The future of critical care: lessons from the COVID-19 crisis

The COVID-19 pandemic has put a huge strain on critical care resources worldwide, as systems have struggled to provide high-quality care for a surge of critically ill patients. The response of clinicians and researchers—in providing care in extraordinary circumstances and in rapidly establishing research programmes to explore the potential of a range of preventive and therapeutic approaches—has been impressive. Lessons can be learned from the challenges encountered and the successes achieved as we consider future directions for critical care.

The crisis has triggered collaborative efforts to develop and implement treatments and vaccines, as seen with the launch of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership. A range of treatments to target the virus or the host response—including small-molecule antivirals, monoclonal antibodies, and cell-based therapies—is being tested in clinical trials. Promising results have been reported for remdesivir, but further developments are eagerly awaited. Testing of interventions should go hand in hand with efforts to understand the pathology, disease mechanisms, clinical features, and clinical course of COVID-19; the identification of phenotypes and treatable traits could ultimately help to facilitate a personalised approach to care. The pandemic has also brought renewed focus to the fundamentals of good clinical practice, including the need to make full use of interventions with proven benefit—eg, lung-protective ventilation for acute respiratory distress syndrome (ARDS)—and to restrict the use of unproven interventions that might do harm to testing in controlled trials, as far as possible.

In low-income and middle-income countries (LMICs), the pandemic has drawn attention to the scarcity of much-needed resources for critical care; importantly, it has also emphasised the need for training and education of health-care workers, modification of guidance developed in high-income settings to establish management approaches that match local resources, and research with a focus on clinical practice in LMICs. Outside the pandemic setting, the Kigali modification of the Berlin definition of ARDS exemplifies the pragmatic adjustments that can be made to facilitate critical care medicine in resource-limited settings. Large, collaborative initiatives such as the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) have also enabled progress in the prevention and management of critical illness on a global scale. Building critical care capacity, responding rapidly to local emergencies, and tailoring diagnostic, prognostic, and therapeutic approaches to a range of settings should be a priority as we move beyond the current crisis.

The substantial heterogeneity of critical care syndromes such as ARDS and sepsis has hindered progress in identifying treatment targets and achieving positive outcomes in clinical trials. A lack of targeted therapeutics and consensus on aspects of management has meant that the needs of critically ill patients are often unmet, with some subgroups exposed to interventions that do harm. In a Review in this issue, Kiran Reddy and colleagues outline advances in the identification of clinical and biomarker-driven subphenotypes of critical care syndromes, which could transform the landscape of critical care as precision medicine approaches are realised. In a second Review, Tom van der Poll and colleagues consider the potential of macrolides in correcting immune dysregulation in critically ill patients, highlighting the need to identify subgroups of patients who might benefit from existing and novel compounds.

Developments in research and clinical practice will bring new challenges, but also opportunities for progress in meeting the needs of individual patients. Large-scale research networks could help to accelerate patient recruitment, achieve larger samples of predicted responders, and improve the generalisability of research findings. Adaptive platform trial designs could improve the efficiency and productivity of testing. And the hope is that new approaches to clinical decision making (eg, use of artificial intelligence) and the delivery of high-quality care (eg, through telemedicine) will help to ensure that patients benefit from emerging therapeutic options.

The COVID-19 crisis has served as a stark reminder of the need for planning and preparedness to allow critical care resources to be mobilised and to enable rapid testing of diagnostic, prognostic, and therapeutic approaches to tackle new disease outbreaks. The high motivation for progress in research and clinical practice—with support from funders and policy makers—must be maintained and expanded as we look beyond COVID-19 to the full range of issues that need to be addressed in critical care medicine worldwide. ■ *The Lancet Respiratory Medicine*

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For more on the **ACTIV partnership** see *JAMA* 2020; published online May 18. DOI:10.1001/jama.2020.8920

For more on **remdesivir for the treatment of COVID-19** see *N Engl J Med* 2020; published online May 22. DOI:10.1056/NEJMoa2007764

For more on the **treatment of COVID-19-related ARDS** see **Comment** *Lancet Respir Med* 2020; **8:** 433–34

For more on the **Kigali modification** see *Am J Respir Crit Care Med* 2016; **193:** 52–59

