Original Article

The efficacy of parenteral fish oil in critical illness patients with sepsis: a prospective, non-randomized, observational study

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Background and Objectives: To investigate the clinical outcomes in septic patients receiving parenteral fish oil. **Methods and Study Design:** A prospective, non-randomized, observational clinical study was carried out in 112 patients with sepsis from March, 2013 to May, 2015 in the surgical intensive care unit (SICU) of a tertiary-referral hospital. The patients were put into one of two groups; either the control or the study group. Patients received the standard treatment of sepsis based on guidelines in the control group. In the study group, patients received parenteral nutrition (PN) containing fish oil. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, the length of ICU and hospital stay, duration of mechanical ventilation, mortality, and re-admission into the ICU were recorded. Tumor necrosis factor (TNF)-α and procalcitonin (PCT) levels were also evaluated. **Results:** The study group showed a significant reduction for all-cause mortality (20.0% vs 10.0% in study and control groups, p=0.034) and APACHE II score on day 5 (p=0.015), day 7 (p=0.036) and day out of SICU (p= 0.045) compared with the control group. The study group tended to show a shortened length of stay in the ICU compared to the control group. However, TNF-α and PCT level, 28 d mortality, the length of hospital stay and the duration of mechanical ventilation did not show statistical differences between the two groups. There were no drug-related adverse effects shown during the study. **Conclusions:** PN with fish oil is probably safe and may improve clinical outcome in critical ill patients with sepsis.

Key Words: parenteral fish oil, sepsis, critical illness, clinical study, nutrition

INTRODUCTION

Sepsis is a common syndrome induced by infection, and has a high mortality and morbidity especially in critical ill patients. The incidence of sepsis is estimated to be 288 per 100,000 persons each year and is on the rise worldwide.[1] The mortality rate of sepsis is as high as 17%, with approximately 5.3 million deaths annually.[1] A total of 20 billion dollars each year is spent on patients with sepsis.[2] Bundle management of sepsis patients has been demonstrated to increase the survival rate.[3] However, new approaches to improve patients' clinical outcomes are still required to reduce the mortality. Since sepsis causes systemic inflammatory response syndrome (SIRS), cytokines might perform important roles in the disease development.[4] Anti-inflammatory and antioxidant treatment should get more attention, and be further investigated.

Fish oil is a kind of marine-derived n-3 polyunsaturated fatty acid (PUFA) with the constituents of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Previous studies have showed that fish oil has anti-inflammatory activity.[5] Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient suggest that fish oil use should be considered in critically ill patients with sepsis.[6] Over the past several years, fish oil administration in sepsis has been explored widely in animals and humans. The findings suggest that fish oil may have the potential to regulate leukocyte function and modulate cytokine release, which may be beneficial for septic patients.[7,8] There have been some randomized control trials (RCTs) conducted to evaluate the effects of fish oil in sepsis, however, the relatively small sample size and strict inclusive principles have to some extent restricted the investigations.[9,10] In this study, we performed a prospective, non-randomized, observational clinical study to assess the clinical outcomes in septic patients receiving parenteral fish oil.

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MATERIALS AND METHODS

Study design

A prospective, non-randomized and observational study was performed in a 28-bed Surgical Intensive Care Unit (SICU) in a single tertiary-referral hospital from March, 2013 to May, 2015. The protocol was reviewed and approved by the ethics committee of Zhongshan Hospital, Fudan University (Identified number: B2013-006). The sepsis patients in SICU or new sepsis cases during the treatment in the SICU were enrolled. A clinical diagnosis of sepsis was defined as the presence (probable or documented) of infection together with systemic inflammatory response syndrome (SIRS).[11] Systemic inflammatory response syndrome is manifested by two or more of the following four variables: (i) fever (>38.3°C) or hypothermia (<36°C); (ii) heart rate >90 beats/min or more than two standard deviation (SD) above the normal value of the similar age; (iii) altered mental status; (iv) significant edema or positive fluid balance (>20 mL/kg over 24 hr); (v) hyperglycemia (plasma glucose level >7.7 mmol/L) in the absence of diabetes; (vi) leukocytosis (white blood cell count $>12.0\times10^9$/L), leukopenia (white blood cell count $<4\times10^9$/L), or normal WBC count with greater than 10% immature forms; (vii) plasma C-reactive protein more than two SD above the normal value; and (viii) plasma procalcitonin (PCT) more than two SD above the normal value[12].

