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Effects of early enteral nutrition on T helper lymphocytes of surgical septic patients

A retrospective observational study

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Abstract

The aim of this study was to investigate the effects of early enteral nutrition (EEN) on T helper lymphocytes and the subpopulations ratios of surgical septic patients.

We performed a retrospective study including 107 eligible patients from February 2014 to December 2015. Patients were divided into EEN, delayed enteral nutrition (DEN), or total parenteral nutrition (TPN) group according to the duration before enteral feeding. Th1, Th2, Th17, and Treg lymphocyte percentages were collected on days 3, 7, and 14 after admission. The disease severity and clinical outcome variables were also recorded.

The Th1, Th17 percentages, and Th1/Th2, Th17/Treg ratios of EEN group were significantly lower than those of DEN or TPN group on the 14th day after admission ($P < .05$). Compared with TPN, DEN might have a tendency to decrease the Th1 and Th17 percentages. EEN could improve the disease severity and clinical outcomes of septic patients, however, no difference on 28-day mortality was found between EEN and DEN group.

EEN could improve the dysregulation of Th1/Th2 and Th17/Treg ratios during early stage of sepsis. Compared with DEN, EEN could improve the disease severity and clinical outcomes, but not decrease the 28-day mortality of surgical septic patients.

Abbreviations: APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, DEN = delayed enteral nutrition, EEN = early enteral nutrition, EN = enteral nutrition, ICU = intensive care unit, MODS = multiple organ dysfunction syndrome, SOFA = sequential organ failure assessment, TPN = total parenteral nutrition.

Keywords: early enteral nutrition, enteral nutrition, immune, sepsis, T helper lymphocytes

1. Introduction

Sepsis is a severe systemic response to infection. Despite the surviving sepsis guidelines having recommended a great deal of therapeutic principles of this fatal disease, its mortality is still about 20% to 50% in adults.[1,2] Recent studies have indicated that immune dysregulation might play a principal role in the development of sepsis, and this dysregulation (immune excess or suppression) is closely associated with T helper lymphocytes during both early and late stage of sepsis.[3–5] Based on the differentiation and different phenotypes, T helper lymphocytes are divided into 4 subtypes: Th1, Th2, Th17, and regulatory T (Treg) cells, induced by naive CD4+ T lymphocytes. Wu et al[6] found that higher Th1 and Th17 differentiation was associated with higher survival rate in severe sepsis. Whereas Li et al[7] reported that the proportions of Th1/Th2 and Th17/Treg were inversed in patients with sepsis and septic shock. Accordingly, some researchers advised using immunomodulatory therapy for septic patients.[8–10] However, no consensus on this strategy has been reached because of conflicting results of experiments and clinical studies.

As an essential treatment for sepsis, enteral nutrition (EN), especially early enteral nutrition (EEN), could modulate inflammatory response, increase antioxidant activity, and decrease the incidences of multiple organ dysfunction syndrome (MODS) and infectious complications of patients in intensive care units (ICUs).[11–13] Therefore, we infer that EEN might regulate the immune function of critical ill patients. Our previous clinical trial[14] also showed that EEN could moderate the excessive immune response during early stage of severe acute pancreatitis. However, whether the improvement of immune function is associated with the alterations of Th1/Th2 and Th17/Treg ratios is unknown. Moreover, the effects of EEN on Th1/Th2 and Th17/Treg ratios of sepsis are still unclear. Therefore, in view of our ICU population (mostly surgical sepsis), the present study aimed to investigate the effects of EEN on Th1, Th2, Th17, and Treg subpopulations, as well as Th1/Th2 and Th17/Treg ratios of surgical septic patients.

2. Materials and methods

2.1. Patients

From February 2014 to December 2015, all adult patients (age ≥18 years) admitted to the surgical ICU of our department,

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Nanjing First Hospital, with sepsis diagnosed and ICU stay ≥48 hours, were included in this clinical retrospective study. The diagnostic criteria of sepsis was accordant with the surviving sepsis guidelines.[1,2] Patients with chronic organ dysfunction (e.g., hepatic or renal dysfunction), coagulation dysfunction, diabetes mellitus, malnutrition or immunodeficiency, and patients who had received artificial nutrition (enteral or parenteral nutrition) before admission were all excluded. The study was approved by the institutional review board of our hospital, whereas written informed consent was waived because this was a retrospective study. Figure 1 showed the flow diagram of the participants. All patients received specialized treatments for sepsis[1] such as intensive monitoring, fluid resuscitation, oxygen administration or mechanical ventilation, antimicrobial therapy, vasopressor administration, glucose control, renal replacement therapy, and so on.