For more on **ISARIC** see https://isaric.tghn.org/

For the **paper by Reddy and colleagues** see **Review** page 631

For the **paper by van der Poll and colleagues** see **Review** page 619

For more on **international research in critical care medicine** see **Spotlight** *Lancet Respir Med* 2019; **8:** 245–46

For more on **adaptive platform trials** see *Nat Rev Drug Discov* 2019; **18:** 797–807

For more on the **use of artificial intelligence in the treatment of sepsis** see *Nat Med* 2018; **24:** 1716–20

For more on **telemedicine in critical care** see *Crit Care Med* 2020; **48:** 553–61

Subphenotypes in critical care: translation into clinical practice

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Despite progress in the supportive care available for critically ill patients, few advances have been made in the search for effective disease-modifying therapeutic options. The fact that many trials in critical care medicine have not identified a treatment benefit is probably due, in part, to the underlying heterogeneity of critical care syndromes. Numerous approaches have been proposed to divide populations of critically ill patients into more meaningful subgroups (subphenotypes), some of which might be more useful than others. Subclassification systems driven by clinical features and biomarkers have been proposed for acute respiratory distress syndrome, sepsis, acute kidney injury, and pancreatitis. Identifying the systems that are most useful and biologically meaningful could lead to a better understanding of the pathophysiology of critical care syndromes and the discovery of new treatment targets, and allow recruitment in future therapeutic trials to focus on predicted responders. This Review discusses proposed subphenotypes of critical illness syndromes and highlights the issues that will need to be addressed to translate subphenotypes into clinical practice.

Lancet Respir Med 2020; 8: 631–43

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Introduction

Most randomised controlled trials (RCTs) of interventions in critical care medicine have not identified a treatment benefit.[1] One potential reason is the heterogeneity of critically ill populations and the broad defining criteria for associated syndromes.[2] In an attempt to address this problem, population enrichment methods are increasingly being used in trials to identify subgroups that are likely to benefit from treatment, thereby amplifying treatment effect, reducing noise, and reducing required sample sizes.[3] Of particular interest is predictive enrichment, a strategy that aims to identify patients with a higher likelihood of treatment response, which is often based on biomarkers. An RCT in patients with sepsis, published in 2019, shows the value of a contemporary approach to biomarker-guided predictive enrichment, using clinical measures of coagulopathy to target treatment with thrombomodulin.[4] The use of robust approaches to subdivision on the basis of biomarker panels is an imminent development in critical care, and will radically change the research landscape in the near future.

In the past few years, the rise of genomics, transcriptomics, proteomics, and metabolomics—coupled with the development of data analytic tools—has seen an exponential growth in the identification of novel disease subgroups (subphenotypes) that has led to numerous clinical and biological insights into acute respiratory distress syndrome (ARDS),[5–18] sepsis,[19–37] and acute kidney injury (AKI).[38,39] The advent of these subphenotypes offers the tantalising prospect of delivering precision-based critical care, as evidenced by developments in other fields, such as oncology[40,41] and asthma,[42–44] in which similar approaches have been successfully applied. If critical care subphenotypes are successfully translated into clinical practice, they could facilitate prospective clinical trials of targeted treatments, allow further understanding of disease classification and pathophysiology, and potentially lead to the clinical use of precision treatments that reduce morbidity and mortality for critical care syndromes.

In this Review, we first aim to summarise advances in the identification of subphenotypes of critical care syndromes. We examine in detail the correlating and discordant data from different research groups, discuss the implications of identified subphenotypes for future clinical trials and clinical care, identify barriers to their translation into clinical practice, and discuss approaches that have the potential to overcome these barriers. Because terminology is particularly difficult in this field, we propose definitions of phenotype, subphenotype, and endotype, and consider the potential application of these definitions (panel; figure 1).

