American Journal of Emergency Medicine 35 (2017) 579–583

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

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

Original Contribution

Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria

Sheng Tao Yan [a], Li Chao Sun [b], Hong Bing Jia [c], Wen Gao [d], Jian Ping Yang [e], Guo Qiang Zhang [f,*]

[a] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[b] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[c] Clinical Microbiology Unit, China-Japan Friendship Hospital, Beijing, China
[d] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[e] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[f] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China

ARTICLE INFO

Article history:
Received 4 September 2016
Received in revised form 20 November 2016
Accepted 9 December 2016

Keywords:
Sepsis
Procalcitonin
Positive blood culture
Gram-positive bacteria
Gram-negative bacteria
Bacterial species
Infection sites

ABSTRACT

Objective: The aim of this study was to evaluate procalcitonin (PCT) diagnostic accuracy in discriminating gram-negative (GN) from gram-positive (GP) bloodstream infections and determining the relationship between PCT levels, infection sites, and pathogen types.

Methods: Clinical and laboratory data were collected from patients with blood culture (BC)-positive sepsis between January 2014 and December 2015. PCT levels at different infection sites were compared, as was the presence of GN and GP bloodstream infection. A receiver operating characteristic (ROC) curve was generated to assess diagnostic accuracy.

Results: Of the 486 monomicrobial BCs, 254 (52.26%) were positive for GN bacteria (GNB), and 202 (42.18%) for GP bacteria (GPB). Median PCT levels were higher in BCs positive for GN (2.42 ng/ml, IQR: 0.38–15.52) than in those positive for GPB (0.49 ng/ml, IQR: 0.13–5.89) ($P < 0.001$). In the ROC analysis to differentiate between GNB and GPB, the area under the curve was 0.628 (95% CI: 0.576–0.679). When the cutoffs for PCT were 10.335 and 15.000 ng/ml, the specificity of GNB infection was 80.2% and 84.2%, respectively. PCT levels caused by GNB differed between *Escherichia coli* and *Acinetobacter baumanni*/*Burkholderia cepacia*, *Klebsiella pneumonia* and *Acinetobacter baumanni*. PCT levels caused by GPB differed between *Staphylococcus epidermidis*/*Staphylococcus aureus* and *Staphylococcus hominis*/*Staphylococcus haemolyticus*, *Enterococcus faecium* and *Enterococcus faecalis*/*S.hominis*/*S. haemolyticus*. Among patients with known infection sites, there were statistical differences in PCT levels between abdominal infection and pneumonia/infective endocarditis, urinary tract infection and pneumonia/catheter-related infection/infective endocarditis.

Conclusion: PCT can distinguish between GNB and GPB infection, as well as between different bacterial species and infection sites.

1. Introduction

Sepsis is a life-threatening condition that can result from infections. The global incidences between 1995 and 2015 were 437 and 237 per 100,000 persons per year for sepsis and severe sepsis, respectively [1], and sepsis contributed to one in every two to three deaths in two complementary hospital cohorts [2]. Early diagnosis and rapid bacterial identification are essential for timely and appropriate clinical management [3-5]. Blood cultures (BCs) are considered the gold standard for detecting pathogens in patients with sepsis; however, given the time required, it cannot be applied to make early therapeutic decisions [6]. Identifying biomarkers with high sensitivity and specificity would be useful for overcoming this problem.

Procalcitonin (PCT) is a 116-amino acid protein with a molecular mass of 13 kDa that is produced by thyroid C cells and converted to calcitonin before being released into the bloodstream. Circulating levels of PCT—which are produced by liver monocytes, macrophages, and lung and intestinal lymphocytes—are generally very low in healthy individuals, but can increase by 100 to 1000 fold in response to systemic bacterial infections [7].

