Original Article

Decrease in Gamma Delta T-Cell with Microbiologically Proven Infection in Septic Oncologic Children

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Objective: Predictors determining septic oncologic patients at high or low risk are helpful in guiding of antimicrobial management. As the number of γδ T-cells decreased in septic adult patients and the degree of change significantly associated with disease severity, the authors applied this concept and explored the association between the number of γδ T-cells and sepsis severity in oncologic children. The association of cell counts with microbiologically proven infection was also investigated.

Materials and Methods: Pediatric oncologic patients admitted with sepsis were prospectively enrolled. T-cell subset numbers were performed by flow cytometry method. Each episode of sepsis was categorized as severe sepsis versus non-severe sepsis or microbiologically proven infection versus non-microbiologically proven infection. Comparison of white blood cell count, lymphocyte count, and lymphocyte subset count between groups was performed.

Results: Forty-eight septic episodes were included. No association between the number of γδ T-cells and sepsis severity was noted. However, the percentage of γδ T-cell/total lymphocytes and absolute neutrophil count (ANC) were significantly lower in patients with microbiologically proven infection. A γδ T-cell greater than 3% of total lymphocytes and ANC greater than 100/uL are proposed as factors associated with non-microbiologically proven episodes in patients presenting with mild sepsis.

Conclusion: The authors proposed that percentage of γδ T-cells in septic oncologic patients, along with ANC may be used as a guide for antibiotic management in septic oncologic children.

Keywords: Sepsis, γδ T-cells, Oncologic children

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Sepsis remains a major complication encountered during chemotherapy for malignancy and is a leading cause of pediatric intensive care unit admission[1]. Appropriate, prompt, specific, and supportive treatments are key factors in patient survival[2]. Bone marrow suppression and breakdown of epithelial integrity contribute to increases in the probability of sepsis in oncologic patients. These patients usually receive broad spectrum antibiotics when presenting with sepsis; however, etiologic organisms may not be detected in many cases. As prolonged antibiotic use certainly leads to development of drug-resistant organisms and increase the cost of treatment, most clinicians face difficulty in deciding how long antibiotics should be prescribed and whether de-escalation is appropriated. Many markers have been developed to predict which patients are at low risk of infection and their antibiotic course can be shortened[3-5].

Innate immune cells are responsible for the frontline combat of invading organisms. Neutrophils are considered to be the main tool for this purpose. In addition, many innate lymphocytes, of which NKT-cells and gamma delta (γδ) T-cells are examples, also contribute to this role[6]. The function of these cells is not yet as clear as those lymphocytes participating in the adaptive immune response. The γδ T-cells have been shown to orchestrate immune regulation and fight against invading pathogens[7,8]. Moreover, γδ T-cells can directly retard micro-organism invasion by phagocytosis[9] and secretion of anti-microbial peptides[10]. Many studies have reported that decrease in number of these cells could be associated with

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severity of infection. In addition, these cells have been shown to function as lymphoid surveillance, recognizing cells injured by stress[11,12]. Since sepsis is the process of organ dysfunction caused by infection, the authors proposed that oncologic patients with severe sepsis or infection may have fewer innate lymphocytes when compared with patients with less severe episodes. The objectives of the study were to ascertain the association of the number of γδ T-cells as well as other T-cell subsets in pediatric oncological patients according to 1) the severity of sepsis, and 2) the category of infection (microbiologically proven or non-microbiologically proven).

Summary of main point

Percentage of γδ T-cell/total lymphocyte is a promising parameter to differentiate microbiologically proven episodes from non-microbiologically proven episodes in oncologic patients presenting with sepsis.

Materials and Methods

Patients

Oncologic patients aged 1 month to 18 years old hospitalized at the Department of Pediatrics, Ramathibodi Hospital, between December 2013 and January 2015 and diagnosed with sepsis were enrolled. After admission, blood cultures were drawn and sent for analysis. Urine cultures, stool cultures, sputum cultures, and chest radiographs were done on the discretion of the attending physicians. All patients participating in the study provided written informed consent. Patients with concomitant HIV infection or autoimmune diseases and those who had undergone stem cell transplant were excluded. The study was approved by the Ramathibodi Hospital Ethics Committee.

Definitions

Sepsis was defined as systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection[13]. Sepsis severity was categorized into severe sepsis and non-severe sepsis (mild sepsis). SIRS was defined as SIRS diagnosed by the presence of at least of the two following items, one of which must be abnormal temperature or leukocyte count, body temperature higher than 38.5°C or lower than 36°C, heart rate more than 2SD of the normal value for age, respiratory rate more than 2SD of the normal value for age, or a white blood cell count elevated or depressed for age, or immature neutrophils higher than 10%.

