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Sepsis Therapies: Insights from Population Health to Cellular Therapies and Genomic Medicine

Emanuele Rezoagli, Bairbre McNicholas, Peter Moran, and John G. Laffey

Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Galway, Ireland

Recommended Reading from the Galway University Hospitals Department of Anaesthesia and Intensive Care Medicine Fellows, John G. Laffey, M.D., Faculty Advisor

ORCID IDs: 0000-0002-4506-7212 (E.R.); 0000-0001-9524-4021 (B.M.).

Seymour CW, *et al.* Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *N Engl J Med* (1)

Reviewed by Emanuele Rezoagli

Sepsis, a syndrome of pathophysiologic abnormalities due to a disordered immune response to microbial infection (2), is a key public health concern (3) and is implicated in 50% of hospital deaths (4). International guidelines for management of sepsis emphasize the importance of early antibiotic therapy and crystalloid fluid resuscitation (5). However, the efficacy of early treatment to improve outcome remains controversial because of the low to moderate quality of the available evidence.

In a large retrospective study from New York, Seymour and colleagues explored the association between timing of treatment and risk-adjusted mortality in patients with sepsis (1). All hospitals included in the study were mandated to develop and adhere to evidence-informed protocols for early identification and treatment of severe sepsis or septic shock (6). The sepsis protocol had two components: The “3-hour bundle” required blood cultures (before antibiotics), serum lactate measurement, and broad-spectrum antibiotic administration. The “6-hour bundle” required a fluid bolus of 30 ml/kg in patients with hypotension or lactate greater than or equal to 4.0 mmol/L, vasopressor therapy for refractory hypotension, and lactate remeasurement. Exclusion criteria were protocol initiation after 6 hours of hospital arrival (focus on community-acquired sepsis), the 3-hour bundle completed over 12 hours, contraindications to the protocol, and centers with fewer than 50 cases of sepsis.

Analysis of data from 49,331 patients demonstrated that faster completion of the 3-hour bundle and each individual component was associated with lower mortality. Each hour of time to completion of

the 3-hour bundle was associated with a 4% hourly increase in mortality. Patients who had the bundle completed during hours 3 to 12 had 14% higher odds of in-hospital death. In contrast, time to completion of the fluid bolus administration was not associated with hospital mortality. A 1.5-fold (from 94.3% to 64.1%) variation in 3-hour completion rates for the bundle occurred across hospitals.

Liu and colleagues recently reported a similar association between the time to antibiotic treatment and hospital mortality in inpatients with sepsis from Northern California (7).

Limitations of the study include its retrospective design (i.e., findings associative, not demonstrating cause and effect), lack of data regarding antibiotic regimen effectiveness, and potential for timing inaccuracies. In addition, strategies targeting rapid antibiotic administration must be balanced to avoid antibiotic overuse and increased resistance (8).

In conclusion, given that randomized clinical trial data regarding timing of antibiotic therapy are unlikely to be forthcoming given equipoise issues, this population-level analysis provides significant support for the contention that faster sepsis recognition and treatment may improve outcome. ■

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Correspondence and requests for reprints should be addressed to John G. Laffey, M.D., School of Medicine, 1-008 Clinical Sciences Institute, National University of Ireland Galway, Newcastle Road, Galway, H91 YR71, Ireland. E-mail: john.laffey@nuigalway.ie.

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Tsoyi K, *et al.* Carbon Monoxide Improves Efficacy of Mesenchymal Stromal Cells during Sepsis by Production of Specialized Proresolving Lipid Mediators. *Crit Care Med* (9)

Reviewed by Bairbre A. McNicholas

Mesenchymal stromal cells (MSCs) demonstrate benefits in multiple sepsis models, including bacterial pneumonia (10, 11) and abdominal sepsis (12–14), and early clinical trials suggest promise (15). MSCs may reprogram the innate immune “hyperinflammatory” response and enhance immune cell function, both directly (16, 17) and indirectly (10, 12–14) enhancing antimicrobial killing. MSC reparative effects may be mediated by specialized proresolving lipid mediators (SPM), which modulate immune cell function.

The potential for, and mechanisms underlying, preconditioning-mediated enhancement of MSC function remain unclear. Tsoyi and colleagues (9) hypothesized that *ex vivo* preconditioning of MSCs with carbon monoxide (CO), which is endogenously produced during heme degradation and directly improves survival in preclinical sepsis models (18, 19), would enhance MSC efficacy in a murine cecal ligation and puncture model.