2.2. Nutrition protocols

A nasogastric or nasojejunal feeding tube (size 10F, Flocare, Nutricia Ltd, Wuxi, China) was placed routinely before starting enteral feeding. In EEN group, the enteral nutrition was established during the first 48 to 72 hours after admission. Patients in delayed EN (DEN) group received EN on the 4th day or later after admission. Peptide-based formula (Peptisorb, Nutricia Ltd.) was used in the first 24 to 48 hours, and if patients were tolerant, whole protein formula (Nutrison Fibre, Nutricia Ltd.) would be performed subsequently. The goal intake was determined as 20 to 25 kcal/kg/d and protein need was calculated as 1.5 g/kg/d.[14] The feeding rate was initiated at 15 to 20 mL/h and increased gradually by 15 to 20 mL every 6 to 8 hours, using a pump.[15] If patients were intolerant because of high gastric residual volume (>500 mL), abdominal distension or diarrhea, we would slow down the feeding rate, dilute the feedings concentration, or use prokinetic agents to improve intestinal motility.

Parenteral nutrition would be used if EN was contraindicated or if patients could not tolerate EN for 3 days or more.[16] The caloric intake of parenteral nutrition was calculated as 20 to 25 kcal/kg/d and the calorie:nitrogen ratio was determined as 120–150:1.[16,17] Fifty to seventy percentages of total energy intakes were provided by glucose, whereas the supply of lipids was based on serum triglyceride levels. Moreover, sufficient vitamins, electrolytes, insulin, and trace elements were also added into the intravenous solution.

2.3. Data collection

Our study was a retrospective reanalysis of the data from a previous clinical observational trail about sepsis and nutrition (not yet published) in our center. On admission, the baseline parameters including age, sex, body mass index (BMI), and etiology of sepsis were recorded. The acute physiology and chronic health evaluation II (APACHE II) scores and sequential organ failure assessment (SOFA) scores were recorded on days 1, 3, 7, and 14 after admission. The Th1, Th2, Th17, and Treg lymphocyte percentages, Th1/Th2 and Th17/Treg ratios in peripheral blood were also collected on days 3, 7, and 14 after admission. The flow cytometry measures of T lymphocytes were performed in our hospital central laboratory. After human peripheral blood mononuclear cells were isolated, the proliferation analysis of Th1, Th2, and Th17 cells subpopulations were executed by using the BD Pharmingen™ Human Th1/Th2/Th17 Phenotyping Kit (BD Biosciences, Franklin Lakes, New Jersey),

