

# The Association between the Level of Antithrombin III and Mortality in Children with Sepsis

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## Abstract

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**BACKGROUND:** Sepsis is a significant cause of morbidity and mortality in children. The diagnosis of sepsis remains continuing to develop which determines treatment and prognostic. Antithrombin III is one of the coagulation markers to evaluate the prognosis of sepsis.

**AIM:** To determine the association between the level of antithrombin III and mortality in children with sepsis in the Pediatric Intensive Care Unit, Haji Adam Malik General Hospital, Medan.

**METHODS:** A cross-sectional study was conducted in Haji Adam Malik General Hospital, Medan from April until June 2015. There were 41 children with sepsis. Sepsis was diagnosed from clinical and laboratory findings. Complete blood count, antithrombin III level, C-reactive protein and procalcitonin were an indicator of unproven sepsis that performed in the laboratory. Meanwhile blood culture was performed in the microbiology laboratory. The association between the level of antithrombin III and mortality was analysed by using chi-square test.

**RESULTS:** Of the 41 participants, the low antithrombin III level was 13 of 41 children (31.7%) meanwhile the normal antithrombin III level was 28 of 41 children (68.3%). There was 8 of 13 (42.1%) and 11 of 28 (57.9%) children in death cases of low and normal antithrombin III level, respectively. Samples with low antithrombin III level had 2.473 higher risk mortality than normal antithrombin III level ( $P = 0.184$ ; 95% CI 0.641 to 9.5421; PR = 2.473).

**CONCLUSION:** There was no statistically significant association between levels of antithrombin III and mortality in children with sepsis.

## Introduction

Sepsis is one of the causes of mortality amongst children worldwide. It is defined as systemic inflammatory response syndrome (SIRS) which caused by infection either proven by clinical examination, blood culture or septic markers [1], [2], [3]. The incidence of sepsis was 0.56 cases per 1000 children per year, the highest amongst infants (5.16 per 1000) and decreased with ages (0.20 per 1000 among 10-14-year-olds) [4]. The development of diagnostic of sepsis is the main key to treatment and prognostic determination [5], [6].

Antithrombin III is an inhibitor of thrombin-mediated vascular injury in the microcirculation during severe sepsis. This endogenous anticoagulant is rapidly depleted in the early phases of sepsis as a result of decreased synthesis, increased destruction,

and enhanced clearance by thrombin-antithrombin complex formation [7]. Examination of antithrombin III (ATIII) will be able to be an objective and reliable examination in detecting sepsis circumstances, in determining the severity and differentiate various possible causes of sepsis and can be used to measure the response to treatment [5], [6].

A study in Turkey, 2007, showed that the value of initial antithrombin III (ATIII) level could be used as a prognostic factor in neonatal sepsis. From this study was reported that the initial antithrombin III (ATIII) level decreased in patients with sepsis and could predict mortality [7].

However, the antithrombin III level, as a prognostic factor, in children has never been reported; this is the background of this study to determine the association between antithrombin III (ATIII) level and mortality in children with sepsis.

## Methods

### Study Design

A cross-sectional study was conducted to determine the association between the level of antithrombin III and mortality in children with sepsis Pediatric Intensive Care Unit, Haji Adam Malik General Hospital, Medan, North Sumatera, Indonesia from April until June 2015. Sepsis was diagnosed with by clinical examination, blood culture or septic markers. The inclusion criteria are children with sepsis from 6 months to 18 years old.

The exclusion criteria are patients with blood disorders because the level of antithrombin III was decreased in blood disorders. Samples were obtained by consecutive sampling. Data were analysed by statistical software, and the result was presented in tables. This study was approved by the Health Research Ethical Committee, Medical School, University of Sumatera Utara.

### Sample Recruitment

All subject who fulfilled the inclusion criteria were enrolled in this study. Data patients about sex, mean age, body weight, stature, nutrition status, data laboratory (Routine blood, antithrombin III, C-reactive protein (CRP), procalcitonin and blood culture) were collected from medical records.

