Procalcitonin levels in children with bloodstream infections caused by different species: a cohort study

José Iván Castillo Bejarano
University Hospital "Dr. José Eleuterio González"  https://orcid.org/0000-0003-4270-2687

Agustín De Colsa Ranero
Hospital Universitario Dr Jose Eleuterio Gonzalez

Oscar Tamez Rivera
Instituto Nacional de Pediatría

Andrés Guillen Lozoya
Hospital Universitario Dr Jose Eleuterio Gonzalez

Napoleón González Saldaña
Instituto Nacional de Pediatría

Alfonso Huante Anaya
Instituto Nacional de Pediatría

Ismael Herrera Benavente
Universidad Autonoma de San Luis Potosi - Facultad de Medicina

Abiel Mascareñas de los Santos  ( a_mascarenas@hotmail.com )
https://orcid.org/0000-0002-4057-9526

Research article

Keywords: Procalcitonin; Sepsis; Bacterial sepsis

DOI: https://doi.org/10.21203/rs.3.rs-25485/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background: Timely diagnosis and accurate identification of the causative microorganism in sepsis is crucial in order to offer targeted treatment and increase survival rates. Previous studies have aimed to identify biomarkers that could potentially predict blood culture positivity in patients with bacteremia; however, most of the research has been performed in adult populations. The aims of this study were to analyze procalcitonin (PCT) levels in confirmed bloodstream infections by species in children and assess their utility in immunocompromised patients.

Methods: Medical records of children younger than 18 years admitted from 2011 to 2018 were reviewed. Subjects who met the diagnostic criteria for sepsis, with PCT levels collected within a 72-hour period prior to obtaining a blood culture were included. Kruskal-Wallis test was used to compare differences among groups. Receiver-operating characteristic curves were used to evaluate PCT cut-offs.

Results: A total of 120 patients were included. Mean age was 55 months. Mean PCT levels in immunosuppressed patients was 26.68 mcg/L, compared to 8.78 in the immunocompetent group. Subjects with bacteremia by Gram-negative bacilli (GNB) had the highest mean PCT levels (18.2 ± 34.2) (p < 0.001). Sensitivity and specificity were 78% and 53% for Gram-positive cocci (GPC), 60.9% and 33.3% for GNB, and 75% and 25% for yeasts, respectively. Subgroup analysis showed 87.5% sensitivity and 16.7% specificity of PCT for predicting documented GNB bacteremia in immunodeficient children.

Conclusions: PCT may be considered as a surrogate biomarker in immunocompromised children, and a viable tool to differentiate etiology by species.

1. Background

Sepsis is a leading cause of morbidity and mortality in the pediatric population (1). Timely diagnosis and accurate identification of the causative microorganism is crucial in order to offer targeted treatment and increase survival rates. Previous studies have aimed to identify biomarkers that could potentially predict blood culture positivity in patients with bacteremia; however, most of the research has been performed in adult populations (1, 2).

Procalcitonin (PCT) is a 116-aminoacid prohormone synthetized and secreted by the thyroid C-cells, although in infectious diseases, PCT can be synthesized and secreted by differentiated cell types and all parenchymal tissues (3-5). High levels of PCT are observed in critically ill infected patients (7-10). It has been reported that PCT levels higher than 3.61 ng/mL predict blood culture-confirmed bacteremia in adults, with a 75% sensitivity and 72% specificity (9). Likewise, previous studies have described a high negative predictive value (95.4%) of normal levels of PCT for predicting bacteremia (10). Furthermore, it has been suggested that PCT levels could be helpful in differentiating among bacterial species in adults, with Gram-negative bacilli (GNB) causing a greater increase of PCT levels compared to Gram-positive cocci (GPC) (11). The objectives of this study were to analyze PCT levels in confirmed bloodstream infections by species in children and assess their utility in immunocompromised patients.
2. Methods

Medical records of all subjects admitted to the National Institute of Pediatrics (INP) in Mexico City from 2011 to 2018 were reviewed. Subjects younger than 18 years of age who met the diagnostic criteria for sepsis, with PCT levels collected within a 72-hour period prior to obtaining a blood culture were included in the analysis. Subjects with polymicrobial blood cultures and/or with isolation of commensal bacteria (coagulase-negative Staphylococci, Gram-positive bacilli, and Micrococcus spp) in a single peripheral blood culture were excluded. Blood cultures with commensal bacteria were only included in central line-associated bloodstream infections (CLABSI), and if the same microorganism was documented in two or more peripheral blood cultures. Samples were processed by the automated blood culture system BD BACTEC™. Bacterial identification and susceptibility testing were performed by BD Phoenix™ 100. PCT levels were obtained using the Thermo Scientific Fisher™ system, with a cut-off value of 0.5 mcg/L.