PCT is used as a biomarker for initiating or terminating antibiotic therapy in various clinical settings, including the emergency department, intensive care unit (ICU), and primary care [8-10]. The present study investigated whether PCT levels in the clinical course of bacterial blood infection can serve as an early diagnostic marker for sepsis. We examined whether the levels differed according to bacterial species

* Corresponding author at: Department of Emergency Medicine, China-Japan Friendship Hospital, No 2 east Yinghua street, Chaoyang district, Beijing 100029, China.
E-mail address: zhangchong2003@vip.sina.com (G.Q. Zhang).

http://dx.doi.org/10.1016/j.ajem.2016.12.017

and site of infection, and evaluated the utility of PCT levels for distinguishing between gram-negative and -positive bacteria (GNB and GPB, respectively) in patients with bloodstream infection.

2. Materials and methods

2.1. Patients and samples

This retrospective study was carried out using clinical and routine laboratory data collected at the Clinical Microbiology Unit of China-Japan Friendship Hospital, China, between January 2014 and December 2015. Inclusion criteria were as follows: (1) fulfillment of diagnostic criteria for sepsis in 2012 [11]; (2) at least one positive blood culture; (3) consecutive blood samples for BC and PCT collected simultaneously; (4) age ≥ 18 years; and (5) only a single bloodstream infection episode (only the first sample of the episode was considered). An episode was defined as the time period associated with one or more positive BCs for the same organism(s) [12,13]. PCT levels may be altered in some non-infectious diseases, such as autoimmune disease [14-18] and malignant tumors [19-21]. Therefore, our exclusion criteria were: (1) a medical history of immune system disease (adult-onset Still's disease, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, or multiple sclerosis) [14-18]; and (2) history of malignant tumor (thyroid carcinoma or lung cancer) [19-21].

2.2. Measurement of PCT level

Serum PCT levels were measured using an automatic analyzer (Vidas B.R.A.H.M.S.; bioMérieux, Marcy l'Etoile, France), according to the manufacturer's instructions. The lower detection limit of the assay was 0.05 ng/ml and assay sensitivity was 0.09 ng/ml.

2.3. BCs

For each sample, an aliquot of 5–10 ml whole blood was inoculated into Bactec aerobic and anaerobic bottles (Becton Dickinson, Sparks, MD, USA) that were incubated in a Bactec FX automated blood culture system (Becton Dickinson). Aliquots were removed from positive cultures for Gram staining and were streaked on solid medium for subsequent analysis. Microorganisms were identified by conventional methods and matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

2.4. Pathogen identification

Microorganisms detected in BCs were considered as clinically relevant pathogens rather than contaminants if they met the following conditions: (i) detection in two or more BCs and reported by the clinician as the cause of the sepsis episode; (ii) detection in only one set of BCs but consistent with the results of cultured samples from suspected infectious foci collected from the same patient during the same infectious episode; (iii) detection in only one set of BCs and belonging to a species included among etiopathogenic agents of the patient's infectious disease; and (iv) detection in only one set of BCs reported by the clinician as the cause of the sepsis episode in the final diagnosis based on clinical, instrumental, and laboratory data. Coagulase-negative staphylococci, *Corynebacterium* spp., and other skin commensals were considered as

Table 1
Demographic and clinical characteristics of patients.

Variable	Value
Age (years)	70 (IQR: 59–80)[a]
Males (%)	253 (61.11)
Females (%)	161 (38.89)
Ward of hospitalization	
ICU (%)	309 (74.64)
EM (%)	105 (25.36)
BCs	
Monomicrobial (%)	486 (92.75)
GNB (%)	254 (52.26)
GPB (%)	202 (42.18)
Fungi (%)	30 (6.17)
Polymicrobial (%)	38 (7.25)
SOFA	4 (IQR: 1–7)[a]
Platelet count ($\times 10^9$/l)	154 (IQR: 75–228)[a]
Creatininemia (mg/dl)	73.70 (IQR: 50.90–137.05)[a]
Total bilirubin (μmol/l)	11.90 (IQR: 7.51–20.84)[a]

BC, blood culture; EM, emergency department; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; ICU, intensive care unit; IQR, interquartile range; PCT, procalcitonin; SOFA, sequential organ failure assessment.
[a] Median value and IQR.

Table 2
Median PCT levels corresponding to pathogens isolated from two or more BCs with monomicrobial infection.