Patients with sepsis requiring total parenteral nutrition (TPN) for at least 3 days were included. Exclusion criteria included: (i) age <18 years old; (ii) pregnancy; (iii) treatment with immunosuppressive drugs, especially with TNF-α inhibitor; (iv) requirement for TPN less than 3 days; (v) disability to accept TPN within 3 days of the initial treatment of sepsis; (vi) hypersensitivity to fish, egg, or soy protein; (vii) HIV-positive patients; (viii) diarrhea in recent 3 days; (ix) APACHE II <5 at the first 24 hours; (x) participation in any other clinical study within 1 month.

Patients were assigned to the study group (40 cases) or control group (72 cases) based on the choice of the patient or their family, and also recommendation from the physicians. The control group received standard TPN which consists of medium and long chain fat emulsion (MCT/LCT) (Lipovenoes per 1000 mL Sino-Swed Pharmaceutical Co. LTD: linoleic acid (18:2ω6) 43.8-58.6 g; α-linolenic acid (18:3ω3) 4.53-11 g; glycerol 25 g; medium chain triglycerides 50 g; egg phospholipids 6.0 g), amino acid, glucose, vitamins and other essential nutrients. The study group received standard TPN with ω-3 fish oil fat emulsion (Omegaven, Fresenius-Kabi, Austria) at the dosage of 100 mL/d. The ingredients in fish oil were listed in Table 1. Each infusion was started at midday or midnight and lasted for 6 hours. The patients in both groups received equal lipid and energy delivery. All included patients received standard care according to the guidelines of the Surviving Sepsis Campaign. In short, the care included initial fluid resuscitation and the use of broad-spectrum antibiotics. The target therapy was initiated when the results of pathogen cultured and drug sensitivity test came out.

Table 1. The constituents of Omegaven

Constituents	Concentration (g/L)
Eicosapentaenoic acid	12.5–28.2
Docosahexaenoic acid	14.4–30.9
Myristic acid	1.0–6.0
Palmitic acid	2.5–10.0
Palmitoleic acid	3.0-9.0
Stearic acid	0.5-2.0
Oleic acid	6.0-13.0
Linoleic acid	1.0–7.0
Linolenic acid	≤2.0
Octadecatetraenoic	0.5–4.0
Eicosaenoic acid	0.5-3.0
Arachidonic acid	1.0-4.0
Docosaenoic acid	≤1.5
Docosapentaenoic acid	1.5–4.5
Other fatty acid	10.5

Data collection and experimental methods

The information of the patients included basic demographic data, comorbidity, infectious diagnosis, and causative pathogen. Venous blood was drawn on day 1 (within 24 hours after admission and before the start of infusion, also supposed as baseline), day 3, day 5 and day 7, and 2 hours after lipid infusion. The serum concentration of tumor necrosis factor (TNF)-α was determined by sandwich enzyme-linked immunosorbent assay. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were assessed for the most aberrant clinical and laboratory parameters in the first 24 hours from admission to the SICU as baseline (day 1) and then every 48 hours. The length of ICU and hospital stay, duration of mechanical ventilation, mortality, and readmission into the ICU were also recorded. Patients were followed up until death or discharge of hospital. The mortality included 28-day mortality, also named mortality in acute phase and all-cause death (Beyond the 28 days). Considering that some of the patients progressed into immune inhibition phase, or had complications due to acute infection in the ICU, there were still some deaths after the 28 days. Therefore, we included the all-cause mortality in this study.

Statistical analysis

Statistical analysis was carried out using SPSS statistics version 22.0 (IBM, USA). Kolmogorov-Smirnov tests were used to estimate the normal distribution of study variables. Continuous variables were presented as the mean ± standard deviations (SD) and analyzed by t-test if they followed normally distribution. Otherwise, the data were presented as the median (range) and analyzed by Wilcoxon rank sum test. Discontinuous variables were expressed as numbers and percentages and analyzed by Pearson χ^2 or Fisher exact test. Comparison of survival days was completed by the log-rank test and was demonstrated as Kaplan-Meier curves. p value <0.05 was considered statistically significant. Multivariate analysis was proceeded to predict some factors which could be associated with all-cause mortality, including age, illness severity (as evaluated by the APACHE II), infection site, the requirement for hemodialysis, etc.

