Estimation of d lactat level as amarker of bacterial translocation in gut failure in critically ill pediatric patients

Thesis

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بسم الله الرحمن الرحيم
وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ
صدق الله العظيم

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Eman Ismaeil Fathy Elgendy

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LIST OF ABBREVIATIONS

ACCM/PALS

AGI	:	Acute gastrointestinal injury
ALT	:	Alanine aminotransferase
AMPs	:	Antimicrobial peptides
APACHE	:	Acute Physiology and Chronic Health Evaluation
APC	:	Antigen presenting cells
ARDS	:	Acute respiratory distress syndrome
C3	:	Complement factor 3
C-BF	:	Cathelicidin-BF
CHD	:	Congenital Heart Disease
CRBSI	:	Catheter related blood stream infection
CSF	:	Cerebrospinal fluid
CT	:	Computed tomography
DAMPs	:	Danger-associated molecular patterns
DCs	:	Dendritic cells
DIC	:	Disseminated-intravascular-coagulation
EN	:	Enteral nutrition
ESPEN	:	The European Society for Clinical Nutrition and Metabolism
FA	:	Fatty acids
GCS	:	Glasgow Coma Scale
GI	:	Gastrointestinal
GLP-2	:	Glucagon-like peptide-2
ICAM	:	Intercellular adhesion molecule 1
ICP	:	Intracranial pressure
ICUs	:	Intensive care units
IECs	:	Intestinal epithelia cells
IF	:	Intestinal failure
IFALD	:	Intestinal failure associated liver disease
IgA	:	Immunoglobulin A.
IM	:	Intramuscular
IV	:	Intravenous
LF	:	Lactoferrin
LIFE	:	Lausanne Intestinal Failure Estimation
LPS	:	Lipopolysaccharide
MALT	:	Mucosa-associated-molecular pattern

MAP	:	Mean arterial pressure
M-cells	:	Microfold cells
MEDS	:	Mortality in Emergency Department Sepsis
MIS	:	Mucosal immune system
MMPs	:	Matrix metalloproteinase
MODS	:	Multiple organ dysfunction syndrome
MOF	:	Multi-organ failure
MUC2	:	Mucin-2
PAMPs	:	Pathogen-associated molecular patterns
PCR	:	Polymerase chain reaction
PEEP	:	Positive End-Expiratory Pressure
PEG	:	Polyethylene glycol
PG	:	Proteoglycan
PIRO	:	Predisposition, Infection, Response and Organ Damage
PK	:	Pharmacokinetic
PN	:	Parenteral nutrition
PRR	:	Pattern recognition receptors
PSCC	:	The Pediatric Sepsis Consensus Congress
ROS	:	Reactive oxygen species
SBS	:	Short bowel syndrome
SIRS	:	Systemic inflammatory response
SOFA	:	Sequential (Sepsis-related) Organ Failure Assessment
SOLE	:	Standard soybean oil lipid emulsion
SP	:	Surfactant protein
SSCG	:	Surviving Sepsis Campaign guidelines
sTNF	:	Soluble TNF
TEDs	:	Trans-epithelial dendrites
TJs	:	Tight junctions
TLR	:	Toll-like receptor
TNF	:	Tumor necrosis factor
VCAM	:	Vascular cell adhesion molecule 1
WFPICCS	:	The World Federation of Pediatric Intensive and Critical Care Societies

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. ***(Singer et al., 2016)***

In critically ill patients, the intestine is a vulnerable organ, and gastrointestinal (GI) dysfunction is common. Conversely, GI dysfunction can indicate a critical condition. It has been reported that almost 50% of patients in intensive care units (ICUs) have enterocyte damage at admission. Among critically ill patients, those with GI dysfunction have higher mortality rates than those without GI dysfunction. It is therefore important to monitor the status of the GI tract in critically ill patients **(Li et al., 2017).**

Gut barrier failure is associated with bacterial translocation, systemic inflammation, and is presumed to be associated with the development of multiple organ dysfunction syndrome. As the gut barrier function is carried out by a monolayer of enterocytes, a minimum requirement is the integrity of the enterocytes, and controlled paracellular permeability between adjacent enterocytes. Many factors can cause critically ill patients to lose gut barrier function by a mechanism of enterocyte damage; for example, small bowel ischemia or hypoxia,

sepsis, systemic inflammatory response syndrome, or absence of enteral feeding **(Piton and Capellier, 2016).**

Lactic acid, like many organic molecules, consists of two mirror-image isomers. L-lactate is produced by the human body and is the isomer tested for in common "lactate" assays **(Adeva-Andany et al., 2014).**

D-lactate, the mirror image of L-lactate, is produced in minute concentrations in human Lactic acid, like many organic molecules, consists of two mirror-image isomers. L-lactate is produced by the human body and is the isomer tested for in common "lactate" assays **(Schippa and Conte, 2014)**.

