ORIGINAL RESEARCH

Clinical Significance of Procalcitonin, Lactic Acid, and Endotoxin Testing for Children With Severe Pneumonia and Sepsis

Yan Lu, MM; Lei Song, MD

ABSTRACT

Context • Sepsis is a common complication of severe pediatric pneumonia, characterized by difficulty in treatment, a high treatment cost, high morbidity and mortality, and poor prognosis. The levels of three indicators, procalcitonin (PCT), lactic acid (Lac), and endotoxin (ET), can vary greatly in children with severe pneumonia complicated by sepsis.

Objective • The study aimed to investigate the clinical significance of PCT, Lac, and ET levels in the serum of children with severe pneumonia complicated by sepsis.

Design • The research team performed retrospective study.

Setting • The study took place at Nantong First People's Hospital in Nantong, Jiangsu, China.

Participants • Participants were 90 children with severe pneumonia complicated by sepsis and 30 children with severe pneumonia only, all of whom had received treatment in the pediatric intensive care unit of the hospital between January 2018 and May 2020.

Groups • At baseline, the research team divided the participants into three groups based on their pediatric clinical illness score (PCIS) at 24 h after admission: (1) the extremely critical group—0-70 points (n = 29), (2) the critical group—71-80 points (n = 31), and (3) the noncritical group—>80 points (n = 30). The 30 children who had received treatment but who had severe pneumonia only became the control group.

Outcome Measures • The research team: (1) measured the serum PCT, Lac, and ET levels for the four groups at baseline, (2) compared those levels by group, (3) compared those levels by clinical outcome, (4) determined the correlation of the three indicators to the PCIS scores, and (5) identified the predictive value of the three indicators. To compare the levels by clinical outcome and to determine the indicators' predictive values, the team divided participants into two groups according to their clinical outcomes on day 28 of the study: (1) 40 children who died became the death group, and (2) 50 children who survived became the survival group.

Results • The serum PCT, Lac, and ET levels in the extremely critical group were the highest, followed by the critical group, the noncritical group, and the control group. The serum PCT, Lac, and ET levels had a significant negative correlation with participants' PCIS scores (r = -0.8203 (PCT), -0.6384 (Lac), -0.6412 (ET), $P < .05$). The area under the curve (AUC) for the PCT level was 0.7732 (95% CI = 0.6214 to 0.9249, $P = .0015$), for the Lac level was 0.9533 (95% CI = 0.9036 to 1.000, $P < .0001$), and for the ET level was 0.8694 (95% CI = 0.7622 to 0.9765, $P < .0001$). These values indicate that all three indicators were significantly predictive regarding participants' prognoses.

Conclusions • The serum PCT, Lac, and ET in children with severe pneumonia complicated by sepsis were abnormally high, and the levels of these indicators were significantly negatively correlated with the PCIS scores. PCT, Lac, and ET may be potential indicators for the diagnosis and prognosis assessment of children with severe pneumonia complicated by sepsis (*Altern Ther Health Med.* 2023;29(3):218-223).

Yan Lu, MM, associate chief physician, and **Lei Song, MD**, chief physician, Department of Pediatrics, Nantong First People's Hospital, Nantong, Jiangsu, China.

Corresponding author: Lei Song, MD
E-mail: ly23691981@163.com

Pediatric pneumonia is a common respiratory disease,[1] which can lead to serious complications if not treated promptly and appropriately, and its morbidity and mortality are high in comparison to other childhood diseases.[2] The deterioration of pneumonia in children can lead to an impaired immune system and induce severe complications, such as shock, sepsis, septicemia, and multi-organ failure.[3]

This can bring great harm to the children and their families and creates a challenge in clinical treatment.

Pneumonia and Sepsis

Sepsis is a common complication of severe pediatric pneumonia, with millions of new cases of sepsis each year worldwide and a mortality rate of up to 25%.[4] It's a major risk factor for death in children with severe pneumonia.[5] Pulmonary infections can be the main source of infection in patients with sepsis.

