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Critical Care Medicine

Volume 2

Recent Advances in Critical Care Medicine

Editors
Atul Prabhakar Kulkarni
Kushal Rajeev Kalvit

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CHAPTER

9

Precision Medicine: Sub-phenotyping in Critical Care

Shaveta Devesar, Prashant Nasa

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INTRODUCTION

The evolving landscape in healthcare is precision-based medicine and patient-centered care with an individualized treatment approach. Historically, critical care has relied on broad syndromic definitions for treatment and research purposes. Constructs or syndromes such as sepsis, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), traumatic brain injury (TBI), and delirium were developed using a combination of clinical, physiological, and biochemical patterns for the identification and grouping of critically ill patients. Although these syndromes help in early diagnosis through easily accessible clinical and physiological variables, the fundamental heterogeneity in underlying etiology and pathophysiological processes challenges their existence. It is further complicated by the inter-individual variation in response to inciting injury and response to interventions. Additionally, these syndromes involve diverse overlapping biological mechanisms, and may present as multiple, yet interconnected critical care syndromes.

The heterogeneity observed in these syndromes is often cited as a significant barrier, both in clinical practice and research. The definition or diagnostic criteria of these syndromes are mainly left broader to improve sensitivity and include the majority of patients, albeit with varied clinical presentations, disease course, and outcomes. Moreover, using these definitions as inclusion criteria for clinical research has its own challenges. The heterogeneity could explain the numerous failed clinical trials on various pharmacological and supportive care interventions that may appear otherwise promising in preclinical models. Furthermore, in some instances, heterogeneity may also account for adverse effects of an intervention observed in certain subgroups of patients while the benefit is observed in others (heterogeneity-of-treatment effect).

A *one-size-fits-all* approach is increasingly viewed as inadequate, prompting a shift toward more personalized interventions that recognize patient and disease heterogeneity.[1,2] Sub-phenotyping these clinical syndromes into distinct subgroups with or without treatable traits offers an opportunity for more targeted, effective interventions in critical care settings. This chapter aims to provide a comprehensive overview of sub-phenotyping

in critical care, highlighting the scientific rationale, methodologies employed, evidence, clinical applications, challenges for sub-phenotyping, and future directions for precision-based medicine.

RATIONALE FOR SUB-PHENOTYPING

Delineate Heterogeneity

Sub-phenotyping involves using various measurable traits such as physiological characteristics, imaging and biomarkers to categorize syndromes (phenotype) into distinct and reproducible subgroups **(Table 1)**. Sub-phenotyping is used in critical care to address patient heterogeneity and enable tailored treatment strategies and prognostic enrichment.

Most syndromes in critical care are inherently heterogeneous, featuring patients with overlapping clinical presentations and pathophysiological mechanisms but heterogeneous etiology, molecular, immunological, and physiological characteristics. Sub-phenotyping helps to delineate heterogeneity of syndromes such as sepsis, ARDS, and AKI, and allows

TABLE 1: Definitions of phenotyping terminology used in this chapter.

Terms	*Definition*	*Example*
Phenotype	Clinically observable set of characteristics	ARDS
Subgroup	Categorization of phenotypes using a *cut-off of clinical or physiological* variable	PaO_2/FiO_2 ratio-based classification of ARDS
Sub-phenotype	Clinically *distinct subgroups* of phenotype which can be reliably discriminated, based on a shared set or pattern of measurable or observable characteristics	Biomarkers-based sub-phenotyping into hyper- or hypoinflammatory
Endotype	Sub-phenotype with *distinct underlying functional or biological mechanisms* (e.g., gene expression, protein levels, or biomarkers) that may or may not be associated with a specific treatment response	Specific profile within hyperinflammatory sub-phenotype (e.g., IL-6, complement pathway)
Treatable traits	Set of measurable clinical characteristics and/or biomarkers representing a pathophysiological process and have been linked to outcomes/interventions	Hyperinflammation in ARDS or sepsis

(ARDS: acute respiratory distress syndrome; IL: interleukin; PaO_2/FiO_2: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen)
Source: Adapted from Nasa P, Bos LD, Estenssoro E, van Haren FM, Serpa Neto A, Rocco PR, et al. Consensus statements on the utility of defining ARDS and the utility of past and current definitions of ARDS-protocol for a Delphi study. BMJ Open. 2024;14(4):e082986.

