Asociación entre hiperprocalcitonemia y disfunción endotelial y microcirculatoria y resultados en niños con sepsis y choque séptico

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Association Between Hyperprocalcitonemia and Endothelial and Microcirculatory Dysfunction and Outcomes in Children with Sepsis and Septic Shock

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ABSTRACT

OBJECTIVES: To evaluate the association between hyperprocalcitonemia and endothelial and microcirculatory dysfunction in children with sepsis and septic shock, along with clinical outcomes.

DESIGN: A prospective observational cohort study.

SETTING: A tertiary care pediatric intensive care unit (PICU) with 15 medical-surgical beds in a university hospital.

PATIENTS: We included children with sepsis and/or septic shock who had serum procalcitonin (PCT) measured at admission, 24 hours, and 48 hours, with simultaneous microcirculatory assessment using sublingual videomicroscopy and evaluation of endothelial injury biomarkers (syndecan-1, angiopoietin-2, [Ang-2] and endocan). Hyperprocalcitonemia (H-PCT) was defined as procalcitonin > 2 ng/mL.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among the 230 included patients, 43.9% (101/230) had H-PCT at PICU admission. After adjusting for confounders, children with H-PCT showed a greater reduction in capillary blood flow at 24 hours (aOR, 1.35 [95% CI, 1.08–1.72]) and 48 hours (aOR, 1.14 [95% CI, 1.04–1.24]) after admission, compared with patients with normal PCT. Children with H-PCT and elevated serum lactate had higher odds of glycocalyx damage (aOR, 1.31 [95% CI, 1.09–1.68]; p = 0.041). At 24 hours, children with H-PCT had higher syndecan-1 levels (125.87 [IQR, 49.56–224.30] vs. 107.71 [IQR, 62.82–156.55] ng/mL, respectively; p < 0.01) and higher odds of Ang-2 elevation (aOR, 2.28 [95% CI, 1.08–5.17]; p = 0.042). Hyperprocalcitonemia with severe endothelial/microcirculatory dysfunction was associated with >10% fluid overload (aOR, 2.01 [95% CI, 1.06–3.80]; p = 0.033), multiple organ dysfunction (aOR, 1.87 [95% CI, 1.01–3.57]; p = 0.041), and mortality (aOR, 1.66 [95% CI, 1.06–2.61]; p = 0.022).

CONCLUSIONS:

Hyperprocalcitonemia in children with sepsis and septic shock represents a phenotype characterized by endothelial and microvascular dysfunction, and is associated with worse clinical outcomes. Our study suggests that preserving

microvascular integrity may be a therapeutic target to reduce microcirculatory damage and improve outcomes.

KEY WORDS: *sepsis, septic shock, endothelium, extracellular matrix, vascular permeability, proteoglycans, outcomes.*

Sepsis is characterized by a dysregulated host inflammatory response to infection (1). It can lead to multiple organ dysfunction and high mortality rates in children (2,3). Among its pathophysiological mechanisms, endothelial dysfunction plays a central role, contributing to increased vascular permeability, fluid extravasation, and impaired microvascular perfusion (4). Procalcitonin (PCT), a widely used biomarker for differentiating bacterial from non-bacterial infections, has recently been implicated in endothelial barrier disruption, suggesting a link between hyperprocalcitonemia (H-PCT) and microvascular damage (5-8). Preclinical and adult studies have associated elevated PCT levels with increased capillary permeability and microcirculatory dysfunction, particularly in systemic inflammation (6,7).

The microcirculation is primarily responsible for the exchange of substances, mainly oxygen, between tissues and the bloodstream. During sepsis, significant capillary-level alterations occur, including endothelial glycocalyx degradation, increased perfusion heterogeneity, impaired capillary recruitment, and loss of blood flow autoregulation (9). Recently, systemic inflammation has been recognized to be associated with poor microvascular control, decreased capillary recruitment and tissue perfusion, factors which may contribute to organ dysfunction (10,11). Furthermore, recent studies on sepsis have linked endothelial dysfunction and altered capillary density with adverse clinical outcomes such as fluid overload, multiple organ dysfunction, and increased mortality (12,13).

