INVESTIGATION OF HUMORAL IMMUNE DISORDERS IN CHILDREN WITH SEPSIS IN PEDIATRIC INTENSIVE CARE UNIT IN DA NANG HOSPITAL FOR WOMEN AND CHILDREN

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ABSTRACT

Background: *Sepsis has a complex pathophysiology with several diverse and nonspecific mechanisms. Objective: To investigate humoral immune disorders and some related factors in the prognosis of 28-day mortality in children with sepsis.*

Subjects and methods: *A descriptive cross-sectional study of 91children with sepsis treated in Pediatric Intensive Care Unit in Da Nang Hospital for women and children from January 2020 to January 2022.*

Results: *29 patients had low levels ofimmunoglobulins, in which the independent decrease of IgG concentrations accounted for the highest rate of 31.1%, the lowest was a decrease of bothIgM + IgA levels(3.5%). There was a statistically significant difference between septic shock, multiorgan dysfunction syndrome, white blood cell count, platelet count, albumin and procalcitonin with IgG and IgM levels, p < 0.05. There was no difference in 28-day mortality between two groups of low and high IgG levels after adjusting for some related factors (p>0.05).*

Conclusion: *There were humoral immune disorders in children with sepsis. However, the levels of immunoglobulinshad no prognostic values for 28-day mortality.*

Keywords: *immune globulin, mortality rate, sepsis.*

1. INTRODUCTION

Sepsis is one of the leading causes of death worldwide especially in children, with an estimated 7.5 million deaths annually [5]. Sepsis has a complex pathophysiology with diverse and nonspecific mechanisms,in which the immune dysregulation between inflammatory and anti-inflammatory responses contributes to Multiple Organ Dysfunction Syndrome (MODS) and death. Intravenous immunoglobulin (IVIG) insepsis support treatment remains controversial, several recent studies show that the use of IVIG does not reduce mortality and the evidences for efficacy are still limited. However, the tests are conducted in small groups and there are not many studies on the degree of humoral immune disorder in pediatric patients with sepsis. Stemming from the above issues, we conduct a study on this topic in order to investigate the status of humoral immunity disorders and some related clinical and subclinical factors and determine the theprognostic value of mortality in 28 days in pediatric patients with sepsis.

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2. RESEARCH SUBJECTS AND METHODS:

2.1. Research subject

Pediatric patients from 1 month to 16 years old diagnosed with sepsis treated at the Pediatric Resuscitation Department - Da Nang Hospital for Women and Children during the period from January 1, 2020 to January 1, 2022.

2.1.1. Inclusion criteria

* Focal or suspected infection with systemic inflammatory response syndrome is defined when at least 2/4 of the criteria are met, 1 of the 2 mandatory criteria is to have abnormal body temperature and peripheral leukocytes:

- Temperature > 38^{O}C or < 36^{O}C

- Tachycardia by age or bradycardia in children under 1 year old.

- Rapid breathing by age

- Leukocytes increase or decrease by age (>12,000/mm^3 or <4,000/mm^3) or leukocytes >10%.

* Diagnosis is confirmed when there are suspicious clinical and subclinical signs of sepsis mentioned above with positive blood culture [1], [5] .

2.1.2. Exclusion criteria

Pediatric patients with a history of confirmed immunodeficiency, nephrotic syndrome, malignancy, use of immunosuppressive drugs, corticosteroids, IVIG within 3 months.

2.2. Research methods

2.2.1. Research design: A cross - sectional descriptive study.

2.2.2. Sample size: Conveniencesampling

2.2.3. Data processing: Using SPSS 20.0 software.

2.2.4. Evaluationcriteria

Concentrations of IgG, IgM, IgA, IgE immune antibodies arecompared with the normal reference range by age according to the protocol ofMinistry of Health in 2015 [1], divided into 3 groups:

- Normal: mean antibody concentration (lower limit - upper limit) by age.

- Decrease: antibody concentration < lower limit by age.

- Increase: antibody concentration > upper limit by age.