Table 2. Demographic and baseline characteristics of the patients.

Characteristics	Control group (n=72)	Study group (n=40)	*p*
Age, mean±SD, year	68.9±12.5	63.1±14.1	0.039
Sex, women/men	24/48	10/30	ns
Comorbidities, n (%)			
Hypertension	35 (48.6)	18 (45.0)	ns
Diabetes	14 (19.4)	8 (20.0)	ns
Cancer	14 (19.4)	6 (15.0)	ns
Hyperuricemia	1 (1.4)	0 (0.0)	ns
Hyperlipidemia	1 (1.4)	0 (0.0)	ns
Cerebral infarction	5 (6.9)	0 (0.0)	ns
Psychiatry	2 (2.8)	0 (0.0)	ns
Chronic obstructive pulmonary disease	2 (2.8)	2 (5.0)	ns
Tuberculosis	1 (1.4)	1 (2.5)	ns
Arrhythmia	5 (6.9)	2 (5.0)	ns
Coronary heart disease	6 (8.3)	1 (2.5)	ns
Gastrointestinal ulcer	3 (4.2)	0 (0.0)	ns
Liver disease	5 (6.9)	4 (10.0)	ns
Chronic kidney disease	3 (4.2)	1 (2.5)	ns
Deep vein thrombosis	4 (5.6)	1 (2.5)	ns
Focus of sepsis, n (%)			
Abdominal	47 (65.3)	33 (82.5)	ns
Respiratory	9 (12.5)	1 (2.5)	ns
Chest	8 (11.1)	4 (10.0)	ns
Blood	0 (0.0)	2 (5.0)	ns
Skin and soft tissue	4 (5.6)	0 (0.0)	ns
Others	4 (5.6)	0 (0.0)	ns
Causative pathogen, n (%)			
Gram positive	16 (43.2)	8 (32)	ns
Gram negative	26 (70.3)	18 (72)	ns
Fungus	4 (10.8)	5 (20)	ns
No reported pathogen	35 (48.6)	15 (37.5)	ns
Initial antibiotics strategy, n (%)			
Cephalosporin/Broad spectrum Penicillin	37 (51.4)	14 (35.0)	ns
Carbapenems	46 (63.9)	30 (75)	ns
Fluoroquinolones	5 (6.9)	3 (7.5)	ns
Vancomycin/Teicoplanin	13 (18.1)	9 (22.5)	ns
Linezolid	3 (4.3)	0 (0.0)	ns
Tigecycline	3 (4.2)	3 (7.5)	ns
Triazole antifungals	6 (8.3)	4 (10.0)	ns
Echinocandins	2 (2.8)	2 (5.0)	ns
Others	2 (2.8)	2 (5.0)	ns
Requirement for hemodialysis, n. (%)	17 (23.6)	4 (10)	ns

RESULTS

A total of 133 patients were enrolled from March, 2013 to May, 2015 and 21 patients were excluded from enrollment because of incomplete data (2 patients), death or discharge from ICU within 3 days (5 patients), APACHE II <5 (8 patients) and inability to accept TPN within 3 days (6 patients). Of 112 patients, 40 patients received fish oil emulsion supplementation. All the patients received at least 3-day parenteral nutrition. The longest was 28 days. The patients in control group received 10.8±5.7 d, while the patients received TPN for 10.3±3.5 d in the experimental group (vs control, $p>0.05$). No adverse effects were observed in the patients who received ω-3 fish oil fat emulsion during the course of the study.

There were no significant differences between the two groups in comorbidities, focus of sepsis, causative pathogen, initial antibiotics strategy, and the requirement for hemodialysis (Table 2). The baseline of APACHE II score (Table 3), PCT (Table 4), and serum TNF-α (Table 4) did not show significant difference between the two groups. However, the average age of the patients in the control group were 5 years older than those of the study group (68.9±12.5 vs 63.1±14.3, $p=0.039$). This could lead to the change of statistical analysis. Therefore, the stratification adjustment was used to eliminate the bias of this difference.

