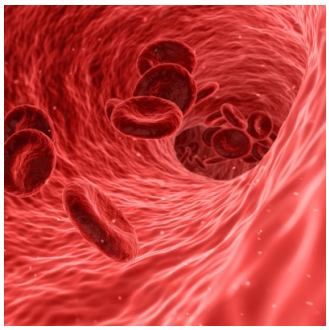
ICU
MANAGEMENT & PRACTICE

Using biomarkers to improve sepsis diagnosis and treatment



Since sepsis was first identified almost three decades ago, the existing definitions remain imprecise and the clinical diagnosis of sepsis corresponds poorly with post hoc presence of infection. Furthermore, the outcome of sepsis depends on factors beyond patient signs and symptoms, including age, the infection source, and the timing and appropriateness of therapeutic interventions.

There is currently a promising shift from predicting outcome to a pathobiology-driven understanding of the heterogeneity in the host response to sepsis, utilising novel translational high throughput tools and analytic methods to define distinct host response subgroups. Also, it is increasingly recognised that biological markers improve the classification of sepsis and can facilitate identification of distinct patient subclasses, or endotypes.

Transcriptomic profiling

Interindividual transcriptome variation in sepsis has been recently evaluated in several large cohorts, with a dysfunctional immune response phenotype being a common theme. With the use of nearly 25,000 genome-wide transcriptomic (gene expression microarray and RNA sequencing) profiles, researchers have identified patterns among expressed genes that define molecular subgroups representing different disease states without reference to clinical outcomes, but which could be associated to them.

In the most recent and comprehensive attempt to identify sepsis subtypes, data from 14 transcriptomic datasets consisting of 700 patients revealed three robust host response clusters across the sepsis spectrum. These were termed: (1) inflammopathic (increased innate and reduced adaptive immune signal marked by increased expression of IL-1 receptor, pattern recognition receptor activity, complement activation); (2) adaptive (reduced innate and high adaptive immune signal with lower mortality, marked by interferon signalling); and (3) coagulopathic (irregularities in the coagulation and complement systems, including platelet degranulation and glycosaminoglycan binding).

Since the transcriptome profile depends on the inflammatory cell type, it is possible that gene expression patterns that distinguish subclasses reflect different leukocyte populations instead of within-cell differences in gene expression. These findings require validation in large cohorts spanning different countries as variation in ethnic background is a strong determinant of gene expression.

Metabolomics

Metabolomics is an expanding and less familiar method to decipher heterogeneity in sepsis. It refers to the global assessment of small metabolites in any biological sample, representing a composite ‘snapshot’ of gene expression, enzyme activity, and the physiological landscape. The metabolites can include both endogenous (lipids, carbohydrates, amino acids, nucleic acids) and exogenous (microbial components and byproducts) compounds. Alteration in endogenous metabolite concentration can be linked to biological pathways and the magnitude of change relates to the stage of illness, significantly magnifying transcriptome and proteome-level shifts. Studies so far included retrospective specimen collection with small sample sizes.

Metabolites also vary based on infection source, with community-acquired pneumonia (CAP) having a different metabolite pattern relative to other sites of infection. A recent analysis of the plasma metabolome in H1N1 pneumonia successfully differentiated viral from bacterial culture-positive pneumonia and ventilated ICU controls. Therefore, whether sepsis endotypes are truly independent of infection type and anatomical source will require large-scale prospective cohort studies with enough power to address this question.

Conclusion

It is possible that the true nature of the heterogeneity of the host response to sepsis will require a combination of molecular, protein, metabolomic and functional signatures that will lead to an integrated, simple, and clinically useful diagnostic model that could be rapidly used at the time of ICU admission. Hopefully, a parsimonious set of biological markers will be useful to categorise patients into specific sub-groups that would be useful for testing specific new therapies. Ultimately, detection of key biological markers along with clinical indicators at the bedside could help with precision medicine-guided therapy and outcomes of patients with sepsis.

Source: Critical Care

Image credit: Pixabay

Published on : Tue, 12 Mar 2019