Sepsis is characterized by difficulty in treatment, a high treatment cost, high morbidity and mortality, and poor prognosis, suggesting that medical practitioners should develop aggressive clinical interventions for such children.[6,7] A study conducted in 163 hospitals showed that the number of patients with severe pneumonia complicated by sepsis had increased by 2.9% in 2017 compared to 2016.[8]

Weiss et al and Yadav et al found that children with pneumonia combined with sepsis could experience specific pathological changes; their immune systems were in a state of imbalance, causing their immune cells to dramatically release a large number of inflammatory factors.[9,10] Those researchers found that a cytokine storm could occur, resulting in disorders of the coagulation and fibrinogen system, with abnormal coagulation causing disseminated intravascular coagulation, shock, multi-organ failure, and acidosis with an imbalance of water and salt metabolism, all of which could increase the risk of death.

Prognostic Indicators

Procalcitonin (PCT). PCT is a commonly used biomarker for bacterial infection or sepsis, and its levels are abnormally elevated in individuals with severe bacterial, fungal, or parasitic infections or sepsis and multiple organ failure. It aids in the clinical diagnosis of severe shock, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome.[11]

Mawji et al's study with 124 children with severe pneumonia combined with sepsis found that the serum PCT level was 18.11 ± 6.16 ng/ml in children in an extremely critical group and 16.11 ± 3.19 ng/ml in children in a critical group, with significant differences between the groups.[12] That study suggested that PCT is a lipopolysaccharide released during bacterial infection and is a factor that can bind to glycoprotein receptors on the surface of the alveolar epithelial cell membrane. Song et al's study found that it can accelerate the diffusion of infectious factors, while its elevation can also release inflammatory signals to the downstream organs and aggravate the injury to them from the inflammatory response.[13]

Lactic acid (Lac). Lac is an intermediate product of glucose metabolism. Under a pathological state, such as respiratory failure or circulatory failure, Lac levels are abnormally elevated, and clinicians often use this indicator as a differential indicator of potential disease.[14]

Downes et al found that abnormally elevated Lac levels can affect the internal environment and induce multi-organ failure.[15]

Endotoxin (ET). ET is invariably associated with gram-negative bacteria and usually produced after lysis of the bacteria, causing fever, microcirculatory disorders, endotoxic shock, and other symptoms. ET is a clinical index reflecting the severity of bacterial infection and is closely related to the damage that bacterial infection can cause.[16] Clinicians also use it in the diagnosis of digestive system diseases, heart disease, respiratory disease, etc..[17]

Clinical Indicators and Sepsis

Goh et al found that the levels of the three indicators can vary greatly in children with severe pneumonia complicated by sepsis and that the condition's severity can directly affect patients' prognosis, resulting in differences in the levels of PCT, Lac, and ET of children with different clinical outcomes.[18]

A clinical study conducted with 110 children with severe pneumonia complicated by sepsis showed that the diagnostic areas under the receiver operating characteristic (ROC) curve (AUCs) of PCT, Lac, and ET were 0.899, 0.794 and 0.898, respectively, with the diagnostic sensitivity and specificity of PCT, Lac, and ET being 76.2% and 91.26%, 66.7% and 83.5%, and 90.5% and 79.6%, respectively.[19]

Another study with children with sepsis resulting from different conditions showed that participants' levels of PCT, Lac, and ET were closely related to the severity of the children's illness.[20] Those researchers found that severity was related to changes in the level of the serum indicators, which medical practitioners could use to evaluate the illness and predict the prognosis of children with sepsis. Poropat et al found that the severity of the activity of pathophysiological mechanisms could lead to higher levels of PCT, Lac, and ET.[21]

Current Study

The routine diagnosis and detection of sepsis in children is insufficient. The use of laboratory indicators in the diagnosis and differential diagnosis of children with sepsis has the advantage of rapidity, strong repeatability, and high sensitivity and specificity, especially for its application at primary medical institutions. The indicators could be a new reference for the clinical diagnosis and prognosis of children with sepsis.

