

# The Role of IgM-Enriched Immunoglobulin (Pentaglobin) in Septic Patients with Hematological Disease

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## ABSTRACT

**Background:** Patients with hematological disease are 15 times more likely to develop sepsis than the general population. The patient with hematological disease and, mainly, those undergoing hematopoietic stem cell transplantation (HSCT), develop a severe secondary humoral immunodeficiency, with low serum levels of IgM, which may take more than a year to be restored.

**Materials and Methods:** This is a retrospective, controlled and observational study that analyzed 51 patients with underlying hematological disease, who were diagnosed with sepsis or septic shock during the study period, to evaluate whether IgM-rich Ig replacement decreases the 30-day mortality.

**Results:** Of the 51 patients, 35 patients received IgM-rich immunoglobulin (group A) and 16 (31%) received conventional therapy. Eleven (69%) patients in the control group were alive after 30 days compared to 11 (34%) patients in the intervention group,  $p=0.013$ .

**Conclusion:** There are no apparent benefits in the use of IgM-rich immunoglobulin in septic patients with hematological disease.

**Keywords:** Pentaglobin; Sepsis; Hematological disease

## INTRODUCTION

Patients with hematological disease are 15 times more likely to develop sepsis than the general population. Mortality from sepsis in this group of patients reaches 60%, more than double than the patients with solid tumors<sup>1-5</sup>. Much has been discussed about the search for adjuvant treatments for sepsis in patients with hematological disease, but little has been advanced.

It is known that immunoglobulins have a fundamental role in the control of the infectious condition, helping in the process of opsonization, toxin neutralization and activation of the complement system. Low serum immunoglobulin levels at the beginning of sepsis are associated with increased mortality. IgM immunoglobulin is, among immunoglobulins, the one responsible for the first fight against the pathogens in the bloodstream<sup>6</sup>.

The patient with hematological disease and, mainly, those undergoing hematopoietic stem cell transplantation (HSCT), develop a severe secondary humoral immunodeficiency, with low serum levels of IgM, and which may take more than a year to be restored and reach again its normal values<sup>6</sup>.

A systematic review in 2018 on the use of IgM-rich immunoglobulin in sepsis identified five studies that showed no benefit from the use of this substance, and nine showed some benefit from this adjunctive therapy in sepsis<sup>7</sup>. A recent meta-analysis on this same topic found 19 relevant studies and concluded that the use of immunoglobulin is associated with lower mortality, but also with a low quality of evidence<sup>8</sup>. It is worth mentioning that, of all the studies evaluated in the two above mentioned reviews, only one involved patients with hematological disease.

So far, it is concluded that immunoglobulin (Ig) enrichment with IgM in sepsis may be beneficial, however, this data has never been proved by robust studies and very little is known about the exact moment to start the replacement and its effect on individuals with hematological disease. Thus, the main objective of this study was to evaluate whether IgM-rich Ig replacement decreases the 30-day mortality of septic patients with underlying hematological disease.

## MATERIALS AND METHODS

This is a retrospective, controlled and observational study conducted at a tertiary care hospital in the city of Sao Paulo, Brazil. Through the review of electronic medical records, patients with hematological disease admitted to the Brazilian Institute for Cancer Control (IBCC) where developed sepsis was identified.

The definition of sepsis was based on Sepsis 3, which defines sepsis as a potentially fatal organ dysfunction caused by an unregulated immune response to an infection and septic shock such as sepsis accompanied by circulatory and cellular abnormalities capable of substantially increasing mortality<sup>9</sup>.

All patients over 18 years of age admitted to the Hematology unit of the IBCC who developed

sepsis and received immunoglobulin enriched with IgM between May 2018 and May 2019 were included. The control group was made up of patients over 18 years also diagnosed with sepsis, from the same unit and who did not receive immunoglobulin in the same period. The use of IgM-rich immunoglobulin was made according to the recommendation of the attending physician responsible for the patient.