Subphenotypes of ARDS

Despite numerous trials of pharmacotherapy, the management of ARDS is limited to supportive therapies at present. ARDS is clinically defined by the Berlin definition.[45] The heterogeneity contained within this

Key messages

- A variety of subgroups (subphenotypes) of acute respiratory distress syndrome, sepsis, and acute kidney injury have been identified that differ in their prevalence and associated mortality
- In retrospective analyses, some subphenotypes have shown differential treatment response to randomised interventions that had no significant effect in the overall population
- Mechanistic studies of subphenotypes of critical illness syndromes might allow us to better understand their pathophysiological basis and develop novel targeted therapies
- To translate subphenotypes for clinical application at the bedside, there is a need to develop rapid real-time assays for subphenotype assignment and to compare disparate subphenotyping strategies prospectively in heterogeneous patient cohorts
- Global cooperation between critical care researchers, with free sharing of data and determinant algorithms, will be needed to validate subphenotypes and realise the potential of precision medicine

Panel: Suggested definitions for subgrouping of patients in critical care

These definitions draw from similar literature in asthma, as described by Lötvall and colleagues.[42]

Phenotype
A set of clinical features in a group of patients who share a common syndrome or condition (eg, the Berlin definition of acute respiratory distress syndrome [ARDS]).

Subphenotype
A set of features in a group of patients who share a phenotype—such as shared risk factor, trait, diagnostic feature, expression marker, mortality risk, or outcome in response to treatment—that distinguishes the group from other groups of patients with the same phenotype (eg, hypoinflammatory *vs* hyperinflammatory ARDS, or sepsis response signature 1 *vs* sepsis response signature 2).

Endotype
A distinct biological mechanism of disease, often associated with an anticipated response to treatment, that is shared by a subgroup of patients and might be indicated by shared mortality risk, clinical course, or treatment responsiveness. As we know little about the mechanisms of critical illness, true endotypes do not yet exist in critical care (eg, allergic asthma *vs* aspirin-sensitive asthma *vs* late-onset hypereosinophilic asthma[42]).

Treatable trait
A subgroup characteristic that can be successfully targeted by an intervention (eg, the *BRAF* Val600Glu mutation of melanoma that is targeted by vemurafenib[41]).

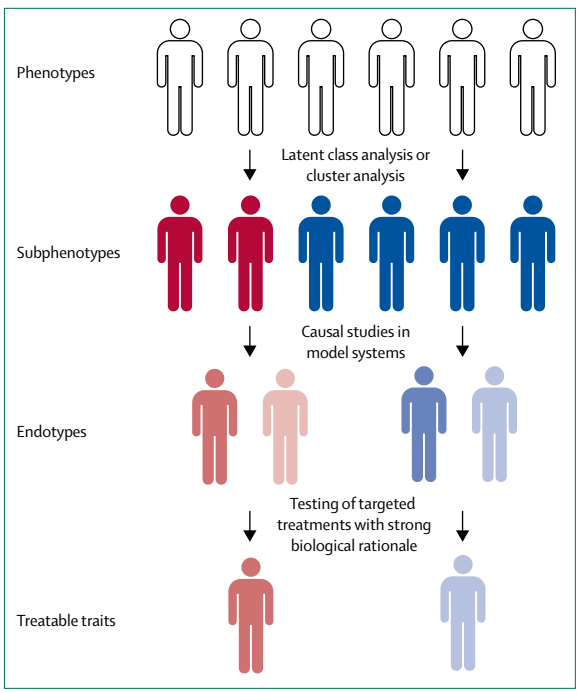

Figure 1: **Potential application of definitions for subgrouping in critical care**
Note that not all subphenotypes are necessarily endotypes. Methods by which subphenotypes, endotypes, and treatable traits might be identified are given. Subphenotypes defined by biomarkers have been repeatedly identified by techniques such as latent class analysis and cluster analysis. Identified candidate markers should then be investigated to identify mechanistic differences between subphenotypes. If these mechanistic differences are proven, the subphenotype becomes an endotype. If a biologically plausible treatment can be successfully targeted to an endotypic mechanism, the endotype becomes a treatable trait.

syndromic definition might explain the absence of observed benefit in RCTs of treatments for which a strong preclinical rationale exists. Methods of subdividing ARDS into meaningful subgroups have therefore been considered. An overview of published ARDS subphenotyping studies is provided in table 1 and the appendix (pp 2–5); important ongoing and planned studies that target or aim to identify ARDS subphenotypes are highlighted in table 2.