The current study intended to investigate the clinical significance of PCT, Lac, and ET in the serum of children with severe pneumonia combined with sepsis.

METHODS

Participants

The research team performed a retrospective study. The study took place at Nantong First People's Hospital in Nantong, Jiangsu, China. Potential participants were children with severe pneumonia complicated by sepsis, as well as children with severe pneumonia only, all of whom had received treatment in the pediatric intensive care unit of the hospital between January 2018 and May 2020. Based on the hospital information system, cases were screened according

to the inclusion criteria, and then unqualified cases (including those with incomplete information) were eliminated according to the exclusion criteria, and then the inclusion objects were determined.

The study included potential participants if they: (1) were aged one month to 12 years, (2) met the diagnostic criteria for pneumonia combined with sepsis;[22] and (3) had received no other therapeutic interventions.

The study excluded potential participants if: (1) they had primary vital organ failure; (2) they had received anti-infective and symptomatic treatment; (3) they had incomplete data available; (4) they had a concurrent malignancy or immune heterogeneity; (5) they had died or abandoned treatment within 24 h of their ICU admission; or (6) their parents had refused to allow them to participate.

The guardians of the participating children carefully reviewed and signed the informed consent form. The ethics committee of Nantong First People's Hospital approved this study after a rigorous review of the trial protocol (No. 2020KT263).

Procedures

Serum samples. The research team: (1) collected fasting, elbow, venous blood samples from all participants using a heparin anticoagulation tube; (2) centrifuged the blood samples at 3000 r/min for 15 min and kept the serum at -80°C; (3) measured the Lac levels using a Radiometer ABL-90 blood gas analyzer with reagents that the team had purchased from Shanghai Shensheng Biotechnology (Shanghai, China); and (4) detected the PCT and ET levels in the blood samples using a DG5033A Elisa Analyzer, a microplate reader for performing an enzyme-linked immunosorbent assay (ELISA), from Wuxi Unitalen Intelligent Technology (Wuxi, China). The team measured each indicator 3 times and used the average value as the final result.

Groups. At baseline, the research team divided the participants into three groups based on their pediatric clinical illness score (PCIS)[23] at 24 h after admission: (1) the extremely critical group—0-70 points (n = 29), (2) the critical group—71-80 points (n = 31), and (3) the noncritical group—>80 points (n = 30). The children who had received treatment but who had severe pneumonia only became the control group.

The Emergency Medicine Group of the Chinese Academy of Pediatrics and the Pediatrics Group of the Chinese Society of Emergency Medicine developed the PCIS assessment tool, which covers 10 indicators, such as heart rate, systolic blood pressure, respiration, pH, blood sodium, and blood potassium. Lower scores represent more critical symptoms.

Outcome measures. The research team: (1) measured the serum PCT, Lac, and ET levels for the four groups at baseline, (2) compared those levels for the four group, (3) compared those levels by clinical outcome, (4) determined the correlation of the three indicators to the PCIS scores, and (5) identified the predictive value of the three indicators. To compare the levels by clinical outcome and to determine the indicators' predictive values, the team divided participants into two groups according to their clinical outcomes on day 28 of the study: (1) 40 children who died became the death group, and (2) 50 children who survived became the survival group.