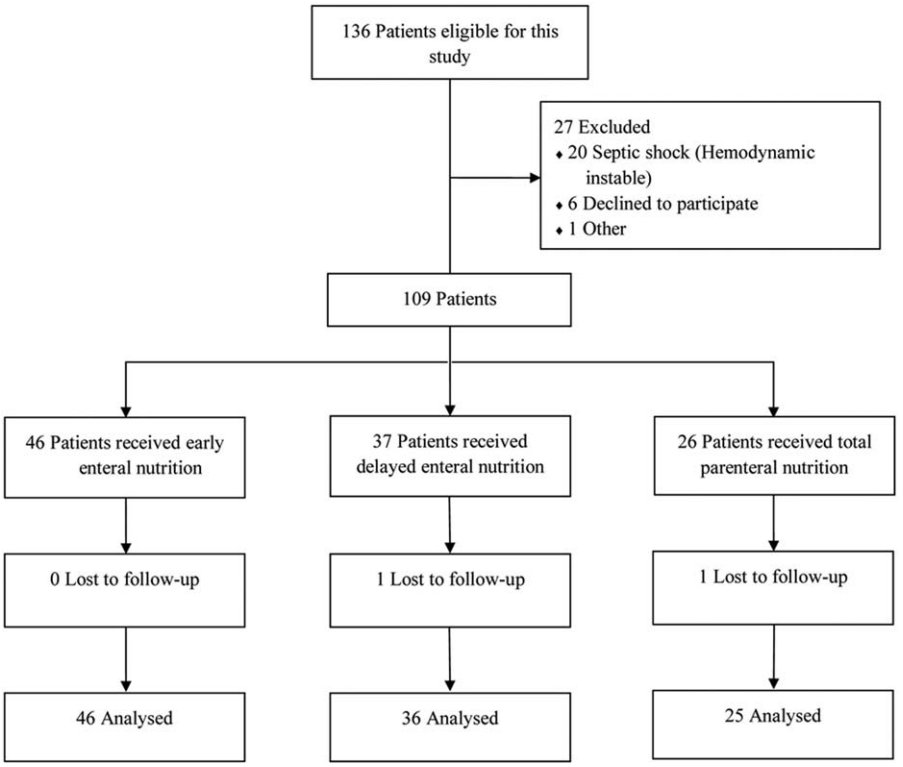

Figure 1. The flow diagram of participants.

and Treg cell subpopulation was detected by using CD4 (antigen presenting cells), CD25 (PE), and Foxp3 (Fluorescein isothiocyanate) labelled antibodies (e-Bioscience, USA). In addition, the clinical outcome variables including 28-day mortality, duration of ICU stay, and the incidence of MODS were also recorded.

2.4. Statistical analysis

Kolmogorov–Smirnov test was performed initially to test normal distribution of the data. Abnormal distributed data were presented as medians (interquartile ranges) and compared by Mann–Whitney *U* test or Kruskal–Wallis test. Normal distributed data were presented as means ± standard deviation and compared by *t* test or one-way variance analysis. The comparisons of 2 paired groups were performed by paired *t* test or Wilcoxon signed-rank test. Categorical variables were expressed as absolute numbers or in percentages, and were analyzed using chi-squared test or Fisher exact test. Survival curves to 28 days after admission were calculated by Kaplan–-Meier method and compared with log-rank test. IBM SPSS Statistics (version 20.0, NY) software was used for statistical analysis. $P < .05$ was considered statistically significant. The statistical methods of this study were reviewed by Qiao Liu, Biostatistician from the Center for Disease Control and Prevention of Jiangsu Province, China.

3. Results

As shown in Fig. 1, a total of 107 eligible patients with sepsis were included in this clinical observational study during the research period. Of these patients, 46 (43.0%) cases received EEN, 36 (33.6%) cases received DEN, and 25 (23.4%) cases received total parenteral nutrition (TPN). The demographic data and clinical parameters of the patients on admission were shown in Table 1. Thirty-six (33.6%) patients developed MODS, and 28 (26.2%) patients died of MODS or infectious complications during hospital stay.

3.1. Th1, Th2, Th17, and Treg lymphocyte percentages

Figure 2A and B showed the differences of Th1 and Th2 lymphocyte percentages among the 3 groups on days 3, 7, and 14 after admission. No differences about Th2 percentages were found during the 14 days ($P > .05$), whereas the Th1 percentages of EEN group were significantly lower than those of the other groups on the 14th day after admission ($P < .001$). Moreover, the Th1 percentages of DEN group were also lower than those of TPN group on day 14 (16.9 [15.0–21.1] vs 19.1 [17.3–22.8], $P = .038$).

Similar to the trends of Th1 and Th2 percentages, the Th17 percentages of EEN group were significantly lower than those of the other groups on the 14th day after admission ($P = .01$), whereas no difference about Treg percentages was found during the 14 days ($P > .05$) (shown in Fig. 3A, B). Though no differences were found, the Th17 percentages of DEN group on day 14 were still numerically lower than those of TPN group (3.7 [1.9–5.7] vs 4.5 [3.1–6.4], $P = .089$).

These phenomena revealed that EEN could decrease the Th1 and Th17 lymphocyte percentages in the early stage of sepsis, and DEN might have similar effects during the same stage.

3.2. Th1/Th2 and Th17/Treg ratios

Figures 2C and 3C showed the differences of Th1/Th2 and Th17/Treg ratios among the 3 groups on days 3, 7, and 14 after admission. No differences about both Th1/Th2 and Th17/Treg ratios were found during the first week after admission ($P > .05$), whereas the 2 ratios of EEN group were significantly lower than those of the other groups on the 14th day ($P = .004$ and .046, respectively). However, no differences were found between DEN and TPN group ($P > .05$) on the 14th day of admission.