See Online for appendix

Clinical subphenotypes

The concept of distinct ARDS subphenotypes based on clinical insult is long standing. So-called direct ARDS results in local lung damage, and is usually caused by pneumonia, aspiration, mechanical ventilation, or contusion. Indirect ARDS occurs in the setting of systemic disorders that cause diffuse vascular endothelial damage, such as sepsis, pancreatitis, or cardiopulmonary bypass.[47] Calfee and colleagues[7] described biomarker differences on the basis of insult pattern in ARDS, showing that although endothelial and epithelial injury were ubiquitous, direct ARDS was characterised by a predominance of epithelial injury and indirect ARDS was characterised by a predominance of endothelial injury and inflammation. Indirect and direct ARDS show divergent radiographic findings, respiratory mechanics, and histopathology; however, little evidence supporting differential treatment response has been found.[48]

Alternatively, ARDS has been subdivided by clinical imaging as a surrogate marker of lung recruitability.[17] Previous work led to the hypothesis that ARDS localised to the lung bases (focal ARDS) would respond favourably to low positive end-expiratory pressure (PEEP), whereas diffuse ARDS would respond favourably to high PEEP and recruitment manoeuvres.[49] The LIVE study[17] compared a personalised approach to ventilation on the basis of CT to standard lung-protective ventilation. No difference in 90 day mortality was found for personalised (PEEP and recruitment manoeuvres based on CT morphology) ventilation strategies, although in a subgroup analysis of the personalised ventilation limb, patients who were incorrectly classified to focal or diffuse ARDS had increased 90 day mortality. This result shows the inherent subjectivity of radiographic imaging to subclassify ARDS. More objective methods of describing subphenotypes are needed in order to avoid potential harm incurred by misclassification.

	Key finding	Prevalence (%)	Mortality (%)	Differential treatment response
ARDS				
Calfee et al (2014)[6]	Hyperinflammatory and hypoinflammatory subphenotypes of ARDS identified	Hypoinflammatory 67–74%; hyperinflammatory 26–33%	Hypoinflammatory 19–23%; hyperinflammatory 44–51%	Differential response to high and low PEEP ventilation strategies for hyperinflammatory and hypoinflammatory ARDS
Calfee et al (2018)[9]	Differential response to pharmacological treatment shown for ARDS subphenotypes	Hypoinflammatory 65%; hyperinflammatory 35%	Hypoinflammatory 22%; hyperinflammatory 46%	Higher 28-day and 90-day survival with simvastatin in patients with hyperinflammatory ARDS
Bos et al (2017)[14]	Uninflamed and reactive subphenotypes of ARDS identified	Uninflamed 48%; reactive 52%	Uninflamed 21·6–22·0%; reactive 37·7–39·1%	Not tested
Sepsis				
Wong et al (2009)[25]	Subphenotypes of sepsis identified in children	Subclass A 29%; subclass B 46%; subclass C 26%	Subclass A 36%; subclass B 11%; subclass C 12%	Not tested
Wong et al (2015)[30]	Differential response to corticosteroids shown for subphenotypes of sepsis in children	Subclass A 34–48%; subclass B 52–66%	Subclass A 17–21%; subclass B 5–10%	Increased mortality with corticosteroid treatment in patients with subclass A
Davenport et al (2016)[33]	Subphenotypes of sepsis identified in adults	SRS1 35–41%; SRS2 59–65%	SRS1 22–59%; SRS2 10–29%	Not tested
Antcliffe et al (2019)[35]	Differential response to corticosteroids shown for subphenotypes of sepsis in adults	SRS1 47%; SRS2 53%	SRS1 33–37%; SRS2 8–42%	Increased mortality with hydrocortisone treatment in patients with SRS2
Scicluna et al (2017)[36]	Mars subphenotypes identified	Mars1 13–29%; Mars2 34–44%; Mars3 23–37%; Mars4 6–13%	Mars1 28·6–43·3%; Mars2 16·2–26·7%; Mars3 7·2–28·2%; Mars4 5·3–32·5%	Not tested
AKI				
Bhatraju et al (2019)[39]	Biomarker-derived subphenotypes of AKI identified	AKI-SP1 58–63%; AKI-SP2 37–42%	AKI-SP1 6–24%; AKI-SP2 25–43%	Decreased mortality with vasopressin as opposed to noradrenaline in patients with AKI-SP1

Biomarker-driven studies were chosen on the basis of novelty, number of citations, relative contribution to the field, and demonstration of differential treatment effect. AKI=acute kidney injury. AKI-SP1=AKI-subphenotype 1. AKI-SP2=AKI-subphenotype 2. ARDS=acute respiratory distress syndrome. PEEP=positive end-expiratory pressure. SRS1=sepsis response signature 1. SRS2=sepsis response signature 2.