Outcome Measures

Predictive value of serum PCT, Lac, ET levels. The research team plotted the predictive receiver operator characteristic (ROC) curves of the serum PCT, Lac, and ET levels for participants with sepsis separately and calculated their areas under the curves (AUCs) separately,

Statistical Analysis

The research team used the Statistical Package for the Social Science (SPSS) 22.0 (IBM, Armonk, NY, USA) to analyze the data in the study. The team: (1) expressed measurement data as means ± standard deviations (SDs), (2) compared the groups using the *t* test for data meeting a normal distribution or the Mann-Whitney U-test for data with variance inconsistency, and (3) expressed the count data as numbers and percentages (%) and compared the groups using the chi-square test , (4) used a Spearman analysis for correlation analysis, and (5) drew a receiver operator characteristic (ROC) curve for evaluation of diagnostic effectiveness. $P < .05$ indicated a significant difference. The team used Graphpad prism 8.3 (La Jolla, CA, USA)[24] as the plotting software.

RESULTS

Participants

No significant differences existed at baseline in the demographic characteristics of the four groups, suggesting that the groups were comparable (Table 1).

PCT, Lac, and ET Levels by Group

Table 2 and Figure 1 show that the serum PCT, Lac, and ET levels in the extremely critical group were the highest, followed by the critical group, the noncritical group, and the control group. The differences in the above indicators were statistically significant between these groups ($P < .05$).

Serum levels by Clinical Outcome

Figure 2 shows that the results showed that the serum PCT, Lac and ET levels of the children in the death group were significantly higher than those in the survival group ($P < .05$).

Correlation Between Serum Levels and PCIS Scores

Table 3 and Figure 3 show that the serum PCT, Lac, and ET levels had a significant negative correlation with the PCIS score (r = -0.8203 (PCT), -0.6384 (Lac), -0.6412 (ET), $P < .05$).

Predictive Value of Serum Levels

Table 4 and Figure 4 show that the AUC for the PCT level was 0.7732 (95% CI = 0.6214 to 0.9249, $P = .0015$), for

Table 1. Comparison of Demographic Characteristics Among the Groups at Baseline (n = 120)

Characteristics	Extremely Critical Group n = 29 n (%) Mean ± SD	Critical Group n = 31 n (%) Mean ± SD	Noncritical Group n = 30 n (%) Mean ± SD	Control Group n = 30 n (%) Mean ± SD	t/χ^2	*P* value
Gender						
Male	16 (55.17)	20 (64.52)	17 (56.67)	19 (63.33)	0.132	.716
Female	13 (44.83)	11 (35.48)	13 (43.33)	11 (36.67)		
Age, y	3.29 ± 0.32	3.35 ± 0.29	3.19 ± 0.28	3.34 ± 0.31	1.796	.152
Weight, kg	16.19 ± 2.11	15.98 ± 2.43	16.02 ± 2.09	16.23 ± 2.14	0.095	.963

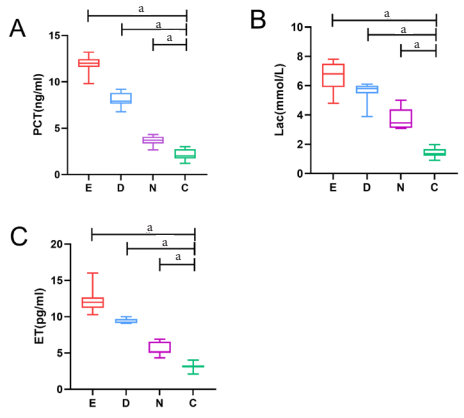
Table 2. Comparison of Serum PCT, Lac, and ET Levels by Group (n = 120). The serum PCT, Lac, and ET levels in the extremely critical group were the highest, followed by the critical group, the noncritical group, and the control group.

Groups	PCT, ng/ml	Lac, mmol/L	ET, pg/ml
Extremely Critical Group (n = 29) Mean ± SD	13.02±2.11	8.78±1.22	12.11±2.11
Critical Group (n = 31) Mean ± SD	8.78±0.98	6.78±1.21	9.78±0.87
Noncritical Group (n = 30) Mean ± SD	4.39±0.21	4.22±0.87	6.12±0.34
Control Group (n = 30) Mean ± SD	2.11±0.19	1.22±0.11	3.28±0.45
t1	28.211	33.809	22.407
P1	<.001	<.001	<.001
t2	36.609	25.069	36.466
P2	<.001	<.001	<.001
t3	44.097	18.738	27.580
P3	<.001	<.001	<.001

Note: P1 represents the comparison between the extremely dangerous recombination and the control group, P2 represents the comparison between the dangerous recombination and the control group, and P3 represents the comparison between the non-dangerous recombination and the control group.

