EDITORIAL

Intensive care medicine in 2050: precision medicine

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By 2050, intensive care medicine will evolve from reliance on treatment protocols, guidelines, consensus definitions, and organ support to regularly applying the principles of precision medicine. Precision medicine entails the customization of therapies based on unique features of an individual patient or of patient subtypes. At a fundamental level, we already practice precision medicine. For example, among patients with cardiovascular shock, we select different pharmacologic agents on the basis of the etiology of shock. However, the hope is that the field can evolve toward a more granular form of precision medicine, wherein we directly address the unique molecular and biological features of an individual patient. For example, the rapidly evolving discipline of pharmacogenomics provides an opportunity to tailor drug selection and dosing based on genetic variants modifying drug response and metabolism [1].

Oncology is a primary area of investment for precision medicine initiatives [2]. This is appropriate given the public health burden of cancer, and the heterogeneous biological features of cancers. Intensive care medicine is an equally valid area in which to develop precision medicine, because it also represents a major health care burden. Further, critical illness typically reflects complex syndromes resulting from heterogeneous and dynamic biological processes.

Enrichment strategies are fundamental for disentangling the biological heterogeneity of critical illness and thus embracing precision medicine. Enrichment refers to the selection of patients in whom an intervention is more likely to be effective, as compared to unselected patients [3]. There are two broad categories of enrichment

strategies. *Prognostic enrichment* entails the selection of patients who are more likely to have a disease-related event, such as mortality. *Predictive enrichment* entails the selection of patients who are more likely to respond to an intervention based on a biological mechanism. This form of enrichment is more challenging because it requires a clear understanding of the biological mechanisms that directly contribute to the disease process of interest. For critical illness, this is an area where there exist many knowledge gaps.

Recent studies in sepsis and acute respiratory distress syndrome (ARDS) provide relevant examples of evolving enrichment strategies for critical illness. The examples highlight opportunities for molecular characterization of dysregulated and variable host responses that lead to critical illness. Using a combination of clinical and metabolomics data, Langley et al. developed a prognostic enrichment strategy to estimate the risk of mortality among patients with sepsis [4]. Similar efforts were developed for children with sepsis, but based on a panel of protein biomarkers [5, 6]. The most recent effort in this area involved a multi-research group collaboration that leveraged publically available transcriptomic data to develop and validate prognostic models for patients with sepsis [7].

With regard to predictive enrichment, Meyer et al. reported a coding variant of the interleukin-1 receptor antagonist (IL1RA) gene associated with increased production of IL1RA and decreased mortality among patients with ARDS or septic shock [8, 9]. This is particularly exciting given the availability of recombinant IL1RA for human use. In a precision medicine approach, this biological agent would be considered mainly for patients without the coding variant. Calfee et al. used clinical and biomarker data to identify subtypes of patients with ARDS [10]. Importantly, subtype membership was

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associated with differential responses to PEEP and fluid management strategies [10, 11]. Similarly, Davenport et al. used transcriptomics to identify two subtypes of patients with sepsis based on a sepsis response signature (SRS) [12]. The SRS1 signature indicates immune suppression, and patients allocated to this group have higher mortality compared to patients allocated to the SRS2 group. The existence of SRS1 and SRS2 sepsis subtypes was recently validated [13]. Analogous subtypes were reported among children with septic shock and the method for subtype identification was simplified for clinical application [14, 15]. These sepsis subtypes could be useful for more precise targeting of immune modulating therapies.

Figure 1 depicts a conceptual approach for applying prognostic and predictive enrichment strategies to enable precision intensive care medicine. Here, an otherwise heterogeneous cohort of patients with sepsis, as an example, is separated on the basis of the risk for poor outcome, using prognostic enrichment. Those with a low risk for poor outcome are treated with standard care and not considered for adjunctive therapies. The higher risk patients are further separated on the basis of a predictive enrichment strategy, which identifies patients who are candidates for therapies beyond standard care, targeting a specific biological mechanism. This approach requires robust and generalizable enrichment strategies in order to be effective. As proof of principle, a recent post hoc analysis combined prognostic and predictive enrichment strategies to identify a subgroup of children with septic shock who are more likely to respond favorably to corticosteroids [3].

Time is a major consideration for developing enrichment strategies for critical illness. Decision-making in

this population is time sensitive because of acuity and rapid clinical trajectories. Accordingly, effective enrichment strategies for critical illness must be developed to generate actionable data within a few hours. The technologies for achieving this capability are evolving rapidly. A related factor is the dynamic nature of critical illness. The technologies of 2050 will allow us to capture rapidly changing biological responses in real time, making it possible to more finely monitor treatment responses and titrate therapies.

Another major consideration is the source of biological materials used for enrichment strategies. All of the aforementioned examples of enrichment strategies rely on blood samples. While the blood compartment is an unquestionably rich source of biological information, it fails to fully capture organ-specific biological processes in critically ill patients. Thus, the technologies of 2050 will allow us to interrogate organ-specific biological mechanisms among critically ill patients. This capability will be represent a major enabler of precision intensive care medicine.

In summary, the complexity and heterogeneity of critical illness are ideally suited for the promises of precision medicine. Bringing these promises to fruition by the year 2050 requires the development of time-sensitive enrichment strategies, founded on a better understanding of the dynamic biological processes that contribute to critical illness.

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Compliance with ethical standards

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Conflicts of interest

The Cincinnati Children's Research Foundation and the author hold US patents and have US patents pending for some of the enrichment strategies described in this manuscript.

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