Severe sepsis was defined as sepsis with at least one of the following, cardiovascular organ dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions. In the present study, patients who were not in the severe sepsis group were classified into non-severe sepsis (mild sepsis) group.

Types of infection were categorized as 1) microbiologically proven episode defined as patients presenting with sepsis and positive bacterial or fungal cultures from normally sterile sites or positive cultures of pathogenic organisms from any sites with signs of infection, and 2) non-microbiologically proven episode defined as patients presenting with signs indicative of infection but without confirmed positive cultures.

Patients diagnosed with sepsis were treated at the discretion of the attending physicians. Demographic data, pediatric risk of mortality scores III (PRISM III), and pediatric logistic organ dysfunction scores (PELOD) were collected. Blood was drawn on day 0, 1, and 2 after admission for T-cell subset enumeration. Ethylenediaminetetraacetic acid (EDTA)-treated peripheral blood was stained with fluorochrome-tagged antibodies diluted in 1:100 against cell surface antigens. All antibodies were derived from eBioscicence (San Diego, USA). Stained cells were lysed by red blood cell lysis buffer (BD Biosciences, San Jose, USA) and analyzed by flow cytometer. The percentage of each T-cell subset in total lymphocytes was calculated using Flowjo v.10 (Ashland, USA).

Statistical analysis

The percentage of each T-cell subset between each group was compared using the Mann-Whitney U test. Associations between groups of patients and other parameters were determined using the Chi-square or Fisher's exact test.

Results

Demographic data

Between December 2013 and January 2015, 36 oncological patients, totaling 48 episodes of sepsis, at the Department of Pediatrics, Ramathibodi Hospital, were enrolled. The data analyses flow chart is shown in Figure 1 and demographic data in Table 1. There were 36 patients, 17 boys, and 19 girls. Of the 48 septic episodes, 42% occurred in male patients, 65% had hematologic malignancy, 77% had neutropenia, 98% had lymphopenia, and 83% had been receiving granulocyte-colony stimulating factor (G-CSF) before enrollment. Death occurred in only one patient who had *Escherichia coli* sepsis.

Thirty-five percent of the episodes were

Table 1. Demographic data of enrolled patients

	Severe sepsis (n = 17) n (%)	Non-severe sepsis (n = 31) n (%)	p-value	Microbiologically proven (n = 16) n (%)	Non-microbiologically proven (n = 32) n (%)	p-value
Age (year), Median (1st, 3rd quartile)	7 (4, 11)	6 (3.5, 10)	0.611	6 (1.8, 8.8)	7 (4, 8.8)	0.468
Male	8 (47.1)	12 (38.7)	0.575	7 (43.8)	13 (40.6)	0.836
Hematologic malignancy	11 (65.7)	20 (64.5)	0.990	13 (81.3)	18 (56.3)	0.088
Lymphopenia+	17 (100)	30 (96.8)	1.000	16 (100)	31 (96.9)	1.000
Neutropenia$	15 (88.2)	22 (71.0)	0.173	14 (87.5)	23 (71.9)	0.225
Receiving G-CSF	15 (88.2)	25 (80.6)	0.500	14 (87.5)	26 (81.3)	0.701
Receiving steroid	11 (64.7)	7 (22.6)	0.004	8 (50.0)	10 (31.3)	0.206
PRISM, Median (1st, 3rd quartile)	14 (11, 16)	8 (6.5, 9)	0.000	11.5 (8.8, 15.5)	9 (7, 15.5)	0.015
PELOD, Median (1st, 3rd quartile)	6 (4, 11)	4 (2, 4)	0.000	5.5 (3.8, 7)	4 (2.8, 7)	0.030

G-CSF=granulocyte-colony stimulating factor; PRISM=pediatric risk of mortality score; PELOD=pediatric logistic organ dysfunction score

+ Lymphopenia: absolute lymphocyte count less than lower normal limits for age

$ Neutropenia: absolute neutrophil count less than 500 cells/uL

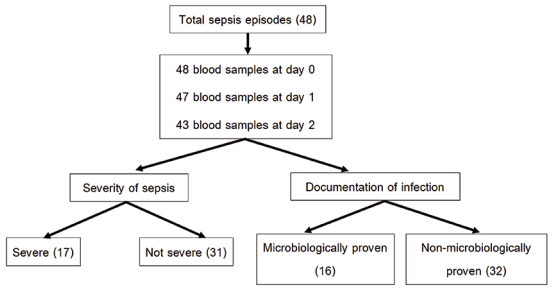

Figure 1. Flow chart of enrolled patients.

categorized as severe sepsis, and 33% of the episodes had microbiologically proven episode. The organisms isolated and sites of infection are summarized in Table 2. Severe sepsis associated significantly with microbiologically proven episode, as shown in Table 3. Accordingly, microbiologically proven episodes had higher PELOD and PRISM III scores on admission day compared with non-microbiologically proven episodes (Table 1).