3.3. The severity markers and outcome variables

At 28 days after admission, 5 of 46 patients (10.9%) in EEN group, 8 of 36 patients (22.2%) in DEN group, and 15 of 25 patients (60%) in TPN group died (relative risk, 2.976; 95% confidence interval, 1.793–4.940; $P < .001$). No difference in the survival probability was found between EEN group and DEN group during the 28 days after admission ($P = .149$) (shown in Fig. 4). The survival probability in TPN group was significantly lower than that of the other groups ($P < .001$ and $P = .002$, respectively) (shown in Fig. 4).

As Table 2 shown, the APACHE II and SOFA scores of EEN group were significantly lower than those of the other groups on the 14th day ($P < .01$). Meanwhile, the APACHE II scores of DEN group were also lower than those of TPN group (15 [12–17] vs 18 [15–20], $P = .013$). The MODS incidences and ICU days of TPN group were significantly higher than those of the other groups during hospital stay ($P < .05$). In addition, the ICU days of EEN group were also lower than those of DEN group (6 [4–10] vs 8 [5.5–14], $P = .031$), whereas no differences about MODS

Table 1

Demographic data and clinical parameters on admission.

	EEN group (n = 46)	DEN group (n = 36)	TPN group (n = 25)	*P*
Age, y	71 (64.5–77)	72.5 (60–82.5)	74 (62.5–82)	.594
Sex, male:female	26:20	22:14	14:11	.894
Etiology, n (%)				
Abdominal infection	28 (60.9%)	24 (66.7%)	18 (72.0%)	.630
Thoracic/pulmonary infection	13 (28.2%)	9 (25.0%)	6 (24.0%)	.909
Urinary infection	4 (8.7%)	2 (5.5%)	1 (4.0%)	.786
Mucocutaneous infection	1 (2.2%)	1 (2.8%)	–	>.99
BMI, kg/m^2	23.0 (21.0–24.6)	22.8 (21.0–25.5)	23.7 (22.3–25.2)	.391
APACHE II scores	20 (17–24)	19 (16–22)	21 (15–25)	.573
SOFA scores	8.5 (6–10)	8 (7–11)	9 (6–12.5)	.876

APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, DEN = delayed enteral nutrition, EEN = early enteral nutrition, SOFA = sequential organ failure assessment, TPN = total parenteral nutrition.

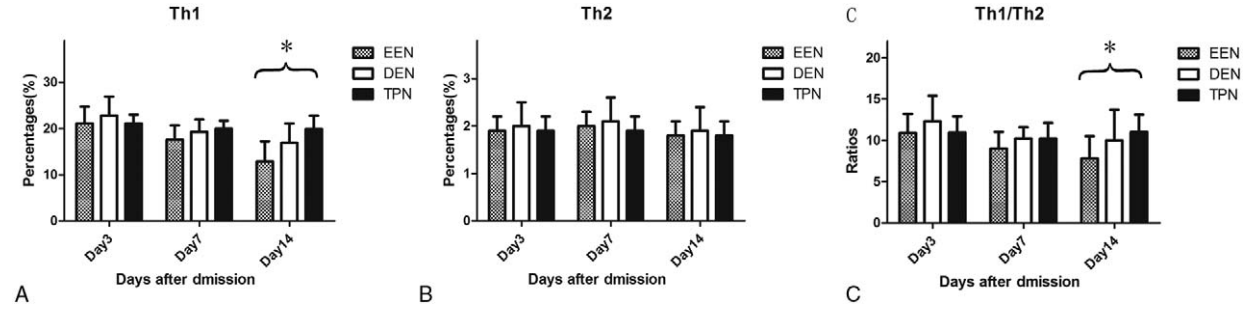

Figure 2. The differences of Th1, Th2 lymphocyte percentages, and Th1/Th2 ratios among the 3 groups. DEN = delayed enteral nutrition, EEN = early enteral nutrition, TPN = total parenteral nutrition. $^{*}P < .05$.

