Soluble CD14 Subtype Presepsin as a Diagnostic Marker in Central Line Associated Blood Stream Infection in Intensive Care Unit Patients

Thesis

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INTRODUCTION

Bloodstream infection is the recovery of a microbial pathogen in blood culture by means of infection, not sample contamination **(*Shah et al.,2013*).** Intravascular catheters are essential to clinical practices and are inserted in critically-ill patients for the administration of fluids, blood products, medication, nutritionalsolutions, and for hemodynamic monitoring ***(Gahlot et al., 2014)***.

Central line-associated blood stream infection (CLABSI) is a laboratory confirmed blood stream infection where central line was in place for > 2 calendar days on the date of event, with day of device placement being day 1, and the line was also in place on the date of event or the day before. If a central line was in place for > 2 days then removed, the date of event must be the day of discontinuation or the next day to be CLABSI ***(CDC,2017)***.In an Egyptian epidemiological study of health care associated infection by ***Talaat et al.(2016)***,CLABSIrepresented 63.4% of total BSIs,the device utilization rate is 0.4 and the incidence of CLABSI is 2.6/1000 central line days.

Dependance on blood culture as a ‘gold standard’ is not the best method for clinical diagnosis of CLABSI because of long turn-around time for results and frequent falsely negative culture results due to low inoculums of bacteria in the small volume of blood sample collections

(Connel et al., 2007). So variousdiagnostic tests, including biochemical and hematological markersare used to help choosing appropriate antibiotic therapy. the most commonly used biomarkers for sepsis are C-reactive protein (CRP) and Procalcitonin (PCT). CRP has been used for many years but its specificity has been challenged. It remains difficult to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome (SIRS) ***(Edgar et al., 2010)***. Procalcitonin (PCT) is widely used in diagnosis of sepsis,but it has some limitations. It rises transiently in patients with non-septic conditions and SIRS (for example, trauma, surgery, andheatstroke) ***(Urbonas et al., 2013)***.

Cluster of differentiation 14 (CD14) is a glycoprotein expressed in macrophage, monocyte, and granulocyte cells and their cell membranes ***(Zamani et al., 2013)***.

During inflammation, soluble CD14 (sCD14) is produced either following phagocytosis or through proteolytic cleavage on activated monocytes***(Ackland et al., 2015)***. Soluble CD14 can be cleaved by proteases, generating a truncated form of 64 amino acid residues known as sCD14 subtype (sCD14-ST), or presepsin ***(Mussap et al., 2011)***. Presepsin is said to be responsible for intracellular transduction of endotoxin signals ***(Shirakawa et al., 2011).*** The reference range forpresepsinin normal adults free from inflammatory diseases is 55–184 pg/mL ***(Giavarina and Carta, 2015).***

After detection of the value of presepsin as a new biomarker of inflammation, it has been reported in many studies as by ***Wu et al.(2015)& Zheng et al.(2015)*** for the prediction of sepsis. Presepsin has a higher sensitivity and specificity than CRP and PCT in the diagnosis and prognosis of sepsis and It plays a crucial role as a supplemental method in the early diagnosis of sepsis ***(Zou et al., 2014)***.

In a meta-analysis done by ***Zhang et al. (2015)***, the sensitivity of presepsin in diagnosis of sepsis was (70-100%) and its specificity ranged from (62-93%) that makes presepsin a good candidate for evaluation of its diagnostic value in cases of Catheter Related Blood Stream Infections.

AIM OF THE WORK

The aim of the study is to measure the serum level of presepsin in patients with CLABSI, compare it with levels in controls and to determine the sensitivity and specificity of serum presepsin level in diagnosis of CLABSI taking positive blood culture either conventionally or by PCR as a gold standard.

Chapter One

CENTRAL LINE ASSOCIATED BLOOD STREAM INFECTIONS

Device-associated healthcare-acquired infections are one of the main threats to the safety of patients, causing patient morbidity, mortality, excess costs and prolonged length of hospital stay, particularly in intensive care settings of limited-resource countries ***(Rosenthal et al., 2012).***

There are two key terms used to define central venous-related infections in the bloodstream: catheter-related bloodstream (CRBSI) and central line associated bloodstream (CLABSI) infections. CRBSI is a clinical definition based on a specific patient-related clinical criterion in which the diagnosis is taken into account. This term is used more commonly in research and clinical treatment in some cases, as it involves advanced microbiological procedures to specifically identify the catheter as the origin of bacteremia that may not be available in all hospitals. In contrast, the diagnosis of CLABSI is a simplified definition based on surveillance criteria that identify bloodstream infections in patients with central lines in which there is no other obvious secondary source for bacteremia ***(O'Grady et al., 2011).***

CRBSI is diagnosed by any of the following 3 criteria:

- Same organism recovered from percutaneous blood culture and from quantitative or semiquanitative(>15, 10 colony-forming units respectively) culture of the catheter tip;

- Same organism recovered from a percutaneous and a catheter lumen blood culture, with growth detected 2 hours sooner (ie, 2 hours less incubation) in the latter = differential time to positivity (DTP);