Association between blood cell count and sepsis severity

Absolute neutrophil count (ANC), total lymphocyte count, each T-cell subset count, and percentage of each subset on admission day are shown in Table 4. No difference in any cell population between the severe sepsis and the non-severe sepsis groups was observed. Total γδ T-cell number and percentage/total lymphocytes of these cells were not different between patients who required ICU stay, inotrope use, or ventilator use, and those did not. Correlations between the number of γδ T-cells or percentage of γδ T-cell/total lymphocytes on admission day and PRISM III score or PELOD score were not observed (data not shown).

Table 2. The organisms isolated and sites of infection in the study

Sites of infection	Organisms isolated	Total number
Bacteremia/candidemia	*Streptococcus mitis*	1
	Staphylococcus aureus (MSSA)	2
	Escherichia coli	2
	Candida tropicalis	1
Catheter related blood stream infection	*Escherichia coli*	1
	Klebsiella pneumonia	1
	Pseudomonas aeruginosa	1
	Acinetobacter baumanii	1
Pneumonia	*Pseudomonas aeruginosa*	1
Urinary tract infection	*Escherichia coli*	1
	Klebsiella pneumonia	1
	Enterobacter cloacae	1
	Enterococcus spp.	1
Gastroenteritis	*Salmonella* group O	1

MSSA=meticillin-susceptible *S. aureus*

Table 3. Association between disease severity and documentation of infection

	Non-microbiologically proven n (% of total episodes)	Microbiologically proven n (% of total episodes)	Chi-square p-value
Non-severe sepsis	25 (81)	6 (19)	0.006
Severe sepsis	7 (41)	10 (59)	

Table 4. Total cell number at admission day in each episode category

	Sepsis severity Median (1st, 3rd quartile)		Microbiologically proven infection Median (1st, 3rd quartile)	
	Non-severe	Severe	No	Yes
Total white cell count (cells/uL)	390 (135, 1095)	430 (210, 850)	435 (267, 1150)	250 (128, 857)
Absolute neutrophil (cells/uL)	132 (23, 691)	52 (19, 170)	160 (46, 687)	35 (13, 93)*
Absolute lymphocyte (cells/uL)	164 (69, 583)	235 (69, 389)	257 (46, 550)	174 (94, 537)
Total CD3 count (cells/uL)	149 (39, 437)	230 (55, 366)	181 (36, 373)	106 (63, 473)
Total CD4 count (cells/uL)	62 (19, 147)	85 (22, 172)	77 (18, 162)	62 (31, 176)
Total CD8 count (cells/uL)	42 (12, 257)	77 (22, 156)	54 (10, 201)	54 (24, 191)
Total DN count (cells/uL)	17 (7, 38)	19 (6, 40)	23 (8, 47)	10 (5, 29)
Total γδ T cell count (cells/uL)	8 (4, 21)	9 (1, 30)	8 (4, 24)	4 (1, 22)
Total CD19 count (cells/uL)	1 (0, 14)	1 (0, 44)	1 (0, 12)	1 (0, 25)
Total CD56 count (cells/uL)	7 (4, 27)	10 (7, 30)	10 (5, 23)	7 (4, 14)
Total CD3/CD56 count (cells/uL)	2 (1, 7)	3 (2, 5)	2 (1, 10)	3 (1, 4)
% lymphocyte	60 (20, 84)	86 (31, 95)	58 (18, 83)	90 (62, 90)*
% CD3	87 (64, 93)	85 (71, 97)	83 (67, 92)	92 (70, 98)
% CD4	37 (27, 50)	39 (21, 47)	37 (25, 40)	39 (33, 49)
% CD8	33 (19, 40)	30 (24, 40)	32 (20, 40)	31 (22, 39)
% DN	11 (4, 14)	9 (5, 10)	12 (9, 14)	5 (4, 8)*
%γδ T cell	5 (2, 9)	4 (2, 8)	6 (3, 10)	3 (1, 6)*
% CD19	1 (0, 2)	0 (0, 7)	1 (0, 4)	0 (0, 6)
% CD56	7 (4, 11)	5 (3, 8)	9 (5, 11)	4 (2, 8)
% CD3CD56	2 (1, 4)	1 (1, 3)	2 (1, 4)	1 (1, 2)

Total cell counts are cell count per microliter of EDTA blood. % lymphocyte is the percentage of lymphocyte population in total white blood cell count, otherwise is the percentage of lymphocyte subset in total lymphocyte count.

