Clinica Chimica Acta 421 (2013) 116–120

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Serum adhesion molecules as predictors of bacteremia in adult severe sepsis patients at the emergency department

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ARTICLE INFO

Article history:
Received 6 November 2012
Received in revised form 3 February 2013
Accepted 22 February 2013
Available online 28 February 2013

Keywords:
Bacteremia
Serum adhesion molecules
Severe sepsis

ABSTRACT

Background: Bacteremia is a severe bacterial infection with significant mortality. Clinical parameters that reliably predict it are less elucidated. We assessed the potential of serum adhesion molecules for predicting bacteremia and compare it with current available infection biomarkers to determine a more timely predictor of adult severe sepsis patients on admission to the emergency department (ED).
Methods: Sixty-seven consecutive non-traumatic, non-surgical adult patients with severe sepsis admitted to the ED were evaluated. Serum samples were collected and assessed while serum adhesion molecules were analyzed.
Results: Thirty-one (46.2%) study patients had bacteremia. There were significant differences in both sICAM-1 and sE-selectin on admission between bacteremic and non-bacteremic patients. By stepwise logistic regression model, only sE-selectin was independently associated with bacteremia and any 1 ng/ml increase in level increased bacteremia rate by 0.8%. The cut-off value of sE-selectin level for predicting bacteremia was 117 ng/ml (84% sensitivity and 69% specificity).
Conclusion: Although serum cell adhesion markers are not specific for predicting bacteremia in septic patients, higher mean serum cell adhesion molecules levels on admission may imply both more severe infection and presence of bacteremia. Assay of serum adhesion molecules may be added as an infectious marker among the panel of bacteremic parameters in clinical practice, especially since early diagnosis and prompt antimicrobial therapy are essentially for survival.

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1. Introduction

Bacteremia, a microbiological finding indicative of severe bacterial infection, is associated with a high fatality rate of up to 30% [1]. Because of variations in both the causative pathogens and the hosts, individual clinical responses and presentations of bloodstream infection vary greatly. A previous report revealed that approximately 50% of adults with undifferentiated hypotension at the emergency department (ED) were ultimately diagnosed with sepsis even though they usually had normal body temperatures and white blood cell counts [2]. Thus, ED physicians are forced to have low thresholds for initiating broad-spectrum antibiotics after blood sampling for blood cultures.

Another previous study suggested that patients diagnosed with bacteremia by blood culture sampling had higher mortality rates than patients without bacteremia [3]. Delays in the initiation of appropriate antimicrobial therapy have also been associated with worse outcomes [4–6]. It is essential to identify patients with bacteremia early when clinicians face various populations in the ED.

Blood culture sampling is required to detect bacteremia and identify the pathogen for further antimicrobial susceptibility tests. However, this method has limited usefulness for the early detection of bloodstream infection because at least 24 h is needed for results to be known. Detailed history-taking, comprehensive physical examination, and basic blood biochemistry tests are also insufficient to identify patients with bacteremia before microbiologic results are available. Several authors have tried to predict bacteremia using immediately available parameters at the ED, but the accuracy of such diagnostic approaches

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http://dx.doi.org/10.1016/j.cca.2013.02.023

are limited [7,8]. Thus, new serum markers like interleukin-10, tumor necrosis factor-α (TNF-α), and procalcitonin are regarded as possible tools for the early detection of bacteremia [9–11].

The endothelium has long been considered both a source and a target of systemic inflammation. Endothelial cells play an essential role in the development of inflammatory processes and in various stimuli, resulting in endothelial activation and endothelial-leukocyte interactions like adhesion and extravasation. These are mediated by the augmented expression of adhesion molecules, including soluble intercellular cell adhesion-molecule-1 (sICAM-1), soluble endothelial-selectin (sE-selectin), soluble platelet-selectin (sP-selectin), and soluble vascular cell adhesion molecule-1 (sVCAM-1). Cytokines regulate the local mobilization of leukocytes into inflammatory sites such that IL-1, IL-4, interferon-gamma (IFN-g), and TNF-α up-regulate the expression of sVCAM-1, sICAM-1, and sE-selectin to promote leukocyte extravasation [12,13]. Increased concentrations of circulating soluble adhesion molecules have been reported in patients with systemic inflammatory response syndrome, sepsis, and septic shock, and have been associated with multiple organ dysfunction, disease severity, and death [14–19].

2. Patients and methods

2.1. Study population and definition

This prospective study on the time course of adhesion molecule levels in severe sepsis and septic shock patients was conducted over a one-year period (January to December 2011). Patients aged ≥18 y who were consecutively admitted from the ED of Kaohsiung Chang Gung Memorial Hospital (CGMH) were screened daily for severe sepsis and septic shock according to specific criteria. The hospital's Institutional Review Committee on Human Research approved the study protocol and all of the patients provided informed consent.