On the first day of treatment, all subjects were suspected as sepsis based on clinical findings; samples had laboratory tests such as routine blood, antithrombin III, C-reactive protein (CRP), procalcitonin and blood culture. Antithrombin III (ATIII) level is part of the coagulation examination. Blood was taken at least 1.8 mL from the cubital vein. The blood inserted into a citrate tube and transported to the laboratory according to the Standard

Operating Procedure. Examination of ATIII level is carried out using Teco Coatron AT III. The 75-150% value of antithrombin III (ATIII) is a normal category, and the < 75% value of antithrombin III (ATIII) is a low category [8]. Samples were followed-up until death or discharged from the paediatric intensive care unit.

### Statistical Analysis

The association between the level of antithrombin III and mortality in children with sepsis was analysed using chi-square with a 95% confidence interval and P-value < 0.05 was considered significant.

## Results

Of 41 patients were enrolled in this study. Baseline characteristics samples were described in Table 1. shows the baseline characteristics of patients, including sex, mean age, body weight, stature, nutrition status, data laboratory (Routine blood, antithrombin III, C-reactive protein (CRP), procalcitonin and blood culture). There was no association between sex, mean age, nutrition status, CRP, blood culture, mean leukocyte, mean platelets, mean procalcitonin to mortality in this study. There was an association ( $p = 0.024$ ) between mean haemoglobin in the death group (10.26 g/dl) and life group (11.54 g/dl).

**Table 1: Baseline characteristics samples**

Characteristics	Mortality	Death Life	p
Sex (n%)			
Boys	12 (52.2)	11(47.6)	0.397 <sup>a</sup>
Girls	7 (38.9)	11(61.6)	
Mean Age (years)	7.95 (5.49)	8.71 (5.38)	0.656 <sup>b</sup>
Nutritional Status (n%)			
Malnutrition	4 (66.7)	2 (33.3)	0.390 <sup>d</sup>
Normal	15 (42.9)	20 (57.1)	
CRP (n%)			
Positive	18 (48)	19 (51.4)	0.610 <sup>d</sup>
Negative	1 (25)	3 (75)	
Blood Culture (n%)			
Positive	1 (20)	4 (80)	0.350 <sup>d</sup>
Negative	18 (50)	18(50)	
Mean Haemoglobin(g/dl)	10.26 (2.17)	11.54 (1.26)	0.024 <sup>b</sup>
Mean leukocyte (mm <sup>3</sup> )	15.165 (9567)	14.927 (5270)	0.979 <sup>c</sup>
Mean Platelets (mm <sup>3</sup> )	276.173 (188.333)	222.256 (129.778)	0.488 <sup>c</sup>
Mean Procalcitonin	9.09 (13.44)	15.56 (41.86)	0.875 <sup>c</sup>

<sup>a</sup> Chi-Square; <sup>b</sup> T independent; <sup>c</sup> Mann Whitney; <sup>d</sup> Fisher's Exact.

**Table 2: Association between the level of antithrombin III and mortality**

Antithrombin III	Mortality		P	PR	95% CI
	Yes	No			
Low	8 (42.1)	5 (22.7)	0.184	2.473	0.641-9.542
Normal	11 (57.9)	17 (77.3)			

Chi-square test was used to determine the association between the value of antithrombin III (ATIII) and mortality in children with sepsis (Table 2). Antithrombin III was classified as normal if the level of antithrombin III was 75% until 150% and low if the level of antithrombin III was < 75% [8]. According to the test's result, there was no statistically significant association between levels of antithrombin III and mortality in this study ( $p = 0.184$ ).

## Discussion

Sepsis is a group of signs of systemic inflammation due to infection based on clinical

examination or proven by blood culture and septic markers [1], [2], [3]. Sepsis is one of the common reason for mortality in infants and children Who reported that 70 per cent of 8 million mortality of children under five years old in developing countries was caused by infectious diseases in which ended up to sepsis [4]. In 2007, Indonesia Basic Health Research reported that sepsis was the most common reason for infant mortality (20.5%) [9].

The sepsis diagnostic approach is currently to determine early signs of sepsis, evaluate treatment and make prognosis [5], [10].