The clinical data evaluated were: Age, gender, hematological disease, whether or not HSCT was performed, date of sepsis diagnosis, hospitalization length in the Intensive Care Unit (ICU), presumed sepsis focus, causative agent of sepsis, in addition to data from blood culture tests, creatinine, blood count, total bilirubins and patient fractions and data (gender, age, underlying disease, HSCT, SAPS3).

The main outcome of the study was 30-day mortality and secondary outcomes were discharge from the ICU and discharge from the hospital.

Qualitative characteristics were described according to the time of immunoglobulin use, discharge from the ICU, hospital discharge, 30-day survival and immunoglobulin use, applying absolute and relative frequencies and the association with the use of chi-square test or exact tests was verified (Fisher's exact test or likelihood ratio test). Quantitative characteristics were described according to the outcomes cited using summary measures (mean, standard deviation, median, minimum and maximum) and compared according to the outcomes using Mann-Whitney tests or Student's t-test. The analyzes were performed using SPSS for Windows version 22.0 and the tests were performed with a 5% significance level.

## RESULTS

Fifty-one patients were diagnosed with sepsis or septic shock during the study period. Of these, 35 patients received IgM-rich immunoglobulin (group A) and 16 (31%) received conventional therapy (group B). Among group A patients, the mean age was  $44 \pm 16$  years and the predominant gender was male (21 male and 14 female patients). The most prevalent primary diagnoses

were Acute myeloid leukemia in nine of the patients (25%), Acute lymphoid leukemia in six of the patients (17%) and Non-Hodgkin's lymphoma in 5 (14%) patients. Twenty-four patients (68%) had undergone allogeneic HSCT and six (17%) had autologous HSCT. The main infectious foci attributed to sepsis were: bloodstream infection in 12 (34%) patients, pulmonary infection in 8 (23%) patients and the focus remained undetermined in 10 (28%) cases. The mean SAPS 3 of admission of this group to the ICU was 71. Circulatory dysfunction was observed in 27 (77%) patients and respiratory in 21 (60%) and 21 (60%) patients had two or more organ dysfunctions. The etiological sepsis agent was identified in 23 (66%) patients in the group that received immunoglobulin, and in 18 (78%) the agent was bacterial. The main isolated agent among the bacteria was Klebsiella, which was observed in six (33%) cases. Fungal infection was identified in four patients, two cases (50%) of candida tropicalis, one (25%) with candida albicans and one (25%) with aspergillosis. The only patient with viral infection identified was cytomegalovirus infection (Tables 1 and 2).

Group B consisted of 16 patients with a mean age of  $54 \pm 18$  years and the predominant gender was female (10 patients). The most prevalent primary diagnoses were multiple myeloma in five patients (31%), non-Hodgkin's lymphoma in 3 (19%) patients. Acute lymphoid leukemia, Hodgkin's lymphoma and myelodysplasia appeared in an equal distribution, with two patients (12%) each. Six patients (38%) had undergone allogeneic HSCT and five of those (31%) had autologous HSCT. The main infectious foci attributed to sepsis were: urinary tract infection in 3 (19%) of the patients, indeterminate focus in three (19%) patients and lung in 8 (50%) patients. The mean SAPS 3 was 65. Circulatory dysfunction was observed in 4 (25%) patients and respiratory in 9 (56%). Five (31%) of the patients had two or more organ disorders. The etiological agent of sepsis was identified in seven (44%) patients in this group who did not receive immunoglobulin, and in five

(71%) the agent was bacterial. The main isolated agent among the bacteria was coagulase negative Staphylococcus, which was observed in three (19%) cases. Fungal infection was identified in one patient and candida tropicalis was isolated. The only patient with viral infection identified was Parainfluenza infection (Tables 1 and 2).