Table 1: **Landmark studies of subphenotypes in ARDS, sepsis, and AKI**

Parsing ARDS by clinical trajectory has also been suggested. A subphenotype of ARDS characterised by rapid improvement of the syndrome in patients who no longer met the Berlin criteria or who were extubated within 1 day of study enrolment has been described in ARDS network clinical trials.[18] This group might consist of patients who have been misclassified as having ARDS because of the poor specificity of the Berlin definition,[50] although this group could also be a novel clinical or biological subphenotype.

Although clinical classifications of ARDS allow disease characteristics to be mapped conceptually and potential benefits of available supportive therapies to be rationalised for subgroups of patients, such subgroups do not have a clear link to the biological mechanisms underlying the development of ARDS.

Biomarker-driven subphenotypes

Biomarker-driven classification approaches based on biological data are yielding insights into potential ARDS mechanisms and subphenotypes. These approaches could lead to targeted treatments with more ambitious therapeutic goals than are possible with clinical classification systems. Unsupervised clustering analyses of large datasets of ARDS that use high-dimensional biological variables might identify subgroups that reveal underlying biological mechanisms and treatable traits.

The most recognised subphenotypes of ARDS are those described by Calfee and colleagues,[6] who identified two distinct groups using latent class analysis of clinical and biomarker data from the ARDSnet trials of lower tidal volume ventilation (ARMA trial[51]) and high versus low PEEP (ALVEOLI study[52]). Latent class analysis is a type of structural equation modelling that identifies unrecognised subgroups in categorical and continuous data. The so-called hyperinflammatory class was characterised by a higher concentration of circulating plasma markers of inflammation (IL-6, IL-8, sTNFR1, and PAI-1), a more frequent use of vasopressors, a higher degree of metabolic acidosis, and a greater prevalence of sepsis. The hypoinflammatory cohort had higher concentrations of serum bicarbonate and protein C, higher systolic blood pressure, higher platelet count, and lower mortality.[6] These findings were confirmed in a retrospective analysis of the FACTT cohort.[53] The hyperinflammatory and hypoinflammatory groups also showed differential treatment response to high versus low PEEP ventilation strategies, and fluid-liberal versus fluid-conservative resuscitation strategies.[6,8]

	Study design (number of participants)	Novelty	Location and recruitment status
ARDS			
PHIND: clinical evaluation of a point of care assay to identify phenotypes in the ARDS (NCT04009330)	Multicentre, prospective cohort study (n=480)	Prospectively validating hyperinflammatory and hypoinflammatory subphenotypes, and allocating them at the bedside	UK and Ireland; recruiting
ProCoCo: procollagen-3 driven corticosteroids for persistent ARDS (NCT03371498)	Multicentre RCT (n=356)	Targeting corticosteroid administration to an ARDS subphenotype (procollagen type III peptide-high) in a randomly allocated, parallel-arm study	France; recruiting
LEOPARDS: linking endotypes and outcomes in paediatric ARDS (NCT04113434)	Multicentre, prospective cohort study (n=500)	Identifying subphenotypes in paediatric ARDS	USA; not yet recruiting
PARDS: identifying paediatric ARDS endotypes (NCT03539783)	Single centre, prospective case-control study (n=60)	Correlating nasal and bronchial epithelial gene expression to serum biomarkers and determining their efficacy in subphenotype identification	USA; recruiting
Sepsis			
REALISM: the reanimation low immune status markers project;[46] IMPACCT: immune profiling of ICU patients to address chronic critical illness and ensure healthy ageing*	Initial single centre, prospective cohort study of patients with sepsis (n=160; REALISM) followed by multicentre, prospective cohort study (IMPACCT)	Clarifying optimal markers to identify immunosuppressed subphenotypes in sepsis; prospectively validating and allocating subphenotypes at the bedside	UK, France, and Sweden; not yet recruiting
SHIPSS: stress hydrocortisone in paediatric septic shock (NCT03401398)	Multicentre RCT (n=1032)	Examining differential response of paediatric subphenotypes A and B to steroids in a randomly allocated manner (exploratory outcome only)	USA and Canada; recruiting

Many of these studies aim to prospectively validate or define subphenotypes. Of note, the PHIND study will prospectively study a rapid assay for subphenotype allocation that could be clinically viable. The ProCoCo trial is the only study that will target treatment to subphenotype, although the subphenotypes used are investigator-defined and based on the hypothesised response to corticosteroids. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. RCT=randomised controlled trial. *The IMPACCT study is not yet referenced online, although it is funded and in the recruitment phase (Gordon A C, unpublished).