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precision-based personalized treatment. For example, sepsis has been redefined by third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3) as life-threatening organ dysfunction caused by a dysregulated host response to infection. Although the definition shifted its focus on organ dysfunction from nonspecific clinical signs grouped as systemic inflammatory response syndrome (SIRS). However, there is no consideration of the underlying etiology, molecular and immunological pathways leading to organ failure and the presence of pre-existing organ dysfunction.[3] Furthermore, many noninfective conditions present with organ failure and overlap considerably with sepsis. This often accounts for the failure of otherwise promising therapies to demonstrate efficacy in large clinical trials, as differential responses among unrecognized patient subgroups dilute observed treatment effects. Sub-phenotyping aims to resolve these differences, allowing clinicians to—(1) predict which patients will respond to specific therapies; (2) identify mechanisms that drive adverse outcomes; and (3) design targeted clinical trials that enrich for likely responders.

Differential Prognostic and Treatment Implications

Patients categorized into distinct sub-phenotypes may demonstrate unique disease trajectories and varying responses to treatments.[4] The identification of these subgroups facilitates prediction of outcomes (prognostic enrichment) and enables the selection of patients who are most likely to benefit from specific therapeutic interventions (predictive enrichment).[5]

Understanding Pathophysiology

Identifying sub-phenotypes based on biological characteristics provides deeper understanding of the pathophysiological mechanisms underlying the various syndromes and insights into heterogeneity of treatment effect. Besides, these mechanistic studies also explain varied patient trajectories within the same condition and help in prognostication.[6]

METHODOLOGIES FOR SUB-PHENOTYPING

Various approaches are employed to uncover distinct patterns within a broader clinical phenotype, thereby identifying sub-phenotypes. These sub-phenotypes often differ in prognosis, treatment response, or biological pathways. The process typically involves statistical modeling using a combination of clinical and physiological characteristics, biomarkers, and imaging.[3]

Statistical and Clustering Methods

Recent advances in big data analytics and computational biology have facilitated the integration of multidimensional datasets that include multiple variables such as clinical, physiological, imaging, and biological (biomarker)

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characteristics. The complex statistical tools such as clustering algorithm and latent class analysis (LCA) are used for large scale analyses of clinical, physiological and molecular data to identify critical illness subphenotypes.

Latent Class Analysis

Latent class analysis is a probabilistic method for partitioning patients into latent subgroups within a heterogeneous cohort based on patterns of observed variables (clinical, physiological, or biological).[3]

Clustering Analysis

It is an unsupervised machine learning method that identifies homogenous subgroups based on similar characteristics (clinical, biological, or physiological).[6]

Dynamic Time Warping

Along with hierarchical agglomerative clustering (HAC), dynamic time warping (DTW) identifies sub-phenotypes by analyzing the trajectory of physiological scores, e.g., temporal evolution of Sequential Organ Failure Assessment (SOFA) score over time in sepsis.[7]

Biomarker and Data-driven Approaches

Machine Learning Models

Unsupervised clustering of large datasets including support vector machines, random forests, and deep learning identifies sub-phenotypes with distinct underlying biological mechanisms.[2]

Multiomics

Integrating information genomics, transcriptomics, proteomics, and metabolomics for better characterization of pathophysiology and patient–environment interactions, thereby, identifies exclusive subgroups (sub-phenotypes).

Real-time Sub-phenotyping

Emerging technologies enable point-of-care diagnostic platforms for rapid biomarker measurement (e.g., portable immunodiagnostic assays), which may facilitate real-time clinical decision-making.

Trajectory-based Methods

Using dynamic evolution of various physiological characteristics, distinct subgroups could be identified for patient prognostication and treatment responses (dynamic trajectory of PaO_2 and FiO_2 ratio, organ dysfunction scores).[8]

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EVIDENCE FOR SUB-PHENOTYPES IN CRITICAL CARE SYNDROMES

In this section, we will discuss the evidence on three common ICU syndromes—sepsis, ARDS, and AKI. There are other conditions where sub-phenotyping has been described such as TBI and delirium. However, these are beyond the scope of this chapter.