DN=double negative T cells (CD3+, CD4–, CD8–)

* Statistically significant difference from non-microbiologically proven group ($p<0.05$)

Association between blood cell counts and microbiologically proven episode

The microbiologically proven episode group had a lower ANC compared with the non-microbiologically proven group. No difference in total cell counts of any lymphocyte subsets was noted between the two groups. Of note, the total number of double negative T-cells and total γδ T-cells was lower in microbiologically proven episodes, but neither reached a statistically significant difference. Regarding the percentage of the lymphocyte subset population, on day 0, the microbiologically proven group had a significantly lower percentage of double negative T-cells (12% versus 5% of total lymphocytes) and γδ T-cells (6% versus 3% of total lymphocytes) compared with the non-microbiologically proven group. The percentage of CD56 cells was also lower in the microbiologically proven group, but the difference did not reach

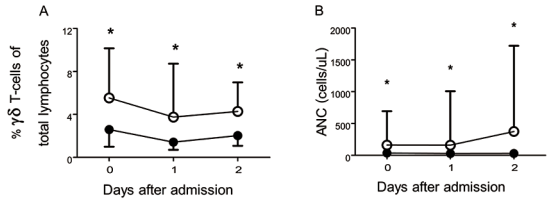

Figure 2. Time course of %γδ T-cell/total lymphocytes (A) and ANC (B).

Values represent median with first quartile (downward bars) or third quartile (upward bars)

* Statistically significant difference between microbiologically-proven ● and non-microbiologically proven ○ groups

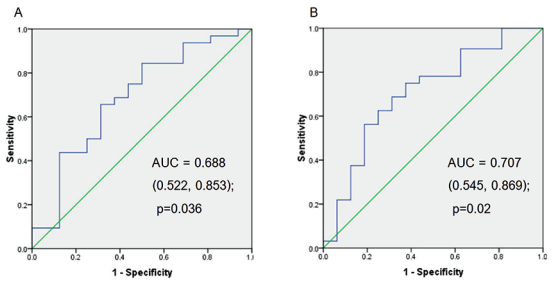

Figure 3. ROC of %γδ T-cell/total lymphocytes (A) and ANC (B) on admission day in discriminating between microbiologically proven and non-microbiologically proven episodes.

Values in the parentheses represent 95% CI

statistical significance.

The dynamic change in percentage of γδ T-cells is shown in Figure 2A. The microbiologically proven group had a significantly lower percentage of γδ T-cells compared with the non-microbiologically proven group from day 0 through day 2 of enrollment. Percentage rate changes of γδ T-cells between days were not different between these two groups (data not shown). Interestingly, the non-microbiologically proven group tended to show more marrow recovery as ANC in this group started to rise at day 2 after admission (Figure 2B). Receiver operating characteristic (ROC) curves of percentage of γδ T-cell/total lymphocytes and ANC on day 0 were constructed to show how well these values can be used to distinguish between microbiologically proven and non-microbiologically proven groups in patients admitted with sepsis (Figure 3). The AUC of both parameters was around 0.7, which is believed to show the fairness of the test's performance.

The authors next sought to determine whether ANC and γδ T-cell percentage on admission day could be useful in differentiating the microbiologically proven group from the other. Generally, oncological patients presenting with severe sepsis will be given empirical broad-spectrum antibiotics. However, those presenting with mild sepsis are possible candidates for narrower spectrum antibiotics. The present study showed that patients presenting with mild sepsis were 5.95 times less likely to have microbiologically proven episode compared with those patients presenting with severe sepsis. When ANC on admission day was also considered, patients with mild sepsis and ANC greater than 100/uL were 5.44 times less likely to have microbiologically proven episodes. Patients with mild sepsis and a percentage of γδ T-cells greater than 3% of total lymphocytes were nine times less likely to have microbiologically proven episodes. Interestingly, if both ANC and percentage of γδ T-cells were considered together, the eight patients with mild sepsis who had ANC greater than 100/uL and percentage of γδ T-cells greater than 3% of total lymphocytes belonged to the non-microbiologically proven group (Table 5). Of note, seven out of eight patients in this group did not have a definite source of infection, while the remaining one patient was suspected to have viral pneumonia. In the patients with mild sepsis, using ANC greater than 100/uL together with percentage of γδ T-cell greater than 3% of total lymphocytes yielded sensitivity of 32% in detection of non-microbiologically proven episodes, and specificity of 100% in excluding microbiologically proven episodes. This means that if antibiotics were given to mild septic patients with either ANC less than 100/uL or percentage of γδ T-cell lower than 3% of total lymphocytes, 74% of patients may have received unnecessary antibiotics. However, when patients had both ANC greater than 100/uL and percentage of γδ

