Value of 1,3-Beta-D-Glucan in Comparison to Culture on Sabouraud Dextrose Agar in the Diagnosis of Fungal Infection in Preterm Neonates

Thesis

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Mahmoud El-Badrawy

List of Contents

List of Abbreviations

Abb.	Full term
AEMs	*Antimicrobial effector mechanisms*
ARDS	*Acquired respiratory distress syndrome*
ART	*Assisted reproductive technology*
BDG	*(1, 3)-β-D-Glucan*
CoNS	*Coagulase-negative Staphylococcus*
CRP	*C Reactive Protein*
CV	*Cardiovascular*
CVC	*Central venous catheter*
DAMPs	*Damage associated molecular patterns*
DIC	*Disseminated intravascular coagulation*
ELBW	*Extremely low birth weight*
ELISA	*Enzyme-linked immune-sorbent assay*
EMA	*European Medicines Agency*
GBS	*Group B Streptococcus*
G-CSF	*Granulocyte colony-stimulating factor*
HMGB-	*High-mobility group box 1*
HSM	*Hepatosplenomegaly*
HSS	*Hematologic scoring system*
IC	*Invasive candidiasis*
IFN	*Interferon*
IL	*Interleukin*
LPS	*Lipopolysaccharide*
LTA	*Lipoteichoic acid*
MCP	*Monocyte chemoattractant protein*
MIP	*Macrophage inflammatory protein*
NICU	*Neonatal intensive care unit*
NLR	*NOD-like receptors*
PAI-1	*Plasminogen activator inhibitor-1*

List of Abbreviations cont...

Abb.	Full term
PAMPs	*Pathogen-associated molecular patterns*
PCT	*Procalcitonin*
PRRs	*Pattern recognition receptors*
PTB	*Preterm birth*
RLR	*Retinoic acid–inducible protein I like receptor*
ROC	*Receiver-operating characteristic*
s1CAM-1	*Soluble intracellular adhesion molecules-1*
SFI	*Systemic Fungal Infection*
SIRS	*Systemic inflammatory response syndrome*
SNAPII	*Score for neonatal acute physiology II*
t PA	*Plasminogen tissue activator*
TAT	*Thrombin – antithrombin III complex*
TLR	*Toll-like receptor*
TNF alpha	*Tumor necrosis factor alpha*
TNF	*Tumor necrosis factor*
UA	*Uric acid*
VCAM-1	*Adhesion molecule- 1*
VLBW	*Very low birth weight*
VOTra	*Vasopressin/oxytocin receptor antagonist*
WBC	*White blood cell*

List of Tables

List of Tables cont...

List of Tables cont...

List of Figures

List of Figures cont...

INTRODUCTION

Neonatal sepsis is the commonest cause of neonatal mortality; It is responsible for about 36% of the total neonatal deaths in developing countries ***(Lawn et al., 2005).*** In Egypt, the incidence of suspected neonatal sepsis is 45.9% with a mortality rate 42.9% for proven late onset sepsis ***(Shehab El-Din et al., 2015)***.

Classically it has been divided depending on the time of onset into early onset and late onset sepsis. The cutoff point between them varies among authors from 24 hours to 7 days ***(Rostenberghe et al., 2009)***, 72 hours is a cutoff time point considered to be adequate ***(Boghossian et al., 2013; Tröger et al., 2014)***.

The pathogens causing late onset sepsis are generally acquired from the postnatal environment, most importantly nosocomial acquired infection in hospitalized babies ***(Wolkowiez et al., 2009).*** Risk of nosocomial infection increase with low birth weight and prematurity ***(Polak et al., 2004)***. The digestive tract is a major site for colonization and systemic translocation by many pathogens especially in preterm neonate ***(Stoll et al., 2002)***.

Candida is the third most-common agent of late-onset infections in critically ill neonates, especially in very low birth

weight (VLBW) and extremely low birth weight (ELBW) ***(Benjamen et al., 2006; Chapman et al., 2007)***.

Numerous risk factors for invasive candidiasis (IC) have been identified in NICU patients, some are related to host factors: (Immunodeficiency resulting from decreased numbers of neutrophils and T cells, immature skin structure, Candida colonization), others to medical care: (central venous catheters, total parenteral nutrition, mechanical ventilation, broad spectrum antibiotic therapy, use of 3rd generation cephalosporin, administration of H2-blockers ***(Cotton et al., 2006; Bendel et al., 2005)***.

Due to the frequency, severity and difficulties in early diagnosis and prompt therapy, prevention is crucial for decreasing the burden of infection-related complications in the NICU. Hygiene measures and cautious use of aggressive procedures as well as drugs are mandatory ***(Kaufman et al., 2010)***.

A positive blood culture for Candida spp. is the mainstay of the diagnosis of candidemia, although the sensitivity of blood cultures may be as low as 50% ***(Arendrup et al., 2008)***, In addition, cultures may take several days to grow, particularly for certain species of Candida, such as C. glabrata. Identification of diagnostic and prognostic factors that are available early during the disease course would improve our ability to individualize anti-fungal strategies ***(Fernandez et al., 2009)***.

Non-culture-based diagnostic techniques for detecting IFD are therefore increasingly used to facilitate timely diagnosis. One of the developed biomarkers is (1, 3)-β-D-Glucan (BG), a major cell wall component of almost all fungi, is present on ***(Jaijakul et al., 2012)***. BG detection has been widely used as a diagnostic tool for invasive fungal diseases in adults ***(Mohr et al., 2011; Goudjil et al., 2013)***.

Until recently, the cell wall of fungi has been viewed as an inert exoskeleton with the primary role to simply provide structure and support to the organism ***(Latgé et al., 2007)***. Based on cumulative data, the fungal cell wall is now viewed as a dynamic structure rather than an inert structure. In other words, the fungal cell wall is continuously undergoing the processes of assembly and remodeling during cell growth as a result of mechanical or chemical stresses.

Glucan is the most important and abundant polysaccharide component of the cell wall of most fungi ***(Latgé et al., 2007)***. Glucans are a major constituent of the cell wall of saprophytic and pathogenic fungi with the exception of *Mucor*, *Rhizopus*, *Blastomyces dermatitidis*, and *Cryptococcus* species ***(Mennink-Kersten et al., 2006; Bowman et al., 2006; Girouard et al., 2007).***

Although the surveillance and diagnosis of invasive fungal infections with beta-glucan testing in high-risk patients seems logical, this surrogate fungal marker may also be useful for therapeutic monitoring ***(Pazos et al., 2005; Kawagishi et al., 2007).***

AIM OF THE WORK

1ry aim is to study the value of 1, 3-β-D-Glucan in comparison with culture on Sabouraud dextrose agar in the diagnosis of invasive fungal infection in preterm neonates.

2ry aim is to study the prevalence and risk factors of invasive fungal infection in preterm neonates.