2.1 Definitions

Sepsis was defined as the presence of systemic inflammatory response syndrome (SIRS) in addition to a documented infection via blood culture. SIRS was defined according to the Society of Critical Care Medicine (4). Subjects who met two or more of the following criteria were diagnosed with SIRS: fever ≥38°C, hypothermia <36°C, tachycardia > 90 beats per minute, tachypnea >20 breaths per minute, hypocapnia PaCO₂ <32 mmHg, and leukocytosis/leukopenia adjusted by age. In order to avoid overestimation of infectious episodes, a second infectious event in the same subject was defined as sepsis after a minimum of six days of hemodynamic stability without antibiotics. Patients with immunodeficiencies, including solid organ transplantation, hematopoietic stem cell transplantation (HSCT), primary immunodeficiency, solid tumors, nephrotic syndrome, Down’s syndrome, severe malnutrition, hematologic immunodeficiency (i.e. leukemia, hemophagocytic lymphohistiocytosis), and drug-induced immunodeficiency were eligible for inclusion in the study.

2.2 Statistical analysis

For the statistical analysis, chi-squared test was used to analyze categorical variables. Kruskal-Wallis test was used to compare differences among groups. Receiver-operating characteristic (ROC) curves were used to evaluate PCT cut-offs. Statistical significance was assumed if the null hypothesis could be rejected at p <0.05. Statistical analysis was performed using SPSS v.21 (IBM Corp., USA).

3. Results

3.3 Demographic characteristics

A total of 41,836 blood cultures were obtained from January 2011 to April 2018, of which 5,059 cultures (12.09%) were positive. PCT levels were available for 311 subjects; 191 of these were excluded due to polymicrobial (n=2), contaminated (n=68), and duplicated (n=121) blood cultures. The final sample included 120 subjects with sepsis and documented PCT levels within a 72-hour period before blood
culture collection (Figure 1). Mean age was 55 months, 54% were male, and 44.2% had an immunodeficiency. Mean PCT level was 15.3 mcg/L.

3.4 PCT levels in immunocompromised children.

Mean PCT level in immunodeficient children was 26.68 mcg/L, compared to 8.78 mcg/L in immunocompetent hosts (p <0.05). PCT level distribution is shown in Table 1. The most frequent immunodeficiencies were hematologic (53.8%), primary immunodeficiency (9.6%), and solid tumors (9.6%). Subjects with hematologic immunodeficiency had the highest PCT mean level (31.4 mcg/L), followed by HSCT recipients (16.9 mcg/L); however, no statistical significance was observed.
| Type of ID\(^1,2\) | n (%) | Median PCT level (mcg/L) | P value |
|---------------------|-------|--------------------------|---------|
| SOT\(^2\)          | 2 (3.8) | 2.4 | 0.15 |
| PID\(^2\)          | 5 (9.6) | 3.8 | |
| Hematology         | 28 (53.8) | 31.4 | |
| HSCT\(^2\)         | 2 (3.8) | 23.8 | |
| Solid tumor        | 5 (9.6) | 9.3 | |
| Nephrotic syndrome | 3 (5.8) | 16.9 | |
| Down syndrome      | 3 (5.8) | 1.14 | |
| Severe malnutrition | 3 (5.8) | 1.9 | |
| Drugs              | 1 (1.9) | 180 | |

1) Kruskal-Wallis analysis

2) Immunodeficiency (ID), Primary Immunodeficiency (PID), Solid Organ Transplant (SOT), Hematopoietic Stem Cell Transplantation (HSCT)

