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Can gram-negative-like biomarker values in *Streptococcus pyogenes* sepsis negatively influence right choice of initial antibiotic therapy?

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ABSTRACT

Introduction: Biomarkers of sepsis are used to facilitate the diagnosis of sepsis and antibiotic stewardship. Gram-negative sepsis has been reported to have a distinct pattern of markedly increased procalcitonin vs. C-reactive protein compared to patients with Gram-positive sepsis. However, selected infective agents may not follow this pattern, possibly leading to inappropriate choice of ATB therapy, (namely in *Streptococcus pyogenes* infection).

Methods: We retrospectively evaluated charts of septic patients infected by *S. pyogenes*, *Escherichia coli* or with *Staphylococcus aureus* sepsis, their biomarker pattern, appropriateness of the initial ATB therapy, and outcome. Biomarker values were compared using Kruskal-Wallis test followed by Dunn Post-Hoc tests and as a threshold was used $p < 0.05$.

Results: Procalcitonin levels were higher in *S. pyogenes* sepsis (12.51 ng/ml, IQR: 6.26–48.38 ng/ml) vs *E. coli* sepsis (4.30 ng/ml, IQR: 1.50–10.00 ng/ml, $p < 0.001$) and vs *S. aureus* sepsis (0.75 ng/ml, QR: 0.34–1.62 ng/ml, $p < 0.001$). Neutrophil to lymphocyte ratio followed the same pattern as procalcitonin. Initial appropriate ATB therapy in *S. pyogenes* cohort was 11.29% compared to 99.3% and 100% in *S. aureus* and *E. coli* group, respectively.

Conclusion: Contrasting previous reports, the highest procalcitonin values were observed in the *S. pyogenes* group rather than in gram-negative sepsis. This has contributed to an inappropriate initial ATB therapy and, we believed, resulted in higher mortality in this group. Therefore, we recommend a re-evaluation of current procalcitonin values in order to improve both survival rate as well as patient's quality of life in general.

KEYWORDS

GAS sepsis – procalcitonin – neutrophil/lymphocyte ratio – initial ATB therapy – biomarkers – clindamycin

SOUHRN

Adámková V., Lahoda Brodská H., Adámková V., Zima T.: Mohou hodnoty biomarkerů, imitující gramnegativní zánětlivou odpověď, negativně ovlivnit iniciální volbu antibiotika u pacientů se sepsí vyvolanou *Streptococcus pyogenes*?

Úvod: Biomarkery jsou u septických pacientů využívány jak k diagnostice sepse, tak k antibiotickému stewardshipu. Sepse vyvolaná gramnegativními bakteriemi má odlišné charakteristiky, především vysoký procalcitonin vs C-reaktivní protein v porovnání se sepsí vyvolanou grampozitivními bakteriemi. Avšak jednotlivá infekční agens, především *Streptococcus pyogenes*, nemusí do tohoto schématu zapadat, což může vést k nesprávné iniciální volbě antibiotika.

Metody: Retrospektivní analýza biomarkerů, iniciální volby antibiotické léčby a výsledků léčby u pacientů se sepsí vyvolanou *S. pyogenes*, *Escherichia coli* a *Staphylococcus aureus*. Hodnoty biomarkerů byly porovnány pomocí Kruskal-Wallis testu s následným Dunn post-Hoc testem s prahem $p < 0,05$.

Výsledky: Hodnoty procalcitoninu byly nejvyšší u sepse vyvolané *S. pyogenes* (12,51 ng/ml, IQR: 6,26–48,38 ng/ml) oproti sepsí vyvolané *E. coli* (4,30 ng/ml, IQR: 1,50–10,00 ng/ml, $p < 0,001$) a *S. aureus* (0,75 ng/ml, QR: 0,34–1,62 ng/ml, $p < 0,001$). Poměr neutrofilů a lymfocytů vykazoval stejné charakteristiky jako procalcitonin. Správná iniciální antibiotická léčba byla v souboru *S. pyogenes* 11,29 % v porovnání s 99,3 % a 100 % u *S. aureus* a *E. coli* skupin.

Závěr: Oproti předchozím studiím byly v našem souboru pozorovány nejvyšší hodnoty procalcitoninu u pacientů se sepsí vyvolanou *S. pyogenes* spíše než gramnegativními bakteriemi. Vysoké hodnoty procalcitoninu imitující gramnegativní zánětlivou odpověď přispěli k ovlivnění výběru iniciální antibiotické léčby (bez znalosti původce), což mohlo vést k vyšší mortalitě u této skupiny pacientů. Proto doporučujeme přehodnocení významu procalcitoninu v diagnostice sepse pro zlepšení přežití i kvality života pacientů.