- Same organism recovered from a quantitative percutaneous and a catheter lumen blood culture, with 3-fold greater colony count in the latter ***(Mermel et al., 2009).***

CRBSI surveillance is complicated by variations in the implementation of diagnostic approaches between providers, patients, groups, and health care facilities that may contribute to differences in CRBSI case finding frequency. This issue is solved by testing for CLABSI instead of CRBSI, so culture of catheter tip is not required to meet the CLABSI case definition ***(Sexton et al., 2010)***. CLABSI defination has functioned with satisfactory stability of sensitivity and specificity of case detection between facilities to help national health care safety network(NHSN) toestablish a benchmarking database ***(Dudeck et al., 2011).***

A- Defination

Central line-associated blood stream infection: A laboratory confirmed bloodstream infection in which a blood stream infection organism is identified and acentral line is in place for more than two consecutive calendar daysand is present on the laboratory confirmed blood stream infection (LCBI) date of event or the day before.

The date of event is the first time that the first item used to satisfy an NHSN site-specific infection criteria (site-specific sign or first-come positive diagnostic test) occurs ***(CDC, 2019).***

An infection is considered a Healthcare-associated Infectionif the date of event of the NHSN site-specific infection criterion occurs on or after the 3rd calendar day of admission to the hospital where day of admission is calendar day 1 ***(CDC, 2019).***

Laboratory-Confirmed Bloodstream Infectionmust meet oneof the following criteria:

In LCBI 1, a patient of any age has a recognized bacterial or fungal pathogen not included on the NHSN common commensal list, identified from one or more blood specimens obtained by aculture or non-culture based microbiologic testing methods and Organism(s) identified in blood is not related to an infection at another site.

While LCBI 2 criteria are that a patient of any age has at least ***one*** of the following signs or symptoms:fever (>38.0°C), chills, or hypotension and Organism(s) identified in blood is not related to an infection at another site and the same NHSN common commensal is identified by aculture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions.

But LCBI 3 criteria are that a patient ≤ 1 year of age has at least ***one*** of the following signs or symptoms: fever (>38.0°C), hypothermia (<36.0°C), apnea, or bradycardia and Organism(s) identified in blood is not related to an infection at another site and the same NHSN common commensal is identified by a culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions.

Taking in consideration that a common commensal organisms include, but not are not limited to, diphtheroids (*Corynebacterium* spp. not *C. diphtheria*), *Bacillus* spp. (not *B. anthracis), Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis),* viridans group streptococci, *Aerococcus* spp. *Micrococcus* spp. and *Rhodococcus* spp ***(CDC, 2019)***.

B- Epidemiology:

Among industrialized countries, Sepsis is the 10th most common caus of death, with an annual incidence of

about 5-10%***(Gonsalves and Sakr, 2010)***. Early accurate diagnosis is important, because every hour of delay of appropriate antibiotic therapy increases mortality by 5–10 % ***(Bauer and Reinhart,2010).***

In a study of device associated infections by ***Rasslan et al. (2012)*** including two Egyptian pediatric intensive care units and an adult respiratory intensive care unit, the CLABSI rate was 18.8 per 1000 central line days in the pediatric intensive care units and 22.5 in the respiratory intensive care units,with an overall rate in the 3 ICUs of 20.8. it represented 20% of all hospital acquired infections.

In a pilot study including 11 egyptian hospitals with 90,515 patient days of surveillance data, 22% ofidentified 472 HAIs were blood stream infections ***(See et al., 2013)***.

A study done by ***Hu et al. (2013)*** between August 2008 and July 2010 on device associated infections,there were a total of 2,631 admissions to the 7 ICUs in the study hospitals. The CLABSI rate was 7.66/1,000 central line days.

In a pilot study by ***Talaat et al. (2016)*** ninety-one ICUs in 28 hospitals contributed to 474,544 patient days and 2,688 HAIs. Of these, 30% were bloodstream infections. CLABSI represented 63.4% of BSIs.

In an egyptian study done in a private hospital to assess rate and risk factors of CLABSI, Nearly 44% ofICUs

patients have central lines placed. The CLABSI rate was 6 cases per 1000 central line-days. The central line utilization rate was 0.94 per 1000 patient-days. The mortality rate among cases with CLABSI was 16.8% during the study period ***(Malek et al., 2018).***

C- Pathogenesis:

Central lines are associated with risk ofexit site infection and subsequent migration of that infection along the extraluminal catheter surface to the bloodstream**.**The most common course of infection for peripherally inserted catheters ismigration of skin organisms at the insertion site into the cutaneous catheter tract with colonization of the catheter tip ***(O'Grady et al., 2011).***

The risks are minimized by subcutaneously tunneling the catheter, expanding the distance between the skin-catheter interface and the catheter-vessel interface, or complete implantation of the catheter.Bacterial or fungal contamination of a catheter hub can also lead to intraluminal infection of the catheter and extension of that infection to the bloodstream ***(Shah et al., 2013).***