Table 1
PCT levels by type of immunodeficiency

3.5 PCT levels by microorganism

Mean PCT levels by microorganism are shown in Table 2. The most commonly isolated microorganisms were GNB (65.8%), followed by GPC (24.2%) and yeasts (10%). Subjects with Gram-negative bacterial sepsis had the highest mean PCT levels (18.2 ± 34.2 mcg/L), compared to GPC (13.1 ± 36 mcg/L) and yeasts (1.9 ± 1.69 mcg/L). We found a statistically significant difference in mean PCT levels among the major microorganism groups (p < 0.001). The bacteria with highest PCT mean levels were Beta-hemolytic
streptococcus (39.3 mcg/L), *Klebsiella pneumoniae* (28.4 mcg/L), and *Streptococcus pneumoniae* (25.8 mcg/L).
| Pathogen                     | n (%) | Median PCT level (mcg/L) | Range       |
|------------------------------|-------|--------------------------|-------------|
| **Gram-negative bacteria**   |       |                          |             |
| *Acinetobacter* spp          | 3 (2.5) | 3.4                      | 0.99–8.16   |
| *Burkholderia cepacia*       | 2 (1.7) | 0.1                      | 0.09–0.21   |
| *Enterobacter cloacae*       | 7 (5.8) | 14.2                     | 0.18–45.8   |
| *E. coli*                    | 18 (15) | 16.9                     | 0.26–93.6   |
| *Klebsiella* spp             | 25 (20.8) | 28.4                    | 0.46–243.4  |
| *Salmonella* spp             | 3 (2.5) | 13.7                     | 0.43–34.9   |
| *Stenotrophomonas maltophiliia* | 6 (5) | 7.9                      | 0.03–40     |
| *Pseudomonas aeruginosa*     | 15 (12.5) | 15.1                    | 0.33–76.6   |
| **Gram-positive bacteria**   |       |                          |             |
| *Enterococcus* spp           | 3 (2.5) | 1                        | 0.4–2.2     |
| *Staphylococcus aureus*      | 8 (6.7) | 0.8                      | 0.7–3       |
| Pathogen                        | n (%) | Median PCT level (mcg/L) | Range     |
|--------------------------------|-------|--------------------------|-----------|
| Coagulase negative *staphylococcus* | 11 (9.2) | 17.3 | 0.1–180 |
| *Staphylococcus lugdunensis*    | 2 (1.7) | 5.1 | 0.03–101 |
| Beta-hemolytic *streptococcus*  | 3 (2.5) | 39.3 | 7.3–65  |
| *Streptococcus pneumoniae*      | 2 (1.7) | 25.8 | 1.2–50.4 |
| **Fungi**                       | 12    | 1.9 | 0.2–5.5 |
| *Candida spp*                   | 12 (10) | 1.9 | 0.2–5.5 |

Table 2
PCT levels corresponding to pathogens isolated

3.6 PCT sensitivity and specificity by microorganism

ROC curves were used to evaluate the diagnostic efficacy of PCT for predicting a positive blood culture. Using a cut-off value of 0.5 mcg/L, we found a sensitivity of 58% and specificity of 35%, with an area under the curve (AUC) of 0.639 (95% CI, 0.519 – 0.760). Higher values were observed in immunocompromised subjects with 82% sensitivity and 53% specificity (AUC 0.635, 95% CI. 0.457-0.812). Sensitivity and specificity by microorganism group were 78% and 53% for GPC, respectively (AUC 0.581, 95% CI, 0.402 - 0.761), compared to 60.9% and 33.3% for GNB (AUC 0.640, 95% CI, 0.429 - 0.851). For yeasts, we found a 75% sensitivity and 25% specificity (AUC 0.734, 95% CI, 0.444 - 1).

Subgroup analysis showed an 87.5% sensitivity and 16.7% specificity of PCT for predicting blood culture-demonstrated GNB infection in immunocompromised patients (AUC 0.906, 95% CI, 0.748 – 1), and a 78.8% sensitivity and 22.2% specificity for GPC infection (AUC 0.744, 95% CI, 0.542 - 0.946).

4. Discussion
The current knowledge about PCT as a biomarker for sepsis in children has been described in previous studies (12-13). Elevation of PCT levels usually occurs earlier during the course of infection, even before the elevation of other biomarkers, peaking at 24-36 hours (12). Pontrelli et al (13) showed a moderate accuracy for the diagnosis of sepsis in neonates with a PCT cut-off of 2.0-2.5 ng/mL (14). A 2015 meta-analysis showed that PCT is highly accurate in differentiating bacterial and viral meningitis in children with 96% sensitivity (12). Studies about PCT levels in blood culture positivity by different microorganism groups in children are scarce, especially in immunocompromised hosts.

