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Serum Soluble Endoglin in Pediatric Septic Shock Associated Multiple Organ Dysfunction Syndrome.

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Genomics of Pediatric Septic Shock Investigators

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Abstract

Background: Endothelial activation is a key driver of multiple organ dysfunction syndrome (MODS). Soluble endoglin (sENG) is expressed by mature and progenitor endothelial cells and thought to have angiogenic properties. We sought to determine the association between sENG and pediatric sepsis associated MODS.

Methods: Prospective observational study of pediatric septic shock. Primary outcome of interest was complicated course -a composite of death by (or) MODS on day 7 of illness. Secondary

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Conflicts of interest: None

outcomes included individual organ dysfunctions. Endothelial biomarkers including sENG were measured using multiplex Luminex assays among patients with existing data on pediatric sepsis biomarker risk model data (PERSEVERE-II). Multivariable regression was used to test the independent association between sENG and clinical outcomes. Serum sENG concentrations across PERSEVERE-II mortality risk strata and correlations with established markers of endothelial dysfunction.

Results: 306 critically ill children with septic shock were included. Serum sENG concentrations were higher among those with primary and secondary outcomes of interest, with the exception of acute neurological dysfunction. sENG was independently associated with increased odds of complicated course [adj OR 1.53 (95% CI: 1.02–2.27), p=0.038] and acute renal dysfunction [adj OR 1.84 (95%CI: 1.18–2.876), p=0.006]. sENG demonstrated graded responses across PERSEVERE-II risk strata and was positively correlated with endothelial biomarkers, except Angiopoietin-1.

Conclusions: Serum soluble endoglin is independently associated with complicated course and acute renal dysfunction in pediatric septic shock. Future studies are required to validate our observational data and mechanistic studies are necessary to elucidate whether endoglin plays a organ-specific role in development or resolution of acute renal dysfunction in sepsis.

Keywords

Critical Illness; Sepsis; Septic Shock; Multiple Organ Dysfunction Syndrome; Endothelial; Endothelial Dysfunction; Endoglin; Biomarker

Introduction:

Complications of sepsis including septic shock and associated multiple organ dysfunction syndrome (MODS) are a leading cause of mortality among critically ill children admitted to pediatric intensive care units across the world.[1,2] Moreover, survivors of the acute phase of the disease suffer considerable morbidity with poor long term quality of life,[3] new medical device acquisition,[4] and neurocognitive effects.[5] Yet our understanding of disease pathobiology and differences across the host developmental age remains incomplete.

Dysregulated host immune and endothelial responses are both critical aspects of sepsis pathobiology.[6,7] Over the previous decade, with advances in high throughput technologies, our understanding of immune dysregulation in sepsis has evolved significantly. For instance, gene-expression based profiling of peripheral whole blood has resulted in the identification of patient subclasses or endotypes as well as the discovery of biomarkers predictive of sepsis mortality and organ dysfunctions.[8] In contrast, our understanding of endothelial dysfunction in critical illness remains in its relative infancy, primarily due to sampling challenges coupled with the tremendous heterogeneity and organ-specificity exhibited by endothelial cells in vivo.[9]

Endoglin (ENG) also known as CD105 is a transmembrane glycoprotein expressed on progenitor and mature endothelial cells and to a lesser extent on cells of the innate (macrophages) and adaptive immune (T-cells) systems.[10] It functions as the co-receptor for several ligands of the transforming growth factor beta (TGF-β) family and is thought to

be involved in cell adhesion and a marker of angiogenesis. Soluble endoglin (sENG), which represents the extracellular domain of the protein cleaved by matrix metalloproteinase-14, is found in circulation.[11] Few small-scale studies to date have evaluated sENG in murine models of systemic inflammation including those by our own group,[12,13] and human sepsis.[14–16] Further, it remains unknown whether sENG is independently associated with development of organ dysfunctions in critical illness.

Accordingly, we sought to test the association between human sENG and pediatric septic shock associated mortality and multiple organ dysfunctions. Further, we sought to test differences in concentration across prospectively validated pediatric sepsis biomarker model (PERSEVERE-II) risk strata.[17,18] Finally, we sought to compare correlation with more established markers of endothelial dysfunction.