Abbreviations: ET, endotoxin; Lac, lactic acid; PCT, procalcitonin.

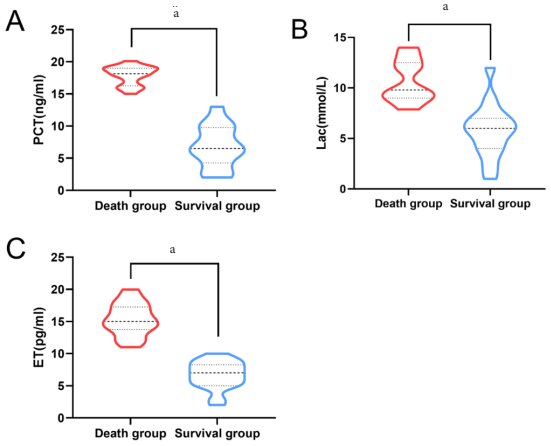
Figure 1. Comparison of the Serum PCT, Lac, and ET Levels Among the Groups. The comparison showed that the levels of serum PCT (A), Lac (B) and ET (C) in the extremely critical, critical and noncritical recombination children were significantly higher than those in the control group, and the difference between the above index groups was statistically significant ($P < .05$).



[a]indicates that compared with the control group, the difference of the same index was statistically significant.

Abbreviations: ET, endotoxin; Lac, lactic acid; PCT, procalcitonin.

Figure 2. Comparison of Serum PCT, Lac, and ET Levels in Children With Different Clinical Outcomes. Figure 2A shows the PCT levels; Figure 2B shows the Lac levels; and Figure 2C shows the ET levels. All three levels in the death group were significantly higher than those in the survival group ($P < .05$)



[a]$P < .05$, indicating that the serum PCT, Lac, and ET Levels were significantly higher in the death group than those of the survival group.

Abbreviations: ET, endotoxin; Lac, lactic acid; PCT, procalcitonin.

Table 3. Correlation of Serum PCT, Lac, and ET Levels with PCIS Scores (n = 120)

Group	PCT	Lac	ET	PCIS
PCT	-	-	-	-0.8203
Lac	-	-	-	-0.6384
ET	-	-	-	-0.6412
PCIS	-0.8203	-0.6384	-0.6412	-

Abbreviations: ET, endotoxin; Lac, lactic acid; PCIS, pediatric clinical illness score; PCT, procalcitonin

Table 4. Predictive Value of Serum PCT, Lac, and ET Levels for Participants With Sepsis (n = 90)

Parameter	Cut-off Value	AUC	*P* value	95% CI	Jorden Index
PCT	12.13 ng/ml	0.7732	.0015[a]	0.6214 to 0.9249	0.972
Lac	7.61 mmol/L	0.9533	<.0001[a]	0.9036 to 1.000	0.892
ET	12.18 pg/ml	0.8694	<.0001[a]	0.7622 to 0.9765	0.949

[a]$P < .05$, indicating that all three indicators were significantly predictive regarding participants' prognoses

Abbreviations: ET, endotoxin; Lac, lactic acid; PCIS, pediatric clinical illness score; PCT, procalcitonin.