Table1. IgA, IgG, IgM, IgE concentrations by age [1]

Age	IgA(g/l)	IgG(g/l)	IgM(g/l)	IgE (UI/ml)	
1 month old	0.1 - 0.3	4.6 - 8.6	0.2 - 0.7	Male	Female
3 months old	0.1 - 0.4	2.9 - 5.5	0.3 - 0.8	0 - 230	0 - 170
6 monthsold	0.2 - 0.6	2.3 - 4.4	0.3 - 0.9		
1 year old	0.2 - 0.8	3.3 - 6.2	0.5 - 1.3		
3 years old	0.3 - 1.2	4.8 - 8.9	0.5 - 1.5		
5 - 9 years old	0.4 - 1.6	5.5 - 11.5	0.5 - 1.5		
15 years old	0.5 - 2.0	6.5 - 12.3	0.5 - 1.6		

3. RESULTS

Through the study of 91 pediatric patients with sepsis from 1 month to 16 years old, treated at the Pediatric Resuscitation Department - DaNang Hospital for Women and Childrenfrom January 2020 to January 2022, we recorded the following results:

3.1. Status of humoral immune disorders in pediatric patients with sepsis

Table 2. Concentrations of immune antibodies in children with sepsis

Antibody concentration		n	Ratio %	Median (25%-75%)
IgG (mg/dl)	Decrease	23	25.3	585.0 (356.0 -818.3)
	Normal	33	36.3	
	Increase	35	38.4	
	Total	91	100.0	
IgM (mg/dl)	Decrease	13	14.3	78.0 (52.0 -133.5)
	Normal	54	59.3	
	Increase	24	26.4	
	Total	91	100.0	
IgA (mg/dl)	Decrease	14	15.4	52.0 (32.0 – 87.0)
	Normal	58	63.7	
	Increase	19	20.9	
	Total	91	100.0	
IgE (UI/ml)	Decrease	0	0.0	50.4 (7.3 – 137.9)
	Normal	81	89.0	
	Increase	10	11.0	
	Total	91	100.0	

Comment:

- The rate of decrease inconcentration ofIgG, IgM, IgA antibodiescompared to the reference values of the respective age groups was 25.3%; 14.3% and 15.4%,respectively.

- The rate of increase inconcentration ofIgG, IgM, IgA, IgE antibodies compared to the reference values of the respective age groups was 38.4%; 26.4%; 20.9% and 11.0%, respectively.

Table 3. Distribution of increased antibody concentration

Antibody concentration	n	%
IgG	12	26.8
IgM	2	4.4
IgA	4	8.9
IgE	2	4.4
IgG + IgM + IgA	8	17.9
IgM + IgA	1	2.2
IgG + IgA	2	4.4

IgG + IgM	6	13.3
IgG + IgM + IgA + IgE	3	6.7
IgG + IgM + IgE	2	4.4
IgG + IgA + IgE	1	2.2
IgM + IgE	2	4.4
Total	45	100.0

Comment:

There were 45 cases of increasedimmune antibody concentration, in which IgG alone accounted for the highest rate (26.8%), followed by simultaneous increase of IgG + IgM + IgA (17.9%).

Table 4. Distribution of decreased antibody concentrations

Decreasedantibody concentration	n	%
IgG	9	31.1
IgM	3	10.3
IgA	2	6.9
IgG+ IgM+ IgA	6	20.7
IgM + IgA	1	3.5
IgG + IgA	5	17.2
IgG + IgM	3	10.3
Total	29	100.0

Comment: **There were 29 cases of decreased immune antibody concentration, in which the decrease of IgG alone accounted for the highest rate of 31.1%, the lowest was the decrease of IgM + IgA (3.5%).**

3.2. Relationship between humoral immune disorders and some clinical and subclinical factors and treatment result

Table 5. Distribution of IgG antibody concentration according to shock status and MODS

Characteristics		IgG concentration						p
		Decrease		Normal		Increase		
		n	%	n	%	n	%	
Shock	Yes	11	47.8	7	21.2	2	5.7	0.001
	No	12	52.2	26	78.8	33	94.3	
	Total	23	100.0	33	100.0	35	100.0	
MODS	Yes	16	69.6	13	39.4	9	25.7	0.004
	No	7	30.4	20	60.6	26	74.3	
	Total	23	100.0	33	100.0	35	100.0	

Comment: **The rate of shock and MODS in the group with decreased IgG was higher than in the other 2 groups; the difference was statistically significant, p<0.05.**

Table 6. Distribution of IgM antibody concentration by shock and MODS

Characteristics		IgM. concentration						p
		Decrease		Normal		Increase		
		n	%	n	%	n	%	
Shock	Yes	5	38.5	14	25.9	1	4.2	0.03
	No	8	61.5	40	74.1	23	95.8	
	Total	13	100.0	54	100.0	24	100.0	
MODS	Yes	8	61.5	28	51.9	2	8.3	< 0.001
	No	5	38.5	26	48.1	22	91.7	
	Total	13	100.0	54	100.0	24	100.0	

Comment: The rate of shock and MODS in the group with decreased IgM was higher than that in the other 2 groups, the difference was statistically significant, $p < 0.05$.