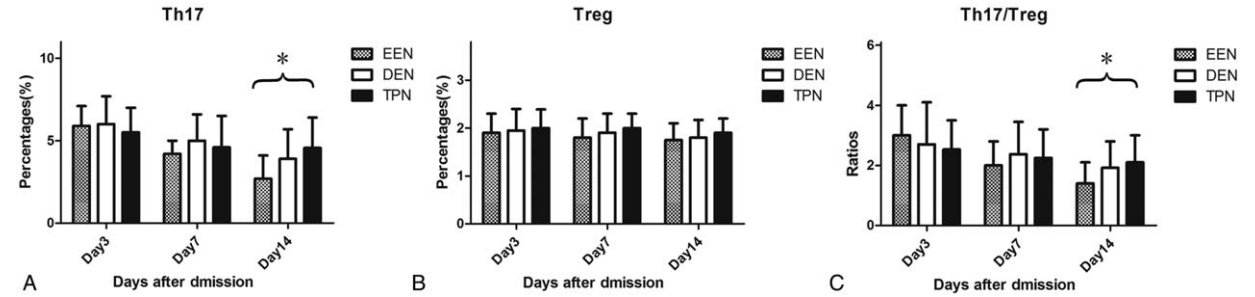

Figure 3. The differences of Th17, Treg lymphocyte percentages, and Th17/Treg ratios among the 3 groups. DEN = delayed enteral nutrition, EEN = early enteral nutrition, TPN = total parenteral nutrition. $^{*}P < .05$.

incidences were found between the 2 groups (10/46 vs 11/36, $P = .364$).

4. Discussion

The clinical retrospective observational study explored the effects of EEN on Th1, Th2, Th17, and Treg subpopulations, as well as Th1/Th2 and Th17/Treg ratios of surgical septic patients. Our results demonstrated that EEN could decrease the Th1, Th17 lymphocyte percentages, and Th1/Th2, Th17/Treg ratios during the early stage of sepsis. Compared with TPN, DEN also had a tendency to decrease Th1 and Th17 percentages. Moreover, EEN could improve the disease severity and clinical outcomes of septic patients. The 28-day mortality of EEN or DEN group was lower than that of TPN group, whereas no difference about mortality was found between the former 2 groups.

A growing number of studies have found that immune (especially cellular immunity) dysregulation was a considerable cause of sepsis.[5,18,19] It is well known that the immune reactions of sepsis can be characterized by pro-inflammatory or anti-inflammatory response during different stages, and T helper lymphocytes are considered to be closely associated with these processes. Wu et al[6] reported that the absolute counts of the 4 subpopulations were decreased in non-survivors with severe sepsis, whereas Li et al[7] found that the transcription factors and related cytokines of the 4 subpopulations were increased in patients with sepsis and severe sepsis. These inconsistent findings suggested that T helper lymphocytes might be changing dynamically in different severity of sepsis. Our study found that both Th1 and Th17 cells percentages as well as Th1/Th2 and Th17/Treg ratios were decreased during the 2 weeks after admission, and these results were consistent with the consensus

Table 2

Clinical severity markers and outcome variables.

		EEN group (n = 46)	DEN group (n = 36)	TPN group (n = 25)	*P*
APACHE II scores	Day 3	19 (16–22)	19 (17–22)	21 (15–22)	.773
	Day 7	17 (14–21)	18 (16–21)	20 (16–22)	.203
	Day 14	13 (9–15)	15 (12–17)	18 (15–20)	<.001
SOFA scores	Day 3	8 (7–10)	8 (7–11)	9 (6–11)	.472
	Day 7	7 (6–9)	7 (6–10)	8 (5–10)	.112
	Day 14	5 (3–6)	5.5 (4–7)	7 (4–8)	.001
MODS, n (%)		10 (21.7%)	11 (30.6%)	15 (60%)	.004
ICU stay, days		6 (4–10)	8 (5.5–14)	13 (7.5–22)	<.001

APACHE II = acute physiology and chronic health evaluation II, DEN = delayed enteral nutrition, EEN = early enteral nutrition, ICU = intensive care unit, MODS = multiple organ dysfunction syndrome, SOFA = sequential organ failure assessment, TPN = total parenteral nutrition.

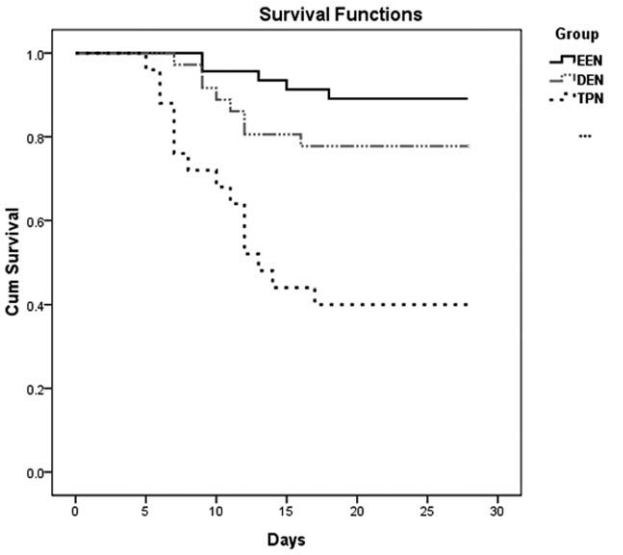

Figure 4. The survival curves to 28 days after admission. DEN = delayed enteral nutrition, EEN = early enteral nutrition, TPN = total parenteral nutrition.

