

# Thyroid Hormone Profile in Children with Sepsis: Does Euthyroid Sick Syndrome Exist?

Gema Nazri Yanni<sup>\*</sup>, Cynthea Prima Destariani, Arlina Nurbaity Lubis, Melda Deliana

*Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Haji Adam Malik General Hospital, Medan, Indonesia*

## Abstract

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**\*Correspondence:** Gema Nazri Yanni, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Haji Adam Malik General Hospital, Medan, Indonesia. E-mail: [gema.nazri.yanni@gmail.com](mailto:gema.nazri.yanni@gmail.com)

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**BACKGROUND:** Alterations in peripheral thyroid hormone metabolism play an eminent role in the development of the euthyroid sick syndrome. Altered solvation may also lead to changes in peripheral thyroid hormones. Data on thyroid hormones in critically ill children remain unclear.

**AIM:** This study was aimed to evaluate thyroid hormone profile in children with sepsis as well as to assess the association between thyroid level and sepsis outcome.

**METHODS:** An observational cohort study was conducted in 80 children with sepsis from October 2015 to January 2016 in Haji Adam Malik General Hospital. T3 and T4 level were measured on day 1 and after > 72 hours of sepsis diagnosed.

**RESULTS:** We recorded length of stay in PICU, patient outcome and analysed the relationship with the chi-square test. Level of T3 and T4 were decreased on day 1 in pediatric sepsis. Of 80 subjects, 57 (71.2%) with low-level T3 and 41 (51.2%) with low T4 were found. The relationship between T3 and T4 level on day 1 with the length of stay were not found ( $P = 0.500$ ;  $P = 0.987$ ). There were a significant relationship between level of T3 and T4 with outcome ( $P = 0.0001$ ; OR 24.706;  $P = 0.014$ ; OR 3.086). Subject with normal T3 and T4 level had 24 and 3 times life chances compare to lower level.

**CONCLUSION:** The Euthyroid Sick Syndrome in children with sepsis does exist. There was a significant relationship between T3 and T4 level on day 1 with patient outcome.

## Introduction

Sepsis is the most common cause of mortality in infants and children. The incidence of sepsis and septic shock were increasing in the last 30 to 40 years [1]. *World Health Organization* (WHO) reported 70% in eight million children under five years mortalities in developing countries caused by infection diseases which commonly ended in sepsis condition. The incidence of sepsis was 0.56% of 1000 children and 5.6% of 1000 infants with the highest mortality rate as 10.6% [2].

Division of Emergency and Intensive Care Medicine, Department of Child Health, Cipto Mangunkusumo Hospital in 2009 reported incidence of sepsis was 19.3% of 502 patients hospitalised in

pediatric intensive care unit (PICU) with mortality rate 10.3% [3]. Mortality rate due to neonatal sepsis in Haji Adam Malik General Hospital in 2008 until 2010 was 32.9% [4].

Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. A hormonal disorder that often affected in sepsis was thyroid hormones which occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) [5]. Euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) is a condition of decreased thyroid hormone levels without disruption of thyroid hormone function that occurs in severe systemic non-thyroid disease. Changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn

will lead to organ system failure and ended in death [6].

The critical disease is characterized by complex and multiple changes in the thyroid pathway. Along with worsening of a critical illness, the decrease occurs in not only triiodothyronine (T3) levels but also thyroxine (T4) and thyroid stimulating hormone (TSH). Decreased levels of T4 and TSH showed an indication of worsening of disease and poor prognosis. The incidence was around 80%, especially in patients with T4 levels < 3 µg/dL. The decreased in thyroid hormone levels is still controversy to date. A study in Greece and the United States reported the decreased level of T4 and TSH affected mortality rate in sepsis and septic shock [7]. A study in the Netherlands showed decreased in T4 that affected mortality, but a study in Belgium showed that T3 was. Decreased in T3 was due to changes in metabolism in thyroid hormones [8], [9], [11].