KLÍČOVÁ SLOVA

S. pyogenes sepsis – procalcitonin – poměr neutrofilů/lymfocytů – iniciální ATB terapie – biomarkery – klindamycin

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INTRODUCTION

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is the major cause of mortality from any infectious disease worldwide [1]. In 2005, the WHO reported a global estimate of 18.1 million cases of severe *Streptococcus pyogenes* (GPOS) disease, with 1.78 million new cases of severe disease and 517,000 deaths per year [2]. Group A streptococci (GAS) not only causes superficial diseases, but it has also the capacity to breach epithelial barriers and cause a variety of invasive diseases which lead to a death of 8 to 23% patients with GAS invasive disease within 7 days of infection [3].

Being the first 3–6 hours after the clinical suspicion critical for establishment of therapeutic measures that improve prognosis, the keystone of sepsis management is timely administration of active microbials, Surviving Sepsis Campaign guidelines [4]. Under routine clinical praxis, patients with suspected sepsis are immediately screened for biomarkers and blood culture is drawn. In the best-case scenario, preliminary results of microbial diagnosis of sepsis from the blood culture are available after 24 h. Therefore, the choice of empiric initial ATB therapy is commonly based on the level of available biomarkers and clinical symptoms [5] and once the microbiological results are available, the initial therapy is evaluated and changed if inappropriate.

In general, empiric initial treatment of a suspected GPOS sepsis consists of a use of glycopeptides. Suspected GNEG sepsis is covered by the administration of carbapenems, aminoglycosides or colistin based on a local epidemiological situation [6]. However, the gold standard for GAS sepsis is a combination of cell wall synthesis inhibitors (i. e. beta-lactams or glycopeptides) with protein synthesis inhibitors (MLS antibiotics) [7]. Although *S. pyogenes* is susceptible to penicillin *in vitro* [8], penicillin monotherapy treatment of GAS infections with toxin production has been associated with high morbidity and mortality [7] due to “Eagle effect” [9]. Addition of clindamycin decreases morbidity and mortality [10] via inhibition of GAS virulence factors production. Worldwide increasing resistance of *S. pyogenes* to clindamycin might decrease its effect, however, data from the Czech Republic do not show the trend in increasing resistance [11, 12]. Furthermore, clindamycin is associated with longer post-antibiotic effect than penicillin and its effect is not influenced by inoculum size [13]. On the other hand, the use of clindamycin is associated with increased risk of post-antibiotic colitis caused by *Clostridium difficile* [14].

Nevertheless, currently there is no single commercially available biomarker that would be 100% specific and sensitive to discriminate between GNEG and GPOS sepsis [15]. This hinders clinical sepsis pathway implementation, potentially leading to an inappropriate choice of ATB therapy, which in the worst-case results in patient’s death [5]. Frequently used biomarkers, such as the total white blood cells, neutrophil count, and CRP, lack the specificity to discriminate between SIRS and sepsis [15]. In this sense, PCT – a prohormone of calcitonin – was shown to have the best accuracy to identify patients with invasive bacterial infections because inflammatory stimuli including severe infection leads to its upregulated production in different tissues [16]. Despite the fact that

elevated PCT serum concentrations are not exclusive to infections (they can also be elevated during paraneoplastic processes, in patients with solid tumours or with major trauma [17], at this moment, PCT is considered among the best clinically available biomarkers to diagnose sepsis [18] and can be used as a guide to fulfil the principles of antimicrobial stewardship (AS). Brodská et al. and other researchers [19, 20] have published that PCT values are significantly higher in GNEG sepsis compared to GPOS and yeast sepsis and currently, if PCT level is > 3 [20], patients are treated for GNEG sepsis until microbiological results are available. Nonetheless, Ruddle et al., 2018 [21] questioned the validity of those findings. The aim of this retrospective study was to evaluate the administration of an appropriate initial ATB therapy based on available biomarkers in patients with microbiologically confirmed cases of GAS sepsis.

METHODS

Patient population

Retrospectively, we identified and reviewed all cases of GAS sepsis ($n = 62$) between 2006 and 2019 in a single tertiary-care centre. Control groups were patients with sepsis between years 2018 and 2019 caused by the most frequent causative GPOS agent ($n = 150$), *Staphylococcus aureus*, and the most frequent GNEG agent ($n = 149$) *Escherichia coli*. Only confirmed cases with complete data (PCT, CRP, NLR, WBC, blood cultures, recommended ATB treatment) were analysed.