that Th1 and Th17 lymphocytes mainly played an important role in pro-inflammatory effects.[18]

Now that the excessive immune response is the main pathophysiological process of sepsis in the early stage, researchers are trying to use immunosuppressive treatment for this fatal disease.[18,20,21] Ono et al[8] reported that removal of Tregs by hemoperfusion with polymyxin B-immobilized fiber could improve the immune suppression in patients with sepsis. Though the immunotherapy might represent future advance in the treatments of sepsis, no consensuses have been obtained due to inconsistent findings in previous studies. In addition, excessive immunosuppression might induce the development of subsequent infectious complications in the late period of sepsis. Given the above, the effects of immunotherapy in sepsis are still indefinite, and further clinical studies are also required.

The intestinal tract is a main immune organ supplying an original barrier against pathogenic microorganism.[22] Recent studies reported that gut immune reaction was closely associated with EN, and lack of enteral stimulation could lead to immune suppression.[23,24] Our previous study also found that EEN could improve the immune imbalance of patients with severe acute pancreatitis,[14] but the underlying mechanisms of this finding were not established. In this study, we investigated the potential mechanisms of EEN influencing immune function of sepsis from the perspective of T helper lymphocytes, and we found that EEN could decrease the Th1 and Th17 lymphocyte percentages as well as Th1/Th2 and Th17/Treg ratios during the early stage of sepsis. Similarly, a clinical pilot study performed by Tan et al[10] showed that enteral administration of probiotics would adjust the Th1/Th2 imbalance and improve clinical outcomes in patients with traumatic brain injury. These phenomena revealed that T helper lymphocytes might be new targets for immunotherapy in sepsis.

The 4 T helper lymphocytes subtypes are divided into 2 sorts according to different pathological effects: I. Pro-inflammatory lymphocytes—Th1 and Th17 cells; II. Anti-inflammatory lymphocytes—Th2 and Treg cells.[5,7] Th1 and Th17 cells can express some pro-inflammatory factors, such as IL-6, IL-17, and TNF-α, whereas Th2 and Treg cells mainly express anti-inflammatory factors, such as IL-10, IL-4, and TGF-β. As shown in our results, the immune imbalance of early sepsis mainly manifested as excessive activation of Th1 and Th17 lymphocytes, however, both Th1/Th2 and Th17/Treg ratios were decreased after EEN treatment, and DEN also had a similar tendency. Li et al[7] observed that the ratios of Th17/Treg in patients with sepsis and septic shock were inversed, and obvious immunosuppression was developed in septic shock. Our results of TPN group were accordant with their findings, but the Th2 and Treg lymphocytes percentages in EEN group were not decreased. Therefore, we concluded that EEN might release the excessive inflammatory response of sepsis without subsequent immunosuppression.

In accordance with previous reports,[1,24,25] the present study also found that EEN could improve the disease severity and clinical outcomes of septic patients. We inferred that the improvement of disordered Th1/Th2 and Th17/Treg ratios might be an important reason for these findings. However, no difference about 28-day mortality was found between EEN and DEN group, probably because this small sample study was not powered to find a difference in mortality.

Some limitations of this study should be discussed. Because of our single-center design and small sample size, the results might be inconclusive for a confirmative conclusion, and the accuracy should be verified by large-scale clinical studies. Moreover, because the study was not based on pathophysiological models, the exact mechanisms of EEN on T helper lymphocytes should be tested by more basic experiments. Finally, because our immune parameters were only collected for 2 weeks, the later effects of EEN on sepsis should also be tested by future randomized controlled clinical trials.

In conclusion, this study suggested that EEN could improve the dysregulation of Th1/Th2 and Th17/Treg ratios during early stage of sepsis. Compared with TPN, DEN also had a tendency to decrease the Th1 and Th17 percentages. Moreover, EEN could improve the disease severity and clinical outcomes of septic patients, however, no difference on 28-day mortality was found between EEN and DEN group. In addition, more basic experiments or large-sample clinical randomized controlled trials were needed to verify our results.

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