Sepsis

Sub-phenotyping in sepsis has been performed based on the immune response, biomarkers, organ dysfunction, and clinical trajectories. Moreover, the evidence supports sub-phenotyping for mortality prediction, guiding personalized interventions, and/or developing targeted therapies.[2]

Inflammatory (Hyperinflammatory versus Hypoinflammatory) Sub-phenotypes

Previously validated models used for sub-phenotyping ARDS, including clinical data and plasma biomarkers, were used for LCA-based sub-phenotyping in two randomized controlled trials (RCTs) of sepsis—Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock (PROWESS-SHOCK) trial and Vasopressin and Septic Shock Trial (VASST) were evaluated. A strong concordance was noted between sepsis and ARDS sub-phenotypes with higher proinflammatory cytokines and lower protein C in the hyperinflammatory sub-phenotype. Moreover, a higher vasopressor requirement and mortality rates were observed in the hyperinflammatory versus hypoinflammatory sub-phenotype ($p < 0.0001$). Notably, significant heterogeneity of treatment effect was found with lower mortality associated with activated protein C in the hyperinflammatory sub-phenotype compared to placebo. However, no treatment interaction was observed in the VASST trial.[9]

Immune Profiling

The immune profiling is based on the host response to the microbial agent. In a large study, four distinct sub-phenotypes were identified across three observational cohorts and three clinical trial populations, and labeled as α, β, γ, and δ. Patients in the α sub-phenotype showed relatively normal laboratory values and minimal organ dysfunction. Those in the β sub-phenotype were typically older, with a greater burden of chronic diseases, and more often presented with AKI. Hypoalbuminemia, higher body temperatures, and elevated markers of systemic inflammation characterized the γ sub-phenotype. In contrast, the δ sub-phenotype was marked by hypotension and elevated serum lactate levels. Importantly, mortality rates were consistently highest among patients in the δ group—up to eight times greater than those in the lowest-risk α group. Additionally, circulating cytokine concentrations

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were found to be elevated in both the γ and δ phenotypes compared with α and β.[10]

In another study using body temperature, four sub-phenotypes were identified—hyperthermic slow resolvers, hyperthermic fast resolvers, normothermic, and hypothermic. Hyperthermic cohorts had higher levels of both pro- and anti-inflammatory cytokines. However, hypothermic patients had lower levels of inflammatory cytokines, instead higher levels of coagulation biomarkers such as thrombomodulin, Ang-1, and tissue factor as well as higher mortality.[11]

The Molecular Diagnosis and Risk Stratification of Sepsis (MARS) consortium described four sepsis sub-phenotypes, termed Mars1–4.[11] Patients classified as Mars1 had the highest SOFA scores, with a greater incidence of shock and mortality. Their gene-expression profile suggested impaired innate and adaptive immune responses, including downregulation of NFκB1, toll-like receptor signaling, T-cell receptor signaling, and antigen presentation.

Trajectory-based

Sub-phenotyping based on the trajectory of vital signs, laboratory variable, and organ function helps to identify sub-phenotypes. Hao et al. identified three sub-phenotypes using time-series clustering analysis and DTW and labeled as type A to C. Type C with severely impaired organ function noted to have highest inflammatory markers and mortality rate, compared to type A and type B.[12]

Acute Respiratory Distress Syndrome

There is no other syndrome like ARDS in critical care, where considerable heterogeneity exists and with extensive work on sub-phenotyping has been performed. Sub-phenotyping ARDS has been performed based on etiological, physiological, radiological, and biological criteria.

Inflammatory Sub-phenotypes

In ARDS, inflammatory sub-phenotyping divides patients into groups with distinct biological and clinical characteristics, most commonly hyperinflammatory and hypoinflammatory. Patients in the hyperinflammatory subgroup tend to experience poorer outcomes, with higher rates of mortality and multiorgan failure, whereas those in the hypoinflammatory subgroup generally show more favorable prognoses. These categories, defined through a combination of biomarkers and clinical variables, also appear to respond differently to specific therapies such as simvastatin and corticosteroids, highlighting opportunities for a more personalized approach to ARDS management. Post-hoc analysis of large

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RCTs indicates that the incidence of hyperinflammatory sub-phenotype is around 30–40%. In a meta-analysis of 12 studies comprising 6,643 patients, based on low certainty of evidence, patients with hyperinflammatory ARDS were found to be associated with a higher risk of death and lower ventilator-free days compared to hypoinflammatory sub-phenotypes.[13]

However, primary challenges with biomarkers are the bedside availability for classification and diagnosis. Besides, most research is retrospective with post-hoc analysis of large RCT. Prospective research and point-of-care biomarker assays are required, before they are adopted in clinical practice.[4]