Methods: Study design and patient selection:

The study protocol was approved by Institutional Review Boards (IRBs) of participating institutions (Cincinnati Children's Hospital IR, Genomic Analysis of Pediatric Systemic Inflammatory Syndrome, IRB ID: 2008–0558, Continuous Review).[18–20] Informed consent was obtained from parent or guardian of patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review boards of participating institutions and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Briefly, patients under the age of 18 years were recruited from 13 pediatric ICUs (PICU) across the U.S. between 2003 and 2019. There were no study-related interventions except for blood draws. Clinical and laboratory data were available between day 1 through 7, including platelet counts on day 1. Baseline illness severity among patients was determined by pediatric risk of mortality (PRISM-III) score.[21] Inclusion criteria for this study were 1) patients meeting pediatric-specific consensus criteria for septic shock[22] and 2) existing pediatric sepsis biomarker (PERSEVERE-II) and risk strata data. Organ dysfunction criteria used are previously described.[20]. The primary outcome of interest was complicated course - a composite of death by (or) presence of ≥ 2 organ dysfunctions on day 7 of septic shock. Secondary outcomes were death or presence of individual organ dysfunctions (cardiovascular, respiratory, renal, hepatic, hematologic, and neurologic) on day 7.

Endothelial biomarker measurements:

Concentrations (in pg/mL) of serum soluble endoglin (sENG), soluble Thrombomodulin (sTM), Angiopoietin-1 (Angpt-1), Angiopoietin-2 (Angpt-2), Tyrosine kinase with immunoglobulin-like loops and Epidermal growth factor homology domains-2 (Tie-2), Inter-Cellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), and Platelet Endothelial Cell Adhesion Molecule (PECAM-1) were measured in serum collected on day 1 of septic shock by Luminex assays (R&D Systems, MN) in a convenience sample from the cohort.

PERSEVERE-II based Risk Stratification:

PERSEVERE-II mortality probability and risk strata were previously determined according to published methods.[17] Briefly, Interleukin-8 (IL-8), Heat shock protein 70 kDA (HSP70),

C-C Chemokine ligand 3 (CCL3), C-C Chemokine ligand 4 (CCL4), Granzyme B (GZMB), Interleukin-1 α (IL-1 α), Matrix metallopeptidase 8 (MMP8) were previously measured in day 1 septic shock serum. Classification And Regression Tree (CART) analyses were used to derive a mortality probability risk score (0.000–0.999) using R software (version 4.2.2). Patients were subsequently classified as low risk (mortality probability score range ≤0.019), intermediate risk (mortality probability score range >0.019 to ≤ 0.300) or high risk (mortality probability score range > 0.300).

Statistical analyses:

Minitab Software (PA, USA, version 21.1.0) was used for data analyses. GraphPad Prism (CA, USA, version 9) was used to generate figures. Demographic data were summarized with percentages or median with interquartile ranges. Differences between groups were determined by χ^2 squared test for categorical variables and by non-parametric Mann-Whitney test for continuous variables. One-way Analysis of Variance (ANOVA) with Dunnett's test for correction for multiple comparisons were used when comparing differences across PERSEVERE-II mortality risk strata. Multivariable logistic regression analyses adjusted for age and PRISM-III score between serum endoglin concentrations and outcomes of interest were determined. We used a p value of 0.05 to determine significance for primary outcome and an adjusted p value with Bonferroni correction for multiple comparisons for secondary outcomes. Spearman's correlation was used to test the association between sENG concentrations and established markers of endothelial dysfunction measured.

Results:

Three hundred and six patients were included in this study. The demographic characteristics and clinical outcomes comparing those with (n=100) and without (n=206) complicated course is presented in Table 1. Those with primary outcome of interest were more likely to be younger, have higher illness severity at onset, greater 28-day mortality, and fewer PICU free days relative to those without. Figure 1 shows box and whisker plots of serum sENG concentrations among those with and without complicated course. Figure 2 shows the differences in sENG concentrations based on occurrence of death by or individual organ dysfunctions on day 7 of septic shock. Serum sENG was higher among those with complicated course (p=0.0003) and each of the organ dysfunctions with the exception of death or neurological dysfunction by day 7.