CO preconditioning enhanced the effects of MSCs, allowing them to remain effective in attenuating sepsis when administered later (6 h) after onset of sepsis. This effect was lost when MSCs deficient in heme-oxygenase gene were pretreated with CO, indicating the role of this pathway in mediating the effects of CO. Markers of organ dysfunction were lower, whereas neutrophil phagocytosis and macrophage efferocytosis were enhanced by CO preconditioning. In cell culture, the investigators induced specific subtypes of SPMs by changing the substrate available to cells—with improved survival only noted when docosahexaenoic acid was used, which produced SPM. HPLC analysis of culture media found the SPM subtype resolvins increased. Resolvins alone increased neutrophil phagocytosis, whereas MSCs treated with resolvin D1 and D2 further enhanced phagocytosis to a degree analogous to CO pretreatment of MSCs. Pharmacologically inhibiting SPM production resulted in a loss of the effect of CO preconditioning MSCs on neutrophil phagocytosis. Silencing of 5-lipoxygenase and 12/15-lipoxygenase mRNA genes reduced production of resolvins, abolishing enhanced activity of CO-pretreated MSCs.

There are some limitations to be considered. This is a mouse model of sepsis, in which standard treatments such as hemodynamic resuscitation or antibiotics were not used. The paracrine versus cell-mediated effect of CO-enhanced MSCs requires further resolution, as not all effects of CO-MSC treatment were replicated by resolvin

treatment. The effect of CO preconditioning on MSC longevity and safety remains to be elucidated.

In summary, CO preconditioning enhances MSC efficacy in a preclinical sepsis model by enhancing lipoxin A4 production, providing an elegant proof of concept for strategies to enhance MSC function. Furthermore, these findings elucidate the role of resolvins in mediating MSC effects and suggest that resolvins may be a useful therapeutic target in sepsis. ■

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Davenport EE, *et al.* Genomic Landscape of the Individual Host Response and Outcomes in Sepsis: A Prospective Cohort Study. *Lancet Respir Med* (20)

Reviewed by Peter Moran

Patient heterogeneity and a lack of specific biomarkers have limited advancements in the development of immunomodulatory treatments for sepsis (21, 22). Genetic associations with response to infectious diseases have previously been recognized, but the functional significance of these genetic associations has not been well established (23–25).

Davenport and colleagues use expression quantitative trait loci (genetic variants that influence gene expression) from

peripheral blood leukocytes to map associations between genetic variants and differences in gene expression in patients with sepsis due to community-acquired pneumonia, first in a discovery (265 patients) cohort and then a validation (106 patients) cohort (20). This enabled investigators to define genes modulated by genetic variation and identify specific functional regulatory polymorphisms.

Gene transcriptional analysis to characterize the interindividual variability in leukocyte transcriptome in the discovery cohort and two groupings of transcriptional sepsis response signatures (SRS1 and SRS2) were defined. Two human endotoxin tolerance data sets were also analyzed to define an endotoxin tolerance gene. A total of 3,080 genes were differentially expressed between the two groups, with 2,260 downregulated in SRS1. Key mediators of endotoxin tolerance were also differentially expressed between SRS groups. For the validation component, just seven genes that predicted SRS group membership were used to assign patients to SRS1 or SRS2. The SRS1 group was characterized by an immunosuppressed phenotype, with T-cell exhaustion, endotoxin tolerance, and HLA-II downregulation. Interestingly, clinical variables did not predict SRS grouping. Patients with SRS1 phenotype had an increased 14-day mortality in both the discovery (22% vs. 10%; hazard ratio, 2.4; 95% confidence interval, 1.3–4.5; $P = 0.005$) and the validation (59% vs. 29%; hazard ratio, 2.8; 95% confidence interval, 1.5–5.1; $P = 0.007$) cohorts.

Study limitations include the relatively small sample size. Samples were taken after ICU admission, which could result in a lead-time bias. Data regarding end-of-life practices and timing of antimicrobials are absent. Only a sepsis cohort was investigated; a critically ill comparator group without sepsis may have provided additional insights.

This study and others (23, 25) highlight the degree of heterogeneity in the host sepsis response, the contribution of variable gene expression to this heterogeneity, and the potential impact on outcome. Although application to clinical practice will take time, this approach could facilitate identification of subsets of patients with sepsis who may benefit from individualized novel targeted therapies. Critical care trials could then potentially focus on testing the efficacy of therapies that address specific defects in the host immune response in these patient subsets, heralding the advent of personalized medicine for sepsis. ■

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