Radiology-based Sub-phenotyping

Imaging (CT chest)-based categorization of ARDS into focal and nonfocal sub-phenotypes have been studied for personalized ventilation strategies. Patients with focal ARDS received a tidal volume of 8 mL/kg, low positive end-expiratory pressure (PEEP), and early prone positioning. On the other hand, nonfocal ARDS patients received a lower tidal volume (6 mL/kg), higher PEEP, as well as recruitment maneuvers. Although there was no survival benefit between the personalized ventilation compared to control, misclassification of patients into wrong sub-phenotype was associated with higher mortality.[14] This study reflects on the challenges of classification of ARDS at the bedside and potential implications of misclassification.

Lung ultrasound provides a noninvasive alternative to categorize ARDS, but challenges such as interobserver variability, difficulties in image acquisition in patients with obesity or subcutaneous emphysema, and its inability to detect hyperinflation limit its utility. A meta-analysis showed pooled sensitivity of 0.631 [95% confidence interval (CI): 0.45–0.782] and specificity of 0.942 (95% CI: 0.86–0.98) for diagnosis of ARDS. However, the data was inadequate for meta-analysis for sub-phenotyping.[15] An ongoing RCT will provide further evidence in this regard.[16]

Beyond imaging, physiological and radiological data have helped identify ARDS sub-phenotypes such as recruitable and non-recruitable groups, which differ in their responses to therapies and in mortality risk—a trend also observed in COVID-19-related ARDS.

Physiological Variables

Tracking respiratory mechanics like ventilatory ratio and mechanical power over time can identify worsening or stabilizing sub-phenotypes**.** Using the machine learning with training in the Chinese ARDS Database and further validation in FACTT, SAILS, ALVEOLI, and MIMIC-IV datasets, three longitudinal oxygenation subgroups were identified. The PaO_2/FiO_2 trajectories over time were characterized as persistently low, gradually increasing, and rapidly improving. Mortality varied significantly across these

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subgroups (62.6% vs. 35.8% vs. 17.4%) and performed better than the Berlin classification of severity. Moreover, treatment heterogeneity with high versus low PEEP was greater in the longitudinal subgroups than the static PaO_2/FiO_2 Berlin-defined groups.[17]

A cluster analysis of 3,875 patients identified three clinical sub-phenotypes of ARDS. Sub-phenotype I (40%) was associated with fewer laboratory abnormalities, less organ failure, lower in-hospital mortality, and the greatest number of ventilator-free and ICU-free days, resembling the hypoinflammatory phenotype. Sub-phenotype II (32%) was characterized by younger age, elevated WBC count, higher temperature, increased heart and respiratory rates, and lower systolic blood pressure—features consistent with the hyperinflammatory phenotype. Sub-phenotype III (28%) included older patients with higher serum creatinine and blood urea nitrogen, lower bicarbonate, fewer ventilator-free and ICU-free days, and the highest mortality, reflecting contributions from organ dysfunction, advanced age, and metabolic acidosis. These findings were validated in three RCTs (ALVEOLI, FACTT, and SAILS), where significant treatment heterogeneity was observed in ALVEOLI and FACTT, though no clear heterogeneity of treatment response was seen in SAILS.[18]

Acute Kidney Injury

Sub-phenotyping AKI has highlighted heterogeneous treatment effects with fluid balance strategies, as well as response to renal replacement therapies.

Creatinine Trajectory

In a cohort of cardiopulmonary bypass, divided into development and validation sets and using LCA, 12 AKI sub-phenotypes were distinguished by different postoperative serum creatinine trajectories over time. The study also incorporated patient demographics, procedural variables, postoperative complications, and long-term outcomes. Importantly, four of these sub-phenotypes were classified as high-risk**,** demonstrating a substantially greater long-term mortality risk compared with lower-risk groups.[19]

In another cohort of 6,816 ICU patients with any stage of kidney disease: Improving Global Outcomes (KDIGO)-defined AKI, the pattern of kidney function over time was more strongly linked to inpatient mortality than the peak KDIGO stage itself. Patients with a lower maximum KDIGO stage but a gradual decline in renal function (sub-phenotypes C and D) experienced higher ICU mortality than those who presented with a high KDIGO stage but showed rapid recovery within three days (sub-phenotypes A and B).[20] Another recent study on AKI in sepsis patients, using creatinine trajectory, noted a persistent AKI sub-phenotype was more likely associated with worse outcomes and chronic kidney disease.[21]

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Biomarker-based Sub-phenotypes

Various biomarkers are used for detection of subclinical AKI, defined as AKI before rise of creatinine. These biomarkers include plasma or urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary kidney injury molecule 1 (KIM-1), urinary tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7).