Comparing the two groups, a statistically significant difference was found in relation to patients who had undergone allogeneic HSCT (68% in group A vs. 37% in group B;  $p$  0.036); the mean total admission bilirubin was higher in group A ( $2.5 \times 0.8$ ;  $p$  0.002); In addition, group A patients had more circulatory dysfunction (77%  $\times$  25%,  $p$  <0.001), more bloodstream infection (34%  $\times$  0%,  $p$  0.003) but less pulmonary infection (23%  $\times$  50%,  $p$  0.003). (Tables 1 and 2).

Regarding the main outcome, 11 (69%) patients in group B were alive after 30 days compared to 11 (34%) patients in group A,  $p$  0.013. Assessing secondary outcomes, nine (56%) of the patients in group B were discharged from the ICU compared with 12 (34%) in group A,  $p$  = 0.139; seven (44%) patients in group B were discharged from the hospital compared to six (17%) patients in group A,  $p$  0.08. (Tables 1 and 2).

Analyzing group A in isolation, 23 (65%) patients received immunoglobulin in the first 24 hours of sepsis and 12 (35%) received it after this period. Comparing these two groups, it is noted that there was no significant difference in the following variables: mean age (44 years in the group which received immunoglobulin less than 24 hours versus 43 years in the group that received more than 24 hours,  $p$  = 0.85); Average SAPS3 (43 versus 53,  $p$  = 0.74), performance and type of transplant, underlying disease, sepsis focus and presence or absence of organ dysfunctions (Tables 3 and 4). On the other hand, the group that received immunoglobulin more than 24 hours after the diagnosis of sepsis tended to have less time between sepsis and transplantation (less than 100 days of HSCT: 78% in patients who received more than 24 hours  $\times$  32% in patients who received less than 24 hours,

p 0.04) and had a higher total bilirubin (4.19 x 1.67, p0.023) (Tables 3 and 4).

received immunoglobulin less than 24 hours compared to 8 (66%) patients who received more than 24 hours, p> 0.99. Analyzing patients who were discharged from the ICU, eight (34%) of those who received immunoglobulin within 24 hours of sepsis and four (33%) patients of those

Regarding the studied outcomes, there was no difference between groups. Among the patients there were 16 (69%) of them alive in 30 days who who received it after that period, p> 0.99. Regarding those discharged from the hospital, four patients (17%) of those who received immunoglobulin within 24 hours and two (16%) patients of those who received it after 24 hours, p> 0.99 (Table 5).

**Table 1.** Comparison between categorical variables in the Groups that received or not Pentaglobin

Variable	Group				Total		p
	Without Pentaglobin		With Pentaglobin		n	%	
	n	%	n	%			
Sex							0.135
Male	6	37.5	21	60.0	27	52.9	
Female	10	62.5	14	40.0	24	47.1	
Alogenic							0.036
No	10	62.5	11	31.4	21	41.2	
Yes	6	37.5	24	68.6	30	58.8	
Autologous							0.288*
No	11	68.8	29	82.9	40	78.4	
Yes	5	31.3	6	17.1	11	21.6	
Disease							0.192#
AML	1	6.3	9	25.7	10	19.6	
ALL	2	12.5	6	17.1	8	15.7	
MM	5	31.3	3	8.6	8	15.7	
NHL	3	18.8	5	14.3	8	15.7	
LH	2	12.5	4	11.4	6	11.8	
CLL	0	0.0	1	2.9	1	2.0	
ATLL	0	0.0	1	2.9	1	2.0	
Myelofibrose	0	0.0	3	8.6	3	5.9	
CML	0	0.0	1	2.9	1	2.0	
MDS	2	12.5	2	5.7	4	7.8	
SAA	1	6.3	0	0.0	1	2.0	
Organic disfunctions							0.154#
1	5	31.3	7	20.0	12	23.5	
2	5	31.3	21	60.0	26	51.0	
3	6	37.5	7	20.0	13	25.5	
Circulatory							<0.001
No	12	75.0	8	22.9	20	39.2	
Yes	4	25.0	27	77.1	31	60.8	

