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ORIGINAL RESEARCH REPORT

Diagnostic value of sepsis biomarkers in hematopoietic stem cell transplant recipients in a condition of high prevalence of gram-negative pathogens

Igor Stoma [a,*], Igor Karpov [a], Anatoly Uss [b], Oleg Rummo [b], Natalia Milanovich [b], Igor Iskrov [b]

[a] Department of Infectious Diseases, Belarusian State Medical University, Minsk, Belarus
[b] City Clinical Hospital No. 9, Minsk, Belarus

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Abstract

Objective/background: A decision about the need for antimicrobial therapy in a patient with febrile neutropenia after hematopoietic stem cell transplantation (HSCT) is often complicated because of the low frequency of culture isolation and reduced clinical manifestation of infection. Usefulness and choice of sepsis biomarkers to distinguish bloodstream infection (BSI) from other causes of febrile episode is still argued in HSCT recipients in modern epidemiological situations characterized by the emergence of highly resistant gram-negative microorganisms. In this study a comparative analysis of diagnostic values of presepsin, procalcitonin (PCT), and C-reactive protein (CRP) was performed as sepsis biomarkers in adult patients after HSCT in a condition of high prevalence of gram-negative pathogens.

Methods: A prospective observational clinical study was performed at the Center of Hematology and Bone Marrow Transplantation in Minsk, Republic of Belarus. The biomarkers (presepsin, PCT, and CRP) were assessed in a 4-hour period after the onset of febrile neutropenia episode in adult patients after HSCT. Microbiologically-confirmed BSI caused by a gram-negative pathogen was set as a primary outcome.

Results: Clinical and laboratory data were analyzed in 52 neutropenic patients after HSCT aged 18—79 years. Out of the biomarkers assessed, the best diagnostic value was shown in presepsin (area under the curve [AUC]: 0.889, 95% confidence interval [CI]: 0.644—0.987, $p < .0001$) with

* Corresponding author at: Prititskogo Street, 2/2-105, Minsk 220073, Belarus.
E-mail address: igor.stoma@gmail.com (I. Stoma).

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75% sensitivity and 100% specificity, then in PCT (AUC: 0.741, 95% CI: 0.573—0.869, $p = .0037$) with 62% sensitivity and 88% specificity. The optimal cut-off value for CRP was set as 165 mg/L, while it had an average diagnostic value (AUC: 0.707, 95% CI: 0.564—0.825, $p = .0049$) with low sensitivity (40%) and should not be routinely recommended as a biomarker in adult patients with suspected BSI after HSCT.

Conclusion: Presepsin may be recommended in adult patients with suspected gram-negative BSI after HSCT as a possible additional supplementary test with a cut-off value of 218 pg/mL. PCT is inferior to presepsin in terms of sensitivity and specificity, but still shows a good quality of diagnostic value with an optimal cut-off value of 1.5 ng/mL. CRP showed an average diagnostic value with low sensitivity (40%) and should not be routinely recommended as a biomarker in adult patients with suspected BSI after HSCT in a condition of high prevalence of gram-negative pathogens.

Introduction

Bacterial bloodstream infections (BSI) are still one the leading causes of infectious complications after hematopoietic stem cell transplantation (HSCT), occurring in approximately 5—10% of autologous and 20—30% of allogeneic HSCT recipients [1]. Despite this, an improved level of supportive care mortality rate due to BSI remains significant, with it being 24—40% in allogenic HSCT [2—6]. Traditional diagnosis of BSI includes results of culturing techniques. Positive blood culture is known to be the most certain method of diagnosis, but it has a number of limitations. For instance, in a large percentage of patients it remains negative despite the typical clinical presentation of sepsis [7]. The other issue of standard culturing techniques is that it still takes significant time for the laboratory to give the results to the doctor. It is well known that the adequate and on-time prescribed antimicrobial therapy is key to success in patients with BSI [8]. But there are a number of cases when it is not clear whether the febrile episode in a concrete patient is a symptom of BSI or if the patient has any other cause (e.g., viral or fungal infection, reaction to chemotherapy infusion, or reactivation of hematologic disease). In patients receiving HSCT the consequences of BSI may be dramatic, taking into account the level of immunosuppression caused by high-dose chemotherapy and total body irradiation. The other issue, which may affect the early diagnosis of BSI in HSCT patients, is the possibility of having a potentially fatal BSI with mild clinical symptoms of infection in such patients; though, the clinical significance of sepsis biomarkers increases in HSCT recipients.