There was a significant difference between the control and study group in all-cause mortality (20.0% vs 10.0%, $p=0.034$). Although 28-day mortality in the study group tended to decrease (15.3% vs 5.0%, $p=0.187$), there was no statistical difference ($p>0.05$) (Table 3). The cause for the 28-day mortality was listed in Table 5. The study group did not show significant reduction in the length of ICU and hospital stay (Table 3). Kaplan-Meier survival curves are shown in Figure 1. The mortality was indicated by K-P diagram and only included the data in hospitalization. The longest hospitalization was 187 days. Therefore, we set the time axis as 200 days. To the end of the recording, 20 cases were died in control group, while 4 cases died in experimental group. There was no significant difference in the days free of mechanical ventilation ($p=0.121$; Table 3). The ICU readmission showed no associated decline between the two groups (18.1% vs 12.5% in control and study groups, $p=0.443$).

Table 3. Clinical outcomes after therapies

Variables	Control group (n=72)	Study group (n=40)	*p*
Mortality, n (%)			
28-day mortality	11 (15.3)	2 (5.0)	ns
All-Cause Mortality	20 (27.8)	4 (10.0)	0.034
Length of stay, median (1st quartile, 3rd quartile), day			
In ICU	10.0 (5.0, 22.0)	8.5 (4.0, 11.50)	ns
In hospital	24.0 (15.0, 56.5)	26.0 (11.0, 46.5)	ns
Days of free of mechanical ventilation, median (1st quartile, 3rd quartile), day	4.0 (1.0, 12.0)	3.0 (1.0, 6.0)	ns
ICU Readmission, n (%)	13 (18.1)	5 (12.5)	ns
APACHE II score			
Day 1	14.1±6.13	13.05±4.89	ns
Day 3	12.0±5.37	10.4±4.65	ns
Day 5	10.9±4.89	8.68±3.54	0.015
Day 7	11.3±4.86	9.12±4.16	0.036
Day out of SICU	8.72±3.59	7.33±2.96	0.045

Table 4. Tumor necrosis factor (TNF)-α and procalcitonin (PCT) levels

Variables	Control group (n=72)	Study group (n=40)	*p*
PCT (pg/mL) (median [range])			
Day 1	4.37 (0.82,14.4)	6.33 (1.68,18.1)	ns
Day 3	2.28 (0.81,10.2)	2.58 (1.02,12.5)	ns
Day 5	1.45 (0.57,4.29)	1.38 (0.53,2.93)	ns
Day7	0.89 (0.3,3.14)	0.53 (0.23,1.17)	ns
TNF-α (ng/mL) (mean±SD)			
Day 1	29.8±27.9	26.9±24.5	ns
Day 3	25.9±20.8	22.2±26.3	0.034
Day 5	23.1±18.4	20.8±14.2	ns
Day 7	28.2±33.4	22.3±14.3	ns
TNF-α (ng/mL) (mean±SD) (excluding patients required for hemodialysis)			
n	46	34	
Day 1	28.1±26.4	24.3±22.3	ns
Day 3	25.5±22.7	22.3±27.5	ns
Day 5	22.4±20.3	21.3±15.2	ns
Day 7	31.8±41.2	22.5±15.9	ns

Following therapies, the APACHE II scores showed a decline in both groups on day 3, day 5, day 7 and the day discharged from ICU (Table 3). When comparing the scores between the two groups, the values showed significant differences on day 5, day 7 and the day out of the ICU (p=0.015, 0.036, 0.045, respectively). In contrast, the scores on day 3 did not reveal significant difference between the control group and the study group (p=0.094).

The median PCT level did not show significant difference on day 3, day 5 and day 7 between the two groups. The decrease of serum TNF-α level on day 3 was more obvious in the study group (p<0.05). However, on day 5 and day 7, the values in the two groups were comparable. Because hemodialysis possibly took inflammatory cytokines away from blood, sub-group analysis by exclusion of hemodialysis cases was used to assess the effects of fish oil on the decline of TNF-α. However, there was no significant difference between the two groups in TNF-α level on day 3, day 5, and day 7 (p=0.071, 0.891, 0.777, respectively, Table 4).