Respiratory							0.801
No	7	43.8	14	40.0	21	41.2	
Yes	9	56.3	21	60.0	30	58.8	
Kidney							0.296*
No	14	87.5	25	71.4	39	76.5	
Yes	2	12.5	10	28.6	12	23.5	
Liver							0.543*
No	16	100.0	32	91.4	48	94.1	
Yes	0	0.0	3	8.6	3	5.9	
Focus							0.003#
BSI	0	0.0	12	34.3	12	23.5	
Lung	8	50.0	8	22.9	16	31.4	
Abdomen	1	6.3	3	8.6	4	7.8	
Skin	1	6.3	1	2.9	2	3.9	
Central Nervous System	0	0.0	1	2.9	1	2.0	
Indeterminate	3	18.8	10	28.6	13	25.5	
UTI	3	18.8	0	0.0	3	5.9	
Bacteria							0.179
No	11	68.8	17	48.6	28	54.9	
Yes	5	31.3	18	51.4	23	45.1	
Fung							>0.999*
No	15	93.8	31	88.6	46	90.2	
Yes	1	6.3	4	11.4	5	9.8	
Virus							0.533*
No	15	93.8	34	97.1	49	96.1	
Yes	1	6.3	1	2.9	2	3.9	
Agent							0.400#
Klebsiella	2	12.5	6	17.1	8	15.7	
Pseudomonas	0	0.0	2	5.7	2	3.9	
Candida albicans	0	0.0	1	2.9	1	2.0	
Candida tropicalis	1	6.3	2	5.7	3	5.9	
Escherichia coli	0	0.0	1	2.9	1	2.0	
Staphylococcus aureus	3	18.8	3	8.6	6	11.8	
Without agent	9	56.3	12	34.3	21	41.2	
Enterococcus	0	0.0	2	5.7	2	3.9	
Haemophilus	0	0.0	1	2.9	1	2.0	
Stenotrophomonas maltophilia	0	0.0	2	5.7	2	3.9	
Serratia marcescens	0	0.0	1	2.9	1	2.0	
Cytomegalovirus	0	0.0	1	2.9	1	2.0	

Aspergillus ssp	0	0.0	1	2.9	1	2.0	
Parainfluenza	1	6.3	0	0.0	1	2.0	
Discharge from the ICU							0.139
No	7	43.8	23	65.7	30	58.8	
Yes	9	56.3	12	34.3	21	41.2	
Discharge from the hospital							0.080*
No	9	56.3	29	82.9	38	74.5	
Yes	7	43.8	6	17.1	13	25.5	
Alive in 30 days							0.013
No	5	31.3	24	68.6	29	56.9	
Yes	11	68.8	11	31.4	22	43.1	
<b>Total</b>	<b>16</b>	<b>100</b>	<b>35</b>	<b>100</b>	<b>51</b>	<b>100</b>	

Chi-square Test; \* Exact Fisher Test; \* Likelihood Ratio

AML: Acute Myeloid Leukemia; ALL: Acute Lymphoid Leukemia; ATLL: Adult T-cells Lymphoma/Leukemia; BSI: Bloodstream Infection; CLL: Chronic Lymphocytic Leukemia; CML: Chronic Myeloid Leukemia; ICU: Intensive Care Unit; LH: Hodgkin Lymphoma; MDS: Myelodysplastic Syndrome; MM: Multiple Myeloma; NHL: Non-Hodgkin Lymphoma; SAA: Severe Aplastic Anemia; UTI: Urinary tract infection.

