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Research Article

Can Routine Laboratory Biomarkers Predict Bloodstream Infections by Gram-negative Bacteria?

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Abstract

Bloodstream infections caused by Gram-negative bacteria (BSI-GN) pose clinical challenges due to their severity and difficulty of treatment. Thus, the present study demonstrated the ability of routine laboratorial biomarkers (RLB) values to detect BSI-GN before the final blood culture (BC) report, including RLB values obtained at the time of BC collection (0h) and also 48 and 24 hours before BC collection from patients who had BSI-GN. We retrospectively analyzed data of 6787 patients who collected BC, admitted in a teaching hospital, in Maringa, Brazil. Correlation between RLB and positive BC was assessed using Student's t test or chi-square test. Values of $p \leq 0.01$ or $p \leq 0.05$ were considered statistically significant. 320 patients (181 BSI-GN and 139 BSI-GP) over 18 years old was included in the study. We evaluated 49 RLB of which 14 showed statistically significant differences ($p \leq 0.01$) at T0h. The intra-abdominal initial infections focus showed OR 2.6 (1.37-4.97); $p = 0.003$, patients with the urinary tract as the initial infectious focus had an OR 2.0 (1.04-4.4); $p = 0.04$. We concluded that RLB data, analyzed mainly together with the initial infectious focus data, could predict BSI-GN. These analyses could direct in empirical treatment while the BC result is not available.

Keywords: Blood Culture; Laboratory Biomarkers; Bloodstream Infections; Gram-negative; Gram-positive

Abbreviations

BSI: Bloodstream Infections; GN: Gram-negative Bacteria; BC: Blood Cultures; RLB: Routine Laboratory Biomarkers; GP: Gram-positive Bacteria; ED: Emergency Department; ICU: General Intensive Care Unit; pH: Hydrogen Potential; PO_2: Oxygen Pressure; RDW: Red Blood Cell Distribution Width; WBC: White Blood Cell Count

Introduction

Bloodstream infections caused by Gram-negative bacteria (BSI-GN) pose clinical challenges due to their severity and difficulty of treatment. This is related to the specific characteristics of this bacterial group, such as the presence of lipopolysaccharide with a specific endotoxin for GN [1,2].

Appropriate antimicrobial therapy has been used to reduce mortality among patients with BSI-GN and when started early has

a favorable effect on critically ill patients. However, the choice of the appropriate antimicrobial class has become complex due to increased antibacterial resistance [2,3].

Although blood cultures (BC) are the gold standard for diagnosing BSI, the delay and low positivity of results can affect treatment and prolong the hospital stay. Certain routine laboratory biomarkers (RLB) could mitigate these problems in daily clinical practice [1,4].

This study evaluated the relationship between RLB values with BSI-GN and the ability of RLB values to detect BSI-GN before the final BC report.

Materials and Methods

This retrospective study included registers from patients that had BSI between 2013-2018. The study was conducted at the Maringa University Hospital, in Maringa, Brazil, which is a public teaching general hospital that provides medical and diagnostic services of medium and high complexity, and public health care for about 1.660.000 residents of Maringa and its surrounding towns. The RLB values were evaluated at the time of BC collection (0h) and also 48 and 24 hours before BC collection from patients. All tests analyzed were performed according to specific standard operating procedures. BC and bacterial identification was perfor medin the BACTEC™ and Phoenix™ systems (BD Diagnostic Systems, Sparks, MD), respectively. Complete blood cell counts were determined using the Sysmex-XE-2100™ (Sysmex-Corporation, Kobe, Japan), and the biochemical laboratory tests were performed using VITROS™ 5.1-FS (Ortho-Clinical Diagnostics, New Jersey, USA). Gasometric and biochemical tests (electrolytes, ionized calcium iCa, glucose, lactate and creatinine) were measured with ABL800 ™ FLEX (Radiometer, Copenhagen, Denmark). Coagulation tests were analyzed using the ACL™ Elite-Pro (Beckman-Coulter, California, USA).

The inclusion criteria were: patients with positive BC with GN or GP bacteremia that were in both collected samples, or when at least one BC was positive with pathogens of clinical interest. Exclusion criteria were as suggested by Hall., *et al*. [5]. The RLB results were entered in the computer program "Sistema de Gestão da Assistência de Saúde do SUS" (GSUS) for patients with BSI at 48 (T48h), 24 (T24h), and 0 (T0h) hours before BC collection. The data were organized in Microsoft Excel 2007 (Microsoft®) software. Correlation between RLB and positive BC was assessed using Student's t test or chi-square test. Values of $p \leq 0.01$ or $p \leq 0.05$ were considered statistically significant.

The study was approved by the local ethics committee under COPEP/COREA Number 0447/2017-HUM, MS (Ministry of Health) Resolution 466/12.

Results and Discussion

A total of 13,374 BC (6787 patients), either BSI-GN or BSI by Gram-positive bacteria (GP), were included in the study. We analyzed 320 patients (181 BSI-GN and 139 BSI-GP) over 18 years old.