Among the widely used biomarkers which have been studied in neutropenic patients are procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 [9—11]. Despite this fact, the use of biomarkers in neutropenic patients remains a controversial question. For instance, the guidelines of the Infectious Diseases Society of America does not include the use of biomarkers in their recommendations [12]. However, the existing studies are based on small samples of patients receiving HSCT in a total group of neutropenic patients, so there is not enough data to be sure about the diagnostic and clinical significance of those biomarkers in HSCT recipients [13,14]. Previously it was shown that biomarkers are not equally effective in special groups of patients; however, important differences in diagnostic characteristics of presepsin were shown in patients with advanced forms of acute kidney injury and in patients on hemodialysis, which served as a need for different cut-off values in such patients [15,16]. Furthermore, there is no compelling information concerning the usefulness of presepsin in adult patients after HSCT, and there is a practical need for results of a comparative analysis of diagnostic parameters for PCT, CRP, and presepsin in HSCT recipients [17,18]. The continuing emergence of gram-negative pathogens as a cause of BSI affects transplant centers worldwide, so the use of biomarkers in patients after HSCT should be reevaluated according to this recent shift from gram-positive microorganisms [3,19,20]. Therefore, it is important to assess and compare the diagnostic value of presepsin, PCT, and CRP as early biomarkers of a gram-negative bacterial BSI in HSCT recipients.

The main objective of the study was to identify the diagnostic value of presepsin, PCT, and CRP and perform a comparative analysis of those biomarkers in a group of HSCT recipients with gram-negative bacterial BSI.

Methods

Study setting and design

The Republican Center for Hematology and Bone Marrow Transplantation is located on the base of the City Clinical Hospital No. 9 in Minsk, Belarus. The center has more than 150 beds including a Department of Bone Marrow Transplantation and Intensive Care Unit for patients with various hematological diseases, with patients preparing and undergoing HSCT. It also includes a microbiology laboratory, laboratory of bone marrow separation and freezing, laboratory of cellular biotechnology, HLA-typing laboratory, and clinical diagnostics laboratory. The study was approved by the Institutional Research Ethics Committee of the hospital, and informed consent was taken from the included patients.

Data relating to age, sex, date, and type of transplantation, conditioning chemotherapy regimen, microorganisms isolated from blood, and antibacterial therapy were prospectively collected in hematopoietic stem cell recipi-

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ents in this observational clinical study. There were 52 adult patients who had undergone autologous or allogeneic HSCT with neutropenia–all of them were inpatients. The study was performed between January 2013 and October 2015.

The inclusion criteria of the study included adult patients with febrile neutropenia during 30 days (pre-engraftment period) after autologous or allogenic HSCT. Febrile neutropenia was assessed by definition of Freifeld et al. [12] as a single oral temperature measurement of >38.3 °C or a temperature of >38.0 °C sustained over a 1-hour period with an absolute neutrophil count (ANC) in peripheral blood of $\leqslant$500 cells/mm^3 or an ANC that is expected to decrease to $\leqslant$500 cells/mm^3 during the next 48 hours. Among the exclusion criteria were diabetes mellitus, acute kidney injury (clinically and/or laboratory confirmed), and acute heart failure. Patients, who had received antithymocytic immunoglobulin during 7 days before the onset of the febrile episode were excluded from the study. BSI was defined as having a microbiologically-proven growth from a blood culture of a patient with febrile neutropenia in a period of 30 days after HSCT, which was taken as an endpoint in the analysis. In a case of fatal outcome, blood samples were still included in the analysis.

Laboratory methods

Blood samples for presepsin, PCT, and CRP were obtained in all of the included patients during the period up to 4 hours after the onset of febrile neutropenia. Blood samples (for microbiological analysis and biomarker detection) were taken before the initiation of empiric antibacterial therapy in all patients included in this study. CRP was measured in blood by automatic biochemical analyzer Architect c8000 (Abbott Laboratories, Abbott Park, Illinois, USA) with the reagents from Dialab (Vienna, Austria). PCT in blood was measured by automatic analisator miniVIDAS/Blue with the reagents VIDAS BRAHMS PCT from BioMerieux (Marcy l'Etoile, France). Presepsin was measured in EDTA — blood taking into consideration the hematocrit level by automatic analisator PATHFAST and PATHFAST presepsin reagent from company Mitsubishi Chemical Medience Corporation (Tokyo, Japan). The cut-offs for the biomarker levels were determined prior to initiating the test. Isolation of pathogens was performed by standard means with BacT/ALERT Standard Aerobic/Anaerobic bottles and BacT/ALERT three-dimensional automated microbial detection system, Biomerieux (Marcy l'Etoile, France). Identification and antibiotic resistance was studied with VITEK 2 system by Biomerieux (Marcy l'Etoile, France), E-tests, and disc-diffusion methods.