Table 2: **Ongoing and planned studies in critical care subphenotyping**

Of note, an erratum has been published for the Famous and colleagues study[8] of the FACTT cohort, correcting an exchange of subphenotype terminology that reversed their differential responses.[54] Regardless, the conclusion that these subphenotypes respond differently to fluids is unchanged.

These subphenotypes were also verified in a post-hoc analysis of two clinical trials of statins in ARDS.[9,10] In an analysis of the HARP-2 cohort,[55] the hyperinflammatory subgroup had increased 28 day survival when randomised to simvastatin.[9] Although subphenotypes were again identified in the ARDSnet SAILS cohort,[56] a differential survival benefit with rosuvastatin was not identified.[10] In 2020, a 3-variable model to prospectively identify two ARDS subphenotypes (hyperinflammatory and hypoinflammatory) was developed through analysis of five clinical trials.[11] A model using IL-8, bicarbonate, and protein C as biomarkers did best, achieving an area under the receiver operating characteristic curve of 0·94; however, different 3-variable models with other biomarkers (sTNFR-1 and IL-6) also did well.[11] The prevalence and mortality of the hypoinflammatory and hyperinflammatory subphenotypes were comparable across five RCTs.[6,8–11] Furthermore, latent class analysis showed similar predictive biomarker panels for these subphenotypes across all analysed RCTs.

Kitsios and colleagues[12] used latent class analysis to retrospectively identify two subphenotypes that closely corresponded to hyperinflammatory and hypo-inflammatory ARDS in a prospectively enrolled convenience sample of patients with respiratory failure. The finding that hyperinflammatory and hypo-inflammatory subphenotypes also exist in a population of patients with respiratory failure that do not meet ARDS criteria is especially intriguing, showing the limitations of clinical classification systems.[12] Similar results were shown by another group in a retrospective latent class analysis of 203 patients in the FACTT cohort and 49 prospectively enrolled ARDS patients.[13] Compared with phenotype B, phenotype A had higher plasma concentrations of ANG-2, IL-8, IL-1RA, and IL-6, as well as higher 28 day mortality.[13]

Disparate subphenotypes in patients with ARDS, termed uninflamed and reactive, have also been identified.[14] These groups were identified in an observational cohort by cluster analysis of biomarker data only. This work used a simplified panel of biomarkers to classify the subphenotypes, consisting of IL-6, IFN-γ, ANG-1 and ANG-2, and PAI-1.[14] Retrospective cohort analysis later showed that the uninflamed subphenotype responded preferentially to therapy with low-dose macrolides compared with the reactive group (although treatment was not randomised).[15] The same investigators, using whole

blood transcriptomics and canonical pathway analysis, found notable differences in gene expression. The reactive subphenotype was associated with the upregulation of genes that map to oxidative phosphorylation and cholesterol synthesis pathways. The uninflamed subphenotype was associated with upregulation of the MAP2K4 and RAF1-dependent MAPK pathways, which are involved in cell proliferation, differentiation, motility, and survival.[16] Although these data come from a large prospective observational study,[14] the uninflamed and reactive subphenotypes have been shown in one cohort only and were derived using a small set of 20 biomarkers.

Equating the reactive subphenotype from Bos and colleagues[14] to the hyperinflammatory subphenotype from Calfee and colleagues[6] is tempting because of the presumed underlying inflammatory state. In fact, the hyperinflammatory and reactive subphenotypes share characteristics, such as increased circulating concentrations of IL-8 and PAI-1, as well as decreased serum bicarbonate.[6,8,14] The study of these similarities could lead to novel insights into ARDS biology.