Multivariable logistic regression analyses adjusted for age and PRISM-III score between sENG concentrations and outcomes of interest are presented in Table 2. Serum ENG was independently associated with increased risk of complicated course; adjusted odds of 1.53 (95% CI: 1.02–2.27) with each log2 fold increase in sENG concentrations (p=0.038). Among the secondary outcomes, only the association between serum endoglin and death (or) kidney dysfunction on day 7 reached statistical significance after correction for multiple comparisons testing [adj OR 1.84 (1.18–2.87), p=0.006] with each log2 fold increase in sENG.

Figure 3 shows the difference in serum sENG concentrations across PERSEVERE-II mortality risk strata. Patients categorized as high- risk had higher serum sENG concentrations relative to those with low- ($p<0.0001$) and intermediate-risk ($p<0.0029$) strata. There were no differences between those with low- and intermediate- PERSEVERE-II risk strata. Figure 4 shows the correlation between serum sENG and established markers of endothelial dysfunction. With the exception of serum Angpt-1, sENG was positively correlated with all other markers of endothelial dysfunction tested with strongest correlation observed with ICAM-1 ($r=0.59$), Angpt-2 ($r=0.52$), and sTM ($r=0.51$).

Discussion:

We present data from a large prospective observational cohort of critically ill children with septic shock that demonstrate independent associations between sENG and complicated course and acute renal dysfunction in septic shock. Further, we demonstrate graded differences in sENG concentrations across PERSEVERE-II mortality strata. Finally, our results indicate a positive correlation between sENG and established markers of endothelial dysfunction in sepsis.

Previous studies which have evaluated the association between sENG and clinical outcomes in sepsis, septic shock, and more recently COVID-19 critical illness have focused on adult patients. Faiotto et al. measured sENG concentrations in a convenience sample of 50 septic patients and 23 controls enrolled in a single center tertiary hospital in Brazil, and reported an 1.5 fold increase in sENG among patients relative to controls.[14] More recently, Helan et al. reported pilot data of sENG measurements from 21 septic shock patients from a single center in the Czech Republic (Czechia) demonstrating an association with study mortality.[15] Tomášková et al. measured sENG among 37 patients with septic shock and 40 patients with severe COVID19 in the same center. The authors reported that sENG concentrations were associated with risk of early mortality and circulatory failure among septic patients but did not note a similar association among those with severe COVID19.[16]

To the best of our knowledge, our study is the first report of sENG measurements in pediatric septic shock. The strengths of our study include a large sample size of critically ill patients, as reflected in the nearly 40% mortality in the subset of patients who developed complicated course, which allowed us to test the independent association with outcomes of interest after adjusting for potential confounding factors.

Our reported findings of increases in sENG across PERSEVERE-II biomarker risk strata, reflective of graded increases in systemic inflammation, and correlation with established markers of endothelial dysfunction provide further credence and biological plausibility to the important role of sENG in critical illness. Our data that sENG was correlated with Angpt-2 but not Angpt-1 is intriguing. Indeed, similar observations have been made among patients with hemophilia[23] and only weak correlations reported in patients with cardiovascular disease and diabetes.[24] Angpt-1 is thought to stabilize the vascular endothelium and inhibit neovascularization. In contrast, Angpt-2 serves to destabilize that endothelial barrier integrity and in concert with vascular endothelial growth factor (VEGF)

promotes angiogenesis.[25] Accordingly, sENG may serve as an indicator of microvascular remodeling among critically ill patients.