A study in Cipto Mangunkusumo Hospital in 2014 reported decreased thyroid hormone levels especially T3 in sepsis, while in Semarang showed the decreased of T3 levels were followed by increased of T4 and TSH which was by the definition of ESS. Both studies showed patients with low thyroid hormone levels associated with poor outcome, as measured by pediatric logistic organ dysfunction (PELOD) or pediatric index of mortality (PIM) score.

This study was conducted to evaluate thyroid hormones changes and the outcome in children with sepsis in PICU Haji Adam Malik General Hospital.

## Methods

This was a cohort study in 80 patients with sepsis hospitalised in PICU Haji Adam Malik Hospital from October 2015 until January 2016. Thyroid hormone levels were observed on the first day and > 72 hours of admission. Diagnosis of sepsis was made based on the criteria of International Consensus on Pediatric Sepsis 2005.

**Table 1: Normal value of T3, T4, and TSH levels [12]**

Age	T3(nmol/L)	Age	T4 (nmol/L)	Age	TSH (µIU/L)
1 – 12 months	1.4 – 4	1 – 12 months	77 – 180	1 – 5 months	0.5 – 6
1 – 6 years	1.4 – 3.7	1 – 5 years	58 – 142	6 months – 18 years	0.5 – 4.5
7 – 11 years	1.4 – 3.6	6 – 18 years	58 – 129		
12 – 18 years	1.5 – 3.3				

Inclusion criteria were patients one month until 18 years with a diagnosis of sepsis. Hormone thyroid levels were examined on the first day and > 72 hours. Patients with hypothyroid and hyperthyroid diagnosed by a pediatric endocrinologist before admission to PICU were excluded. Subjects were

taken consecutively. Age, gender, PELOD score, length of stay, and outcome were noted. Data were analysed using SPSS version 20. Chi-square test was done to evaluate the association of thyroid hormones and length of stay and outcome. P value < 0.05 was considered statistically significant.

Normal value thyroid hormone levels were shown in Table 1.

## Result

During the study period there were 80 patients with sepsis were included (Table 2).

**Table 2: Subjects Characteristics**

Variable	n = 80
Gender	
Male	46 (57.5%) <sup>a</sup>
Female	34 (42.5%)
Age	7 (1-17) <sup>b</sup>
PELOD score	
High (≥ 20)	31 (38.75%) <sup>a</sup>
Low (< 20)	49 (61.25%)
Length of stay	
< 7 days	37 (46.25%) <sup>a</sup>
≥ 7 days	43 (53.75%)
Outcome	
Alive	38 (47.5%) <sup>a</sup>
Died	42 (52.5%)

<sup>a</sup> categorical data: n (%); <sup>b</sup> numerical data not normal distribution: median (minimum-maximum); <sup>c</sup> numerical data normal distribution: mean ± standard deviation (SD).

Decreased in T3 hormone on the first day of admission was found in 57 patients (71.2%) and decreased in T4 was in 41 patients (51.2%). On the > 72 hours of admission, patients with low T3 hormone levels were decreased to 49 patients (61.2%), on the other side patients with low T4 hormone levels were increased to 41 patients (56.35%), (Table 3).

**Table 3: Profile of thyroid hormones**

	T3		T4		TSH	
	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD
Day 1						
Normal	23 (28.8%)	1.71 ± 0.53	39 (48.8%)	7.26 ± 1.16	80 (100)	3.49 ± 0.36
Low	57 (71.2%)	0.83 ± 0.22	41 (51.2%)	4.29 ± 1.08	0	0
Day 4						
Normal	31 (38.8%)	1.8 ± 0.46	35 (43.8%)	7.36 ± 1.12	80 (100)	3.41 ± 0.39
Low	49 (61.2%)	0.75 ± 0.27	45 (56.3%)	4.56 ± 1.15	0	0

There was no statistically significant relationship between hormone thyroid levels on the first day of admission and length of stay, where p-value for T3 and T4 were 0.5 and 0.987, respectively (Table 4).

