Journal of Critical Care 42 (2017) 304–309

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Endothelial glycocalyx biomarkers increase in patients with infection during Emergency Department treatment☆

Lisa Smart, BVSc [a,b,*], Stephen P.J. Macdonald, MBChB [a,b,c], Sally Burrows, BMath [d], Erika Bosio, PhD [a,b], Glenn Arendts, MBBS, PhD [a,b], Daniel M. Fatovich, MBBS, PhD [a,b,c]

[a] Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research, Perth, Western Australia, Australia
[b] Division of Emergency Medicine, University of Western Australia, Perth, Western Australia, Australia
[c] Emergency Department, Royal Perth Hospital, Perth, Western Australia, Australia
[d] School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia

ARTICLE INFO

Keywords:
Glycocalyx
Endothelium
Sepsis
Infection
Fluids

ABSTRACT

Purpose: Endothelial glycocalyx (EG) shedding may promote organ failure in sepsis. This study describes temporal changes in EG biomarkers from Emergency Department (ED) arrival, and associations with clinical characteristics.
Materials and Methods: This prospective observational study included 23 patients with simple infection, 86 with sepsis and 29 healthy controls. Serum EG biomarkers included syndecan-1, syndecan-4 and hyaluronan. Samples were taken on enrolment in the ED (T0), 1 hour (T1), 3 hours (T3) and 12 to 24 hours (T24) later.
Results: Syndecan-1 concentration increased incrementally over time (T0-T24, both patient groups, $P < .001$) whereas hyaluronan concentration peaked at T3 (T0-T3, sepsis group, $P < .001$). Hyaluronan was positively associated with cumulative fluid volumes ($P < .001$) at T0, T1, and T3, independent of illness severity. Both syndecan-1 (OR 1.04, 95% CI 1.01-1.07, $P = .017$) and hyaluronan (OR 1.83, 95% CI 1.46-2.30, $P < .001$) were associated with organ failure, independent of age and comorbidity.
Syndecan-4 concentration was not different between groups or over time.
Conclusions: In contrast to previous ICU studies, EG biomarkers increased during the first 24 hours of sepsis treatment and were associated with fluid volumes and organ failure. Further investigation is required to determine if interventions delivered in the ED contribute to EG shedding.

1. Introduction

Multiple organ failure is central to the morbidity and mortality associated with sepsis [1]. A key player in the pathogenesis of organ failure is endothelial dysfunction, featuring increased fluid extravasation, microthrombosis, and loss of vasomotor tone. Increased endothelial activation early in the treatment of sepsis is associated with organ failure severity and mortality [2-4]. More recently, it has been discovered that endothelial activation is preceded by shedding of its luminal surface layer, the endothelial glycocalyx (EG). Shedding of the EG can be initiated by inflammatory cytokines and pathogen-associated molecules, such as lipopolysaccharide [5-7], and is associated with endothelial-leukocyte adhesion and increased vascular permeability [8,9]. Therefore, it has been postulated that EG shedding is an important part of the pathogenesis of multiple organ failure in sepsis [10].

Biomarkers of circulating EG components, such as syndecan-1 and hyaluronan, are increased in patients with sepsis [2,11-18] and are associated with illness severity [2,11,15,16], sequential organ failure assessment (SOFA) score [2,11-13,17], and mortality [11,13,15,18]. Studies in the intensive care unit (ICU) assessing EG biomarker concentrations over time have reported the highest concentrations at ICU admission, with a decreasing trend during the ICU stay [11,12,14]. Patients admitted to the ICU from the emergency department (ED) represent the greatest proportion of ICU patients with sepsis [19]. Interventions given to patients in the ED may increase EG biomarkers in the first 24 hours of treatment, partly explaining high concentrations found at ICU admission.

Abbreviations: CCS, Charlson Comorbidity Score; CISS, Critical Illness and Shock Study; ED, Emergency department; EG, Endothelial glycocalyx; ELISA, Enzyme-linked immunosorbent assay; ICU, Intensive care unit; NGAL, Neutrophil gelatinase-associated lipocalin; SOFA, Sequential organ failure assessment.

☆ Conflicts of Interest and Source of Funding: There are no conflicts of interest to declare. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The results of this study were, in part, presented in abstract form at the Eighth Congress of the International Shock Societies, Tokyo, Japan (October 2016).

* Corresponding author at: Centre for Clinical Research in Emergency Medicine, Level 6, MRF Building, Royal Perth Hospital, Rear 50 Murray St. Perth, WA 6000, Australia. Tel.: +61 8 9224 0356; fax: +61 8 9224 1494.
E-mail address: Lisa.smart@research.uwa.edu.au (L. Smart).