We identified an independent association between sENG and risk of acute renal dysfunction, after accounting for multiple comparisons testing. Interestingly, septic adults with urinary tract infections as a primary source had higher median sENG than those with lower respiratory tract or abdominal infections.[16] While speculative, it remains plausible that ENG may be overexpressed specifically in the kidney microvascular endothelium and that sENG measured may reflect either shed endothelial microparticles or kidney-specific circulating endothelial cells. Thus, preclinical data are required to determine whether modulating ENG results in resolution of endothelial dysfunction and reverse acute kidney injury in septic models. Future clinical studies will need to assess (1) sENG biomarker thresholds of clinical utility, (2) determine whether sENG alone or in combination with other endothelial markers can be used for early identification of patients at high risk of sepsis associated acute kidney injury, and (3) determine whether sENG measurements can inform targeted therapeutic drug delivery to modulate related biological pathways and ameliorate endothelial dysfunction among critically ill patients.

Our study has several limitations: 1) the observational nature of study limit any inference on causality, 2) organ dysfunctions were defined based on modifications to consensus criteria and not reflective of the recently defined PODIUM criteria for organ dysfunctions among critically ill children.[26] Of note, our dataset lacked oxygen saturation data, degree of non-invasive ventilator support, ventilator settings including PEEP to measure oxygenation index, as well as neurological criteria including delirium scores, (3) Measurement of biomarkers at a single-time point. It is conceivable that change in biomarker concentrations over time may be further informative given the dynamic nature of sepsis, (4) it is plausible that given the small molecular size (65kda) of sENG that biomarker concentrations are affected by capillary leak, fluid overload or altered with receipt of renal replacement therapy. However, one would expect low rather than high levels and a bias toward the null in the latter, and 4) potential residual confounders may explain the association between sENG and outcomes reported.

Conclusion:

Serum sENG is independently associated with complicated course and acute renal dysfunction in a large cohort of critically ill children with septic shock. Serum sENG demonstrated graded responses across PERSEVERE-II mortality risk strata and are correlated with established markers of endothelial dysfunction. Further pre-clinical studies are necessary to elucidate whether endoglin has organ-specific roles in critical illness and prospective validation in human sepsis is required to establish the utility of sENG as a prognostic or predictive tool.

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Abbreviations:

sENG	soluble Endoglin
sTM	soluble Thrombomodulin
Angpt-1	Angiopoietin-1
Angpt-2	Angiopoietin-2
Tie-2	TEK tyrosine kinase
Angpt-2/Angpt-1	Angiopoietin-2/Angiopoietin-1 ratio
Angpt-2/Tie-2	Angiopoietin-2/Tie-2 ratio
ICAM-1	Intercellular Adhesion Molecule 1
VCAM-1	Vascular Cell Adhesion Molecule 1
PECAM-1	Platelet Endothelial Cell Adhesion molecule-1

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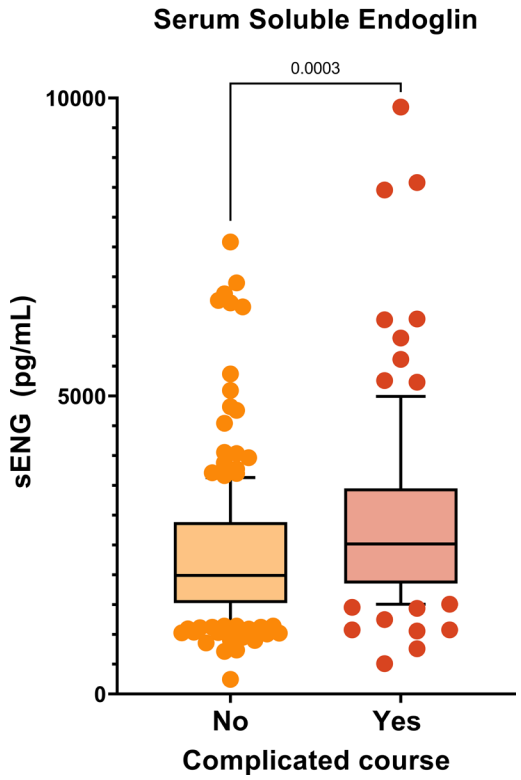

Figure 1.
Box and whisker plots of serum soluble endoglin (sENG) concentrations among patients with and without complicated course.