A common cause of both short- and long-term central venous catheters related infection ishub colonization and intraluminal migration of pathogens ***(Mermel et al., 2011).*** Intrinsic contamination of infusates and hematogenous seeding from distant infection have been identified as

uncommon causes of CLABSI ***(Beekmann and Henderson, 2005).***

The material of which the device is made and the intrinsic virulence factors of the infecting organism are important pathogenic determinants of catheter-related infection. In vitro studies demonstrate that catheters made of polyvinyl chloride or polyethylene are less resistant to the adherence of microorganisms than are cathetersmade of Teflon, silicone elastomer, or polyurethane ***(O'Grady et al., 2002).***

The microbial adherence of certain species which have the ability to form biofilm (e.g., coagulase-negative staphylococci, *Acinetobactercalcoaceticus*, and *Pseudomonas aeruginosa*) is facilitated by surface irregularities that are present in certain catheter materials ***(Nandakumar et al., 2013)***.

Risk factors:

1- Host related: chronic illnesses (hemodialysis, malignancy, gastrointestinal tract disorders, pulmonary hypertension), immune compromised states (bone marrow transplant, end-stage renal disease, diabetes mellitus), malnutrition, total parenteral nutrition, extremes of age, loss of skin integrity (burns), prolonged hospitalization before line insertion increase the risk of CLABSIs ***(Haddadin and Regunath, 2019).***

2- Device related: multi-lumen catheters infection have been shown to be more that single lumen catheter infection by some studies of variable patients, including the critically ill and cancer patients ***(Templeton et al., 2008).*** Nevertheless, there were no significant differences when a meta-analysis excluded many studies assessed as low-quality ***(Dezfulian et al.,2003).***

Central line is associated with infectious, thrombotic and mechanical complications ***(Parienti et al., 2012)*** femoral line has the highest, followed by internal jugular, then subclavian ***(Parienti et al., 2015)***. However, if patient have coagulopathies or anatomic considerations such as lymphadenopathy, which distort normal anatomical features, the patient may not be an appropriate candidate for subclavian access.Femoral catheterisation may be preferred in acute circumstances where vascular access is required rapidly to avoid the risk of pneumothorax with either subclavian or internal jugular catheterization. In the end, subclavian catheterization should be avoided in patients with end stage renal disease, as subclavian stenosis may compound long term access to arteriovenous fistula ***(O'Grady et al., 2011).***

3- Care giver related: the rate of CLABSI is affected by conditions of insertion (emergent versus elective, use of full barrier precautions versus limited), catheter site care,

and skill of the catheter inserter ***(Haddadin and Regunath 2019).***

4- Pathogen related: *Pseudomonas* is commonly seen in association with neutropenia, severe illness, or known prior colonization. *Candida* is associated with the following risk factors: femoral catheterization, TPN, prolonged administration of broad-spectrum antibiotics, hematologic malignancy, or solid organ or hematopoietic stem cell transplantation. Certain bacteria such as *staphylococci*, *Pseudomonas*and *Candida* produce extracellular polysaccharide(biofilm) which favor increased virulence, adherence to catheter surface and resistance to antimicrobial therapy ***(Bell and O'Grady, 2017).***

Univariate analysis identified risk factors for CLABSI and included related co-morbidities such as heart failure, APACHE (Acute Physiology and Chronic Health Evaluation) II scores of > 15, an ICU stay of 5 days or more, central line placement length, subclavian insertion of central line, and mechanical ventilation ***(Malek et al., 2018).***

Types of micro organisms could be isolated from blood:

Based on the NHSN data from January 2006 to October 2007 the order of selected pathogens associated with causing CLABSI areas follows. Gram-positive organisms (coagulase-negative *staphylococci*, 34.1%; *enterococci*, 16%;

and *Staphylococcusaureus*, 9.9%) are the most common, followed by Gram negatives (*Klebsiella spp.*, 5.8%; *Enterobacter* spp., 3.9%; *Pseudomonas spp.*, 3.1%; E.coli, 2.7%; *Acinetobacterspp.*, 2.2%), *Candida*spp. (11.8%), and others (10.5%) ***(Wright et al., 2018).***

Gram-negative bacilli are isolated in infections of patients with cancer, and they are typically the pathogens recovered in instances of infusate contaminations. Gram-negative bacilli and yeast have been associated with catheters placed in femoral veins ***(Khalil and Azqul, 2018).***

There is significant differences between organisms isolated in non neutropenicand neutropenicCLABSI patientsespecially following chemotherapy.The organisms that were overrepresented in the neutropenic group include common residents of the gastrointestinal tract. The lack of relapse of CLABSI in any patient whose line was not removed during or immediately following treatment of the BSI, particularly for *E. coli* and streptococcal BSIs, also suggests a source of infection other than the catheter. Proposing that the organismsattributed is due to translocationand should be excluded from the CLABSI definition in the setting of neutropenia and mucosal disruption. They include*E. coli*, streptococci, and enterococci ***(Steinberg et al., 2013).***