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Age-related immune responses after burn and inhalation injury are associated with altered clinical outcomes

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ABSTRACT

This prospective study aimed to address changes in inflammatory response between different aged populations of patients who sustained burn and inhalation injury. Plasma and bronchoalveolar lavage (BAL) samples were collected from 104 patients within 15 h of their estimated time of burn injury. Clinical variables, laboratory parameters, and immune mediator profiles were examined in association with clinical outcomes. Older patients were at higher odds for death after burn injury (odds ratio (OR) = 7.37 per 10 years, p = 0.004). In plasma collected within 15 h after burn injury, significant increases in the concentrations of interleukin 1 receptor antagonist (IL-1RA), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), granulocyte colony-stimulating factor (G-CSF), interferon-gamma-induced protein 10 (IP-10) and monocyte chemoattractant protein 1 (MCP-1) ($p < 0.05$ for all) were observed in the ≥ 65 group. In the BAL fluid, MCP-1 was increased three-fold in the ≥ 65 group. This study suggests that changes in certain immune mediators were present in the older cohort, in association with in-hospital mortality.

1. Introduction

According to the National Burn Repository, there are over 40,000 burn admissions every year. In an epidemiological study using this repository's data, it was determined that 14% of these patients are over the age of 65 years (Pham et al., 2009). Burn injury in the elderly carries increased risk of death and morbidity (Davis et al., 2013; Hassan et al., 2010; Navar et al., 1985; Enkhbaatar et al., 2016; Bessey et al., 2014; Pruitt and Mason, 1996; Latenser et al., 2007; Klein et al., 2014; Hazeldine et al., 2015). The relationship between advanced age and poorer outcomes in burn injury is characterized in the Baux Score, used commonly to predict mortality risk among burn patients. The Baux score may be tabulated by adding the age of the patient and the percentage of total body surface area (%TBSA) affected by the burn (Osler et al., 2010), indicating the relatively linear relationship between aging and worsened survival in this setting. The reason why prognosis is so poor in elderly burn patients has proven to be elusive, despite associated morbidity and mortality.

Of the organ systems at risk for failure after burn and inhalation injury, the lungs are particularly vulnerable and are usually one of the first organs to fail, a phenomenon increased by inhalation injury (Shirani et al., 1987). The presence of inhalational injury adds an additional 17 points to the Baux equation, and is known as the Revised Baux Score, illustrating the relative importance of not just aging but inhalational injury as contributors to mortality in the setting of burn injury.

Abbreviations: BAL, bronchoalveolar lavage; OR, odds ratio; IL-1RA, interleukin 1 receptor antagonist; IL-1β, interleukin 1 beta; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IL-12, interleukin 12; IL-13, interleukin 13; IL-17, interleukin 17; G-CSF, granulocyte colony-stimulating factor; IP-10, interferon-gamma-induced protein 10; MCP-1, monocyte chemoattractant protein 1; AUC, area under the curve; ROC, receiver operating characteristics; %TBSA, percent total body surface area; ICU, intensive care unit; COHB, carboxyhemoglobin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor alpha

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Table 1
Patient demographics and characteristics.

Characteristic	Total (n = 104)	< 50 years (n = 55)	50–64 years (n = 26)	≥ 65 years (n = 23)	p-Value
Sex (male), n (%)	67 (64.4)	37 (67.3)	17 (65.4)	13 (56.5)	0.66
Race (white), n (%)	64 (61.5)	29 (52.7)	18 (69.2)	17 (73.9)	0.14
#Admission SOFA Score, median (IQR)	5 (4–8)	4 (4–7)	6 (4–8)	7 (4–9)	0.19
Mechanism (flame), n (%)	98 (94.2)	52 (94.6)	24 (92.3)	22 (95.7)	0.87
Inhalation injury (yes), n (%)	87 (83.7)	44 (80.0)	23 (88.5)	20 (87.0)	0.56
Inhalation injury grade, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	0.55
TBSA, % median (IQR)	12.8 (1.0–30.0)	16.0 (1.0–31.0)	10.3 (1.6–40.0)	7.0 (0–15.0)	0.21
*Revised Baux Score, median (IQR)	93.9 (75.1–121.2)	91.7 (76.0–118.2)	104.3 (72.5–136.5)	93.7 (69.4–115.4)	0.40
Baux Score	83.8 (66.0–104.5)	67.0 (51.0–93.0)	84.8 (78.0–114.0)	99.5 (89.0–106.0)	< 0.001
Lowest PaO_2:FiO_2 ratio (initial 48 h), median	182 (131.8–253.8)	196.0 (136.0–277.5)	143.0 (105.0–200.0)	182.7 (157.5–217.5)	0.12
% COHB, median (IQR)	5.7 (2.5–13.4)	5.0 (1.6–10.9)	5.0 (2.6–13.7)	9.0 (3.5–40.0)	0.10
24 h fluid resuscitation (cc/kg), median (IQR)	79.5 (38.8–156.1)	81.8 (42.2–146.6)	68.4 (34.9–208.3)	99.7 (40.1–146.9)	0.92
72 h fluid resuscitation (cc/kg), median (IQR)	194.7 (112.7–323.0)	196.1 (99.7–310.8)	186.9 (142.9–365.3)	194.7 (91.5–264.3)	0.42
Blood products transfused (units)⊥, median (IQR)	0 (0–5)	0 (0–6)	0 (0–3)	0 (0–4)	0.44