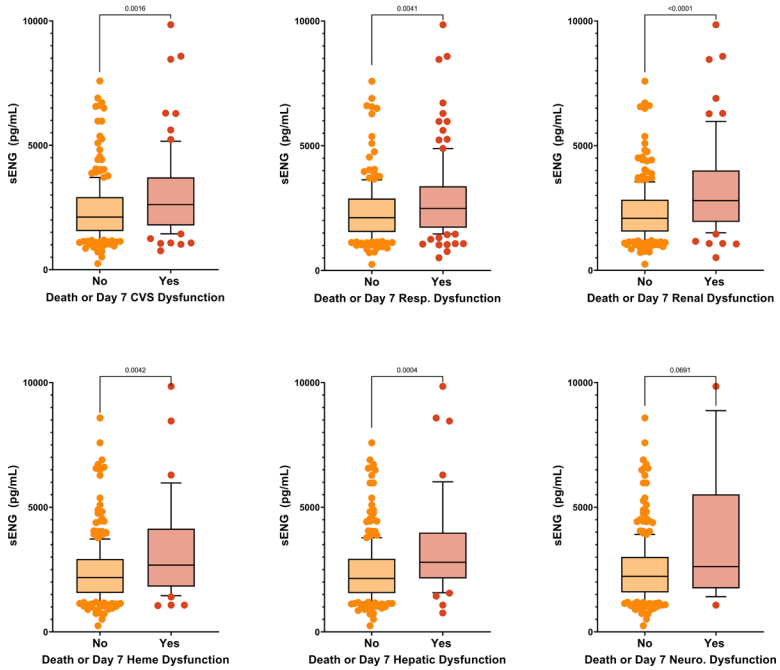

Figure 2. :

Box and whisker plots of serum soluble endoglin (sENG) concentrations among patients with a composite of death by (or) presence of individual organ dysfunctions (Cardiovascular (CVS), Respiratory (Resp), Renal, Hepatic, Hematologic (Heme), Neurologic (Neuro).

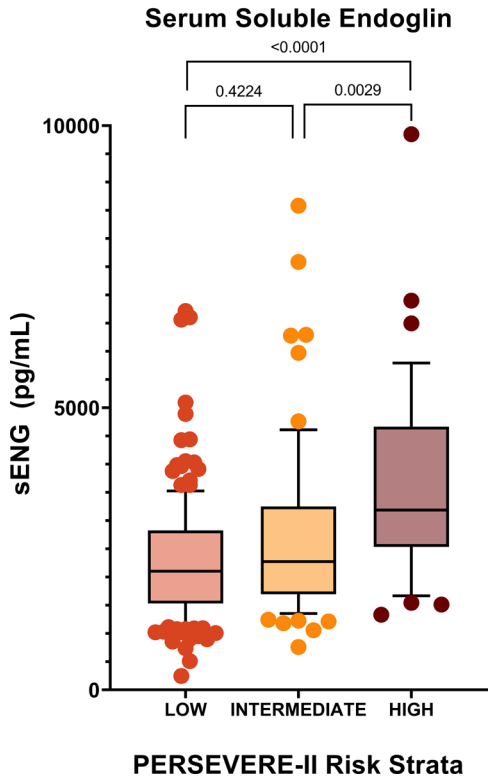

Figure 3.

Box and whisker plots of serum endoglin concentrations (sENG) among patients categorized as low-, intermediate-, or high-mortality risk strata based on Pediatric Sepsis Biomarker Risk Model (PERSEVERE-II).