Pathogen	Number of BCs	Median PCT level (IQR) (ng/ml)
GNB		
Escherichia coli [1-5]	97	4.48 (0.86–23.32)
Acinetobacter baumannii [1,6-9]	39	0.94 (0.17–8.44)
Klebsiella pneumoniae [2,6,10-12]	36	3.42 (0.61–21.96)
Pseudomonas aeruginosa [3,7,10,13,14]	17	1.48 (0.42–10.69)
Burkholderia cepacia [4,8,11,13,15]	18	0.44 (0.24–4.57)
Enterobacter cloacae [5,9,12,14,15]	13	1.50 (0.46–19.10)
Serratiamarcescens	6	1.06 (0.08–2.34)
Klebsiellaoxytoca	2	8.32 (1.57–15.06)
Acinetobacterlwoffii	2	0.45 (0.29–0.61)
Proteus mirabilis	4	0.44 (0.24–9.68)
Salmonella spp.	2	1.90 (0.05–3.74)
Stenotrophomonasmaltophilia	4	9.54 (4.31–16.95)
Aeromonashydrophila	2	2.54 (0.61–4.47)
GPB		
Staphylococcus epidermidis 16,17,18,19,20,39	39	0.31 (0.08–5.32)
Staphylococcus aureus [16,21,22,23,24]	35	1.18 (0.3–11.97)
Staphylococcus hominis [17,21,25,26,27]	35	0.21 (0.08–1.17)
Enterococcus faecium [18,22,25,28,29]	25	3.36 (0.48–23.07)
Enterococcus faecalis [19,23,26,28,30]	18	1.24 (0.24–2.28)
Staphylococcus haemolyticus [20,24,27,29,30]	11	0.41 (0.1–0.82)
Staphylococcus capitis	9	0.44 (0.25–3.54)
Streptococcus mutans	2	0.12 (0.10–0.14)
Paratyphoid C coli	2	0.20 (0.16–0.24)
Streptococcus viridans	2	4.19 (1.42–6.96)
Streptococcus pneumoniae	3	7.39 (5.90–19.58)
Streptococcus mitis	2	0.17 (0.05–0.29)
Streptococcus oralis	3	0.05 (0.05–0.16)
Streptococcus salivarius	2	31.97 (29.32–34.62)
Streptococcus agalactiae	2	9.36 (0.28–18.43)
Fungi		
Candida albicans	19	1.11 (0.41–2.24)
Candida parapsilosis	5	0.79 (0.40–1.70)
Candida tropicalis	2	5.37 (0.29–10.45)

1, $Z = -2.909$, $P = 0.004$; 2, $Z = -0.468$, $P = 0.639$; 3, $Z = -1.042$, $P = 0.297$; 4, $Z = -2.152$, $P = 0.031$; 5, $Z = -0.935$, $P = 0.350$; 6, $Z = -2.321$, $P = 0.020$; 7, $Z = -0.849$, $P = 0.396$; 8, $Z = -0.115$, $P = 0.908$; 9, $Z = -0.726$, $P = 0.468$; 10, $Z = -0.696$, $P = 0.487$; 11, $Z = -1.798$, $P = 0.072$; 12, $Z = -0.589$, $P = 0.556$; 13, $Z = -0.306$, $P = 0.318$; 14, $Z = -0.126$, $P = 0.902$; 15, $Z = -0.601$; $P = 0.567$; 16, $Z = -0.028$, $P = 0.978$; 17, $Z = -3.055$, $P = 0.002$; 18, $Z = -0.998$, $P = 0.318$; 19, $Z = -1.246$, $P = 0.213$; 20, $Z = -2.014$, $P = 0.044$; 21, $Z = -2.933$, $P = 0.003$; 22, $Z = -0.967$, $P = 0.333$; 23, $Z = -1.259$, $P = 0.208$; 24, $Z = -2.03$, $P = 0.043$; 25, $Z = -3.190$, $P = 0.001$; 26, $Z = -1.665$, $P = 0.096$; 27, $Z = -0.490$, $P = 0.629$; 28, $Z = -2.143$, $P = 0.032$; 29, $Z = -2.456$, $P = 0.013$; 30, $Z = -1.237$, $P = 0.220$.
BC, blood culture; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; IQR, interquartile range; PCT, procalcitonin.