**Table 2.** Comparison between numerical variables between groups that received or not Pentaglobin

Variable	Group	Average	SD	Median	Minimum	Maximum	N	p
Age	Without Pentaglobin	54.56	18.02	58	21	85	16	<b>0.050</b>
	With Pentaglobin	44.31	16.33	40	19	75	35	
	Total	47.53	17.37	47	19	85	51	
SAPS3	Without Pentaglobin	65.30	12.77	65	47	93	10	0.241
	With Pentaglobin	71.74	14.78	70	44	107	23	
	Total	69.79	14.32	69	44	107	33	
Leucocytes	Without Pentaglobin	5060.00	5600.04	3000	30	21000	16	0.775
	With Pentaglobin	6298.00	16700.51	380	10	83000	35	
	Total	5909.61	14120.96	940	10	83000	51	
Lactate (mmol/L)	Without Pentaglobin	2.16	1.21	2.05	0.78	4,7	16	0.091
	With Pentaglobin	3.68	4.90	1.8	0.6	26	35	
	Total	3.20	4.16	1.9	0.6	26	51	
Creatinine mg/dL	Without Pentaglobin	1.65	1.09	1.55	0.4	4,7	16	0.670
	With Pentaglobin	1.84	1.62	1.3	0.4	9	35	
	Total	1.78	1.47	1.5	0.4	9	51	
TB mg/dL	Without Pentaglobin	0.81	0.93	0.5	0.22	4	16	<b>0.002</b>
	With Pentaglobin	2.53	2.83	1.4	0.16	11	35	
	Total	1.99	2.52	1.02	0.16	11	51	

Student t-Test

TB: Total Bilirubin

SD: Standard deviation

**Table 3.** Comparison between categorical variables in Pentaglobin groups,  $\leq 24$  h or  $> 24$  h

Variable	Pentaglobin				n	Total	p
	$\leq 24$ h		$> 24$ h				
	n	%	n	%			
Sex							0.721
Male	13	56.5	8	66.7	21	60.0	
Female	10	43.5	4	33.3	14	40.0	
Alogenic							>0.999
No	7	30.4	4	33.3	11	31.4	
Yes	16	69.6	8	66.7	24	68.6	
Autologous							0.640
No	18	78.3	11	91.7	29	82.9	
Yes	5	21.7	1	8.3	6	17.1	
Transplant, 100 days							0.042
No	13	68.4	2	22.2	15	53.6	
Yes	6	31.6	7	77.8	13	46.4	
Disease							0.354*
AML	5	21.7	4	33.3	9	25.7	
ALL	3	13.0	3	25.0	6	17.1	
MM	2	8.7	1	8.3	3	8.6	
NHL	3	13.0	2	16.7	5	14.3	
LH	4	17.4	0	0.0	4	11.4	
CLL	1	4.3	0	0.0	1	2.9	
ATLL	0	0.0	1	8.3	1	2.9	
Myelofibroze	2	8.7	1	8.3	3	8.6	
CML	1	4.3	0	0.0	1	2.9	
MDS	2	8.7	0	0.0	2	5.7	
Organic Disfunctions							0.379*
None	3	13.0	4	33.3	7	20.0	
One	5	21.7	2	16.7	7	20.0	
Two or more	15	65.2	6	50.0	21	60.0	
Circulatory							0.091
No	3	13.0	5	41.7	8	22.9	
Yes	20	87.0	7	58.3	27	77.1	
Respiratory							0.477
No	8	34.8	6	50.0	14	40.0	
Yes	15	65.2	6	50.0	21	60.0	
Kidney							>0.999
No	16	69.6	9	75.0	25	71.4	
Yes	7	30.4	3	25.0	10	28.6	
Liver							0.266