While H-PCT is a marker of increased capillary permeability and microcirculatory dysfunction in adults, the specific relationship between H-PCT and microcirculatory dysfunction in children with sepsis has not yet been

characterized. In this study, we hypothesize that H-PCT is associated with microcirculatory dysfunction in children with sepsis and septic shock due to its direct effects on the microvasculature. Hyperprocalcitonemia is also a reflection of the severity of systemic inflammation and is associated with poor outcomes. Our objective was to evaluate the association between elevated procalcitonin levels and microcirculatory alterations, endothelial dysfunction, and clinical outcomes in children with sepsis.

MATERIALS AND METHODS

Study design and context

This was a prospective observational cohort study in children with sepsis and septic shock who were hospitalized in the pediatric intensive care unit (PICU) of Fundación Cardioinfantil in Bogotá, Colombia. Patients admitted between January 2021 and June 2024 were included. This study was approved by the Fundación Cardioinfantil Research and Ethics Committee (DDI-4947-2024). All parents or legal guardians signed informed consent prior to enrollment in the protocol, and all research procedures followed the ethical standards of the Fundación Cardioinfantil-IRB and were consistent with the Declaration of Helsinki 1975.

Patient population

Patients aged 1 month to 18 years, with a diagnosis of sepsis and/or septic shock, were included. Initially, patients met the International Consensus Criteria for Pediatric Sepsis and Septic Shock. After the introduction of the Phoenix criteria, they were reclassified, including only those with two or more points on the Phoenix Sepsis Score. Septic shock was established when at least one criterion belonged to the cardiovascular domain (1).

Children with shock of other etiologies and those with underlying conditions that could be associated with endothelial glycocalyx alterations were excluded (14). A total of 14 patients were excluded, including those with head trauma (n=4), ketoacidosis (n=2), inborn errors of metabolism (n=2), and a history of chronic kidney disease (defined as a glomerular filtration rate of less than 60 mL/min/1.73 m^2 for more than three months) (n=6).

Protocol

All patients received oxygen therapy, ventilatory support, fluid resuscitation, and vasopressors based on the attending physician's criteria and in accordance with the recommendations of the Surviving Sepsis Campaign (SSC) (*Figure S1 Supplemental material*) (2).

Data collection and microcirculation measures

Microcirculation assessment was performed considering the main variables affected in inflammatory states: capillary density, capillary blood flow, and glycocalyx degradation, which are related to convective and diffusive alterations (15). Dark-field videomicroscopy (*GlycoCheck System® - Microvascular Health Solutions Inc, 2014, Salt Lake City, UT, USA*) was used to obtain the images. This device has a very good inter- and intra-observer correlation (16). The software (*GlycoCheck System®*) analyzes the acquired data and reports the "perfused boundary region" (PBR) in µm, a variable that is inversely proportional to the dimensions of the endothelial glycocalyx. In healthy subjects, a normal PBR is considered to be less than 2.0 microns (17).

Additionally, the software provides the capillary blood volume (CBV), a microvascular flow variable for blood vessels smaller than 25 microns, and the Microvascular Health Score (MVHS), which integrally reports microvascular health. In healthy adults, an MVHS value greater than 4 points is considered normal (17).

Finally, the system processes and reports the 4-6 micron capillary density (CD 4-6µm [mm/mm²]), which indicates the capacity of the capillary network to deliver nutrients to the tissues.

Study variables

Plasma procalcitonin was measured using an electrochemiluminescence immunoassay (*ECLIA-COBAS Pro®).* Hyperprocalcitonemia was defined as PCT levels > 2 ng/mL, a cutoff associated with sepsis in previous studies and reviews (18-20). Measurements were taken at admission, 24 hours, and 48 hours,

simultaneously with other biomarkers and sublingual videomicroscopy assessments.