Table 7. Distribution of IgG antibody concentration according to some subclinical characteristics

Characteristics Of Median (25%-75%)	IgG			p
	Decrease	Normal	Increase	
WBC (x 10^9/L)	10.6 (4.8-18.5)	13.6 (8.3 - 17.9)	17.1 (11.2 -22.4)	0.025
HGB (x 10^{12}/L)	95.6(88.0 -107.0)	96.8(83.0-105.0)	99.2(83.3-109.5)	0.832
PLT (x 10^9/L)	195.0(42.5-351.0)	238.0(130 - 420)	380.0(234-533)	0.007
Lactate (mmol/l)	3.6 (2.5 -6.6)	3.1 (2.2 - 4.4)	3.2 (2.5 – 4.1)	0.295
Albumin (g/l)	25.6 (23.1 – 26.7)	30.0 (26.3-33.0)	31.3 (26.9-32.8)	0.002
Procalcitonin (ng/ml)	51.7 (14.8 -100.0)	24.0 (5.4 - 91.9)	21.8 (5.5 – 47.7)	0.008
CRP (mg/ml)	144.0 (72.0-192)	72.0 (24.0-144)	72.0 (51.3 - 144)	0.160

Comment: There was a statistically significant difference between leucocyte count, platelet count, albumin and procalcitonin concentration with IgG antibody concentration, $p < 0.05$.

Table 8. Distribution ofIgM antibody concentration according to some subclinical characteristics

Characteristics Of Median (25%-75%)	IgM			p
	Decrease	Normal	Increase	
WBC (x 10^9/L)	8.3 (2.6 -17.9)	13.4 (9.1-19)	18.7(11.2–24.5)	0.033
HGB (x 10^{12}/L)	96 (78 - 105)	96.3 (84.4-105.9)	102.5(84.3-115)	0.625
PLT (x 10^9/L)	130 (31- 339)	244 (140 – 443)	371.5(261.5-514)	0.006
Lactate (mmol/l)	3.4 (2.8 – 5.8)	3.2 (2.4 – 4.8)	3.3 (2.3 - 4.3)	0.618

Albumin (g/l)	26.5 (22.6 -30.5)	27.8 (25 – 32)	32 (29.7 – 34)	0.007
Procalcitonin(ng/ml)	21.6(1.7 -50.7)	41.1 (12.6 -99.7)	14.8 (1.2 - 44.9)	0.014
CRP (mg/ml)	144 (72 – 192)	75.9 (36 -144)	72 (36 – 144)	0.543

Comment: There was a statistically significant difference between leucocyte count, platelet count, albumin and procalcitonin concentration and IgM antibody concentration, $p < 0.05$.

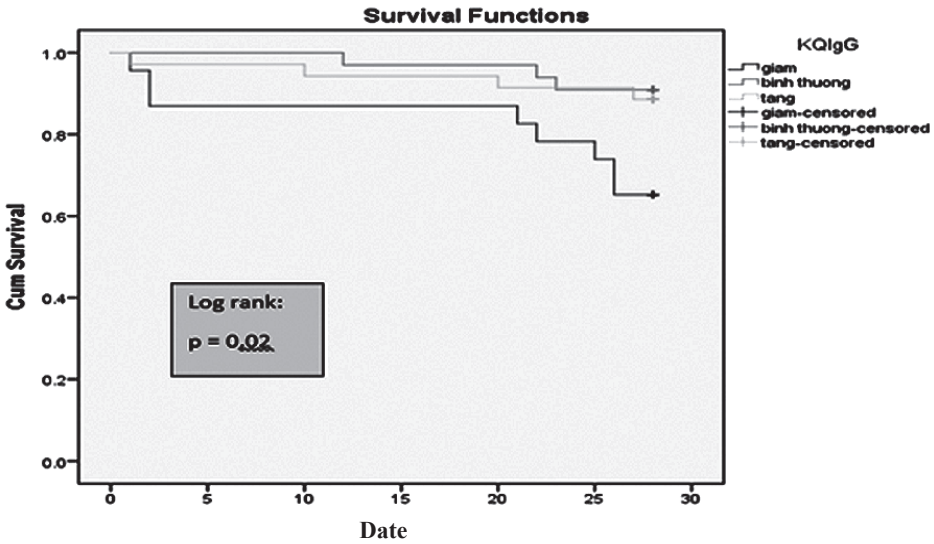

Chart 1. Kaplan–Meier curve of IgG antibody concentration and 28-day survival

Comment: The 28-daysurvival in the group with normal IgG antibody concentration was the highest, the lowest was in the group with decreased IgG, $p = 0.02$.