Table 5. Odds ratio of oncologic patients who were likely to be in non-microbiologically proven group

	OR	95% CI	p-value
Not severe#	5.95	1.60 to 22.15	0.006
Not severe + ANC >100/uL	5.44	1.06 to 28.01	0.030
Not severe + %γδ >3%	9.00	1.75 to 46.30	0.004
Not severe + ANC >100/uL + %γδ >3%*	-	-	-

OR=odds ratio; CI=confidence interval; ANC=absolute neutrophil count

Not severe: patients in non-severe (mild) septic group

* Could not be calculated as all patients in this group belonged to non-microbiologically proven group

Table 6. Performance of using ANC and %γδ T-cell/total lymphocytes to predict non-microbiologically proven episodes in oncologic patients presenting with mild sepsis

	Non-microbiologically proven	Microbiologically proven	
Both ANC >100/uL and %γδ >3%	8	0	PPV=100%*
ANC <100/uL or %γδ <3%	17	6	NPV=26% (95% CI 21.24 to 31.59)
	Sensitivity=32% (95% CI 14.95 to 53.5)	Specificity=100% (95% CI 54.07 to 100)	

ANC=absolute neutrophil count; PPV=positive predictive value; NPV=negative predictive value; CI=confidence interval

* 95% CI cannot be calculated

T-cell greater than 3%, nearly all of them had a non-microbiologically proven episodes (Table 6).

Discussion

To the authors knowledge, the present study is the first study to demonstrate the association between percentage of γδ T-cell/total lymphocytes and microbiologically proven infection in oncological patients. Oncologic patients presenting with sepsis proven to be culture-documented infections tended to have a lower percentage of γδ T-cells compared with those who did not. The implication of the finding is that enumeration of this cell is promising in the prediction of culture-documented infections in this group of patients.

The fact that the percentage of γδ T-cells was different between microbiologically proven and non-microbiologically proven episodes but not different between mild and severe sepsis episodes implies that the response of γδ T-cells depends upon the presence of microbes but not the severity of host response. Another possibility is that a lower amount of γδ T-cells predisposes patients to microbial invasion but not to severity of immune response. The results also showed that the percentage of double negative T-cells was lower in microbiologically proven episodes than in non-microbiologically proven episodes. The γδ T-cells are actually a member of double negative T-cells. Decrease in the percentage of double negative T-cells may represent the decrease in the percentage of γδ T-cells. Another possibility is that the percentages of other innate T-cells which are also members of double negative T-cells may decrease in microbiologically proven episodes as well.

Several reasons may explain why patients with microbiologically proven infections had a lower percentage of γδ T-cells. Since γδ T- cells can fight against bacteria[9,10], their suppression after chemotherapy can predispose patients to bacterial infection. The study performed in mice demonstrated that γδ T-cells were indeed essential in the recruitment of neutrophils[14]; therefore, suppression of γδ T-cells can lead to poor neutrophil infiltration at infection sites. Another reason is that a higher amount of γδ T-cells may be a sign of bone marrow recovery. The authors' results showed that patients who did not have microbiologically proven infections had better marrow recovery as they had higher ANC. However, more evidence is needed to support the correlation between the amount of γδ T-cells and marrow recovery. Furthermore, another reason for lower percentage of γδ T-cells is that the presence of microbes may be responsible for γδ T-cell suppression in septic patients. Some evidence has suggested that pathogens could induce T-cell apoptosis on T cell receptor activation[15] or via caspase activation[16,17]. Many studies have shown the beneficial role of γδ T-cells in infection related complications. Perko et al found that pediatric post-hematopoietic stem cell transplant patients with a higher number of γδ T-cells had lower infection rates compared to those with lower number[18]. Venet et al found that adult patients with septic shock had a lower percentage of γδ T-cells compared with healthy adults, and 70% of patients in that study had microbiologically proven infection[19]. Another study of adult patients showed that the total number of γδ T-cells was markedly reduced in severe septic patients and 36% of them were culture positive[20]. However, only one study showed that γδ T-cell frequency increased in septic patients[21].