Multivariate survival analysis using Cox's regression model were performed to determine the factors for the all-causative mortality, including gender, age, infection site, requirement for hemodialysis, WBC count, serum TNF-α, APACHE II score and fish oil. However, none of those factors demonstrated independent significance (Table 6).

DISCUSSION

In this study, we carried out a single-center, prospective, non-interventional observation study to determine the efficacy of fish oil in critical illness with sepsis. Although some studies investigated the use of fish oil in critical illness,[13,14] including patients with acute respiratory distress syndrome (ARDS),[15] there was not enough evidence to support the beneficial effects of fish oil on septic patients. In this study we enrolled 112 patients with sepsis to investigate the clinical effect of fish oil.

Sepsis at its early phase develops systemic inflammatory response syndrome (SIRS). This is caused by an over-activation of the inflammatory system or excessive release of inflammatory cytokines, such as TNF-α, while

Table 5. The cause of death in the 28-day period

Causes	Control group (n=10)	Study group (n=2)
Disseminated intravascular coagulation (DIC)	1	1
Atrial fibrillation	0	1
Respiratory failure	2	0
Liver failure	1	0
Multiple organ failure	4	0
Metabolic acidosis	1	0
Brain death	1	0

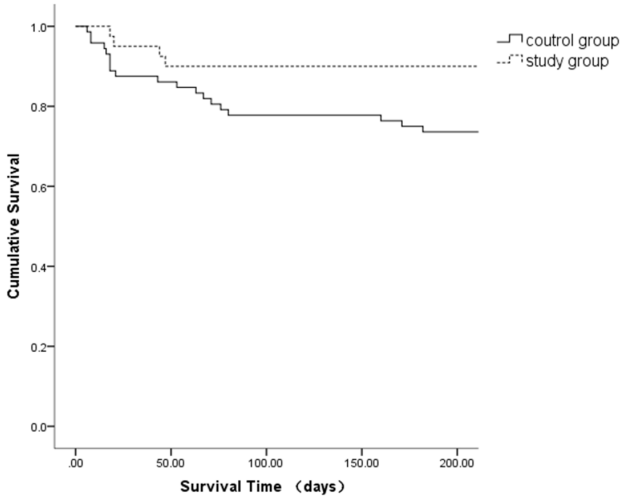

Figure 1. Kaplan-Meier curves of all-cause mortality. A significant difference was observed between study group and control group ($p<0.05$).

Table 6. Multivariable analysis for independent factors for all-cause mortality

Variety	HR	95%CI		*p*
Gender	1.20	0.31	4.58	ns
Age	1.00	0.95	1.07	ns
Infection site	0.62	0.18	2.18	ns
WBC count	0.93	0.83	1.03	ns
Hemodialysis	0.62	0.17	2.27	ns
TNF-α	0.98	0.95	1.01	ns
APACHE II score	1.10	0.98	1.22	ns
Study group	1.61	0.45	5.69	ns

turn into Compensatory Anti-inflammatory Response Syndrome (CARS) at the later phase.[16] Fish oil, containing DHA and EPA, is able to regulate NF-κB expression and decrease the level of inflammatory cytokines.[17] Therefore, fish oil may result in immunosuppression, which is harmful for sepsis patients in CARS condition. To this aim, it would be more beneficial to use fish oil in the early sepsis rather than the late sepsis. We excluded the patients with the disability to accept TPN within 3 days.

In our study, all patients were treated according to the surviving sepsis campaign guideline, including fluid resuscitation and early broad-spectrum antibiotic prescription.[18] Infection is the primary reason for sepsis, therefore antibiotic were considered as the key step to treat sepsis. The initial antibiotic regimen may affect overall clinical outcomes, however, through statistical analysis there were no differences found between the empirical antibiotics used. The baseline clinical characteristic and laboratory inflammatory level had no significant difference between the two groups. The only difference was the age, which was accounted for through stratification adjustment.