Transplantation procedure and management of infections

Transplantation was performed according to institutional protocols. Briefly, the most frequent myeloablative conditioning regimens were busulfan and cyclophosphamide, cyclophosphamide, and total body irradiation (cyclophosphamide + total body irradiation). Nonmyeloablative and reduced intensity conditioning mainly included fludarabine with melphalan or treosulfan and BEAM regimen (carmustine, etoposide, cytarabine, melphalan). Graft versus host disease prophylaxis regimens included cyclosporine, methotrexate, and tacrolimus. Antithymocyte globulin was administered in cases of unrelated donors. Standard antibacterial prophylaxis in the department was based on fluoroquinolones (mainly ciprofloxacin 0.5 g orally twice a day) starting from the initiation of conditioning regimen until the time when level of neutrophils in peripheral blood exceeded 500 cells/mm^3. No routine antibacterial prophylaxis against *Streptococcus pneumoniae* was administered. Antifungal prophylaxis with fluconazole was prescribed to patients undergoing autologous HSCT and micafungin was used as antifungal prophylaxis in patients undergoing allogeneic HSCT. Prophylaxis against *Pneumocystis jirovecii* with trimethoprim—sulfamethoxazole was administered to all patients until immunologic recovery after HSCT. Prophylaxis of infections caused by the herpes viruses was performed by acyclovir. Real-time quantitative polymerase chain reaction was used for monitoring cytomegalovirus (CMV) DNA levels in HSCT patients weekly during the pre-engraftment period, with ganciclovir used as first line pre-emptive therapy in case of possible active CMV infection and exclusion of such patients from the conducted study. During the period of severe neutropenia (ANC <100 cells/mm^3) all patients were isolated in single rooms with positive pressure, laminar air flow and high-efficiency particulate air filtration. After the ANC exceeded 100 cells/mm^3 some of the clinically stable patients were moved to the intensive care department, with two patients remaining in a room and positive air pressure.

The institution's standard protocols of initial empirical antibiotic therapy for febrile neutropenia included cephalosporins (cefepime or cefoperazone/sulbactam) or carbapenems (imipenem/cilastatin or meropenem) depending on the risk group of the patient with an addition of vancomycin in case of possible infection caused by gram-positive pathogens [19].

Statistical analysis

Data processing and analysis were performed using MedCalc Statistical Software version 14.10.2 (MedCalc Software bvba, Ostend, Belgium). Receiver operating characteristic (ROC) analysis was performed with the DeLong et al. [21] method. Probabilities <.05 were considered significant. Classification of quality levels of diagnostic models is shown in Table 1.

Results

In total, there were 52 patients with febrile neutropenia after HSCT included. The age of patients was 18—79 years with a median age of 41 years (25—75 years, percentiles: 28—51 years). Among them were 28 (53.8%) women and 24 (46.2%) men. Among the primary diagnoses were acute myeloid leukemia, Hodgkin's lymphoma, multiple myeloma, and nonHodgkin lymphomas. Among the patients, eight received related allogeneic HSCT, four patients received unrelated allogeneic HSCT, and 40 patients received autologous HSCT. Microbiologically gram-negative BSI was proven in 30 patients, and in 22 patients bacterial etiology of the febrile

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Table 1 Levels of quality of diagnostic models in receiver operating characteristic (ROC) analysis

Area under ROC curve	Quality of model
0.9—1.0	Excellent
0.8—0.9	Good
0.7—0.8	Average
0.6—0.7	Poor
0.5—0.6	Unsatisfactory

episode was excluded by way of multiple blood (or sputum) sample microbiological analysis and additional clinical investigation (chest X-ray, urine analysis). After exclusion of bacterial BSI, the causes of febrile neutropenia in the other 22 patients were discussed individually. Most of them were noninfectious febrile reactions: only three of them had CMV reactivation proven by means of quantitative polymerase chain reaction and one patient had candidemia caused by *Candida albicans*. Table 2 shows the baseline demographic and clinical characteristics of the patients included in the study.