Within the study population, the largest number of patients identified with bacteremia were from the emergency department (ED) totaling 164/320 (52%), followed by the general intensive care unit (ICU), with 65/320 (21%). The median age was 61 years (25th to 75th percentile: 43-73 years). Regarding sex, 190/320 (59%) were male and 130/320(41%) were female. In terms of frequency, the most common initial infectious focus was pulmonary, totaling 106/320 (33%), followed by abdominal focus with 58/320 (19%) and the urinary tract as the initial infectious focus with 42/320 (14%), as shown in table 1.

The microorganisms most frequently detected in BSI-GN were *Escherichia coli* (29.6%), *Klebsiella pneumoniae* (17.4%), *Pseudomonas aeruginosa* (11.6%), and *Acinetobacter baumanni* (10.64%). Among BSI-GP, *Staphylococcus aureus* (51%) was the major isolate.

We evaluated 49 RLBs (hydrogen potential, pH; oxygen pressure, PO_2; red blood cell distribution width (RDW); white blood cell count (WBC); bilirubin; creatinine; lactate; methemoglobin; bands-eosinophils-neutrophils-lymphocytes-monocytes (%/mm_3); p50; activated partial thromboplastin time; aspartate-aminotransferase; alanine-aminotransferase; carbon dioxide; C-reactive-protein; oxygen content; sodium bicarbonate;

		T0h				T24h				T48h			
		Gram-negative		Gram-positive		Gram-negative		Gram-positive		Gram-negative		Gram-positive	
Biomarkers	n		n		p-value*	n		n	p-value*	n		n	p-value†
Bands (/mm^3)	131	914 (262-2332)	131	986 (92.5-2336)	≤0.001	74	458 (98-1732)	63	458 (84-1706)	0.52	63	134 (0-661)	58	241 (0-866)	≤0.001
Bands (%)	131	10 (2-21)	131	7.5 (1-14)	0.01	74	4.5 (1-14)	63	3 (1-10)	0.92	63	1.5 (0-5)	58	2 (0-6)	≤0.001
Bilirubin (mg/dl)	141	1.45 (0.7-2.9)	108	0.9 (0.3-1.7)	≤0.001	53	0.95 (0.3-4.3)	39	0.6 (0.3-1.4)	≤0.001	45	0.8 (0.3-2.45)	36	0.8 (0.3-1.4)	≤0.001
Creatinine (mg/dl)	155	1.55 (0.92-2.8)	118	1.14 (0.66-1.89)	0.004	72	1.06-(0.77-2.07)	56	1.0 (0.64-1.48)	≤0.001	59	1.17 (0.86-1.94)	44	1.14 (0.66-1.89)	0.40
Eosinophils %	160	1 (0-1)	131	1 (0-1)	≤0.001	74	1 (0-2)	63	1 (0-3)	0.001	63	1 (1-4)	58	1 (0-3)	≤0.001
Lactate (mmol/L)	141	2.6 (1.6-4.9)	108	2.0 (1.2-3.2)	0.008	53	1.7 (1.2-2.9)	39	1.25 (0.9-1.87)	≤0.001	45	1.45 (1.2-2.2)	36	1.4 (0.9-1.8)	0.03
Methemoglobin (%)	141	1.1 (0.8-1.4)	108	1.05 (0.7-1.4)	0.003	53	0.9 (0.6-1.2)	39	0.85 (0.5-1.2)	0.17	45	0.9 (0.6-1.2)	36	1.0 (0.7-1.4)	0.38
Neutrophiles (10^3/mm^3)	160	11 (5.6-16)	131	11 (7-16)	≤0.001	74	9.5 (6.7-14.4)	63	9.5 (6.6-13.3)	0.02	63	8.9 (5.5-12.9)	58	8.6 (5.5-15)	0.73
Oxyhemoglobin (%)	141	94 (91.2-95.5)	108	94.6 (93.3-98.2)	0.006	53	94.7 (91.4-95.9)	39	94 (91.5-96.2)	0.65	45	94.6 (92-96)	36	94 (91-95)	0.91
pH	141	7.37 (7.25-7.4)	108	7.41 (7.32-7.46)	≤0.001	53	7.4 (7.33-7.45)	39	7.43 (7.36-7.47)	0.07	45	7.4 (7.35-7.44)	36	7.41 (7.32-7.46)	0.45
pO_2 (mmHg)	141	93 (73.1-119.6)	108	90.7 (69.4-123)	≤0.001	53	86.8 (71.2-116)	39	87.7 (72.7-111)	0.31	45	97 (76-118)	36	90 (69-122)	0.11
p50 (mmHg)	141	27 (24.8-31.8)	108	26.18 (25-28.6)	≤0.001	53	25.9 (24.5-28.9)	39	25.2 (24.2-27.4)	0.99	45	26 (24.6-27.2)	36	26 (24.7-28.6)	0.43
RDW (%)	160	15.5 (14.2-17.2)	131	14.9 (13.8-16.4)	0.01	74	16.2 (15-18)	63	15.6 (13.9-17)	0.59	67	16 (14.4-18.5)	58	15.1 (13.9-16.7)	0.01
WBC (10^3/mm^3)	160	13.1 (6.9-19.7)	131	11.4 (8.5-18)	≤0.001	74	12.4 (8.5-16.9)	63	12.3 (8.5-15.1)	0.01	67	11.3 (7.3-15.8)	58	11.4 (8.5-18)	0.06