Plasma biomarkers of endothelial activation and increased microvascular permeability were measured at admission and 24 hours after PICU admission. These included syndecan-1 (ELISA Kit CD138; Abcam Lab®), angiopoietin-2 (Ang-2) (ELISA Kit ANG-2; Abcam Lab®), and endocan (ELISA Kit ESM-1 [human endothelial cell-specific molecule 1]; Abcam Lab®). Severe microvascular dysfunction was defined by the presence of microcirculatory alterations assessed by videomicroscopy (CBV, PBR, and MVHS greater than the 75th percentile) and elevated endothelial biomarkers (syndecan-1, endocan and Ang-2 greater than the 75th percentile). Demographic data, vital signs, fluid balance, and capillary refill time were collected, the latter being measured in a standardized manner by applying pressure to the index finger for 10 seconds with a glass slide. Pediatric Index of Mortality-2 (PIM-2) and Pediatric Logistic Organ Dysfunction-2 (PELOD-2) scores were calculated at PICU admission.

Outcomes

The primary outcome was the evaluation of microcirculatory changes, including microvascular flow, endothelial glycocalyx degradation, and capillary density in children with sepsis with and without H-PCT. Secondary outcomes analyzed endothelial injury biomarkers (syndecan-1, Ang-2, endocan) and clinical outcomes such as fluid balance and multiple organ dysfunction 24 hours after admission, as well as mortality throughout the entire hospital stay, comparing them between groups.

Statistical analysis

Qualitative variables were reported as frequencies and percentages. A bivariate analysis was conducted according to the variables' nature and distribution. Chi² or Fisher's exact test were used for qualitative variables. The PBR, CBV, capillary density, and MVHS values were compared between groups with PCT ≥2 ng/mL and <2 ng/mL using the Mann-Whitney U or t-test. A receiver operating

characteristic (ROC) curve determined the PCT level associated with microcirculatory changes, and the Youden method identified the optimal cutoff for microcirculatory damage. Due to the nonlinear behavior of endothelial damage biomarkers, locally estimated scatterplot smoothing (LOESS) regression was applied. To analyze PCT and Ang-2 trends over time, logistic regression models with cubic splines captured nonlinear effects without parametric restrictions. A multivariate logistic regression identified independent microcirculatory damage predictors, adjusting for confounders such as age, PIM-2, and vasoactive index score (VIS), reporting the adjusted odds ratio (aOR) with its 95% confidence interval (CI).

Additionally, a random forest machine learning model explored nonlinear relationships between PCT levels and microcirculatory changes assessed via sublingual videomicroscopy, particularly in H-PCT patients with altered CBV and MVHS, and their association with increased organ dysfunction (PELOD-2 score). Statistical analyses were conducted using R software (v. 4.4.0), with $p<0.05$ considered significant.

RESULTS

Altogether, 230 children with sepsis and septic shock were included during the study period. The median age of the study group was 2.0 years (interquartile range [IQR], 0.5–10.1). Of the total population, 43.9% (101/230) had H-PCT at the time of PICU admission. No differences were observed between the groups regarding the site of infection or the definition of sepsis with a local or remote source ($p = 0.331$). A total of 66.5% (153/230) of the children had associated comorbidities, with no differences between the groups ($p = 0.231$) (**Table 1**).

Microcirculatory changes in children with hyperprocalcitonemia

Children with H-PCT had a lower CBV (6.92×10^3 µm³; IQR: 4.01 – 10.20) compared to those with normal PCT levels (7.92×10^3 µm³; IQR: 5.10 – 12.10) ($p = 0.021$), 24 hours after admission. The PCT level with the best predictive ability for CBV reduction at 24 hours post-admission was a value greater than 5.8 ng/mL (area under the curve [AUC]-ROC 0.81; 95% CI 0.72-0.84; $p < 0.011$).

Children with H-PCT above this threshold had higher odds of CBV reduction (aOR 1.35; 95% CI 1.08-1.72; p = 0.001). At 48 hours post-admission, persistent H-PCT levels above 2 ng/mL were associated with a greater reduction in microvascular flow, as measured by CBV (aOR 1.14; 95% CI 1.04-1.24; p < 0.001).

Another variable evaluated in the microcirculation was CD 4–6μm. We were unable to demonstrate differences in CD 4–6μm between groups with and without H-PCT upon PICU admission (p = 0.941), at 24 hours (p = 0.472), or at 48 hours (p = 0.491). However, a relationship was identified between CD 4–6μm and endothelial activation biomarkers within the first 24 hours. Children with lower CD 4–6μm (below the 25th percentile [16.31 mm/mm²]) had higher odds of elevated syndecan-1 (aOR, 1.39 [95% CI, 1.30–1.48]; p < 0.001), Ang-2 (aOR, 1.03 [95% CI, 1.02–1.04]; p < 0.001), and endocan levels (aOR, 1.02 [95% CI, 1.01–1.03]; p < 0.001).