CRP showed a poor level of sensitivity (40%), while it had 91% specificity in the analysis. The positive likelihood ratio of CRP was 4.40 (95% confidence interval [CI]: 1.1—17.7), while the negative likelihood ratio was 0.66 (95% CI: 0.5—0.9). The specificity of CRP was 100% at the level of 225.7 mg/L, and the optimal cut-off value in such patients was 165 mg/L. Area under the ROC curve (AUC) for CRP was 0.707 (95% CI: 0.564—0.825, $p = .0049$), which can be used to assess the quality of the model as an average. ROC-curve for CRP as a biomarker of gram-negative BSI is shown in Fig. 1.

The optimal cut-off value for PCT as a biomarker of gram-negative BSI in patients after HSCT was shown at 1.5 ng/mL, while the sensitivity was 62% and specificity 88%.

Table 2 Demographical and clinical baseline characteristics of patients with febrile neutropenia in the pre-engraftment period after hematopoietic stem cell transplantation (HSCT)

Baseline characteristics	Absolute No. ($n = 52$, %)
Age, y (median, interquartile range)	41 (28—51)
Sex (male)	24 (46.2)
Type of HSCT:	
Autologous	40 (76.9)
Allogeneic	12 (23.1)
Conditioning regimen:	
Myeloablative	9 (17.3)
Nonmyeloablative/reduced intensity	43 (82.7)
Primary diagnosis:	
Acute myeloid leukemia	12 (23.1)
Hodgkin's lymphoma	6 (11.5)
Multiple myeloma	9 (17.3)
NonHodgkin's lymphoma	25 (48.1)

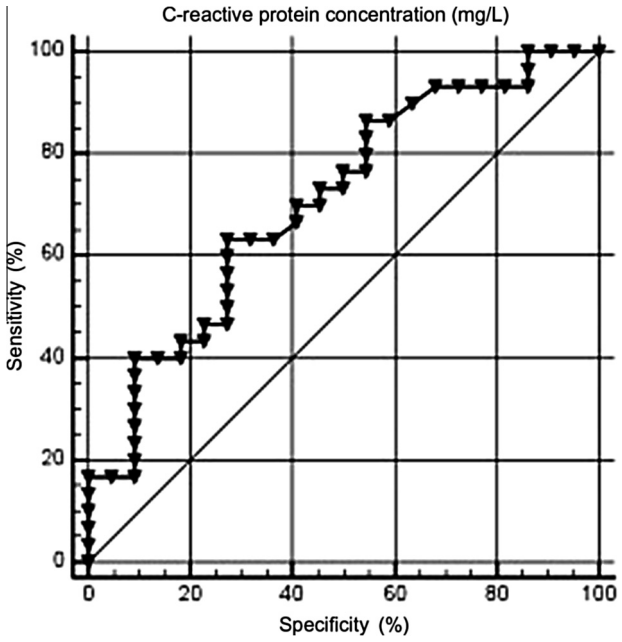

Fig. 1 ROC curve for C-reactive protein.

The specificity was shown to be 100%, while PCT was 26.7 ng/mL. The AUC for PCT was 0.741 (95% CI: 0.573—0.869, $p = .0037$), which can be used to assess the quality of this model as an average. The positive likelihood ratio for PCT was 5.26 (95% CI: 1.4—20.2) with a negative value of 0.43 (95% CI: 0.2—0.8).

The optimal cut-off value for presepsin as a biomarker of gram-negative BSI was shown to be at 218 pg/mL, while its sensitivity was 75% and specificity was 100%. The negative likelihood ratio for presepsin was 0.25 (95% CI: 0.08—0.80), while the positive likelihood ratio was not calculated due to the 100% specificity parameter. The AUC for presepsin was shown to be 0.889 (95% CI: 0.644—0.987, $p < .0001$), which can be used to assess the quality of this model as good. Results of the comparative analysis of diagnostic parameters of presepsin, CRP, and PCT as biomarkers of gram-negative BSI in adult patients after HSCT are presented in Table 3. The spectrum of pathogens which caused gram-negative BSI in patients after HSCT is shown in Table 4.