		Age	Gender n (%)		Initial Infection site n (%)					Admission n (%)			
	n	Years, median (interquartile range)	Female	Male	Pulmonary	Intra-abdominal	UT	Skin and soft tissue	Others or unknown	SC	MC	ICU	Emergency
Gram-negative	181	60 (45-73)	74 (41)	107 (59)	56 (31)	43 (24)	30 (17)	15 (8)	37 (19)	20 (11)	37 (20)	37 (20)	87 (49)
Gram-positive	139	61 (41-73)	56 (40)	83 (60)	50 (36)	15 (11)	12 (9.0)	28 (20)	34 (19)	11 (8)	23 (17)	28 (20)	77 (55)
p-value†		0.48	0.91			0.003	0.04	0.002	0.39	0.34	0.37	0.94	0.19

Odds ratio			2.6 (1.37-4.97)	2.0 (1.04-4.41)	0.4 (0.17-0.69)	

Table 1: General characteristics of eligible patients and univariate evaluation of biomarkers in relation to the time (T0h), (T24h) and (T48h) before blood culture collection.

Data given as median with interquartile range (Q1, Q3); Two-Sample Student's t test or chi-square test; OR = Odds ratio (95% Confidence Interval); n = numbers of patients; pH = hydrogen potential; pO_2 = oxygen pressure; RDW = red blood cell distribution width; WBC = white blood cell count; UT = Urinary tract; SC = Surgery clinic; MC = Medical clinic; ICU = General intensive-care unit. *Values of $p \leq 0.01$ were considered statistically significant. †Values of $p \leq 0.05$ were considered statistically significant.

mean corpuscular hemoglobin; mean corpuscular volume; mean corpuscular hemoglobin; neutrophiles/lymphocytes; carbon dioxide pressure; platelet count; red blood cell count; prothrombin time; international standardized ratio; base excess; ionic calcium; carboxy hemoglobin; oxyhemoglobin; chloride; glucoses; hematocrit; hemoglobin; magnesium; oxygen saturation; potassium; sodium; urea), of which 14 showed statistically significant differences ($p \leq 0.01$) at T0h and are described in table 1.

In relation to initial infections, intra-abdominal infections showed OR 2.6 (1.37-4.97); p = 0.003, indicating more than 150% chance to BSI-GN in relation to BSI-GP. Patients with the urinary tract as the initial infectious focus had a moderate risk for BSI-GN; OR 2.0 (1.04-4.4); p = 0.04, that is, 100% more likely for a GN bacterium to be responsible for BSI (Table 1). According to Levy., *et al*. [6], early knowledge of the presence of an infectious focus may help to indicate the microorganism in BSI. Total bilirubin was among the RLBs analyzed in our study that showed an association with BSI-GN 48h before BC collection (Table 1). Chand., *et al*. [7] found that hyperbilirubinemia was generally associated with infections caused by GN, mainly related to the initial intra-abdominal and urinary tract infectious focus. Our data agree with that of Chand., *et al*. since both parameters were associated with a greater chance of BSI-GN.

Although studies involving RLBs to predict the bacterial group involved in BSI are few and inconclusive [2,3], the RLB data obtained here can help in detection of BSI-GN.

Biomarkers associated with low tissue oxygen demand, such as increased lactate ($p \leq 0.001$), since T48h,in addition to marked changes in pO_2, p50, and oxyhemoglobin and lower pH (metabolic acidosis, T0h) can predict impairment of the oxygenation status in patients with BSI-GN (Table 1) [8].

Parameters pertaining to the blood count exam can be useful due to their ease, speed and low cost [3]. Our study demonstrated that eosinopenia ($p \leq 0.001$ since T48h) associated with an increase in WBC and neutrophils (both $p \leq 0.001$ since T24h) as well as an increase in RDW were related to BSI-GN. These changes in the blood count should be carefully analyzed, as they indicate the severity of the clinical condition, which have been reported by some authors as a predictor of mortality [9,10].

Conclusion

Considering the importance and increase in BSI-GN worldwide and the high morbimortality attributed, we concluded that RLB data, analyzed mainly together with the initial infectious focus data, could predict BSI-GN. These analyses could direct in empirical treatment while the BC result is not available. The rational empirical treatment increases therapeutic success, preventing complications and infections by resistant microorganisms [1]. We believe that further studies are needed so that these data can be used in clinical routine.

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Conflict of Interest

All authors report no conflict of interest for this publication.

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