*Revised Baux Score = Age + TBSA + 17 * (inhalation injury, 1 = yes, 0 = no). # n = 84 for this characteristic. TBSA, total body surface area; COHB, carboxyhemoglobin; IQR, interquartile range; SOFA, sequential organ failure assessment; PaO_2:FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; Inhalational injury score is based on bronchoscopy visualization and ranges from 0 to 4 (no injury, mild, moderate, severe, and massive injury).
⊥ Blood products = packed red blood cells, fresh frozen plasma, and platelets.

Table 2
Outcomes.

Characteristic	Total (n = 104)	< 50 years (n = 55)	50–64 years (n = 26)	≥ 65 years (n = 23)	p-Value
Sepsis	20 (19.4)	12 (21.8)	2 (7.7)	6 (27.3)	0.18
28-Day ventilator-free days	3.5 (0.0–23.5)	6.0 (0.0–24.0)	6.5 (0.0–25.0)	0.0 (0.0–19.0)	0.36
28-day ICU-free days	0 (0–15)	0.0 (0.0–16.0)	1.0 (0.0–19.0)	0.0 (0.0–9.0)	0.47
Acute respiratory distress syndrome	69 (67.0)	40 (72.7)	18 (72.0)	11 (47.8)	0.08
In-hospital death	22 (21.4)	6 (10.9)	6 (23.1)	10 (45.5)	0.004

*Revised Baux Score = Age + TBSA + 17 * (inhalation injury, 1 = yes, 0 = no).
TBSA, total body surface area; IQR, interquartile range. Inhalational injury score is based on bronchoscopy visualization and ranges from 0 to 4 (no injury, mild, moderate, severe, and massive injury).

Previously, we have evaluated the inflammatory response to burn and inhalation injury, both systemically and in lung, via measurements in plasma and bronchoalveolar lavage (BAL) fluid (Davis et al., 2013; Davis et al., 2012; Albright et al., 2012). We observed significant differences in concentrations of both pro- and anti-inflammatory immune mediators that varied with severity of inhalation injury and mortality. To the author's knowledge, there is no report in the literature that specifically addresses differences in the immune response between various age groups in burn patients.

Advanced chronological age is associated with increased mortality, but reasons for these observations are still incompletely understood (Davis et al., 2013; Hassan et al., 2010; Enkhbaatar et al., 2016; Bessey et al., 2014; Pruitt and Mason, 1996). We hypothesized older patients with burn and inhalation injury would exhibit alterations in their systemic and pulmonary inflammatory responses in comparison to younger patients, in association with worse clinical outcomes and increased mortality.

2. Materials and methods

2.1. Patient selection and sample collection

From January 2007 to April 2015, blood samples were collected from 104 patients admitted to the burn intensive care unit at Loyola University Medical Center within 15 h of burn injury. Patients were excluded from the study for the following reasons: age < 18 years, malignancy, immunosuppressive medication, or known autoimmune disease. Diagnostic Bronchoscopy and BAL were performed by a standardized protocol upon admission to the burn intensive care unit in patients where inhalation injury was suspected by history and/or physical findings (Ettensohn et al., 1988). BAL fluid that was not required for routine clinical analysis was obtained for use in research. All BAL samples were collected before aerosolized pulmonary medications (e.g. heparin) were administered. The bronchoscope was directed into a subsegment of the right middle lobe and wedged; the first 50 mL aliquot of saline was instilled, and the aspirate discarded. Subsequent 50 mL aliquots were instilled into the same subsegment, and immediately aspirated with gentle hand aspiration into sterile syringes. These were immediately transferred into sterile 50 mL conical tubes, placed on ice, and transported to the laboratory for additional processing. An average of 8.3 mL (standard deviation of 5.4 mL) of BAL fluid was collected for research. Blood samples were collected at the same time as bronchoscopy. Samples were collected an average of 7.6 h (standard deviation of 3.6 h) after injury. This study and associated consent documents were approved by Institutional Review Board.

2.2. Variables

Clinical variables were collected including age, sex, race/ethnicity, % total body surface area (%TBSA) burn, grade of inhalation injury, mechanism of injury, Baux score (Age + %TBSA), Revised Baux Score (Age + %TBSA + 17), admission sepsis-related organ failure assessment (SOFA) score, lowest partial pressure of oxygen in arterial blood to fraction of inspired oxygen (P:F) ration in the first 48 h, admission % carboxyhemoglobin in the blood, initial 24 and 72 h fluid requirements (Osler et al., 2010; Vincent et al., 1996). The degree of inhalation injury was determined using a standardized bronchoscopic scoring system based on Abbreviated Injury Score criteria (grade 0–4, no visible injury,