Our outcome was the incidence of an appropriate initial ATB therapy, which was based on the levels of PCT and NLR.

Biomarkers determination

PCT, CRP, NLR, WBC measurements were performed in hospital laboratory using commercially available assays as part of routine care. All PCT values and other laboratory parameters were recorded within the first 24h after the onset of sepsis as baseline data. Blood cultures were drawn at sepsis onset before the start of antimicrobial therapy and processed and analysed according to local standards. The investigators considering all available clinical and microbiological data identified the focus of infection retrospectively. For analysis, foci of infection were grouped into four categories (bones/soft tissue, respiratory, urogenital and other).

Statistical analysis

Data analysis was performed in RStudio. Categorical data were expressed as percentage and continuous variables as the mean and medians with interquartile range (IQR) between 25th and 75th percentile. For the comparison of nonparametric data, Kruskal-Wallis test followed by Dunn Post-Hoc tests were used. The threshold for significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Patient’s population

During the 13-years long study period, 62 patients with GAS sepsis were hospitalized in the General University Hospital, Prague. Demographic and outcome clini-

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Table 1. Patient's demographic and clinical data

Characteristics	All patients	STPY group (GPOS)	STAU group (GPOS)	ESCO group (GNEG)
Number	361	62	150	149
Age - Mean (Range)	60 (8-93)	62 (11-93)	63 (0-96)	65,4 (0-94)
Sex - male	226 (62.6%)	35 (56.5%)	95 (63.3%)	96 (64.4%)
Origin of infection				
Community aquired		59 (95.2%)	84 (56.0%)	71 (47.7%)
Nosocomial		3 (4.8%)	66 (44.0%)	78 (52.3%)
Focus of infection				
Soft tissue		57 (91.9%)	72 (48.0%)	0
Urogenital		0	0	82 (55.0%)
Respiratory		5 (8.1%)	15 (10.0%)	5 (3.3%)
Other		0	63 (42.0%)	62 (41.7%)
Mortality				
28 - Day mortality		12 (19.4%)	10 (7.7%)	15 (10.0%)
Appropriate therapy -Number (%)		7 (11.29%)	149 (99.3%)	149 (100%)
Inappropriate- Number (%)		55 (88.71%)	1(0.7%)	0

STPY - *Streptococcus pyogenes*, STAU - *Staphylococcus aureus*, ESCO - *Escherichia coli*, GPOS - Gram-positive bacteria, GNEG - Gram-negative bacteria

cal data are summarized in Table 1. GAS sepsis with positive blood culture is rare [22, 23] and therefore, our cohort was unique due to its large number of GAS patients.

Biomarker levels associated with bacterial sepsis

PCT, NLR and CRP median values for three bacterial species (*Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*) are summarized in Table 2 and shown in Figure 1a, 1b and Figure 1c, respectively. PCT median value of GAS sepsis 12.51 ng/ml (IQR: 6.26-48.38 ng/ml) was significantly higher than the values obtained for both *E. coli* and *S. aureus* sepsis 4.30 ng/ml (IQR: 1.50-10.00 ng/ml, $p < 0,001$) and 0.75 ng/ml (IQR: 0.34-1.62 ng/ml, $p < 0,001$), respectively. Up to our knowledge, we are the first to report that *S. pyogenes* can produce an inflammatory response similar to or higher than GNEG bacteria. *S. pyogenes* GNEG-like inflammatory response might be explained via recognition of GAS pore-forming toxin streptolysin O by TLR4 leading to high expression of pro-inflammatory cytokines [24].

TLR4 is a receptor for lipopolysaccharide of GNEG bacteria, while peptidoglycan of GPOS bacteria activates TLR2 [25] and it has been shown that administration of lipopolysaccharide leads to increased PCT mRNA expression in peripheral blood mononuclear cells [26]

Furthermore, there was also a significant difference in PCT median values between *E. coli* and *S. aureus* sepsis ($p < 0.001$). Data from control groups are in agreement with other studies showing that generally, patients with GNEG sepsis have significantly higher PCT values compared to GPOS septic patients [27]. Due to a very low incidence of *S. pyogenes* positive blood cultures [3], even their inclusion in GPOS group does not significantly increase PCT level (computational modelling, data not shown). Similarly, there was a significant difference in NLR median value between GAS sepsis 22.5 (IQR: 14.00-31.00) and both *E. coli* and *S. aureus* sepsis 11.23 (IQR: 3.47-26.62, $p < 0.001$) and 11.15 (IQR: 6.40-22.40, $p < 0.001$), respectively. In contrast to PCT, there was no significant difference in NLR median values between *E. coli* and *S. aureus* ($p > 0.05$). Although there was no significant difference in median CRP values between septic patients with *E. coli* and *S. aureus*

nor between patients with *S. pyogenes* and *E. coli*, CRP levels of patients with *S. pyogenes* 177.00 mg/ml (IQR: 86.58-330.62 mg/ml) were significantly increased compared to patients with *S. aureus* 130.00 mg/ml (IQR: 96.90-212.00 mg/ml), $p = 0.016$. WBC median values showed no significant difference between any of the groups confirming the findings by Brodská et al [19].

