Equitable endotyping is essential to achieve a global standard of precise, effective, and locally-relevant sepsis care

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Over the past two decades, elucidation of the host response to severe infection has uncovered the complex and dynamic derangements in immune, endothelial, and metabolic homeostasis that underlie sepsis pathobiology.[1,2] Leveraging advances in high-dimensional host response profiling and computational methods (e.g., machine learning, structural equation modelling), identification of patient subgroups defined by distinct clinico-molecular features ("subphenotypes") and pathobiological mechanisms ("endotypes") represents a promising approach to achieve biological deconvolution of the heterogenous sepsis phenotype.[1,2] As *post hoc* analyses of randomized clinical trials suggest that sepsis subphenotypes and endotypes may drive differential responses to host-directed therapies, patient classification based on these subgroups could enable development and precise deployment of therapeutic agents targeting treatable traits.[1,2]

While improved accessibility to advanced laboratory and bioinformatics pipelines has increased the likelihood of integrating a precision medicine approach to sepsis management, the presence and theranostic applicability of sepsis subphenotypes and endotypes have been studied almost exclusively in high-income countries (HICs).[1,2] With nearly 85% of global sepsis cases occurring in low-and-middle-income countries (LMICs), however, incomplete understanding of sepsis pathobiology in these settings is a major barrier to addressing a global health crisis that claims 11 million lives annually.[3] Development of innovative and effective sepsis treatment strategies tailored to LMIC settings is particularly urgent since sepsis treatment protocols developed in HICs have been associated with poor clinical outcomes when implemented in disparate settings (e.g., sub-Saharan Africa).[4] In this context, it is plausible that differential treatment responses may be driven, in part, by the presence of unrecognized phenotypic profiles reflective of immune-, host-, and pathogen-driven factors unique to specific LMIC settings. For example, compared to HIC settings, key features that may contribute to the divergence of sepsis profiles in sub-Saharan Africa include demographics, such as the young age of hospitalized adults, a diversity of microbiologic aetiologies, and HIV co-infection as a predominant driver of pathogen diversity and patient outcomes.[5]

Despite the preponderance of sepsis endotyping data generated from HICs, emerging evidence suggests that pathobiologically-distinct sepsis subgroups are present in LMICs. In sub-Saharan Africa, sepsis subgroups distinguished by pro-inflammatory immuno-metabolic pathway activation, T-cell exhaustion, and endothelial dysfunction have been identified among Ugandan adults and further characterized by differential risk for disseminated HIV-associated tuberculosis, multi-organ failure, and mortality.[6,7] Among adults in Thailand with severe melioidosis, a common cause of sepsis in Southeast Asia, prognostically-relevant subgroups with divergent trajectories of inflammatory cytokines have been reported, with similar findings observed in adults with diverse causes of sepsis in Brazil.[8,9] Forthcoming results from the Molecular Diagnosis and Risk Stratification of Sepsis in India study [NCT03727243 registered with ClinicalTrials.gov] will further elucidate the theranostic relevance of immunopathologically-defined sepsis subgroups in South Asia.

Considering the distinctive features of sepsis in LMICs and often under-resourced health systems in which acute care is delivered, how can advances in endotyping be leveraged to achieve a global standard of precise, effective, and locally-relevant sepsis care? In our view, equitable uptake of sepsis endotyping requires a three-fold approach. First, it is imperative to illuminate sepsis pathobiology in microbiologically diverse LMIC settings using cutting-edge multi-omic and computational methods, with a goal to establish conserved and pathogen-specific mechanisms of infection-related organ dysfunction. Second, mechanistic insights must be translated using clinical, microbiological, and actionable host response data readily available to and easily interpretable by clinicians. Conceivably, such an approach would integrate physiologic parameters (e.g.,

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temperature, blood pressure, capillary refill time), rapid diagnostics for high-burden and priority pathogens (e.g., HIV, malaria, tuberculosis, and other locally-relevant etiologic targets) and a parsimonious panel of host biomarkers, all quantifiable at the point-of-need and reflective of causal and treatable pathobiological mechanisms. Endotype development using locally accessible data is essential to facilitate validation across diverse and variably-resourced settings. In parallel, rapid assessment of microbiology and host response, which are likely to drive prognostic and treatment-predictive endotype assignment, is necessary for real-time enrichment of homogenous patient groups for comparison in adaptively-designed randomized clinical trials. For example, recent data suggest that rapid and quantitative molecular blood testing for *Mycobacterium tuberculosis*, coupled with inflammatory biomarker measurements, can identify, prognosticate, and immunologically stratify adults with disseminated tuberculosis, a leading cause of sepsis in high HIV-burden settings.[10] If further validated, rapid assessment of this candidate pathogen-driven endotype could facilitate innovative treatment strategies including enhanced anti-tuberculosis therapy (informed by systemic bacillary load) and immunomodulation (e.g., targeting pro-inflammatory host responses).[10] Finally, growing capacity related to genomic science and bioinformatics in sub-Saharan Africa (e.g., African Centre of Excellence in Bioinformatics and Data-intensive Sciences [Uganda]; Microsoft Africa Research Institute [Kenya]; H3Africa Hubs [throughout the region]) and other LMIC settings suggests that accessibility to the resources required to identify and interrogate sepsis endotypes should no longer be a region-specific limitation. In combination with expanding access to rapid and low-cost pathogen diagnostics, host immunoassays, and sequencing platforms, deployment and evaluation of sepsis endotyping strategies should be viewed as an achievable goal regardless of income setting.

In an era defined by the promise of precision critical care, utilization of endotyping strategies tailored to the distinct presentations of sepsis in the highest burden settings is essential to ensure that the benefits of translational science reach the bedsides of patients with the greatest need. In parallel with improvements in acute care capacity, an equitable approach to endotyping represents a fundamental step towards delivery of precise, effective, and locally-relevant sepsis care worldwide.

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