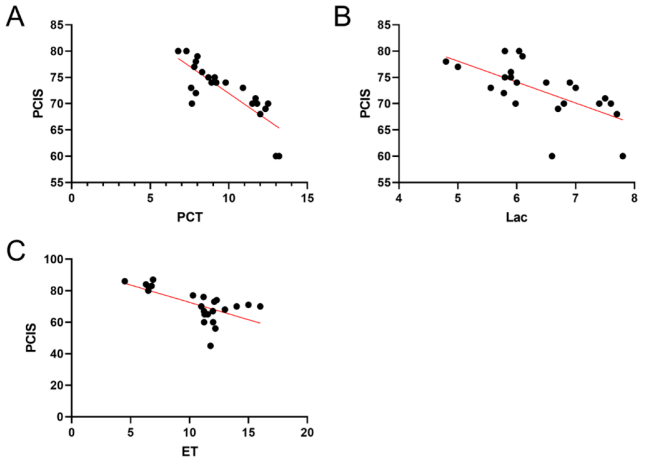
the Lac level was 0.9533 (95% CI = 0.9036 to 1.000, $P < .0001$), and for the ET level was 0.8694 (95% CI = 0.7622 to 0.9765, $P < .0001$) for ET. These values indicate that all three indicators were significantly predictive regarding participants' prognoses.

DISCUSSION

The current study found that the levels of PCT, Lac, and ET were significantly higher in the extremely critical group, critical group and non-critical group compared with the control group, indicating that medical practitioners can use PCT, Lac, and ET not only to identify severe pneumonia complicated by sepsis but also to identify the severity of the disease.

The current research team believed that the elevation of Lac in the current study may have been related to the ischemia and hypoxia of tissues and organs and that the abnormally elevated Lac levels could affect the internal environment and induce multi-organ failure, as Downes et al had found.[15] Some studies believe that PCT is the lipopolysaccharide released during bacterial infection. This factor can combine with the glycoprotein receptor on the surface of alveolar epithelial cell membrane to accelerate the diffusion of infection factors. At the same time, the rise of PCT will also release inflammatory signals to the downstream and aggravate the damage of inflammatory reactions to the body organs, which is similar to the results of this study.[16] The authors believe that the increase of Lac in the body may be

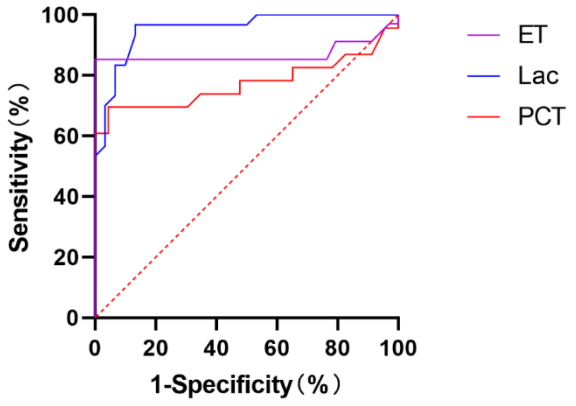
Figure 3. Correlation Between Serum PCT, Lac, and ET levels and PCIS Scores. Figure 3A shows the PCT levels; Figure 4B shows the Lac levels; and Figure 5C shows the ET levels. A negative correlation existed for all three variables with the PCIS score (r = -0.8203, -0.6384, -0.6412, $P < .05$).



Note: The serum PCT, Lac, and ET levels were negatively associated with the PCIS score

Abbreviations: ET, endotoxin; Lac, lactic acid; PCT, procalcitonin; PCIS: pediatric clinical illness score.

Figure 4. The Predictive Value of Serum PCT, Lac, and ET Levels in Children With Severe Pneumonia Complicated by Sepsis. The AUC for PCT was 0.7732 (95% CI = 0.6214 to 0.9249, $P = .0015$), for Lac was 0.9533 (95% CI 0.9036 to 1.000, $P < .0001$), and for ET was 0.8694 (95% CI = 0.7622 to 0.9765, $P < .0001$).



