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Precision Medicine for Sepsis Management in Low- and Middle-Income Countries—Melioidosis as a Model?

Advances in translational critical care have revealed limitations in the current clinical management of critical illness, which is syndrome based (1). Studies evaluating the host response using immunoassays, multi-omics platforms, and bioinformatics analysis have identified heterogenous subgroups (subphenotypes) as well as distinct pathogenic features (endotypes) among patients diagnosed with sepsis (2, 3). This has led to the aim of utilizing a precision medicine approach, where targeted therapeutic management is based on the utilization of assays to identify subphenotypes or clinical correlates of endotypes. This approach has been used in oncology with significant improvement in outcomes by targeting the underlying biological mechanism in individual patients (1).

The overwhelming majority of studies that have characterized the different subphenotypes or endotypes in patients with sepsis have been conducted in high-income countries (2, 3). Annually, there are an estimated 49 million cases of sepsis, resulting in 11 million deaths, which represents close to 20% of deaths globally (4). Almost 85% of the global incidence of sepsis are in low- and middle-income countries, with the highest burdens in South Asia, East Asia, Oceania, and sub-Saharan Africa (4). The characteristics of patients with sepsis in these regions, which may affect the outcomes, differ in demographics, pathogen etiology, and comorbidities compared with those in developed countries and even between the regions. However, the lack of studies conducted in these settings highlight a major limitation if a precision-based approach to sepsis management is to be implemented globally.

Melioidosis resulting from infection with the Gram-negative saprophytic pathogen *Burkholderia pseudomallei* is endemic in Southeast Asia, Northern Australia, and the Indian subcontinent, with a poorly defined epidemiology in many parts of the world (5). Melioidosis has distinct clinical features compared with other Gram-negative bacterial infections, with a varying proportion progressing to sepsis requiring management in ICUs (6). However, despite supportive care, organ replacement therapy, and the use of effective antimicrobial therapy, the mortality rate remains high, ranging from 14.6% in Northern Australia to 30–42% in Thailand (7, 8). These suggest that the host response in melioidosis may differ from that of other bacterial pathogens and that specific adjunctive agents may be required to improve outcomes.

In the study by Xia and colleagues (pp. 288–298) in this issue of the *Journal*, the metabolomic profile of patients enrolled from a single health care center in northeast Thailand who were microbiologically confirmed to have melioidosis was compared with a variety of other bacterial pathogens (9). The demonstration of several significant differences between the groups suggests that in subjects with other etiologies of sepsis in the region, mainly Gram-negative pathogens, melioidosis represents a subphenotype. This may have diagnostic and therapeutic implications, as a distinct host response in melioidosis may respond differently to supportive and adjunctive interventions. The pathways characterized by the metabolomics approach may provide clues as to the pathogenesis of melioidosis, particularly those associated with severe or fatal melioidosis. Although our understanding of these pathways is still rudimentary, better delineation may provide targets for intervention in the future. Although performing metabolomics routinely to guide therapy is not feasible, even in developed countries, technology is rapidly advancing, and it may be feasible in the near future.

This observation is consistent with other studies that have compared host gene expression in patients with melioidosis with that in patients who have other infections (10). In addition, melioidosis has several clinical characteristics that are not commonly seen in other Gram-negative pathogens, such as the high proportion of abscess formation in multiple organs and the need for prolonged antimicrobial therapy to prevent recurrences. The significant differences between survivors and nonsurvivors also suggest that there may be different endotypes in the melioidosis patients with sepsis. This observation is supported by a study conducted in Thailand that showed divergent longitudinal cytokine profiles being linked to outcome (11).

The aforementioned study by Xia and colleagues was performed as a collaboration between clinical researchers based in Thailand and

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overseas collaborators on a pathogen of major regional importance but globally neglected. Several features of *B. pseudomallei* sepsis in melioidosis make it a suitable model to develop a precision medicine approach to better define endotypes that may translate into the improved clinical management of melioidosis. These include a high rate of microbiological confirmation in health care settings with access to microbiology laboratories, a high burden of disease in endemic countries, and a high mortality rate. Achieving this will require a systematic approach with the establishment of clinical networks for enrollment of an adequate number of study subjects; facilities for sample storage; and establishment or access to immunoassays, multi-omics platforms as well as bioinformatic expertise. However, these are currently lacking in the wider Southeast Asia region, along with variable access to microbiology facilities, and we concur with the authors of a recent commentary that an "equitable approach to endotyping" is required for locally relevant clinical management of sepsis and melioidosis could be a suitable model (12). ■

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