In cohorts of septic patients, LCA identified two distinct AKI sub-phenotypes using biomarkers. Patients with elevated biomarker levels [(TIMP–2) · (IGFBP7) > 0.3] following fluid resuscitation were at increased risk of a composite outcome comprising progression to severe AKI (Stage 2/3), need for dialysis, or death. Notably, the incidence of this composite endpoint was comparable among patients with elevated postresuscitation biomarkers, regardless of their preresuscitation biomarker status, and was also similar between those with or without AKI at enrolment as defined by serum creatinine and urine output.[22,23]

Analysis of data from the VASST trial (vasopressin versus norepinephrine in septic shock) further revealed treatment effect heterogeneity, with differing responses to the early initiation of vasopressin between the sub-phenotypes. Patients with less severe septic shock, potentially benefited with early vasopressin initiation, with no survival benefit observed in more severe septic shock.[24]

TABLE 2: Challenges in implementation of current sub-phenotyping of critical care syndromes.

Pitfall	*Description*
Clinical utility	Sub-phenotypes must be prospectively identifiable, measurable, actionable, predictive of treatment response, and reproducible across populations
Generalizability	Models identified and validated in high-resource settings may not translate directly to low-resource environments; global validation is needed
Practicality	Complex sub-phenotypes should be approximated using simple, pragmatic, readily available and point-of-care measurable data for routine implementation
Equity and representation	Underrepresentation of ethnic minorities, children, and pregnant women can limit applicability and exacerbate disparities; patient-centered outcomes are essential
Transparency	Artificial intelligence/machine learning models may be "black boxes," complicating clinician understanding and patient communication
Trial feasibility	Selecting cohort for treatment evaluation increases screening burden, sample size requirements, and raises ethical considerations regarding equipoise

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CHALLENGES WITH SUB-PHENOTYPING

The major challenges in data-driven phenotyping are the heterogeneity of current methods, with no standardized or reproducible approaches to identify sub-phenotypes and endotypes across different datasets, and a lack of consolidated strategies to translate these findings into clinical practice. Most models have been developed in specific cohorts and settings, so their generalizability across various health systems and ICUs remains unclear. Prospective validation in diverse populations will, therefore, be essential, before their widespread adoption. Any proposed sub-phenotype should be evaluated for—(1) consistency and reproducibility in independent datasets, (2) biological plausibility, and (3) clinical utility, such as predicting high-risk patients or guiding treatment response **(Table 2)**.

Ultimately, an ideal phenotyping algorithm should inform real-time clinical decision-making and offer added value compared with existing severity scoring systems.

FUTURE DIRECTION

Future direction for sub-phenotyping in critical care includes translating promising research findings into clinically meaningful strategies at bed side that improve patient outcomes. A key priority is the prospective validation of identified sub-phenotypes through large, multicenter international studies. The primary objective is to determine whether sub-phenotypes reliably predict treatment response and improve patient-centered outcomes across diverse populations and healthcare settings. Therefore, the reproducibility and generalizability of the research findings will be critical, particularly as current models have largely been derived from high-resource settings in west (North America and Europe), which may not reflect patient characteristics or critical illness epidemiology in low- and middle-income countries. Adapting and validating sub-phenotyping approaches in these settings will be necessary to ensure global relevance and equity in critical care research.[1]

Another important direction is the development of pragmatic and simplified approaches that facilitate bedside implementation. While many sub-phenotypes have been derived from complex, multimodal data, future efforts should focus on translating these into clinically feasible tools using routine clinical parameters or limited biomarker panels. This will allow clinicians to readily identify sub-phenotypes and tailor interventions without requiring extensive laboratory or computational resources. Another related issue is the integration of sub-phenotyping into precision medicine, where patients can be stratified for targeted interventions in both clinical trials and routine practice. Sub-phenotypes may guide therapeutic decisions, optimize treatment allocation, and improve the efficiency and success of critical care trials.[2,3]

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Equity and inclusion must also guide future work. Underrepresentation of specific population subgroups such as racial and ethnic minorities, children, and pregnant women in existing trials limits generalizability and may perpetuate disparities in access to novel therapies. Future research should actively incorporate these populations and focus on patient-centered outcomes relevant across diverse groups. At the same time, the use of machine learning and artificial intelligence to define sub-phenotypes must become more transparent and interpretable. Clinicians should be able to understand and communicate the rationale behind model-derived treatment recommendations, ensuring informed decision-making and fostering trust in precision approaches.