**Table 4: Association of T3 and T4 hormone levels and length of stay**

Day 1	Length of stay		Total	p	OR (95%CI)
	< 7 days	≥ 7 days			
T3 levels					
Normal	12 (52.2%)	11(47.8%)	23 (100%)	0.500	1.396 (0.529-3.688)
Low	25 (43.9%)	32 (56.1%)	57 (100%)		
T4 levels					
Normal	18 (46.2%)	21 (53.8%)	39 (100%)	0.987	0.992 (0.412-2.391)
Low	19 (46.3%)	22 (53.7%)	41 (100%)		

Thyroid hormone levels on the first day of admission had a statistically significant relationship with sepsis outcome, where a p-value of T3 and T4 were 0.0001 and 0.014 respectively. Patients with normal T3 levels on the first day of admission were 24 times more likely to live than patients with low T3 levels, where patients with normal T4 levels were three times more likely to live than patients with low T4 levels (Table 5).

**Table 5: Association of T3 and T4 hormone levels and outcome**

Day 1	Outcome		P	OR (95%CI)
	Alive	Died		
<b>T3 levels</b>				
Normal	21 (91.3%)	2 (8.7%)	0.0001*	24.706 (5.205-117.272)
Low	17 (29.8%)	40 (70.2%)		
<b>T4 levels</b>				
Normal	24 (61.5%)	15 (38.5%)	0.014*	3.086 (1.239-7.686)
Low	14 (34.1%)	27 (65.9%)		

## Discussion

Thyroid hormones have an important role in the adaptation of metabolic functions to stress and critical illnesses such as sepsis and septic shock. Thyroid hormone will decrease at the onset of infection and will decrease as the disease progresses. Thyroid hormone levels will be normal again after the systemic disease cured [6]. A study in Turkey in 2004 showed decreased T3 and T4 levels in patients with sepsis [13]. Another study in Jakarta 2014 showed thyroid hormones would decrease in sepsis condition, especially T3 levels [14]. In this study, T3 levels were examined on the first day and > 72 hours of admission in 80 patients with sepsis, and decreased levels of T3 and T4 were found on the first day of admission.

At the beginning of illness there will be decreased in T3 levels due to the enzyme 5'-deiodinase defect which converts T4 to T3, decreased number of thyroid receptors mediated by interleukin 1 $\beta$ , the presence of thyroid binding protein inhibitors and increased in TNF- $\alpha$  [15]. Normal T3 levels during the acute phase might be due to a T3 decreased at the beginning of infection (36-72 hours) will return to normal after more than 72 hours, because after 72 hours post infection TSH will increase due to peripheral thyroid hormone secreted by the feedback mechanism of low T3 levels. This mechanism is called the recovery of metabolic activity [16]. Profile of thyroid hormones in this study showed a decreased in T3 and T4 on the first day of admission that described the acute phase of sepsis, and after > 72 hours T3 levels returned to normal in approximately 10% patients (71.2% to 61.2%), but not on T4 levels.

Medications in critically ill patients also affected thyroid function. Medications such as dopamine will lower TSH levels [17]. Dopamine in neonates and children had been reported to suppress

the function of the pituitary gland. [14], [18], [19] The use of catecholamines and noradrenaline is also reported to lower TSH [20]. The TSH levels reduction in critically ill patients will be proportional to the decreases in levels of T3 and T4 [17].

A study in Semarang 2014 showed there was no significant relationship between thyroid hormone levels in patients with sepsis and the outcome whether it was improvement or deterioration [21]. A study in Switzerland 2010 reported decreased in T3 could not be used as a prognostic marker [22]. Different results obtained from this study, there were a statistically significant relationship between thyroid hormone levels of T3 and T4 on the first day with sepsis outcome. But, many factors affected the outcome of patients with sepsis, for example, disease severity, nutritional status on admission, and sepsis itself whether it had progressed into severe sepsis [23].

That results were similar to this study, where patients with normal thyroid hormone levels on the first day of admission were more likely to live, normal T3 levels were 24 times, and normal T4 levels were three times more likely to live than low thyroid hormones.

Limitation of this study was no differentiation in the severity of sepsis and did not analyze patients with inotropic drugs which might affect thyroid hormone levels.

In conclusion, this study showed that euthyroid sick syndrome (ESS) was found in patients with sepsis. There was a significant relationship between thyroid hormone levels, T3 and T4, on the first day of admission with sepsis outcome.

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