A previous study suggested APACHE II was related to the mortality in the ICU.[19] Lee et al[20] have reported that the discharged APACHE II score may predict post-ICU mortality and was superior to apply APACHE II score to predict early ICU readmission. Our study showed a significant reduction in the score of APACHE II and all-cause mortality in the study group. However, there were no significant differences in ICU readmission between the two groups. These results were consistent with the findings from Khor et al.[10] In another clinical study,[9] the result suggested fish oil was related to a significant reduction in Sepsis-related Organ Failure Assessment (SOFA) scores, which also implicated that fish oil was useful to protect organ function and improve clinical outcome. In our study, we also found that fish oil had a trend to shorten the length of ICU stay. However, our data was unable to support the effects of fish oil on the length of hospital stay and days free of mechanical ventilation.

PCT is a 116-amino acid peptide precursor or prohormone of calcitonin, which is thought to be a specific marker for severe bacterial infection.[21] The study by Li et al[22] demonstrated that there was a positive correlation between APACHE II and PCT concentration, and PCT was a significant risk factor for sepsis mortality. In our study, however, we did not find significant differences in PCT levels between groups. Our results might implicate that the anti-inflammation effect of fish oil was not PCT-dependent. TNF-α is considered as an important inflammatory biomarker related to sepsis, especially in the early phase (SIRS phase).[23] TNF-α was dramatically decreased during fish oil therapy.[24] In this study, TNF-α level decreased in both groups after therapy and there was a significant difference between the two groups on day 3. Hemodialysis can eliminate TNF-α from the blood.[25] Subgroup analysis was used to subtract the hemodialysis effect. However, the results failed to illustrate that fish oil could lower the serum TNF-α level in septic patients without hemodialysis, compared with regular fatty acids. Another meta-analysis[26] also did not find the relationship between n-3 PUFA and TNF-α, which was consistent to our study.

Fish oil was safe in patients with sepsis, as no adverse effect was found during the treatment. Nevertheless, the sample size of this study might be insufficient to distinguish the adverse reaction or the dose of fish oil was still under the safe range. Heller et al[27] found that intravenous fish oil administration at the dosage of 10 g/d is associated with reduced number of infections, and severity of infections. Regression analysis suggested an optimum dose of 0.1-0.15 g/kg/d in abdominal septic patients with a short ICU stay. In our study, 100 mL Omegaven containing 10 g refined fish oil was given to patients every day, making the prescribed dose 0.11-0.25 g/kg/d. In addition, the n-3:n-6 PUFA ratio also affects the anti-inflammatory and anti-oxidative effects. Yang et al[28] reported that low n-6/n-3 PUFA ratio (1:1 and 5:1) had a beneficial effect on cardiovascular risk factors, which implicated that n-6/n-3 PUFA ratio was also important in patients with sepsis or critical illness.

Fish oil might be beneficial for patients after surgery[29] and those with ARDS.[30] Manzanareset al[13] showed that fish oil containing emulsions were associated with a trend toward a reduction in mortality and a reduction in the duration of mechanical ventilation in critically ill patients. However, there were no large RCTs or systematic review to confirm the benefits of fish oil in septic patients. The treatment regimen of sepsis emphasizes early bundle therapy which means comprehensive therapy including liquid resuscitation, antibiotic usage, glucose control and

nutrition. Since our study and previous studies imply that fish oil may improve clinical outcomes in patients with sepsis, larger RCTs are needed to investigate if fish oil could be included as part of bundle therapy.

Previous report implicated that the fish oil could be metabolized into fat inhibitors, such as resolvins and protectin D, which have abilities to regulate TNF-α and Interleukin family and other inflammatory factors.[5,31] Different from TNF-α antibody or glucocorticoid, fish oil does not have strong anti-inflammation effect. Therefore, the acute effect of fish oil in the prognosis was not obvious. However, the long effect of fish oil especially due to the inflammation inhibition deserves further investigation.

Several limitations of this study should be mentioned. Firstly, like the other observational study, some results, especially the APACHE II score, might have subjective deviation. Second, the related small sample size and imbalance cases in the control and study groups may also affect the accuracy of analysis. Thirdly, the dosage of fish oil in future studies should be standardized. Finally, the influence of glucocorticoids and other anti-inflammatory drugs should be considered in later studies.

In conclusion, this prospective observational study showed that parenteral fish oil was relevant to the reduction of all-cause mortality and APACHE II score, and tends to decrease the length of ICU stay in critically illness patients with sepsis. Fish oil might be safe and have the ability to improve the clinical outcome in patients with sepsis.

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AUTHOR DISCLOSURES

None.

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