http://dx.doi.org/10.1016/j.jcrc.2017.07.001
0883-9441/

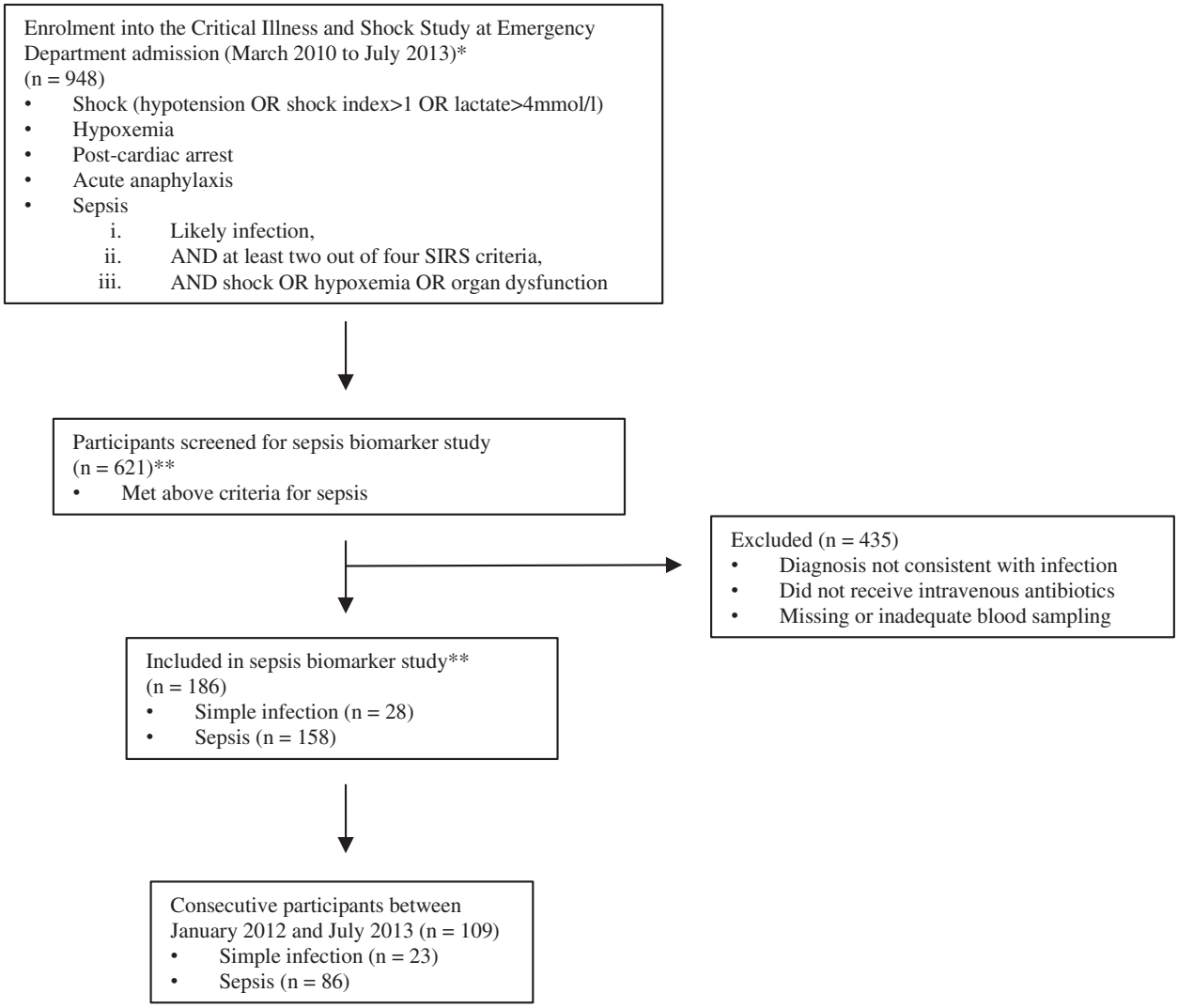
A frequent intervention given early in the treatment of sepsis is intravenous fluid boluses, with most volume loading occurring in the first 6 hours of treatment [20]. Crystalloid fluid boluses have been associated with EG shedding in multiple studies [21-24]. Therefore, it is plausible that the initial resuscitation period of treating sepsis may be associated with increasing EG biomarker concentrations. Understanding the time course of EG shedding in sepsis, and any relationships with therapeutic intervention, is important for devising strategies aimed at mitigating this injury and improving clinical outcomes.

The main objective of this study was to compare the pattern of EG shedding in patients with either simple infection or sepsis over the first 24 hours from ED arrival, as determined by three different EG biomarkers. We hypothesized that EG biomarker concentrations would increase during this time period. A secondary objective was to investigate associations of each EG biomarker with fluid volumes administered, independent of infection severity and degree of inflammation, as well as clinical outcomes.

2. Materials and methods

2.1. Study design

Patients meeting criteria for sepsis in the ED were identified from the Critical Illness and Shock Study (CISS) (HREC permit number 2009-080), which is an observational database of patients meeting physiologic criteria consistent with critical illness (Fig. 1). As previously described [25], CISS enrolment criteria focused on patients with evidence of shock or organ failure. Formal written consent was obtained from patients or next-of-kin. Patients underwent real-time data collection and research blood sampling during the initial 24 hours from enrolment, and were then followed for clinical outcomes. Recruitment into CISS occurred during rostered research nurse hours 0700-2100, up to 7 days of the week. This study included sequential CISS enrolments meeting sepsis criteria between January 2012 and July 2013 that were a subset of a larger sepsis biomarker study [26]. Sepsis was defined as meeting at least 2 of 4 SIRS criteria [27]; temperature >38°C or <36°C,



* Arendts G, Stone SF, Fatovich DM, et al. Critical illness in the emergency department: lessons learnt from the first 12 months of enrolments in the Critical Illness and Shock Study. Emerg Med Australas 2012;24(1):31-6.
** MacDonald SPJ, Bosio E, Neil C, et al. Resistin and NGAL are associated with inflammatory response, endothelial activation and clinical outcomes in sepsis. Inflamm Res 2017;66(7):611-619.

Fig. 1. Flow-chart describing selection of Emergency Department patients with simple infection or sepsis.