Bacteria are almost always the predominant generator of D-lactate in mammals. Normal human gut flora is governed by a complex and still incompletely understood balance of factors. Normal human flora consists predominantly of *Bacteroides* and *Firmicutes* species; other species make up approximately 10% of the remainder. Concentrations of bacteria progressively increase by orders of magnitude from the stomach and duodenum to the colon (**Adeva-Andany et al., 2014).**

Lactoferrin has antimicrobial activity and can stimulate cytokine production, enhance cell proliferation, and regulate mucosal immunity **(Legrand et al., 2012).**

Lactoferrin is safe in amounts consumed in food. Consuming higher amounts of lactoferrin from cow's milk might also be safe for up to a year. Human lactoferrin that is made from specially processed rice appears to be safe for up to 14 days. Lactoferrin can cause diarrhea. In very high doses, skin rash, loss of appetite, fatigue, chills, and constipation have been reported (**Roseanu et al., 2010)**

AIM OF WORK

Our aim was to test effect of lactoferrin supplementation for improving gut barrier function, prognosis and the outcome of septic patients using d lactate as a marker of bacterial translocation in patients with sepsis and gut failure.

CHAPTER 1

PEDIATRIC SEPSIS

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis is condition that affects many children regardless of some underlying healthcare issues. Sepsis is said to be one of the leading causes of death among children even in advanced countries. Al-though demographic data does not clearly show it, many children who are reported to die from other underlying conditions actually die directly from sepsis. The management of pediatric sepsis was comprehensively advocated through systematic review process in the Surviving Sepsis Campaign guidelines (SSCG) 2008 and 2012. Unfortunately, however, many recommendations and suggestions were still based on low-quality evidence and expert consensus, and sometimes only on evidence in adult sepsis. Furthermore, the latest version of SSCG did not include a specific description of the management of pediatric sepsis ***(Kawasaki, 2017).***

Definition of pediatric sepsis

New sepsis criteria were advocated as"Sepsis-3", which redefined sepsis as infection complicated by one or more organ dysfunctions. Organ system dysfunctions are assessed with an increase in the Sequential Organ Failure Assessment (SOFA) score by 2 or more points. The main purpose of this transition is to focus on more severe patients for the recruitment in future intervention studies (**Singer et al., 2016).**

In 2015, Pediatric sepsis was defined as 'the systemic inflammatory response syndrome in the presence of, or as the result of, suspected or proven infection'. It is a syndrome shaped by both pathogen

and host factors. The most common type of pathogens are bacteria (viruses and fungi can result in a similar presentation), which vary according to host factors, including age, comorbidity and geographic location (**Plunkett and Tong, 2015).**

Prior to 2005, there was not a standard definition for pediatric sepsis, which resulted in a lack of uniformity among sepsis studies. In 2005, the Pediatric Sepsis Consensus Congress (PSCC) met to standardize the definition of sepsis; however, as seen with adults, the definition requires continuous reconsideration and modification as this area of research grows. Defining sepsis in the pediatric patient is made more difficult due to age specific vital signs, and their tremendous physiologic reserve, which often masks the seriousness of their condition **(Sankar et al., 2019).** The PSCC divided age into six distinct categories in order to take into account age specific vital signs as well as age specific risk factors for invasive infections, which in turn affect antibiotic coverage guidelines **(Sankar et al., 2019).**

However, Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality. It is identified by sepsis and cardiovascular organ dysfunction, acknowledging that hypotension is a late sign in children (**Singer et al., 2016)**.

Pediatric severe sepsis is defined as

1- two or more systemic inflammatory response syndrome criteria (Table 1)
2- confirmed or suspected invasive infection

(Weiss et al., 2014)

Determination of altered physiology is specific to age dependent vital signs.

Table (1): Age-specific vital signs and laboratory variables Pediatric SIRS Criteria (Weiss et al., 2014)

Age Group	Heart Rate (Beats/Min)		Respiratory Rate (Breaths/Min)	Leukocyte Count (Leukocytes × 10^3/mm)	Systolic BP (mm Hg)
	Tachycardia	Bradycardia			
0 d to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 y	>180	<90	>34	>17.5 or <5	<100
2–5 y	>140	NA	>22	>15.5 or <6	<94
6–12 y	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 y	>110	NA	>14	>11 or <4.5	<117

Table (2): Organ dysfunction criteria (Weiss et al., 2014)

Cardiovascular dysfunction	Despite administration of isotonic intravenous fluid bolus40 mL/kg in 1 hour • Decrease in BP (hypotension)5th percentile for age or systolic BP2SDbelow normal for age **OR** • Need for vasoactive drug to maintain BP in normal range (dopamine or dobutamine, epinephrine, or norepinephrine at any dose) **OR** • Two of the following Unexplained metabolic acidosis: base deficit5.0 mEq/L Increased arterial lactate2 times upper limit of normal Oliguria: urine output0.5 mL/kg/hr Prolonged capillary refill:5 secs