No	22	95.7	10	83.3	32	91.4	
Yes	1	4.3	2	16.7	3	8.6	
Focus							0.602*
BSI	9	39.1	3	25.0	12	34.3	
Lung	5	21.7	3	25.0	8	22.9	
Abdomen	2	8.7	1	8.3	3	8.6	
Skin	1	4.3	0	0.0	1	2.9	
Central Nervous System	0	0.0	1	8.3	1	2.9	
Indeterminate	6	26.1	4	33.3	10	28.6	
<b>Bacteria</b>							>0.999
No	11	47.8	6	50.0	17	48.6	
Yes	12	52.2	6	50.0	18	51.4	
Negative Gram							>0.999
No	16	69.6	8	66.7	24	68.6	
Yes	7	30.4	4	33.3	11	31.4	
Fung							>0.999
No	20	87.0	11	91.7	31	88.6	
Yes	3	13.0	1	8.3	4	11.4	
Virus							>0.999
No	22	95.7	12	100.0	34	97.1	
Yes	1	4.3	0	0.0	1	2.9	
Agent							0.272*
Klebsiela	4	17.4	2	16.7	6	17.1	
Pseudomonas	2	8.7	0	0.0	2	5.7	
Candida albicans	1	4.3	0	0.0	1	2.9	
Candida tropicalis	2	8.7	0	0.0	2	5.7	
Escherichia coli	1	4.3	0	0.0	1	2.9	
Estafilococos aureus	1	4.3	2	16.7	3	8.6	
Without agent	7	30.4	5	41.7	12	34.3	
Enterococos	2	8.7	0	0.0	2	5.7	
Haemofilos	1	4.3	0	0.0	1	2.9	
Stenotrophomonas maltophilia	1	4.3	1	8.3	2	5.7	
Serratia marcescens	0	0.0	1	8.3	1	2.9	
Cytomegalovirus	1	4.3	0	0.0	1	2.9	
Aspergillus ssp	0	0.0	1	8.3	1	2.9	
<b>Total</b>	<b>23</b>	<b>100</b>	<b>12</b>	<b>100</b>	<b>35</b>	<b>100</b>	

Exact Fisher Test; \* Likelihood Ratio

AML: Acute Myeloid Leukemia; ALL: Acute Lymphoid Leukemia; ATLL: Adult T-cells Lymphoma/Leukemia; BSI: Bloodstream Infection; CLL: Chronic Lymphocytic Leukemia; CML: Chronic Myeloid Leukemia; LH: Hodgkin Lymphoma; MDS: Myelodysplastic Syndrome; MM: Multiple Myeloma; NHL: Non-Hodgkin Lymphoma



**Table 4.** Comparison between numerical variables in Pentaglobin groups, ≤ 24 h or > 24 h

Variable	Pentaglobin	Average	SD	Median	Minimum	Maximum	N	p
Age	≤ 24h	44.70	16.69	41	19	75	23	0.852*
	> 24h	43.58	16.33	38.5	21	71	12	
	Total	44.31	16.33	40	19	75	35	
SAPS3	≤ 24h	43.70	38.00	55	0	107	23	0.745
	> 24h	53.75	34.15	65	0	94	12	
	Total	47.14	36.54	62	0	107	35	
Leucocytes	≤ 24h	5281.30	17162.15	500	10	83000	23	0.905
	> 24h	8246.67	16330.75	290	10	50000	12	
	Total	6298.00	16700.51	380	10	83000	35	
Lactate (mmol/L)	≤ 24h	3.34	3.42	1.8	0.6	13	23	0.959
	> 24h	4.33	7.08	1.8	0.8	26	12	
	Total	3.68	4.90	1.8	0.6	26	35	
Creatinine mg/dL	≤ 24h	2.05	1.83	1.6	0.4	9	23	0.234
	> 24h	1.43	1.07	0.99	0.5	3,7	12	
	Total	1.84	1.62	1.3	0.4	9	35	
TB mg/dL	≤ 24h	1.67	2.02	1.1	0.16	10	23	<b>0.023</b>
	> 24h	4.19	3.47	3.4	0.6	11	12	
	Total	2.53	2.83	1.4	0.16	11	35	