We also assessed PBR in both groups. At 24 hours post-admission, children with H-PCT and lactate levels >2 mmol/L had a significantly higher likelihood of abnormal PBR (aOR 1.31; 95% CI: 1.09–1.68; p = 0.041). Additionally, persistent elevated PCT levels (>14.44 ng/mL) at 48 hours were associated with increased odds of endothelial glycocalyx damage (aOR 1.42; 95% CI: 1.09–1.84; p = 0.001).

Changes in endothelial injury biomarkers in children with hyperprocalcitonemia

We found that higher PCT levels were associated with a progressive increase in syndecan-1 at 24 hours (p < 0.01) (**Figure 1A**). Additionally, a minimum reduction in PCT levels of 24% (95% CI, 18.6%–28.5%) at 24 hours, compared to baseline, was associated with normalization of syndecan-1 levels (p < 0.001). We failed to identify an association between serum endocan levels in the H-PCT group (1.35 [IQR, 0.90–2.70] ng/mL; p = 0.431) compared with normal PCT (1.81 [IQR, 1.01–3.21] ng/mL; p = 0.322) at 24 hours after admission.

The time evolution of Ang-2 was biphasic (**Figure 1B**). At admission, no association was found between Ang-2 and H-PCT (aOR, 1.24 [95% CI, 0.63–2.43]; p = 0.541). At 24 hours, children with persistent H-PCT had higher odds of Ang-2 elevation compared to those with normal PCT (11.61 [IQR, 8.11–24.11] vs. 10.95 [IQR, 6.95–24.75] mg/dL, respectively; aOR, 2.28 [95% CI, 1.08–5.17]; p = 0.042). A logistic regression model with cubic splines showed that the relationship between PCT levels and the probability of elevated Ang-2 varied over time. A significant interaction was found between PCT and admission time (aOR, 2.90 [95% CI, 1.39–6.07]; p < 0.001), suggesting that PCT's effect on endothelial dysfunction changes during the first 24 hours of evolution.

Clinical outcomes in children with sepsis with hyperprocalcitonemia

Children with H-PCT and severe microcirculatory dysfunction had higher odds of a positive fluid balance exceeding 10% (aOR: 2.00; 95% CI: 1.06–3.80; p = 0.033) 24 hours after admission, regardless of age and disease severity (**Table 2**). Similarly, a multivariable logistic regression analysis showed that H-PCT was associated with a higher VIS at baseline (p < 0.001) and on day 1 (p < 0.001) (**Figure 2A**). However, we were unable to demonstrate an association between H-PCT and a high VIS 48 hours after admission (p = 0.452). Additionally, children with H-PCT had higher odds of prolonged CRT at baseline (p = 0.021) and at 24 hours (p = 0.042), but this association was not observed at 48 hours (p = 0.236) (**Figure 2B**).

The Phoenix Total Score was higher in the H-PCT group than in patients with normal PCT (aOR 2.05, 95% CI 1.10–3.83; p < 0.021) (*Supplemental Material eTable 1*). Additionally, patients with H-PCT had higher odds of having a positive Phoenix Cardiovascular Score (aOR 1.49, 95% CI 1.05–2.10; p = 0.022). Furthermore, patients with H-PCT had higher odds of elevated PELOD-2 scores (aOR 1.87; 95% CI: 1.01–3.57; p = 0.041). An interaction analysis was conducted to evaluate the combined effect of H-PCT and CBV dysfunction on predicted organ dysfunction, measured using PELOD-2 (**Figure 3A**). In patients with low CBV, there was a sharp increase in PELOD-2 as PCT levels rose, suggesting that worsened microcirculation amplifies the impact of inflammation on organ dysfunction. A random forest model was used to evaluate the interaction between

PCT and MVHS in predicting PELOD-2. Predicted PELOD-2 values were generated across different PCT levels for three categories of MVHS (**Figure 3B**), illustrating how progressive microvascular dysfunction exacerbates the impact of PCT on organ dysfunction. Finally, children with H-PCT and severe microcirculatory dysfunction had higher odds of in-hospital mortality (aOR 1.66; 95% CI: 1.06–2.61; p = 0.022) (**Table 2**).