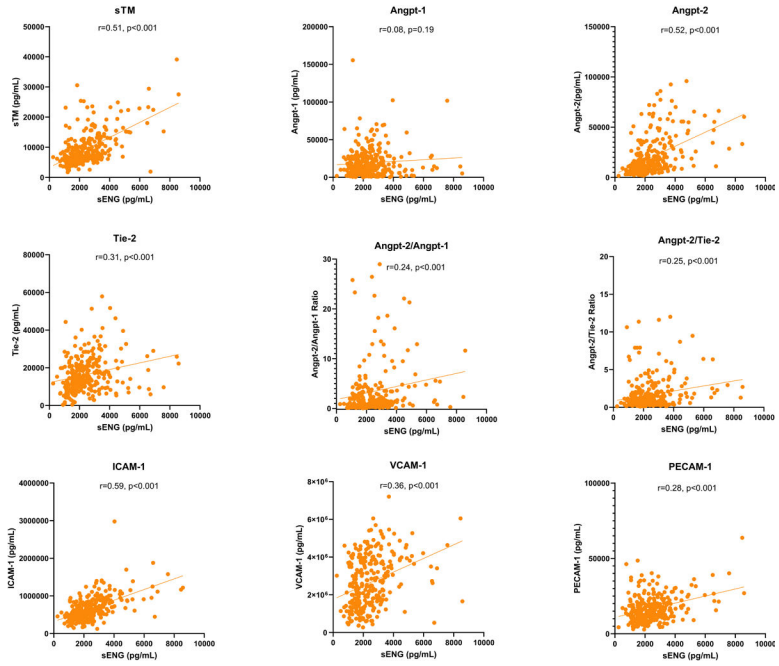

Figure 4.

Spearman correlation between serum soluble endoglin (sENG) concentrations and established markers of endothelial dysfunction including soluble thrombomodulin (sTM), Angiopoietin-1 (Anpgt-1), Angiopoieitin-2 (Anpgt-2), TEK tyrosine kinase (Tie-2), Angiopoietin-2/Angiopoietin-1 ratio (Angpt-2/Angpt-1), Angiopoietin-2/Tie-2 ratio (Angpt-2/Tie-2), Intercellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1), Platelet Endothelial Cell Adhesion molecule-1 (PECAM-1).

Table 1.

Demographic and clinical characteristics of the cohort based on occurrence of death or Day 7 multiple organ dysfunction syndrome (MODS).

Death or Day 7 MODS	Yes (n=100)	No (n=206)	P Value
Age (Years)	4.8 (1.6, 10.9)	8.2 (3.7, 16.2)	0.003
Sex (Female)	49 (49.0%)	101 (49.1%)	0.996
PRISM III	13 (7, 21)	8 (5, 13)	<0.001
Race			0.941
White/Caucasian	72 (72%)	150 (67.6%)	
Black/African American	11 (11%)	24 (11.7%)	
Other	17 (17%)	32 (15.6%)	
Ethnicity			0.274
Hispanic or Latino	8 (8.0%)	25 (12.2%)	
Non-Hispanic or Latino	92 (92%)	181 (87.8%)	
Comorbid conditions:			
Oncological Diagnoses	11 (11.0%)	28 (13.6%)	0.524
Bone Marrow Transplantation	13 (13.0%)	15 (7.3%)	0.104
Solid Organ Transplantation	6 (6.0%)	9 (4.4%)	0.535
Hospital LOS	18 (7, 29)	13 (7, 23)	0.013
PICU LOS	12 (7, 22)	4 (2, 8)	<0.001
PICU Free Days	17 (6, 21)	24 (20, 26)	<0.001
28-day mortality	37 (37.0%)	2 (1.0%)	<0.001

Table 2.

Multivariable logistic regression analyses to test the independent influence of serum endoglin on death or persistent multiple organ dysfunctions on day 7 of pediatric septic shock.

Outcome	Adj. OR (95%CI)	P value
Primary Comparison:		
Death or Day 7 MODS	1.53 (1.02–2.27)	0.038 *
Secondary Comparisons:		
Death or Day 7 CVS Dysfunction	1.42 (0.93–2.18)	0.105
Death or Day 7 Resp. Dysfunction	1.38 (0.95–2.00)	0.088
Death or Day 7 Renal Dysfunction	1.84 (1.18–2.87)	0.006 **
Death or Day 7 Hepatic Dysfunction	1.68 (0.99–2.84)	0.051
Death or Day 7 Heme. Dysfunction	1.50 (0.89–2.52)	0.124
Death or Day 7 Neuro. Dysfunction	1.35 (0.63–2.87)	0.439

All models were adjusted for age in years and PRISM-III mortality risk score.

Serum human endoglin values were log2 transformed for analyses.

* P value of 0.05 was used for the primary comparison of interest.

** Adjusted p value for multiple comparisons (n=6) using Bonferroni correction (0.05/6) of 0.008