDS), hemorrhage, cancer, or surgical removal
- Suppression of hypothalamic-pituitary-adrenal axis by exogenous steroid, usually with doses at 20 mg daily or higher
- Hypopituitarism
- Metabolic failure in hormone production due to congenital conditions or drug-induced inhibition of synthetic enzymes (eg, metyrapone, ketoconazole**)**

(Zaloga and Marik,2001).

Anaphylaxis

Anaphylaxis can develop as a result of Drugs such as penicillins and cephalosporins. Heterologous proteins such as Hymenoptera venom, foods, pollen, and blood serum products **(Angus et al.,2001)**