Our results show a statistically significant difference between mean PCT values for each microorganism group. Mean PCT levels in children with GNB infections were significantly higher than those with GPC and fungal infections. These findings are consistent with previous studies performed in adults (14-16). Yan et al (1) reported a 72.4% sensitivity and 51% specificity of PCT as a predictor of blood culture positivity in adults, using a 0.495 mcg/L PCT cut-off value. Watanabe et al (17), reported a 74.5% sensitivity and 59.1% specificity of PCT for predicting blood culture-proven bacteremia. In our study we found a 75% sensitivity and 53% specificity of PCT as a predictor of GNB infection, using a PCT cut-off value of 0.5 mcg/L.

Thomas-Rüddel et al (18) reported a median PCT significantly higher in GNB compared to GPC (26 ng/ml vs 7.1 ng/ml, p<0.001). The AUC in the ROC analysis was 0.69 (0.67-0.72) for differentiating GNB from GPC or candidemia, and 0.73 (0.71-0.74) for the prediction of GNB compared to all other blood culture results. Bassetti M et al (19), reported similar findings with a median PCT concentration of 25.1 ng/ml in GNB bacteremia compared to 8.9 ng/ml in GPC. The AUC was 0.7 (0.62-0.77) among GNB and 0.46 (0.39-0.53) among GPB. In a previous study, Shuhua et al (20) found a median PCT level of 7.47 ng/ml in GNB sepsis from fungal sepsis, led to a sensitivity of 63.9% and specificity of 93.3%.

The role of PCT as a predictor of GPC in blood cultures, mainly in infections caused by Staphylococci was evaluated by Shomali et al, reporting higher mean PCT levels in infections by S. aureus compared to coagulase-negative Staphylococci (0.85 mcg/L versus 0.26 mcg/L, respectively) (21). In contrast, when comparing PCT levels of patients with bacteremia by S. aureus and by coagulase-negative Staphylococci, we found higher mean PCT levels in the latter (17.3 vs 0.8 ng/mL). This difference may be attributed to a higher isolation rate of coagulase-negative Staphylococci in our hospital.

Studies that analyze PCT as a biomarker for invasive fungal infection by Candida spp are scarce and show conflicting data (22-25). In our study, mean PCT levels in Candida spp infections were 1.9 mcg/L, with a 75% sensitivity and 25% specificity. Previous studies by Cortegiani et al (25) report higher sensitivity and specificity of PCT for predicting fungal infection by Candida spp, with 86.8% and 87.4% respectively. Identification of Candida species was not performed in our study; however, previous authors have not found any difference regarding PCT levels in infections by different Candida species. Thomas-Rüddel et al (18) reported a median PCT level of 4.7 ng/ml, compared to 2.1 ng/ml by Bassetti et al (19). Median PCT levels of 0.6 ng/ml, 0.5 ng/ml, 1 ng/ml and 0.5 ng/ml were reported by Shuhua et al (20),
Miglietta et al (26), Oussalah et al (27) and Leli et al (29), respectively. Consistent with previous studies, we report lower PCT levels in fungal infections compared to bacterial events (26). It has been suggested that fungal infections could trigger an alternate inflammatory response route that does not involve PCT, explaining its modest rise.

Studies on PCT in immunocompromised patients are scarce (30-34). A recent systematic review and meta-analysis in children with chemotherapy-induced neutropenic fever showed that PCT levels >0.5ng/mL have a 67% sensitivity (CI 0.53-0.79), and 73% specificity (CI 0.66-0.77) for predicting microbiologically defined infections (34). In our study according to mean PCT levels, we found a statistically significant difference between immunocompromised (26.68 mcg/L) and immunocompetent (8.78 mcg/L) children with sepsis (p <0.05). We also report an 87.5% sensitivity of PCT for predicting blood culture-proven GNB infection, making PCT a useful resource in clinical practice. PCT levels were also increased in different types of immunosuppression.

Our study has several limitations. A prospective design would aid in having better control of the variables and include a larger sample, to avoid heterogeneity of the cases. Likewise, PCT measurements were not serial, which would have allowed us to analyze PCT behavior in relation to variables such as time, isolated microorganism, treatment, and outcome.

