AIN SHAMS UNIVERSITY
Faculty of Medicine
Department of Anaesthesia, Intensive Care, Pain Management

Recent advances in sepsis-induced Disseminated Intravascular Coagulation

An Essay

Submitted for partial fulfillment of Master degree in General Intensive Care

By

Mohammed Mahmoud Elsayed Abd-Elhadi

(M.B., B.CH.)(Zagazig University)

Under supervision of

Prof. Mohammed Abd-Elkhalik Mohammed Ali

Professor of Anesthesiology, General Intensive Care and Pain Management

Faculty of Medicine - Ain Shams University

Prof. Mohammed Anwar Elshafie

Professor of Anesthesiology, General Intensive Care and Pain Management

Faculty of Medicine - Ain Shams University

Dr.Mohammed Saleh Ahmed

Lecturer of Anesthesiology, General Intensive Care and Pain Management

Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

2018

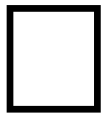
بسم الله الرحمن الرحيم

"قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا

إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ

الْعَلِيمُ الْحَكِيمُ"

(سورة البقرة:آية٣٢)



Dedication

To

My Family

Acknowledgement

Thanks Allah Almighty, the Gracious for blessing me with such a wonderful group of professors who instructed and guided me throughout my work.

I would like to express my sincere thanks to Dr. Mohammed Abd-Elkhalik Mohammed Ali, Professor of Anesthesiology, General Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, for his supervision, guidance, valuable advice, helpful directions and continuous interest throughout the whole work.

My thanks and gratefulness to Dr. Mohammed Anwar Elshafie, Professor of Anesthesiology, General Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, for his keen interest, beneficial advice and constant support during the conduction of this work.

I wish also to extend my warmest and deepest appreciation to Dr.Mohammed Saleh Ahmed, Lecturer of Anesthesiology, General Intensive Care and Pain Management, Faculty of Medicine - Ain Shams University, for his unlimited, endless help and for the tremendous effort he has done in the meticulous revision of this work.

At last, I am indebted for my family and sincere friends for their great support, patience and continuous encouragement.

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a2PI	a2-plasmin inhibitor
Adamts-13	disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
APACHE II	Acute Physiology And Chronic Health Evaluation II
APC	activated protein C
aPTT	activated partial thromboplastin time
AT	Antithrombin
COX-1	cyclooxygenase-1
CRP	C-reactive protein
DIC	disseminated intravascular coagulation
EPCR	endothelial protein C receptor
FDPs	fibrin degradation products
HMGB1	high-mobility group box 1 protein
HMWK	high molecular weight kininogen
ICU	Intensive care unit
JAAM	Japanese Association for Acute Medicine
MODS	Multiple Organ Dysfunction
MPs	Microparticles
NETs	Network microbial trapping
PAI-1	plasminogen activator inhibitor-1
PARs	protease activated receptors
PIC	plasmin inhibitor complex
PPK	plasma prekallikrein
ROTEM	rotational thromboelastometry

RRT	renal replacement therapy
SF	soluble fibrin
SISET	Italian Society for Thrombosis and Haemostasis
SOFA	sequential organ failure assessment score
TAFI	thrombin activatable fibrinolysis inhibitor
TAT	Thrombin-antithrombin complex
TCK-1	Thymus chemokine-1
TEG	Thromboelastography
TF	tissue factor
TFPI	Tissue factor pathway inhibitor
TIMP-1	Tissue inhibitor of metalloproteinase-1
TM	Thrombomodulin
tPA	tissue-type plasminogen activator
TSP	Thrombospondin
TxA2	thromboxane A2
UFH	unfractionated heparin
VCAM-1	Vascular cell adhesion protein 1
VWF	von Willebrand factor

Introduction

Severe sepsis accounts for approximately 2.9% of admissions to hospital, 10% of admissions to the intensive care unit, and is the tenth leading cause of death in the intensive care unite (ICU) ***(Martin et al., 2003)***, despite several decades of intense therapeutic investigation, the mortality remains up to 50% ***(Wittebole et al., 2010)***.

Severe sepsis is a common life-threatening condition in which an infectious agent triggers a series of pro-inflammatory reactions that manifest as hemodynamic imbalance, organ dysfunction and almost universal signs of coagulation abnormalities ***(Angus et al., 2013)***.

The most severe form of coagulation disturbance is disseminated intravascular coagulation (DIC), which accompanies 20 to 40% of all sepsis patients ***(Beale et al., 2009)***.

At the end of the 1970s, it was pronounced that DIC equals a sign that 'Death Is Coming' ***(Spero et al., 1980)***. Since then, DIC has been recognized as an independent disease entity caused by diverse insults, including inflammatory diseases, such as severe sepsis, trauma,

organ destruction (e.g. pancreatitis) and obstetric emergencies ***(Marder et al., 2006)***.

The overwhelming host inflammatory response is the key event underlying life-threatening complications ***(Semeraro et al., 2012)***.

However, the pathophysiology of sepsis-induced DIC is extremely complex and under extensive investigation ***(Slofstra et al., 2003)***, and is important to consider in the clinical and laboratory approach to its diagnosis, management and relevant therapeutic strands.

Aim Of The Essay

The aim of this essay is to throw light on the recent advances in sepsis-induced disseminated intravascular coagulation regarding pathophysiology and management.

Chapter (1)

Physiology of Hemostasis

❖ Overview

Cardiovascular disease, including intravascular clot formation, represents the primary cause of death in the world. Blood coagulation is essential to our health; however, when it proceeds abnormally, myocardial infarction, stroke, or pulmonary embolism can result.

Maintaining blood in a fluid state is vital in order to deliver oxygen, nutrients, and physiological messengers throughout the body. The hemostatic system achieves this balance between the fluid and solid states of blood. The components of the hemostatic system include blood flow, blood vessels, vascular endothelium, platelets, the coagulation system, and the fibrinolytic system (Table 1) ***(Fareed and Iqbal, 2016).***

Table 1: Components of the hemostatic system ***(DeLoughery. 2015).***

Cellular elements		
	• Blood vessel	• Platelets
	• Endothelial cells	• Leukocytes
	• Erythrocytes	•
Plasma-based elements		
	Coagulation system	
	• Activators	• Cofactors
	• Inhibitors	•
	Fibrinolytic system	
	• Activators	• Inhibitors
Blood flow/viscosity		

When the integrity of the vascular system has been compromised, the blood clots to preserve the continuity of the vasculature and the blood supply ***(*Lawrence, et al., 2017*).***

The coagulation system is a network of coagulation factors, their activators and inhibitors that work together to ultimately form fibrin, the physical structure of the blood clot. Traditionally coagulation has been viewed as having two distinct branches, the intrinsic and the extrinsic pathways depending on the initiating source of activation. However, interdependence of the different proteases is known to amplify the action of proteases which contribute to

the eventual formation of thrombin ***(Fareed and Iqbal, 2016).***

❖ Phases of the hemostatic process:

Although the clotting process is a dynamic, highly interwoven array of multiple processes, it can be viewed as occurring in phases (**DeLoughery, 2015**):

A. Endothelial injury and formation of the platelet plug.

B. Propagation of the clotting process by the coagulation cascade.

C. Termination of clotting by antithrombotic control mechanisms.

D. Fibrinolysis and clot dissolution.

➢ Vascular Endothelium

Endothelial cells form the inner lining of the vascular endothelium and act as a selective barrier, controlling the trans-cellular exchange of fluids, ions, and bioactive molecules between circulating blood and perivascular tissues. Under typical physiological conditions, endothelial cells actively sense and respond to signals around from their extracellular environments. Endothelial cells regulate