Therefore, among the causes of gram-negative BSI in adult patients after HSCT in the conducted study gram-negative nonfermenting microorganisms had 33.33%, and the members of the *Enterobacteriaceae* family had 66.67% in a total etiological spectrum.

Discussion

PCT is used as a biomarker of systemic bacterial infections in adults and children [22,23]. There have been described nonspecific elevations of PCT in certain groups of patients, for example, elevation was described in neonates during the 1st 18—30 hours up to 20 ng/mL with a decrease of biomarker to 1.5 ng/mL by 72 hours [24]. Nonspecific elevations of PCT were also described in patients with severe trauma, burns, massive surgical interventions, even with chronic kid-

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Table 3 Diagnostic parameters of presepsin, c-reactive protein, and procalcitonin as biomarkers of gram-negative bloodstream infection in adult patients after hematopoietic stem cell transplantation

Diagnostic parameter	Biomarker		
	C-reactive protein	Procalcitonin	Presepsin
Cut-off value	165 mg/L	1.5 ng/mL	218 pg/mL
Sensitivity (%)	40	62	75
Specificity (%)	91	88	100
Positive likelihood ratio	4.40 (95% CI: 1.1—17.7)	5.26 (95% CI: 1.4—20.2)	—
Negative likelihood ratio	0.66 (95% CI 0.5—0.9)	0.43 (95% CI: 0.2—0.8)	0.25 (95% CI: 0.08—0.80)
Area under the ROC curve	0.707 (95% CI: 0.564—0.825)	0.741 (95% CI: 0.573—0.869)	0.889 (95% CI: 0.644—0.987)
Stand. error	0.0735	0.0831	0.085
p	.0049	.0037	<0.0001
Quality of model	Average	Average	Good

Note: CI = confidence interval; ROC = receiver operating characteristic; Stand. = standard.

Table 4 Causes of gram-negative bloodstream infection after hematopoietic stem cell transplantation in the study

Pathogen	Absolute No.	Frequency of isolation (%)
Klebsiella pneumoniae	12	40
Escherichia coli	8	26.67
Acinetobacter baumannii	6	20
Pseudomonas aeruginosa	4	13.33

ney failure [25]. There are data published concerning the use of PCT in patients after solid organ transplantation, for example, researchers have shown that the use of PCT as a biomarker of bacterial infection is possible in patients after liver transplantation and heart transplantation [26,27]. Nonspecific elevation of PCT and CRP were demonstrated in patients receiving antithymocytic immunoglobulin, T-cell therapy, certain chemotherapy regimens [28,29]. C-reactive protein is a widely used inflammatory marker–one of the so-called acute phase proteins. It was shown to increase at various conditions: infections, trauma, autoimmune diseases, acute cardiologic diseases, and graft versus host disease [18]. Presepsin is a novel sepsis biomarkers recently being implemented in clinical practice. Shozushima et al. [30] have shown that presepsin is an effective diagnostic marker in case of a BSI, but large enough samples of patients after HSCT have not been evaluated yet as a separate group in various studies on presepsin use. In other populations it was shown that the level of presepsin shortly decreases after initiating antibacterial therapy, which makes it important to study this aspect in HSCT recipient populations [31]. All of the patients included in the study had their blood samples taken up to 4 hours after the onset of the febrile episode, so the results may be used to assess the early diagnostic characteristics of biomarkers in HSCT recipients. As it was shown previously, the time to prescribing antibiotics is extremely important: in septic patients antibiotics should be started within 1 hour from the diagnosis, and if the antibacterial therapy is delayed in a patient with septic shock, mortality may increase by 7.6% per hour [32].