Note: The serum PCT, Lac, and ET levels were significantly predictive regarding participants' prognoses

Abbreviations: AUC, area under the curve; ET, endotoxin; Lac, lactic acid; PCT, procalcitonin; PCIS: pediatric clinical illness score

related to the ischemia and hypoxia of tissues and organs. The abnormal increase of Lac level will affect the internal environment of children and induce the occurrence of multiple organ failure, which is also the important reason that Lac level is closely related to the patient's condition.

The current study found that the AUCs of the three indicators were high, suggesting that they could have good diagnostic value for severe pneumonia complicated by sepsis. The current study also found that PCT, Lac, and ET levels are closely related to the condition of severe pneumonia complicated by sepsis and that the more severe the condition, the more severe the activity of pathophysiological mechanisms, as Poropat et al had found.[21]

The limitations of the current study were as follows: (1) the source of patients was limited in region, and the sample size is small; (2) the testing for the Lac should with blood from arteries, which is painful for the children; (3) the results of long-term follow-up are lacking. The above deficiencies may have affected the results' accuracy, and the current research tea proposes to correct them and improve the study in the future.

CONCLUSIONS

The serum PCT, Lac, and ET levels in children with severe pneumonia complicated by sepsis were abnormally high, and the levels of these indicators were significantly negatively correlated with the PCIS scores. PCT, Lac, and ET may be potential indicators for the diagnosis and prognosis assessment of children with severe pneumonia complicated by sepsis.

AUTHORS' DISCLOSURE STATEMENT:

The authors have no conflicts of interest related to the study.