Table 2. Laboratory results of biomarkers in *S. pyogenes* and control groups

Characteristics	Median STPY group	IQR STPY group	Median STAU group	IQR STAU group	Median ESCO group	IQR ESCO group
Clinical data and scores						
PCT (ng/ml)	12.51	62.60-48.38	0.75	0.34-1.62	4.30	1.50-10.00
CRP (mg/ml)	177.00	86.58-330.62	130.00	96.90-212.00	145.00	89.00-225.0
WBCs ($\times 10^9$)	12.70	6.95-18.00	11.63	7.03-15.40	10.49	6.60-15.24
NL ratio	22.50	14.00-31.00	11.15	6.40-22.40	11.23	3.47-26.62

STPY - *Streptococcus pyogenes*, STAU - *Staphylococcus aureus*, ESCO - *Escherichia coli*, IQR - inter-quartile range, PCT - procalcitonin, NLR - neutrophil to leukocyte ratio, CRP - C-reactive protein, WBC - white blood cells

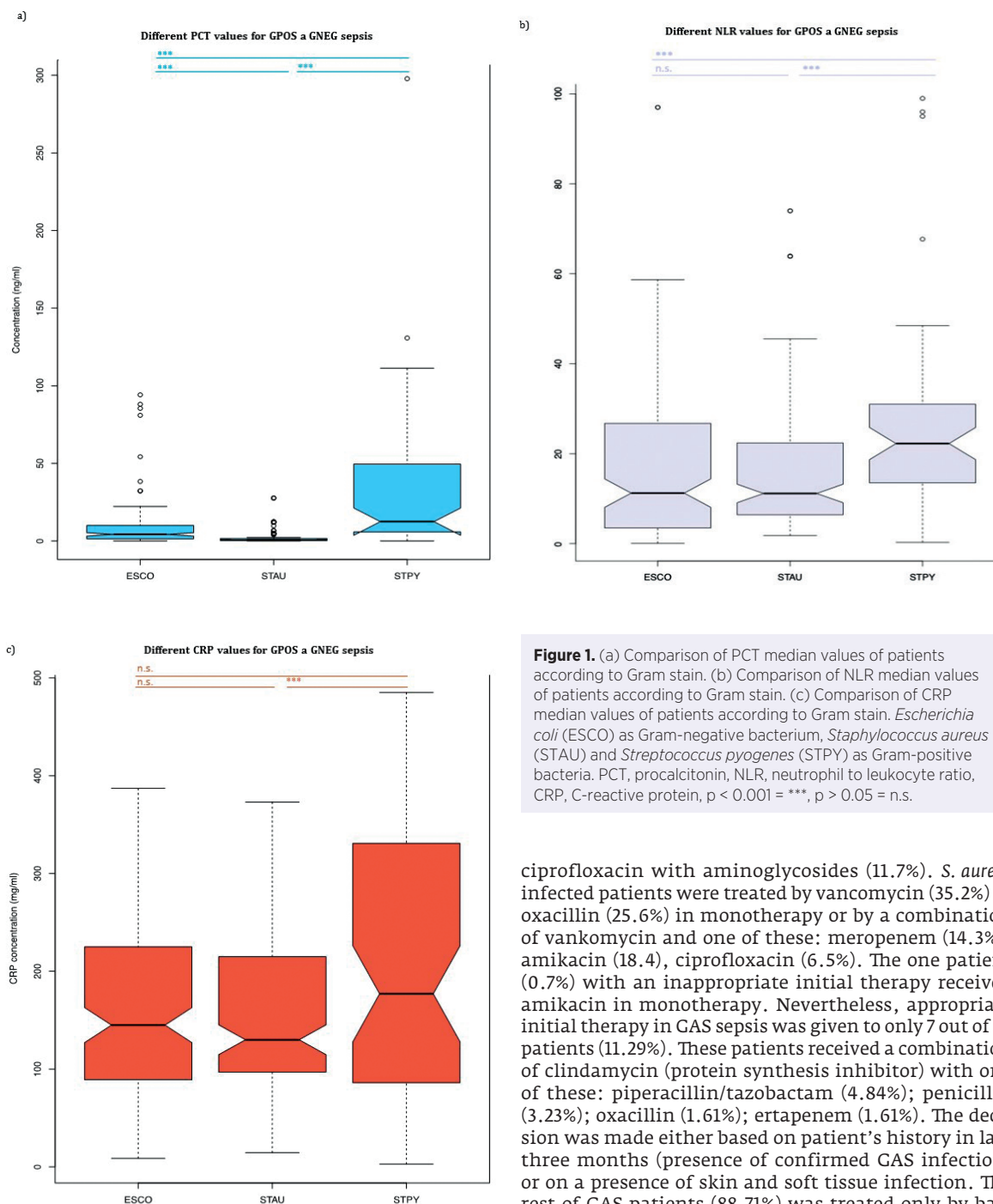


Figure 1. (a) Comparison of PCT median values of patients according to Gram stain. (b) Comparison of NLR median values of patients according to Gram stain. (c) Comparison of CRP median values of patients according to Gram stain. *Escherichia coli* (ESCO) as Gram-negative bacterium, *Staphylococcus aureus* (STAU) and *Streptococcus pyogenes* (STPY) as Gram-positive bacteria. PCT, procalcitonin, NLR, neutrophil to leukocyte ratio, CRP, C-reactive protein, $p < 0.001 = ***$, $p > 0.05 = n.s.$

ATB therapy

According to patient's records, all patients with *E. coli* sepsis and 149 out of 150 patients with *S. aureus* received an appropriate initial therapy. Patients with *E. coli* received either a monotherapy (meropenem, 34.3%) or a combination of: beta-lactams with aminoglycosides (38.8%); carbapenems with aminoglycosides (15.2%) or

ciprofloxacin with aminoglycosides (11.7%). *S. aureus* infected patients were treated by vancomycin (35.2%) or oxacillin (25.6%) in monotherapy or by a combination of vancomycin and one of these: meropenem (14.3%), amikacin (18.4), ciprofloxacin (6.5%). The one patient (0.7%) with an inappropriate initial therapy received amikacin in monotherapy. Nevertheless, appropriate initial therapy in GAS sepsis was given to only 7 out of 62 patients (11.29%). These patients received a combination of clindamycin (protein synthesis inhibitor) with one of these: piperacillin/tazobactam (4.84%); penicillin (3.23%); oxacillin (1.61%); ertapenem (1.61%). The decision was made either based on patient's history in last three months (presence of confirmed GAS infection) or on a presence of skin and soft tissue infection. The rest of GAS patients (88.71%) was treated only by bactericidal antibiotics without the agent inhibiting protein synthesis as their PCT levels were high, currently acknowledged as an indicator of GNEG sepsis [20], and the source of infection was unknown. 28-Day mortality in GAS patients was 19.4% but all of them died in the first 7 days. On the other hand, mortality of patients in the control groups in the first 7 days was < 5% which increased to 7.7% in *S. aureus* cohort and to 10.0% in *E. coli* cohort after 28 days.

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CONCLUSION

Contrasting previous reports, the highest PCT and NLR were observed in *S. pyogenes* cohort. This contributed to a high percentage of initial inappropriate choice ATB therapy. Therefore, if the etiology of sepsis is unknown, the PCT and/or NLR values are high and microbiological results are not yet available, addition of protein synthesis inhibiting antibiotic is required. This therapy would prevent a worsening of symptoms in case the sepsis was not caused by GNEG bacterium but *S. pyogenes* mimicking GNEG immune response. Furthermore, our data highlight an urgent need for a development of fast diagnostic tests based on next-generation sequencing and implementing them into a routine clinical praxis in order to prevent deaths related to a wrong initial ATB therapy due to bacterial sepsis misclassification.

Abbreviations

STPY	– <i>Streptococcus pyogenes</i>
STAU	– <i>Staphylococcus aureus</i>
ESCO	– <i>Escherichia coli</i>
GPOS	– Gram-positive bacteria
GNEG	– Gram-negative bacteria
CRP	– C-reactive protein
PCT	– procalcitonin
GAS	– Group A <i>Streptococcus</i>
WBC	– white blood count
NLR	– Neutrophil lymphocyte ratio
AS	– antimicrobial stewardship
MLS	– macrolide-lincosamide-streptogramin B

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Conflicts of Interest

The authors declare no conflict of interest.

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