DISCUSSION

In this cohort of children with sepsis and septic shock, we found that H-PCT, as compared with ??, was associated with microcirculatory dysfunction and endothelial damage, suggesting a sepsis phenotype with greater microvascular involvement. Patients with H-PCT exhibited lower microvascular blood flow volume, greater endothelial glycocalyx degradation, and elevated endothelial activation biomarkers associated with low capillary density. Hyperprocalcitonemia with severe microvascular dysfunction was associated with a positive fluid balance, greater vasoactive drug requirements, increased multiple organ dysfunction, and higher mortality.

Microcirculatory and endothelial alterations in children with sepsis and increased inflammation can be understood within the framework of August Krogh's theory (10). This theory postulates that microcirculatory regulation depends on the capillaries' ability to be dynamically recruited in response to tissue metabolic demand. In adult patients with sepsis, studies have shown greater heterogeneity in blood flow, impaired capillary recruitment capacity, and reduced red blood cell transit velocity at the microcirculatory level (11). These changes disrupt the convective and diffusive mechanisms of oxygen transport in the microvasculature, leading to tissue hypoxia (21,22). In our patients, increased procalcitonin levels were associated with decreased flow-related variables and endothelial glycocalyx degradation, as assessed by sublingual videomicroscopy. Additionally, capillary density was low in these patients with elevated endothelial biomarkers, suggesting profound impairment in the diffusive component of tissue oxygen delivery. This aligns with emerging evidence indicating that progressive capillary recruitment may be altered in severe systemic inflammation, leading to a mismatch between perfusion and metabolic demand (23,24).

In this regard, Brabenec L et al. (7) characterized the clinical signs of capillary leak syndrome and microvascular dysfunction in patients with H-PCT following elective cardiac surgery. They found that elevated PCT acts directly on the endothelium, destabilizing adherent endothelial junctions (via phosphorylation of VE-cadherin), which contributes to increased microvascular permeability. Patients with PCT >1 ng/mL in the early postoperative period required more vasopressors and crystalloid resuscitation, along with a higher frequency of microcirculatory alterations, as assessed by sublingual videomicroscopy. These results suggest that PCT may play an active role in endothelial dysfunction and vascular hyperpermeability, beyond being merely a marker of infection. Our patients with H-PCT and severe microvascular dysfunction also had more positive fluid balances, greater vasopressor requirements, and multiple organ dysfunction. These findings support the hypothesis that sepsis with H-PCT represents a clinical phenotype with greater microvascular involvement, in which endothelial dysfunction and impaired capillary flow not only contribute to tissue hypoxia but also amplify the progression of organ dysfunction.

In this context, our data support the idea that microvascular dysfunction in sepsis is not merely a consequence of global hemodynamic dysfunction. Instead, it appears to be a primary phenomenon, driven by early endothelial damage associated with inflammation, with specific PCT elevation directly affecting microvascular permeability (25,26). This could also be explained by previous findings showing that macro/microcirculatory dissociation has been associated with worse outcomes in sepsis (27,28). The interrelation between capillary hyperpermeability, decreased functional capillary density, and elevated endothelial biomarkers suggests that microcirculation is not merely a reflection of systemic hemodynamic instability but rather a key determinant of disease severity and progression. Identifying these pathophysiological patterns could improve risk stratification and guide future interventions aimed at protecting the endothelium and restoring microvascular autoregulation in children with sepsis (19,29).

In this study, we found that syndecan-1, but not endocan, was associated with H-PCT in children with sepsis, suggesting distinct pathophysiological mechanisms.

Syndecan-1, a marker of endothelial glycocalyx degradation, reflects increased vascular permeability and early microvascular dysfunction, key characteristics of the H-PCT phenotype. In contrast, endocan, a marker of endothelial activation, showed no significant association, indicating that endothelial activation alone may not be sufficient to induce H-PCT. These findings reinforce the role of glycocalyx damage in the pathophysiology of pediatric sepsis and suggest that syndecan-1 could be a better biomarker for identifying a subgroup of patients with greater microvascular dysfunction and capillary leakage, and higher fluid and vasopressor requirements.