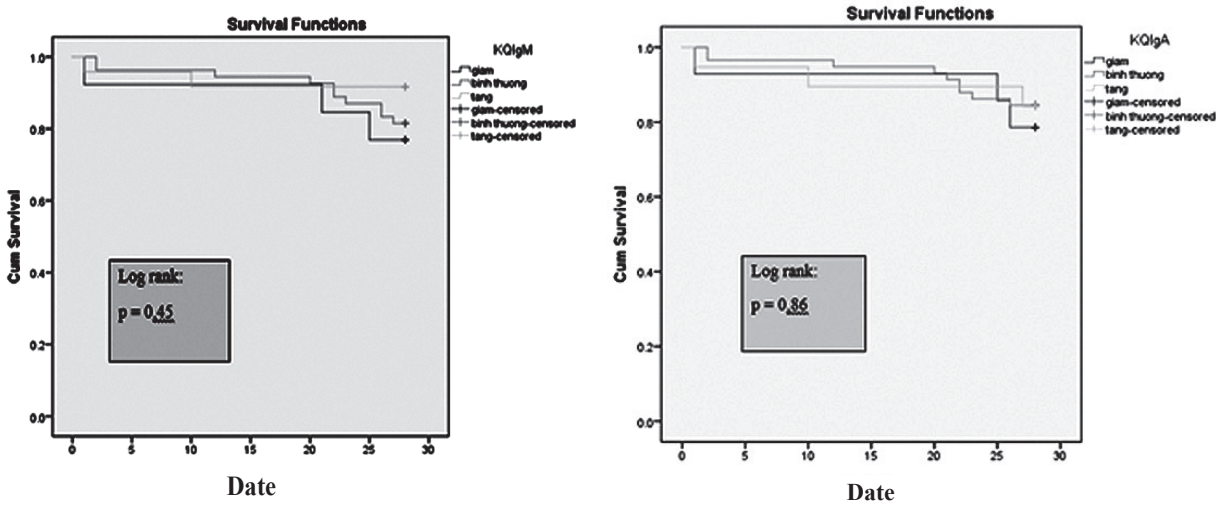

Chart 2. Kaplan-Meier curve of IgM antibody concentration; IgA 28-day survival

Comment: There was no statistically significant difference in 28-day survival between the groups of IgM and IgA antibody concentration with $p = 0.45$ and $p = 0.86$.

Table 9. Cox regression model in 28-day mortality

Factor		HR	95% CI	p
IgG	Decrease	2.61	0.56 - 12.11	0.22
	Increase	4.19	0.69 – 25.18	0.12
WBC		0.92	0.84 -1.02	0.11
PLT		1.0	0.99 – 1.01	0.87
Lactate		1.01	0.86 -1.19	0.85
Creatinine		0.98	0.97 – 1.01	0.14
Albumin		0.99	0.87 – 1.14	0.98
MODS		3.77	0.58 – 24.3	0.16
Shock		9.56	1.50 -60.84	0.01

Comment: There was no difference in 28-day mortality between the 2 groups with decreased and increased IgG concentration after adjusting some related factors, with p>0.05.

4. DISCUSSION

Our study showed that the number of cases of pediatric patients with decreased concentrations ofIgG, IgM, and IgA antibodies compared to the reference values of the respective age groups accounted for 25.3%, 14.3% and 15.4%, respectively. Moreover, the rate of increase in the concentration of IgG, IgM, IgA, IgE antibodies was 38.4%, 26.4%; 20.9% and 11.0%, respectively. In 29 cases with decreased immune antibody concentration, the decrease in IgG alone accounted for the highest rate (31.1%), followed by the decrease in both IgG + IgM + IgA (20.7%), the lowest was the decrease in IgM + IgA (3.5%). Some other studies also showed that there was a disorder of humoral immunity in patients with sepsis. The ALBIOS study showed that the rate of decreasein IgG, IgM, IgA antibody concentration was 63.6%, 22.9% and 8.9%, respectively, while the rate of increase in concentration of these antibodies accounted for 2.8%, 4.2% and 4.8%respectively[4].The study by Bermejo-Martin on patients with severe sepsis and septic shock, there were 27.9% decrease in IgG1, 39.2% decrease in IgM, 19.2% decrease in IgA, 17.4% decrease in IgG1+IgM and 10.5% decrease in IgG1+IgM+IgA [2].