Teste Mann-Whitney; \* Teste t-Student

TB: Total Bilirubin

SD: Standard desviation

**Table 5.** Main outcomes between the participants of the study

Variable	Discharge from the ICU				Total	p
	n	No %	n	Yes %		
Pentaglobin						>0.999
≤ 24h	15	65.2	8	34.8	23	
> 24h	8	66.7	4	33.3	12	
Total	<b>23</b>	<b>65.7</b>	<b>12</b>	<b>34.3</b>	<b>35</b>	
Variable	Discharge from the hospital				Total	p
	n	Não %	n	Sim %		
Pentaglobin						>0.999
≤ 24h	19	82.6	4	17.4	23	
> 24h	10	83.3	2	16.7	12	
Total	<b>29</b>	<b>82.9</b>	<b>6</b>	<b>17.1</b>	<b>35</b>	
Variable	Alive in 30 days				Total	p
	n	Não %	n	Sim %		
Pentaglobin						>0.999
≤ 24h	16	69.6	7	30.4	23	
> 24h	8	66.7	4	33.3	12	
Total	<b>24</b>	<b>68.6</b>	<b>11</b>	<b>31.4</b>	<b>35</b>	

Exact Fisher Test; \*Likelihood Ratio

## DISCUSSION

It is known that patients with hematological diseases undergoing chemotherapy treatment experience severe humoral and cellular immunodeficiency. The reconstitution of cellular immunity happens more quickly than the reconstitution of humoral immunity since neutrophils recover after three weeks of chemotherapy, lymphocytes around 100 days and immunoglobulin levels tend to normalize only after 180 days treatment. The rationale for adjuvant therapy with immunoglobulin in sepsis is not just the replacement of a substance in which the levels are reduced. It is known that, in patients with severe inflammatory diseases, Immunoglobulin is related to the blocking of Fc receptors of proinflammatory cells, leukocyte stimulation, and modulation of lymphocyte production of cytokines.<sup>10</sup>

The use of immunoglobulin during neutropenia, however, has its effectiveness impaired because in this period humoral immunodeficiency is not the only factor nor the main factor related to immunosuppression and the patient's susceptibility to infections.

There are two previous studies, to our knowledge, that evaluated the use of immunoglobulin in sepsis after chemotherapy and with significant impairment of humoral and cellular immunity.<sup>11,12</sup> In the work of Hentrich et al of 2006,<sup>12</sup> the inclusion criterion was for patients with less than a thousand leukocytes, unlike our study that included patients in the various stages of immunosuppression and where the average leukocyte was 5000, varying from 10 to 83 thousand.

Therefore, our group carried out the first study that aimed to evaluate the use of immunoglobulin in patients outside the context of neutropenia. The main conclusion was that the use of IgM-rich immunoglobulin did not show any benefit in the mortality of septic patients with hematological and non-neutropenic diseases.

It is important to note that in the subgroup analysis, the time gap between the onset of sepsis and the administration of immunoglobulin also did not seem to have an impact on the evaluated outcomes, but our results showed that

patients who received immunoglobulin, compared to those who did not, presented greater severity since most of them had previously undergone bone marrow transplantation, were identified with bloodstream infection and had two or more organ dysfunctions. This data makes us believe that, in order to guarantee a greater efficiency of the use of immunoglobulin, its administration should be instituted before the patient progresses to a very serious condition, since its administration in already more critical patients has not shown significant results. This reflection differs from that discussed in the work of Hentrich et al of 2006<sup>12</sup> in which the author comments that perhaps the use of the substance in more severe patients could be beneficial. The benefit of using immunoglobulin in septic patients with hematological disease remains open, requiring randomized and prospective studies and our group believes that the focus of the investigation to try to elucidate the role of immunoglobulin replacement in these patients is to evaluate its use early and outside neutropenia context. The present study has limitations because it is a retrospective study, with a small number of participants, developed in a single treatment center where a historical control group was used. In addition, the decision regarding the use of immunoglobulin was made by the attending physician, making the work susceptible to selection bias.

## CONCLUSION

Our work has not shown any significant benefit in the use of IgM-rich immunoglobulin in septic patients with hematological disease.

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