Formosan Journal of Surgery (2016) 49, 208–216

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-fjs.com

ORIGINAL ARTICLE

Enteric bacterial loads are associated with interleukin-6 levels in systemic inflammatory response syndrome patients

Tzyy-Bin Tsay [a,e], Ming-Chieh Yang [b,e], Jen-Tang Sun [c,d], Pei-Hsuan Chen [b], Ying-Sheng Lin [b], Meng-Hung Shih [a], Lee-Wei Chen [b,c,*]

[a] Department of Surgery, Zuoying Armed Forces General Hospital, Kaohsiung, Taiwan
[b] Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[c] Institute of Emergency and Critical Care Medicine, National Yang-Ming University, Taipei, Taiwan
[d] Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan

Received 22 February 2016; received in revised form 9 April 2016; accepted 27 April 2016
Available online 14 November 2016

KEYWORDS
enteric bacterial loads;
IFABP;
IL-6;
SIRS;
trauma

Abstract *Background:* Loss of intestinal integrity is a critical contributor to excessive inflammation following severe trauma or major surgery. In the case of enterocyte damage, intestinal fatty acid-binding protein (IFABP) is released into the extracellular space. Excessive production of interleukin (IL)-6 can induce systemic inflammatory response syndrome (SIRS). However, the correlation of IL-6 with gut barrier failure and bacterial translocation in critically ill patients has not been well characterized.
Purposes: To define the relationship between enteric bacterial loads and IL-6 levels in patients with SIRS.
Methods: Variables related to prognosis and treatment were measured in 85 patients with SIRS upon admission to the emergency room. IL-6 and IFABP were measured using an enzyme-linked immunosorbent assay. Enteric bacterial loads in blood were measured through quantitative real-time polymerase chain reaction with primers specific for enteric bacteria.
Results: Multivariate analysis revealed a positive correlation between enteric bacterial loads and IL-6 levels in blood. Elevated IFABP concentration was associated with low blood pressure, high respiration rate, hyperglycemia, and high Sequential Organ Failure Assessment score. Elevated C-reactive protein concentrations were associated with higher soluble CD14 levels in blood.

Conflict of interest: The authors have declared that no conflict of interest exists.

* Corresponding author. Department of Surgery, Kaohsiung Veterans General Hospital, 386, Ta-chung 1st Road, Kaohsiung, Taiwan.
E-mail address: lwchen@vghks.gov.tw (L.-W. Chen).
[e] T.-B. Tsay and M.-C. Yang contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.fjs.2016.04.007

Conclusion: Enterocyte damage is associated with hypotension and tachypnia in patients with SIRS. Gut function failure may permit enteric bacteria to enter the blood, thereby elevating IL-6 levels and inducing a systemic inflammatory response, resulting in multiple organ failure.

1. Introduction

Excessive production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8 by immunocompetent cells can induce systemic inflammatory response syndrome (SIRS).[1] Among these proinflammatory cytokines, IL-6 has a longer half-life than TNF-α and IL-1β do, and blood IL-6 levels remain consistently elevated in people with various diseases.[1] IL-6 has been implicated as being responsible for increased gut mucosal permeability in mice with a condition associated with systemic inflammation, namely, polymicrobial peritonitis induced by cecal ligation and perforation.[2] IL-6 is a pleiotropic cytokine involved in both proinflammatory and anti-inflammatory responses by regulating leukocyte function and apoptosis.[3,4] It is a crucial cytokine associated with inflammatory bowel disease as well as other chronic inflammatory diseases and cancer.[5] However, the correlation of IL-6 with gut barrier failure and bacterial translocation in critically ill patients has not been well characterized.

The intestinal tract acts as a major physical barrier between the microflora and internal host tissue, and it responds to the mucosal innate system through commensal microflora.[6] The mucosal barrier is composed of epithelial apical junction complexes, consisting of tight junctions and adherence junctions.[7] Gut barrier function failure due to a major stress insult permits bacterial and endotoxin translocation, which triggers systemic cytokines and exacerbates a systemic immunoinflammatory response that results in organ failure.[8] Intestinal barrier failure is a crucial issue in the treatment of critically ill patients. Bacterial translocation from the intestinal tract is a major cause of thermal injury-induced sepsis and mortality.[9] Providing enteral nutrients shortly after injury alters the gut flora and protects the immunocompromised, stressed, or thermally injured patients through an unknown mechanism.[10] However, small intestine dysfunction is frequently underdiagnosed and associated with poor prognosis in critically ill patients.[11]

Intestinal fatty acid-binding protein (IFABP), which is a small cytoplasmic protein specifically localized in small bowel enterocytes and involved in fatty acid transport, is normally undetectable in plasma.[12] In healthy adults, small bowel hypoperfusion during submaximal effort was shown to cause acute reduction of enterocyte mass.[13] In the case of enterocyte damage, IFABP is released into the extracellular space, leading to increased concentrations of IFABP in plasma and urine. Patients with septic shock show increased urinary IFABP concentrations, suggesting that the shock condition is associated with enterocyte damage.[14] Failure of the gut mucosal barrier to exclude bacteria and endotoxins from the portal and systemic circulation is responsible for the development of sepsis and multiple organ failure.[8] Although experimental data are compelling, corroborative evidence from studies involving patients with sepsis is scarce.

Intestinal failure is one the most frequent complications among patients with sepsis. However, treatment interventions aimed at improving gastrointestinal (GI) perfusion have failed to improve outcomes.[15] We hypothesize that gut barrier function failure due to a major stress insult may permit bacterial translocation, triggering IL-6 release and resulting in organ failure. To test this hypothesis, we examined the IFABP levels, IL-6 levels, enteric bacterial loads, and soluble CD14 (sCD14) in the blood of patients with SIRS and defined the relationship with variables related to prognosis and treatment. The primary objective of this study was to evaluate the changes in blood IL-6 levels in these patients and the relationship of the changes with enteric bacterial loads. The second objective was to identify the factors associated with plasma IFABP concentrations in a population of patients with SIRS. In the future, controlling the contributing factors of enterocyte damage to reduce enteric bacteria translocation in patients with SIRS could be a useful therapeutic strategy for preventing multiple organ failure in patients with severe trauma or those having undergone major surgery.

2. Methods

2.1. Study setting and patients

This prospective study was conducted at the emergency department of the Zuoying Armed Forces General Hospital, Kaohsiung, Taiwan. This study was approved by the local ethics committee (EC-No. ZAFGH 101-06) and conducted in accordance with the guidelines of the Declaration of Helsinki (1964), including current revisions. Patients admitted to the emergency department were screened for the following inclusion criteria: two or more SIRS criteria [temperature, $>38^{\circ}C$ or $<36^{\circ}C$; pulse, >90 beats/min; respiratory rate, >20 breaths/min; or $Paco_2$, <32 mmHg; WBC count, $>12{,}000$ or <4000 cells/μL or $>10\%$ immature (band forms)], age >20 years, and able to give consent. The exclusion criteria for participation in the study were as follows: malignancies; surgery within 72 hours prior to admission; infection with HIV, fungi, or parasites; or inability to sign the consent form. The patients were informed about the trial, and they signed a consent form to confirm their participation. To ensure anonymity, every participant was consecutively assigned an identification number, which was used for further analysis.