The results of the comparative analysis of diagnostic parameters of sepsis biomarkers in adult patients with gram-negative BSI after HSCT showed that the best level of quality in this condition demonstrates more of a diagnostic model with presepsin (AUC: 0.889, 95% CI: 0.644—0.987, $p < .0001$) than PCT (AUC: 0.741, 95% CI: 0.573—0.869, $p = .0037$). CRP does not have an adequate enough sensitivity (40%) to be widely recommended as a sepsis biomarker in adult patients with gram-negative BSI after HSCT and its cut-off value in this condition should be at concentration of 165 mg/L. It is important to underline that these data concern the levels of biomarkers only at the first 24 hours after the onset of febrile neutropenia, as a most important period, because the outcome of BSI in neutropenic patient significantly depends on adequate empiric antibacterial therapy prescribed in the first 24 hours of possible infectious complication. Results of the microbiological part of the study confirm that gram-negative BSI in patients after HSCT are mostly caused by members of the *Enterobacteriaceae* family (66.67%), with an important influence from nonfermenters (33.33%). Results of recent meta-analysis including 2159 sepsis cases, conducted by Wu et al. [31] showed a pooled sensitivity of presepsin for sepsis to be 78% (95% CI: 76—80%), while pooled specificity was 83 (95% CI: 80—85%), pooled positive likelihood ratio was 4.63 (95% CI: 3.27—6.55), and pooled negative likelihood ratio was 0.22 (95% CI: 0.16—0.30); the AUC of the summary ROC curve was 0.89 (95% CI: 0.84—0.94), which is close to the data achieved in our study. Zhang et al. [33] have also conducted a meta-analysis, including 11 published studies, with the overall diagnostic sensitivity of presepsin for sepsis being 83% (95% CI: 77—88%), specificity of 78% (95% CI: 72—83%), and the AUC of 88% (95% CI: 84—90%). Still, it is important to state that the sensitivity of presepsin in HSCT in our study was slightly lower than in the above named meta-analyses (75% vs. 78%; 75% vs. 83%).

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As limitations of the study we may mention the relatively small sample, which is too small to build a firm conclusion from it, but concerning the cost of every HSCT procedure and high risk of fatal outcome in case of BSI, even such numbers of observations may be important. The other limitation was that the measurement of biomarkers was only during the first 4 hours after onset of febrile episode, because multiple measurements were not possible to perform in all of the patients. Finally, this study was conducted in one clinical center, but it is important to mention that this center performs HSCT for patients from all parts of our country. The end-point in the conducted study also has some important limitations, because it is based only on BSIs and concerns only gram-negative pathogens, while in some regions of the world gram-positive infections still remain as leading causes of sepsis in immunocompromised hosts [1] and we could still have been missing active infections without bacteremia (pneumonia or urinary tract infections in neutropenic patients may not have the clear manifestations). Although presepsin is the receptor of lipopolysaccharide-lipopolysaccharide binding protein complexes-an important component of gram-negative bacterial cell wall-previous studies showed no disparity of serum presepsin concentration between infections caused by gram-negative and gram-positive pathogens [31,34]. Therefore, research questions remain important to study in future works with HSCT recipients.

Conclusions

In comparison with the rest of the biomarkers, presepsin determined in the first 24 hours after the onset of the febrile episode has shown a relatively higher diagnostic value as a marker of BSI caused by gram-negative pathogens in adult patients after HSCT with an optimal cut-off value of 218 pg/mL. PCT was also effective in diagnosing BSI with a cut-off value of 1.5 ng/mL, but its relatively low sensitivity (62%) may become a cause of clinically dangerous false-negative results of test. The use of CRP as a biomarker of gram-negative BSI should not be routinely recommended in adult patients after HSCT because of average diagnostic quality and low sensitivity (40%); still, in such cases an optimal cut-off value for CRP should be at 165 mg/L.

Common clinical practice in the area of febrile neutropenia management is based on an immediate search for infectious foci and a haste to initiate antibiotic therapy after taking samples for cultures. Later, the decision to modify or stop antibacterial therapy depends on the workup, which often takes a lot of time. This means that the patient would be committed to broad-spectrum antibiotics for some time before the culture results reveal a pathogen-a practice that has led to the worldwide antimicrobial resistance catastrophe. Furthermore, cultures may turn out to be negative in 40% of patients with sepsis [35]. Therefore, there is a need for a rapid test that could help to rule out an infectious cause quickly. Hence, a biomarker would be most useful as a screening test (i.e., a negative value confirms the absence of infection). A good screening test is characterized by a great sensitivity. However, the sensitivities found in this study are still not high enough to recommend them among the tests that should be taken in face of febrile neutropenia in HSCT patients (presepsin sensitivity was 75%). Therefore, presepsin may only be recommended as a possible additional supplementary test in a febrile neutropenic patient after HSCT to rule out sepsis, caused by gram-negative pathogen, when the pretest probability of sepsis is already borderline, and clinicians are hesitant about keeping the patient off antibiotics.

Conflicts of interest

The authors have no relevant affiliations or financial involvement with any organization with the subject matter or materials discussed in the manuscript. All the authors are responsible for the entire content of this submitted manuscript and approved submission.

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