The Immunopathological Profile of HIV-Associated Sepsis in Uganda: A Prospective Propensity-Matched Cohort Study

M. J. Cummings¹, B. Bakamutumaho², A. Price³, N. Owor², J. Kayiwa², J. Namulondo², T. Byaruhanga², S. Sameroff³, K. Jain³, R. Tokarz³, W. Wong³, M. Muwanga⁴, C. Nsereko⁴, S. Shah⁵, M. Larsen⁶, W. Lipkin³, J. Lutwama², M. R. O’Donnell⁷; ¹Department of Medicine, Division of Pulmonary, Allergy, Critical Care, Columbia University Medical Center, New York, NY, United States, ²Uganda Virus Research Institute, Entebbe, Uganda, ³Columbia University, New York, NY, United States, ⁴Entebbe Regional Referral Hospital, Entebbe, Uganda, ⁵Columbia University Medical Center, New York, NY, United States, ⁶Albert Einstein College of Medicine, Bronx, NY, United States, ⁷Columbia University, New York City, NY, United States.

Rationale: The global burden of sepsis is concentrated in sub-Saharan Africa (SSA), where sepsis-related morbidity and mortality disproportionately affect HIV-infected adults. Although HIV-related immune activation and exhaustion may contribute to sepsis pathogenesis, little is known about the biological mechanisms that uniquely define HIV-associated sepsis in SSA. In this context, we sought to determine the influence of HIV-infection on illness severity and the host immune response among adults hospitalized with suspected sepsis in SSA. Methods: In a prospective cohort of adults (age ≥18 years) hospitalized with suspected sepsis at a public referral hospital in Uganda, we compared microbiological, organ dysfunction, and clinical outcome profiles of patients with and without HIV-infection. We quantified 14 soluble immune mediators, reflective of key domains of sepsis immunopathology, and performed whole-blood RNA-sequencing on samples collected within 24 of admission. We used propensity-score methods to match HIV-infected and uninfected patients by age, sex, illness duration and initial severity, and compared immune mediator concentrations and gene expression profiles across these propensity-matched groups. Results: Among 301 adults with suspected sepsis, 157 (52%) were HIV-infected (clinical stage 3 or 4 in 126/157 [80%], 92/157 [59%] on antiretroviral therapy). HIV-infected patients, 49 (31%) of whom had severe and frequently disseminated tuberculosis, were older (median age 35 [interquartile range, IQR: 28-43] vs. 29 years [IQR 24-42]; p=0.002) with more severe physiologic derangement (median MEWS score 4 [IQR 3-5] vs. 3 [IQR 2-3]; p<0.001), higher prevalence of shock (32/157 [20%] vs. 9/142 [6%]; p=0.001), and higher 30-day mortality (49/142 [35%] vs 13/128 [10%]; p<0.001). In propensity-matched groups, HIV-infected patients exhibited greater pro-inflammatory innate immune activation, including upregulation of IL-6, IL-8, IL-15, IL-17, MIF and HMGB1 pathways, with evidence of concomitant T-cell exhaustion, endothelial dysfunction, prothrombotic pathway activation, and HIF1-α-induced metabolic reprogramming (Figure 1AB). Conclusion: Sepsis-related organ dysfunction and mortality in Uganda are concentrated among HIV-infected adults, who demonstrate exaggerated activation of multiple immunometabolic pathways implicated in sepsis pathogenesis. Further investigations are needed to define modifiable immunopathologic mechanisms in HIV-associated sepsis, including those amenable to therapeutic manipulation.
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