The implication of the present study is that the percentage of γδ T-cells may be used for the prediction of episodes of microbiologically proven infection in oncologic patients presenting with sepsis. Undoubtedly, patients presenting with severe sepsis require broad spectrum antibiotics as soon as possible. In these patients, the source of infection should be sought[22], and the predictors may not be helpful in this regard. The duration of antibiotic treatment also depends upon patient response and the results of

cultures. For oncologic patients presenting with only mild sepsis, the predictors could be helpful in many aspects of antibiotic administration. Patients may be treated on an outpatient basis with oral antibiotics, they may not require very broad-spectrum antibiotics empirically, or their antibiotic treatment course may be shortened if all cultures are proven to be sterile. The present study showed that if patients presenting with mild sepsis had a γδ T-cell percentage greater than 3% of total lymphocytes and ANC greater than 100/uL upon admission, it was less likely they had microbiologically proven episode. These patients may not need very board spectrum antibiotics empirically. Using these two parameters on the first day of admission should be very helpful in decision making regarding antibiotic administration and planning the monitoring of oncological patients presenting with only mild sepsis. However, following this step could lead to the unnecessary administration of broad-spectrum antibiotics in 74% of patients presenting with mild sepsis. Given the fact that these patients are very vulnerable to severe complications if infection does occur, a short duration of broad-spectrum antibiotics followed by de-escalation would be preferable.

The limitation of our study was the small sample size. This reduced the power to detect the difference in many parameters. The total number of γδ T-cells tended to be lower in microbiologically proven episodes, but this did not reach a statistically significant difference. The authors also observed that NK cells (CD56+ cells) tended to be lower in microbiologically proven episodes as well. However, these findings would serve as a good preliminary result for further validating steps requiring a larger sample size. In addition, it would also be worthwhile combining other known factors[23-26] proven to be correlated with infection to better shape the prediction model. Another important point is that a new definition of sepsis has been launched recently[22]. The Sequential Organ Failure Assessment (SOFA) score was proposed for better defining sepsis episodes. However, these criteria have not yet been defined for pediatric populations. A new definition of sepsis for pediatric populations would lead to a new categorization of pediatric patients suspected of having sepsis. Factors proposed to associate with sepsis severity may be changed according to new sepsis definition.

Conclusion

In conclusion, to our knowledge, the present study is the first report demonstrating that septic pediatric oncological patients with microbiologically proven episodes had a lower percentage of γδ T-cell/total lymphocyte compared with those without microbiologically proven episodes. Delayed γδ T-cell reconstitution after chemotherapy or infection inducing suppression of these cells may be responsible for this. The implication of our study is that, along with ANC greater than 100/uL, a γδ T-cell percentage greater than 3% of total lymphocyte on the first day of admission in pediatric oncologic patients presenting with mild sepsis indicates a very low possibility of microbiologically proven infection. Narrower spectrum antibiotics may be considered, and the duration of the antibiotic course can also be shorter. This should lessen the course of treatment.

What is already known on this topic?

Fever in pediatric oncologic patients are very concerning as this may represent serious bacterial infection. However, some episodes are considered mild and caused by non-infectious inflammatory reaction. Currently, broad spectrum antibiotics have been generally used when oncologic patients present with fever. There have been no good markers used to discriminate between culture positive and culture negative episodes leading to prolonged antibiotic use. Previous studies showed that adult patients with sepsis had lower γδ T-cell count. These cells can function as innate immune cells and can eliminate bacteria. It is therefore interesting to see whether γδ T-cell number is changed in pediatric oncologic patients who are proved to have bacterial infection.

What this study adds?

This study showed that septic pediatric oncologic patients who had microbiologically proven infection had lower percentage of γδ T-cell/total lymphocyte compared with those who had non-microbiologically proven infection. In addition, patients in microbiologically proven infection also had lower absolute neutrophil count. Using these two parameters together, an absolute neutrophil count greater than 100/uL, a percentage of γδ T-cell greater than 3% of total lymphocyte on the first day of admission in pediatric oncologic patients presenting with mild sepsis indicates a very low possibility of microbiologically proven infection. This can help physician streamline antibiotic use in these patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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