Antithrombin III is a useful prognostic marker in sepsis, due to its potential inhibitor of thrombin which occurs when there is a vascular injury in microcirculation during the process of infection. Many previous studies have reported that initial AT levels of patients with sepsis who developed septic shock and DIC are an indicator of prognosis and cases with very low AT levels have a higher mortality rate [7]. A study in Europe, 2006, showed that low activity of antithrombin III was correlated with severity and survival rate in patients with sepsis [11].

A study in Korea, 2014, showed that antithrombin and protein C were strong prognostic markers patients with DIC, sepsis or severe sepsis [12]. The same conclusion also found in a study in Thailand, 2006, where the reduced level of protein C, protein S and antithrombin might predict the survival rate of gram-negative sepsis due to *Burkholderia pseudomallei* [13].

This study shows that there is no statistically significant association between levels of antithrombin III and mortality in this study ( $p = 0.184$ ). Low level of antithrombin III in the subjects who died was 8 subject (42.1%) and with normal levels were found in 11 subject (57.9%). Although not statistically significant, there showed that subjects with a low level of antithrombin III in patients with sepsis had 2.473 higher risk for caused mortality compared with the normal level of antithrombin III ( $P = 0.184$ ; 95% CI 0.641 to 9.5421; PR = 2.473).

The limitation of this study did not compare to other haematology markers examinations, so it could not evaluated that specificity and sensitivity. This study was needed more fourth researches to determine the level of antithrombin III as a prognostic marker in children sepsis.

## References

- Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in paediatrics. *Pediatric critical care medicine*. 2005; 6(1):2-8. <https://doi.org/10.1097/01.PCC.0000149131.72248.E6> PMID:15636651
- Carvalho PRA, Trotta EA. Advances in sepsis diagnosis and treatment. *Curr Opin in Pediatr*. 2003; 79:95-204.
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Pediatr Crit Care Med*. 2013; 41(2):580-637. <https://doi.org/10.1097/CCM.0b013e31827e83af> PMID:23353941
- Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005; 6(1):2-4. <https://doi.org/10.1097/01.PCC.0000149131.72248.E6> PMID:15636651
- Melendez E, Bachur R. Advances in emergency management of pediatric sepsis. *Curr Opin in Pediatr*. 2006; 18:245-53. <https://doi.org/10.1097/01.mop.0000193305.55635.ff> PMID:16721143
- Carcillo JA, Planquois JM, Golstein B. Early markers of infection and sepsis in newborn and children. *Advances in Sepsis*. 2006; 5(4):118-25.
- Ersoy B, Nehir H, Altinoz S, Yilmaz O, Dundar PE, Aydogan A. Prognostic value of initial antithrombin levels in neonatal sepsis. *Indian Pediatr*. 2007; 44:581-4. PMID:17827633
- Wiedermann CJ. Clinical review: molecular mechanisms underlying the role of antithrombin in sepsis. *Crit Care*. 2006; 10(209):1-9.
- Kementrian Kesehatan Republik Indonesia. Riset Kesehatan Dasar 2007. Departemen Kesehatan Republik Indonesia. 2007:1-4.
- Ng PC. Diagnostic markers of infection in neonates. *Arch Dis Child Fetal Neonatal*. 2004; 89:229-35. <https://doi.org/10.1136/adc.2002.023838> PMCID:PMC1721679
- Lauterbach R, Pawlik D, Radziszewska R, Wozniak J, Rytlewski K. Plasma antithrombin III and protein C levels in early recognition of late-onset sepsis in newborns. *Eur J Pediatr*. 2006; 165:585-9. <https://doi.org/10.1007/s00431-006-0139-7> PMID:16636814
- Choi Q, Ki Ho Hong, Ji-Eun Kim, Hyun Kyung kim. Changes in plasma levels of natural anticoagulants in disseminated intravascular coagulation: High prognostic value of antithrombin and protein C in patients with underlying sepsis or severe infection. *Ann Lab Med*. 2014; 34:85-91. <https://doi.org/10.3343/alm.2014.34.2.85> PMID:24624342 PMCID:PMC3948838
- Larosa S, Steven O, Barbara U, Sau CBY, Jeffrey H, Andrew J,dkk. Decresed protein C, protein S and antithrombin levels are predictive of poor outcome in gram-negative sepsis caused by *Burkholderia pseudomallei*. *Infect Dis*. 2006; 10:25-31.