According to the study result, the rate of shock and MODS in the group with decreased concentrations of IgG and IgM antibodies was also higher than that in the group with normal and increased concentrations (p < 0.05). The ALBIOS study also showed that the rate of septic shock in the group with decreased IgM and IgG was higher than that in the 2 groups with normal and increased concentrationss, the rate was 59.4%, p=0.017 and 62.6%, p = 0.038, respectively[4].

The results of tables 7 and 8 showed that there was a statistically significant difference of WBC, PLT, albumin and procalcitonin with IgG and IgM immune disorders; p < 0.05. The ALBIOS study also showed that there was a statistically significant difference between the concentrations of IgG, IgM and WBC, albumin (p < 0.05) [4].The result of Venet's study also showed that decreased IgG and IgM were correlated with a decrease in blood protein levels at days 1-2 and 3-4 of the disease [9].In patients with sepsis, there was a decrease in albumin due to an increase in catabolism, extravasation. In many studies on the mechanism of immunoglobulin decrease in patients with sepsis, some authors also proposed the same mechanism of immunoglobulin decrease with albumin, which may explain the relationship

between blood albumin concentration and disorder of immune antibody concentration in sepsis [2],[6],[7].

According to charts 1 and 2, when analyzing the Kaplan-Meier curve, we found that the change in IgG concentration was associated with a decrease in 28-day survival (p = 0.02). In addition, there was no difference between IgM and IgA concentrations with survival (p = 0.45 and p = 0.86). However, when conducting multivariate analysis by Cox regression model to perform adjustment for factors related to mortality (including: WBC, PLT, lactate, creatinine, albumin, MODS, shock), we found no difference in 28-day mortality in decreased or increased IgG group (p=0.22; HR=2.61 and p=0.12; HR=4.19, respectively), while septic shock had a prognostic value for mortality with p=0.01; HR=9.56. The relationship between immune antibody concentration and mortality in Sepsis patientswas controversial. The studyof Bermejo – Martin showed that low IgA, IgG and IgM concentration were associated with decreased survival rate (p=0.003; OR 5.27) [2]. According to Prucha's study: mortality in patients with sepsis, IgG <40 g/dl was higher than in patients with IgG from 40-60 g/dl (p = 0.001). Furthermore, the author's result showed that the mortality in patientssufferring from septic shock with decreased IgM was significantly higher than in patients with normal IgM, while there was no significant difference in the group of patients withsevere sepsis [7]. The study of Taccone also showed similar result with the mortality in the group of patients sufferring from septic shock with decreased IgG was 50%, the group with normal IgG was 0% (p = 0.01) [8]. However, more recently, result from the SBITs study demonstrated that decreased IgG was not correlated with survival in 543 patients with severe sepsis and septic shock (p>0.05). Furthermore, patients with high IgG>1190 mg/dl had a higher mortality (OR=1.68; CI: 1.01-2.81; p = 0.05) [3]. In the ALBIOS study, the Cox regression analysis also showed that the group with increased IgA and IgG concentrations was associated with a higher risk of 28-day mortality (p=0,001; HR=1,50 and p<0,001; HR=1.83, respectively)[4].

Thus, the failure to find an association between concentration of immune antibodies and 28-day mortality in our study, together with the dissimilarity in results among other studies may be due to differences in sample size, race and because other authors studiedmainly onadult subject and chose different age-specific normal values, especially in children, there have not been many exhaustive studies. Therefore, further studies, including larger numbers of pediatric patients, are needed to help clarify the influence of immune antibody concentrations and various factors on mortality and potential benefit of the immunoglobulin therapy in children with sepsis.

5. CONCLUSION

Through the study, we found that the rate of increase in the concentration of IgG, IgM, IgA, IgE antibodies compared to reference values of the respective age groups was 38.4%; 26.4%; 20.9% and 11.0%, respective. The number of cases of pediatric patients with decreased concentrations of IgG, IgM and IgA antibodies accounted for 25.3%, 14.3% and 15.4%, respectively. There was a statistically significant difference between shock status, MODS, leucocyte count, platelet count, albumin and procalcitonin concentrations and IgG and IgM antibody concentrations, p<0.05. The concentration of immune antibodies in pediatric patients with sepsis had no prognostic value for 28-day survival (p > 0.05).

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