5. Conclusions

Our study found that PCT could be a viable tool to predict blood-culture proven sepsis, particularly in immunocompromised patients with GNB infection. The use of PCT could be considered as a surrogate biomarker of bacterial infection, and PCT levels could offer a general prediction of the possible microbial etiology (GNB, GPC and yeasts). Further prospective studies are needed in order to expand the available evidence on the use of PCT as a predictive value for blood culture-proven by species infection in children.

List Of Abbreviations

PCT - Procalcitonin

GNB - Gram-negative bacilli

GPC - Gram-positive cocci

CLABSI - Central line-associated bloodstream infections

SIRS - Systemic inflammatory response syndrome

HSCT - Hematopoietic stem cell transplantation

ROC - Receiver-operating characteristic
AUC - Area under the curve

Declarations

Ethics approval and consent to participate: The authors confirm our study was submitted to and approved by the Academic Group of the National Institute of Pediatrics, Mexico, with the code: GA/094/18. No informed consent was obtained due to the nature of the retrospective data according to the Academic Group of the National Institute of Pediatrics, Mexico. The data used in this study was anonymized before its use.

Consent for publication: Not applicable

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests: The authors declare that they have no competing interests

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors’ contributions: CBJI conception and analysis of data; CRA interpretation of the data, TRO analysis and writing, GLA statistical analysis, GSN design of the work, HAA creation of a software used in the work, HBI have substantively revised the work, MSAH work coordination and analysis.

Authors’ information: Not applicable

Acknowledgements: Not applicable

References

1. Yan ST, Sun LC, Jia HB, Gao W, Yang JP, Zhang GQ. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. Am J Emerg Med. 2017;35(4):579–83.
2. Liu HH, Zhang MW, Guo JB, Li J, Su L. Procalcitonin and C-reactive protein in early diagnosis of sepsis caused by either Gram-negative or Gram-positive bacteria. Ir J Med Sci. 2017;186(1):207–12.
3. Fran Balamuth, Scott L. Weiss, Mark I. Neuman, Halden Scott, Patrick W. Brady, Raina Paul, Reid W.D. Farris, Richard McClead, Katie Hayes, David Gaiieski, Matt Hall S, S. Shah; Elizabeth R. Alpern. Pediatric Severe Sepsis in US Children's Hospitals. Pediatr Crit Care Med. 2014;15(9):798–805.
4. Singer, M. et al., Bellomo R, Bernard GR, Chiche J, Craig M, Hotchkiss RS, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
5. Hawiger J, Veach RA, Zienkiewicz J. New paradigms in sepsis: From prevention to protection of failing microcirculation. J Thromb Haemost. 2015;13(10):1743–56
6. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. Clin Infect Dis. 2004;39(2):206–17.

7. Casado Flores J, Blanco Quirós Procalcitonia: un nuevo marcador de infección bacteriana. An Pediatría. 2001;54(1):69–73.

8. Cha JK, Kwon KH, Byun SJ, Ryoo SR, Lee JH, Chung J, et al. Clinical value of procalcitonin for suspected nosocomial bloodstream infection. Korean J Intern Med. 2017.

9. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. Am J Clin Pathol. 2011;135(2):182–9.

10. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med. 2017;1–11.

11. Díez-Padrisa N, Bassat Q, Morais L, O’Callaghan-Gordo C, Machevo S, Nhampossa T, et al. Procalcitonin and C-reactive protein as predictors of blood culture positivity among hospitalised children with severe pneumonia in Mozambique. Trop Med Int Heal. 2012;17(9):1100–7.

12. Lanziotti VS et al. Use of biomarkers in pediatric sepsis: literature review. Rev Bras Ter Intensiva. 2016; 28 (4): 472-82.

13. Pontrelli G et al. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonate and children with systemic inflammatory syndrome: a meta-analysis. BMC Infectious Diseases. 2017; 17: 302.

14. Kim MH, Lim G, Kang SY, Lee WI, Suh JT, Lee HJ. Utility of procalcitonin as an early diagnostic marker of bacteremia in patients with acute fever. Yonsei Med J. 2011;52(2):276–81.

15. Liu HH, Zhang MW, Guo JB, Li J, Su L. Procalcitonin and C-reactive protein in early diagnosis of sepsis caused by either Gram-negative or Gram-positive bacteria. Ir J Med Sci. 2017;186(1):207–12.