Finally, there is considerable potential to refine sub-phenotypes by integrating multiomics data, including genomics, proteomics, metabolomics, and real-time physiologic parameters. Combining molecular and clinical data may identify mechanistic endotypes that not only predict outcomes but also reveal novel therapeutic targets. Ultimately, successful implementation will require developing clinical decision support systems and protocols that incorporate sub-phenotyping into routine care, alongside rigorous evaluation of their impact on patient outcomes, resource utilization, and cost-effectiveness. Through these efforts, sub-phenotyping can evolve from a research concept into a practical and equitable tool for personalized critical care.[7]

CONCLUSION

Sub-phenotyping is ushering in a new era of precision-based critical care medicine. By acknowledging and delineating patient heterogeneity, this approach holds promise for optimizing therapeutic strategies, enhancing trial efficiency, and ultimately improving patient prognostication and outcomes. While numerous methodological, practical, and ethical challenges remain, the combined advances in data science, diagnostics, and global collaboration highlight a future where individualized care is not only possible, but routine.

Transforming practice from a "one-size-fits-all" to a "personalized" approach in the ICU will require not just innovations in technology and science but also a commitment to equity, collaboration, and continuous learning. As the field progresses, clinicians are encouraged to remain engaged with emerging evidence, embrace data-driven care pathways, and contribute to collaborative efforts that will drive the next wave of progress in critical care.

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Recent Advances in Critical Care Medicine

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This book is aimed at introducing new entrants in the field of critical care medicine to the intricacies of art; as well as for the old hands to update their skills.

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Atul Prabhakar Kulkarni MD (Anesthesiology) is currently Professor and Head, Division of Critical Care, Department of Anesthesiology, Critical Care, and Pain at the Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India. A recognized postgraduate Teacher for MD (Anesthesiology), he is now a Teacher for DM (Critical Care Medicine). He has received Training in Intensive Care at St George Hospital, Sydney, Australia (2002–2003). He finished his Postgraduate Diploma in Health and Healthcare Management from the prestigious Symbiosis Institute. He has participated in many conferences on critical care and anesthesiology at international, national, and state levels. He was the Organizing Secretary for anesthesia review course, since 2004–2018. He has held various positions in the National Executive Committee of the Indian Society of Critical Care Medicine: Treasurer (2004–2010), General Secretary (2010–2014), and lastly the President (2015–2017). He, at the same time, was the Chancellor of the Indian College of Critical Care Medicine. He was a Member of the Editorial Board of the Indian Journal of Critical Care Medicine (IJCCM), a Reviewer for IJCCM, and the past Editor-in-Chief of the IJCCM. He is also the past President of Association of South Asian Association for Regional Cooperation (SAARC) Critical Care Societies and Secretary General. After serving as the honorary Secretary General of the Asia Pacific Association of Critical Care Medicine (APACCM), he took over as the President of the prestigious organization. He handed over the reins of Society July (2024) to his successor. Apart from many publications in the national and international journals in Anesthesia and Critical Care Medicine, he has published many books, including the very popular *Objective Anesthesia Review* (6 editions), *Textbook of Hemodynamic Monitoring and Therapy* (2 editions), and *Case-based Review in Critical Care Medicine* (2 editions).

Kushal Rajeev Kalvit MD DM EDIC EDEC PGDMT is a Physician–Intensivist and is currently working as a Senior Consultant, Department of Critical Care Medicine, Sir HN Reliance Foundation Hospital, Mumbai, Maharashtra, India. He completed his internal medicine residency followed by training in critical care medicine at the Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra. He went on to pursue a Fellowship in Critical Care at Guys and St Thomas' Hospital at London. He has authored/co-authored more than 45 chapters in various textbooks of critical care and has numerous national and international publications to his credit. He has served as the Editor of the first edition of *Recent Advances in Critical Care* book and the *Indian Society of Toxicology's Poisoning Protocols Handbook*.

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