REFERENCES

1. Frenzen FS, Kutschan U, Meiswinkel N, Schulte-Hubbert B, Ewig S, Kolditz M. Admission lactate predicts poor prognosis independently of the CRB/CURB-65 scores in community-acquired pneumonia. *Clin Microbiol Infect.* 2018; 24(3):301-306. doi: 10.1016/j.cmi.2017.07.007
2. Baker AH, Monuteaux MC, Madden K, Capraro AJ, Harper MB, Eisenberg M. Effect of a sepsis screening algorithm on care of children with false-positive sepsis alerts. *J Pediatr.* 2021; 231:193-199.e1. doi: 10.1016/j.jpeds.2020.12.034
3. Li H, Guo J, Wang K, Zhang NR, Zheng ZN, Jin SQ. [Effect of open-lung ventilation strategy on oxygenation-impairment during laparoscopic colorectal cancer resection]. *Zhonghua Wei Chang Wai Ke Za Zhi.* 2020; 23(11):1081-1087. doi: 10.3760/cma.j.issn.441530-20191209-00507
4. Prout AJ, Talisa VB, Carcillo JA, Angus DC, Chang CH, Yende S. Epidemiology of readmissions after sepsis hospitalization in children. *Hosp Pediatr.* 2019; 9(4):249-255. doi: 10.1542/hpeds.2018-0175
5. Pinheiro KHE, Azedo FA, Areco KCN, Laranja SMR. Risk factors and mortality in patients with sepsis, septic and non-septic acute kidney injury in ICU. *J Bras Nefrol.* 2019; 41(4):462-471. doi: 10.1590/2175-8239-JBN-2018-0240
6. Mithal LB, Arshad M, Swigart LR, Khanolkar A, Ahmed A, Coates BM. Mechanisms and modulation of sepsis-induced immune dysfunction in children. *Pediatr Res.* 2022; 91(2):447-453. doi: 10.1038/s41390-021-01879-8
7. Ramos-Sevillano E, Ercoli G, Brown JS. Mechanisms of naturally acquired immunity to Streptococcus pneumoniae. *Front Immunol.* 2019; 10:358. doi: 10.3389/fimmu.2019.00358
8. Kalil AC. Sepsis and septic shock. *Semin Respir Crit Care Med.* 2021; 42(5):639-640. doi: 10.1055/s-0041-1735218
9. Weiss SL, Balamuth F, Thurm CW, Downes KJ, Fitzgerald JC, Laskin BL. Major adverse kidney events in pediatric sepsis. *Clin J Am Soc Nephrol.* 2019; 14(5):664-672. doi: 10.2215/CJN.12201018
10. Yadav B, Bansal A, Jayashree M. Clinical profile and predictors of outcome of pediatric acute respiratory distress syndrome in a PICU: A prospective observational study. *Pediatr Crit Care Med.* 2019; 20(6):e263-e273. doi: 10.1097/PCC.0000000000001924
11. Sole A, Jordan I, Bobillo S, et al. Venoarterial extracorporeal membrane oxygenation support for neonatal and pediatric refractory septic shock: More than 15 years of learning. *Eur J Pediatr.* 2018; 177(8):1191-1200. doi: 10.1007/s00431-018-3174-2
12. Mawji A, Li E, Komugisha C, et al. Smart triage: Triage and management of sepsis in children using the point-of-care Pediatric Rapid Sepsis Trigger (PRST) tool. *BMC Health Serv Res.* 2020; 20(1):493. doi: 10.1186/s12913-020-05344-w
13. Song J, Cho H, Park DW, et al. The effect of the intelligent sepsis management system on outcomes among patients with sepsis and septic shock diagnosed according to the sepsis-3 definition in the emergency department. *J Clin Med.* 2019; 8(11):1800. doi: 10.3390/jcm8111800
14. Butler DF, Myers AL. Changing Epidemiology of Haemophilus influenzae in Children. *Infect Dis Clin North Am.* 2018; 32(1):119-128. doi: 10.1016/j.idc.2017.10.005
15. Downes KJ, Fitzgerald JC, Weiss SL. Utility of procalcitonin as a biomarker for sepsis in children. *J Clin Microbiol.* 2020; 58(7):e01851-19. doi: 10.1128/JCM.01851-19
16. Lestari IN, Yoel C, Lubis M. The association between the level of antithrombin III and mortality in children with sepsis. *Open Access Maced J Med Sci.* 2019; 7(6):959-961. doi: 10.3889/oamjms.2019.211
17. Becker AE, Teixeira SR, Lunig NA, et al. Sepsis-related brain MRI abnormalities are associated with mortality and poor neurological outcome in pediatric sepsis. *Pediatr Neurol.* 2022; 128:1-8. doi: 10.1016/j.pediatrneurol.2021.12.001
18. Goh C, Burnham KL, Ansari MA, et al. Epstein-Barr virus reactivation in sepsis due to community-acquired pneumonia is associated with increased morbidity and an immunosuppressed host transcriptomic endotype. *Sci Rep.* 2020; 10(1):9838. doi: 10.1038/s41598-020-66713-3
19. Bouras M, Asehnoune K, Roquilly A. Contribution of dendritic cell responses to sepsis-induced immunosuppression and to susceptibility to secondary pneumonia. *Front Immunol.* 2018; 9:2590. doi: 10.3389/fimmu.2018.02590
20. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev.* 2019; 12(12):CD002243. doi: 10.1002/14651858.CD002243.pub4
21. Poropat G, Radovan A, Peric M, et al. Prevention of infectious complications in acute pancreatitis: Results of a single-center, randomized, controlled trial. *Pancreas.* 2019; 48(8):1056-1060. doi: 10.1097/MPA.0000000000001368
22. Sapey E, Patel JM, Greenwood H, et al. Simvastatin improves neutrophil function and clinical outcomes in pneumonia: A pilot randomized controlled clinical trial. *Am J Respir Crit Care Med.* 2019; 200(10):1282-1293. doi: 10.1164/rccm.201812-2328OC
23. Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: Prevention, diagnosis, treatment. *Crit Care.* 2019; 23(1):214. doi: 10.1186/s13054-019-2491-9
24. Liu QY, Wang YX, Wu ZS, et al. High mobility group protein 1 reverses immune system paralysis in late-phase sepsis. *Infect Immun.* 2018; 86(9) doi: 10.1128/IAI.00455-18