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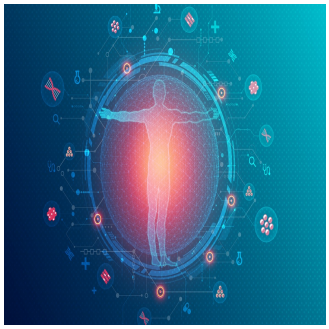
ICU Syndromes and Subphenotypes - Sepsis, ARDS and AKI



Critical care has traditionally focused on clinical practice and research around syndromes such as sepsis, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and traumatic brain injury (TBI). However, these syndromes, while familiar to clinicians, are inherently diverse and encompass various pathophysiological processes that vary among individual patients. This heterogeneity has posed challenges for pharmacological and supportive care interventions, many of which, despite promising preclinical results, have failed to demonstrate efficacy or even caused harm in critically ill patients.

Recent integrated biological and physiological data reveal identifiable subpopulations or "subphenotypes" within these syndromes that may respond differently to treatments tested in clinical trials. Adopting a precision medicine approach holds promise for improving therapeutic outcomes in critical care, although its widespread implementation remains limited.

The concept of biologic subphenotypes in critical care syndromes such as sepsis, ARDS, and AKI reflects their inherent heterogeneity. Traditional approaches based on clinical severity or organ dysfunction have often failed to predict treatment outcomes effectively. Recent machine learning and molecular testing studies have identified distinct subphenotypes within these syndromes. For instance, in sepsis, transcriptomic clusters and immune biomarkers like monocyte HLA-DR expression have shown promise in predicting treatment responses, influencing trial designs towards precision medicine. Similarly, in ARDS and AKI, subphenotyping using clinical, inflammatory biomarkers, and genetic data has delineated groups with differential treatment responses, suggesting a shift towards more tailored therapeutic approaches in critical care.

Precision medicine in critical care extends beyond molecular measurements to include physiologic data. Physiological measures linked to underlying intervention mechanisms and outcomes identify treatable traits and define subgroups benefiting from specific therapies. For instance, in ARDS, patients with differing respiratory system compliance may show varying survival benefits from ventilation strategies. Similarly, monitoring ventilatory efficiency aids in selecting patients for interventions like extracorporeal CO2 removal. In traumatic brain injury (TBI), physiologic monitoring informs therapy intensity, such as decompressive craniectomy, based on intracranial pressure dynamics and metabolic markers like brain tissue Po2 and microdialysis.

In sepsis and ARDS, studies have identified multiple subphenotypes beyond initial stratifications, reflecting diverse inflammatory states in different compartments like alveolar fluid versus plasma. This heterogeneity is particularly evident in ARDS, where respiratory outcomes correlate more closely with the alveolar inflammatory state. In paediatric populations, distinct subphenotypes exist due to developmental differences in immune systems and disease susceptibilities influenced by age-related immune maturation and rare primary immune deficiencies. Transcriptional profiling in sepsis highlights differences between paediatric and adult subphenotypes, influencing clinical outcomes and responses to treatments like glycemic control. Unique AKI subphenotypes distinguish children from adults, underscoring the need for age-specific approaches in critical care.

Recent studies in subphenotyping within critical care have shown promising results, identifying distinct subgroups with implications for prognosis and predictive enrichment. However, further research is needed to validate and compare the various subphenotyping schemas published thus far.

While preclinical studies continue to identify potentially treatable traits, retrospective analyses of clinical trial data have uncovered many subphenotypes and traits that respond differently to therapies. Machine learning techniques, such as causal forests and AI algorithms, aid in identifying treatment heterogeneity across large datasets. These methods are crucial for optimising trial designs and implementing adaptive strategies to maximise treatment benefits in responsive patient subsets.

Realising precision medicine in critical care requires a paradigm shift towards global research collaboration. Emerging models include national clinical trials groups, international platform trials, and collaborative biologic consortia. These networks facilitate research beyond individual institutions, focusing on data sharing, standardising research metrics, defining outcomes, and engaging stakeholders like funders and patients.

Overcoming differences in regulatory frameworks and funding mechanisms across jurisdictions remains a significant hurdle. Balancing industry and academia's roles is crucial, as industry-driven models often emphasise competitive knowledge generation, while academic institutions face challenges adapting to large-scale collaborations.

Ultimately, it is paramount to incorporate the patient perspective throughout research design and implementation. Involving patients and families in subphenotype-driven research ensures that clinical trials align with patient needs and preferences, fostering a comprehensive approach to advancing precision medicine in critical care.

Source: AJRCCM

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