Our study has some limitations, including its single-center design, which may limit the generalizability of the findings to other populations. Additionally, as an observational study, it does not allow for definitive causal inferences. However, when conducted with a rigorous and methodologically sound design, such studies can provide valuable insights, particularly in scenarios where clinical trials are not feasible or ethically viable (30). Additionally, microcirculation assessment was performed using sublingual videomicroscopy, a technique that, while providing detailed insights into microvascular perfusion, does not allow for direct evaluation of critical organs, such as the lungs or kidneys. Although image analysis was processed using investigator-independent software, some variables were measured indirectly. Nevertheless, sublingual videomicroscopy has demonstrated good inter- and intra-observer reproducibility in previous sepsis studies (16). Finally, we only conducted follow-up for the first 48 hours after PICU admission. We do not know what happens to microcirculation and H-PCT beyond this period.

CONCLUSION

Sepsis with H-PCT in children is associated with significant endothelial and microvascular dysfunction, which correlates with fluid overload, greater vasopressor requirements, multiple organ failure, a longer hospital stay, and higher mortality. These findings support the hypothesis that endothelial injury plays a critical role in sepsis pathophysiology, suggesting that microcirculatory alterations could be a potential target for future interventions.

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AT THE BEDSIDE

-Hyperprocalcitonemia (H-PCT) in pediatric sepsis is associated with increased endothelial and microvascular dysfunction.

-Sepsis with H-PCT represents a clinical phenotype characterized by significant microvascular impairment, which not only compromises tissue oxygenation but is also associated with worse outcomes, including fluid overload, multiple organ dysfunction syndrome, a prolonged PICU stay, and increased mortality.

-Identifying these pathophysiological patterns could enhance risk stratification and guide targeted interventions to improve clinical outcomes and reduce mortality in critically ill children.

RESEARCH IN CONTEXT

-Procalcitonin in sepsis serves as a diagnostic, severity, and monitoring biomarker, helping to guide antibiotic use.

-Capillary leak syndrome in pediatric sepsis contributes to organ dysfunction, worse clinical outcomes, and increased mortality. Preclinical and adult studies have shown that procalcitonin affects the endothelium, inducing vascular hyperpermeability by destabilizing endothelial adherens junctions.

-The specific relationship between hyperprocalcitonemia, microcirculatory dysfunction, and endothelial impairment in children with sepsis has not yet been fully characterized.

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Table 1. Baseline characteristics of children with sepsis according to PCT levels.

Table 2. Multivariable logistic regression of biomarkers and outcomes associated with the presence of H-PCT and microcirculatory dysfunction in children with sepsis.

Figure 1. Association between PCT and endothelial biomarkers.
Scatter plots with LOESS regression are shown for endothelial biomarkers in relation to log PCT. Each point represents a patient. The red line is a LOESS smoothing, which captures the trend without assuming a linear relationship. Figure 1A: Syndecan-1. Figure 1B: Ang-2. PCT: procalcitonin.

Figure 2. Forest plot of odds ratios for the association between H-PCT and VIS and CRT.

Figure 2A. VIS. Figure 2B. Prolonged CRT greater than 2 seconds. aOR: adjusted odds ratio for age and PIM -2. 95% CI: 95% confidence interval.

Figure 3. Interaction between procalcitonin, microvascular flow and Microvascular Health Score with the presence of organ dysfunction

Figure 3A: The impact of PCT on organ dysfunction depends on the state of the microcirculation. Patients with low CBV have a higher risk of elevated PELOD-2 in the presence of H-PCT. *Figure 3B*: In patients with normal MVHS, increasing PCT has a lesser impact on PELOD-2, suggesting preserved microcirculation. In contrast, in patients with mild to moderate alterations, PELOD-2 progressively increases with rising PCT, reflecting evolving microvascular deterioration. CBV: capillary blood volume MVHS: Microvascular Health Score. PELOD-2: Pediatric Logistic Organ Dysfunction-2.