16. Charles PE, Ladoire S, Aho S et al. Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis. 2008; 8: 38.

17. Watanabe Y; Oikawa N; Hariu M, Fuke R; Seki M. Ability of procalcitonin to diagnose bacterial infection and bacteria types compared with blood culture findings. International Journal of General Medicine. 2016; 9: 325-331.

18. Thomas-Rüddel D et al. Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. Critical Care. 2018; 22: 128.

19. Bassetti et al. Comparision between procalcitonin and C-reactive protein to predict blood culture results in ICU patients. Critical Care. 2018; 22.

20. Shuhua Li; Heng Rong; Qinliang G; Yifei C; Zhang G; Jiong Y. Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. Journal of Research in Medical Sciences. 2016; 21: 39.

21. Shomali W et al. Can procalcitonin differentiate Staphylococcus aureus from coagulase-negative staphylococci in clustered gram-positive bacteremia?. Diagnostic Microbiology and Infectious
22. Martini A, Gottin L, Menestrina N, Schweiger V, Simion D, Vincent J-L: Procalcitonin levels in surgical patients at risk of candidemia. J Infect 2010,60(6):425–430.
23. Brodská H, Malíčková K, Adámková V, Benáková H, Stťastná MM, Zima T: Significantly higher procalcitonin levels could differentiate Gram-negative sepsis from Gram-positive and fungal sepsis. Clin Exp Med 2012:1–6.
24. Montagna M, Coretti C, Caggiano G: Procalcitonin: a possible marker of invasive fungal infection in high risk patients? J Prev Med Hyg 2011,52(1):38.
25. Cortegiani A, Russotto V, Montalto F, Foresta G, Accurso G, Palmeri C, et al. Procalcitonin as a marker of Candida species detection by blood culture and polymerase chain reaction in septic patients. BMC Anesthesiol. 2014;14(1):9.
26. Miglietta et al. Procalcitonin, C-reactive protein and serum lactate dehydrogenase in the diagnosis of bacterial sepsis, SIRS and systemic candidiasis. Le infezioni in Medicine. 2015; 3: 230-237.
27. Oussalah et al. Diagnostic accuracy of procalcitonin for predicting blood culture results in patients with suspected bloodstream infection. Medicine. 2015; 94 (44): 1-8
28. Leli C, Ferranti M, Moretti A, et al. Procalcitonin levels in Gram-positive, Gram-negative, and fungal bloodstream infections. Dis Markers. 2015;2015:701480.
29. Charles PE, Ladoire S, Aho S et al (2008) Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis 8:38
30. Fleischhack G, Cipic D, Juettner J, Hasan C, Bode U. Procalcitonin—a sensitive inflammation marker of febrile episodes in neutropenic children with cancer. Intensive Care Med. 2000;26 Suppl 2:S202-11.
31. Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U. Procalcitonin in paediatric cancer patients: Its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor and soluble tumour necrosis factor receptor II. Br J Haematol. 2000;111(4):1093–102.
32. Staehler M, Hammer C, Meiser B, Reichart B (1997) Procalcitonin: a new marker for differential diagnosis of acute rejection and bacterial infection in heart transplantation. Transplant Proc 29:584-585
33. Al-Nawas B, Shah PM (1996) Procalcitonin in patients with and without immunosuppression and sepsis. Infection 24:434–436
34. Arif T, Phillips RS. Updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer. Pediatric Blood & Cancer. 2019; 66 (10): e27887.

Figures
Selection of eligible patients and blood culture samples between January 1, 2011 and April 1, 2018

41,836 blood cultures

5,059 blood cultures

4,748 not enrolled due to not drain blood samples for PCT before 72 hours

191 excluded
- 2 polymicrobial
- 68 contaminated
- 121 duplicated

311

120

Gram-negative
79

Gram-positive
29

Candida spp.
12

Figure 1

Selection of eligible patients and blood culture samples between January 1, 2011 and April 1, 2018
Figure 2

A) ROC curve of PCT, AUC 0.639 (95% CI, 0.519 – 0.760). B) ROC curve of PCT for CGP AUC: 0.581 (95% CI, 0.402 – 0.761). C) ROC curve for BGN, AUC: 0.640 (95% CI, 0.429 – 0.851). D) ROC curve for molds, AUC: 0.734 (95% CI, 0.444 – 0.1).