Patients with hematologic disease or those under chemotherapy were excluded. Severe sepsis on ED admission was defined according to the American College of Chest Physicians/Society of Critical Care Medicine criteria: a) suspicion or confirmed infection; b) two or more manifestations of systemic inflammatory response syndrome; and c) at least 1 sepsis-induced acute organ dysfunction or signs of hypo-perfusion (i.e., oliguria, encephalopathy, and lactic acidosis). All patients who met these three criteria were included.

Septic shock was defined as severe sepsis associated with hypotension not controlled by vascular expansion and requiring vasopressive agents (e.g., dopamine ≥7.5 mg/kg/min; epinephrine or norepinephrine at any dose) to maintain SBP >100 mmHg [20].

2.2. Clinical assessment and treatment

Information collected were demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score, which was calculated during the first 24 h of admission to assess the severity of organ dysfunction. Basic laboratory tests, lactate concentration, B-type natriuretic peptide, and inflammatory markers like plasma C-reactive protein (CRP) and procalcitonin were taken on ED admission. Data regarding the source of infection and antibiotic treatments were recorded, and the course of various organ dysfunctions and supportive treatments like vasoactive and ventilator therapies and renal replacement therapies were recorded.

Physicians evaluated the association between existing organ dysfunction and severe sepsis daily. Severe organ dysfunction or organ failure was defined as SOFA score ≥3. Patients under chronic dialysis treatment on admission and those with severe chronic liver disease were excluded from the acute organ dysfunction assessment. An infectious disease specialist was consulted for microbiologic treatment during the first 24 h, which was prescribed according to guidelines of different infectious etiologies.

2.3. Microbiology

Based on clinical indication, blood samples were taken for culture examination upon admission to the ED prior to the start of antibiotic treatment. Two pairs of aerobic and anaerobic bottles were routinely obtained and incubated for at least 5 days (ID GN 32 System; Biomérieux Vitek Inc., Hazewood, MO). All isolates were identified by standard microbiologic procedures. The study group consisted of bacteremic patients, defined as those with the same pathogen isolated from both bottles of a single blood culture set, or from one or more bottles in each of two or more blood culture sets, with at least one positive culture obtained in the ED. Growth of coagulase-negative staphylococci or Corynebacterium species were assumed to be contaminants. Mixed cultures were considered significant if organisms other than contaminants were isolated.

2.4. Assessment of infection biomarkers

All tests were conducted by the quality-controlled central laboratory of the hospital. Concentrations of CRP were determined by enzyme immunoassay (EMIT; Merck Diagnostica; Zurich, Switzerland) and PCT was measured by Enzyme-Linked Fluorescent Assay (VIDAS; bioMerieux; Ponte a Ema, Italy). Serum lactate levels were measured using a serum-based assay catalyzed by lactate oxidase (UniCel Integrated System; Beckman Coulter INS; Boulevard, Brea, CA).

2.5. Blood sampling and assessment of serum adhesion molecules

Blood samples for serum adhesion molecule determinations were obtained from patients with severe sepsis in the ED (Day 1) by venipuncture into Vacutainer SST tubes during the day shift (8:00–16:00) before the start of antibiotics. Blood was allowed to clot at room temperature for a minimum of 30 min. The clot was then removed by immediate centrifugation at 3000 rpm for 10 min at 4 °C. Samples for serum adhesion molecules were collected and measured immediately. Five hours was needed to measure serum levels. Other serum samples were collected after centrifugation, isolated, and stored at −80 °C in multiple aliquots.

Serum sICAM-1, sVCAM-1, sE-selectin, sL-selectin and sP-selectin levels were determined by commercially available ELISA (R & D Systems, Minneapolis, MN). In the assay, standards, controls and unknown samples were incubated in micro-titration wells that were coated with marked antibodies (i.e., anti-ICAM-1, VCAM-1, P-selectin, E-selectin, and L-selectin). After incubation and washing, the wells were treated with another anti-Ag detection antibody labeled with enzyme horseradish peroxidase (HRP).

After a second incubation and washing, the wells were incubated with the substrate, tetramethylbenzidine (TMB). An acidic stopping solution was then added and the enzymatic turnover rate of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. Absorbance was directly proportional to the concentration of antigens present. A set of antigen standards was used to plot a standard curve of absorbance vs antigen concentration, from which antigen concentrations in the unknowns were calculated.

2.6. Statistical analysis

Data were expressed as mean ± SD or median (inter-quartile range). Univariate analyses were compared using Student's *t*-test, while categorical variables were compared using χ^2 test or Fisher's exact test, as appropriate. Multiple comparisons among pairs of means were performed by multiple significant tests with Bonferroni method. Repeated measures of analysis of variance (ANOVA) were used to compare plasma cell-free DNA at 3 different time points after severe sepsis. Analysis of covariance (ANCOVA) was used to compare groups after controlling for potential confounding variables. Correlation analysis was used to explore the relationship among 24-h APACHE II score, SOFA score, lactate, CRP,

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