Subphenotypes of sepsis

In sepsis, the limited utility of clinical definitions to detect underlying biological heterogeneity has been implicated in trials that show no treatment benefit.[57] Newly outlined sepsis-3 definitions improve clarity by differentiating sepsis from simple infection and shock from hypotension, but do little to reduce heterogeneity.[58] An overview of landmark trials and upcoming studies in sepsis subphenotyping is provided in table 1, table 2, and the appendix (pp 6–12).

Clinical subphenotypes

Several investigators have sought to subdivide sepsis using readily available clinical data. Zhang and colleagues[19] developed sepsis subgroups using latent profile analysis, a technique similar to latent class analysis that identifies subgroups with only continuous variables. Four sepsis subphenotypes were identified: profile 1 (baseline group; low mortality), profile 2 (respiratory dysfunction), profile 3 (multiple organ dysfunction; highest mortality), and profile 4 (neurological dysfunction).[19] Profile 3 seemed to respond favourably to intravenous fluids in terms of mortality, whereas profile 4 responded poorly.

In another clinical classification, Bhavani and colleagues[20] identified sepsis subphenotypes using group-based trajectory modelling of repeated temperature measurements. Four subtypes were identified: hyperthermic, slow resolvers (mortality 10·2%); hyperthermic, fast resolvers (mortality 3%); normothermic (mortality 4·5%); and hypothermic (mortality 9·0%). The hypothermic group were older, whereas the hyperthermic, fast resolvers had higher serum C-reactive protein concentrations and a faster erythrocyte sedimentation rate.[20]

Investigators have used k-means clustering to develop sepsis subphenotypes from clinical data at emergency department presentation.[21] A composite database comprising 47712 patients was used to identify four subphenotypes that differed in prevalence, mortality, and clinical characteristics. The α subphenotype (prevalence 33%; mortality 2%) had fewer abnormal laboratory values and less organ dysfunction; the β subphenotype (prevalence 27%; mortality 5%) were older, had more chronic illness, and more renal dysfunction; the γ subphenotype (prevalence 27%; mortality 15%) had more inflammation, lower albumin serum concentrations, and higher temperature; and the δ subphenotype (prevalence 13%; mortality 32%) had higher lactate, higher aminotransferases, and more hypotension.[21] Further analyses suggest that the subphenotypic heterogeneity of recruited patients could explain previous equivocal results in sepsis trials, although it should be noted that this study relied heavily on multiple imputation and the results should be interpreted cautiously.

In another study, latent class analysis on a database of 36390 patients was done to define subphenotypes based on multimorbidity state.[22] Identified groups were the cardiopulmonary (prevalence 6·1%) and cardiac subphenotypes (prevalence 26·4%), consisting of older patients with cardiopulmonary conditions; the young subphenotype (prevalence 23·5%), consisting of young, healthy patients; the hepatic–addiction subphenotype (prevalence 9·8%), consisting of middle-aged patients with high rates of depression, substance abuse, and liver failure; the complicated diabetics subphenotype (prevalence 9·4%); and the uncomplicated diabetics subphenotype (prevalence 24·8%).[22] The groups with highest mortality were the hepatic–addiction subphenotype, followed by the cardiac subphenotype, then the cardiopulmonary and complicated diabetics subphenotypes. This study is the first to apply latent class analysis to multimorbidity and provides robust evidence for differing clinical outcomes based on multimorbidity cluster.

As in ARDS, subphenotypes derived with clinical data provide minimal mechanistic insight. Biomarker-driven approaches to subphenotyping and unbiased statistical analyses could provide a better understanding of sepsis biology than is afforded by a clinical classification system alone.

Biomarker-driven subphenotypes

Secondary analyses of sepsis RCTs have yielded insight into biomarker-defined subphenotypes. Shakoory and colleagues[23] defined a group of patients with hepatobiliary dysfunction and disseminated intravascular coagulation, and re-analysed data from an RCT of IL-1RA (anakinra) to show that this group probably benefited from the trial drug. In a separate trial that also focused on the IL-1 pathway, Meyer and colleagues[24] did a retrospective subgroup analysis of recombinant human IL-1RA in sepsis, showing that patients with a baseline high level of

endogenous IL-1RA benefited from this treatment. This counterintuitive result highlights our insufficient understanding of the pathophysiology of sepsis. Because of the complexity of the syndrome, it is likely that a single biomarker such as IL-1RA is inadequate to precisely identify subgroups. To that end, researchers have employed biomarker panels to classify sepsis into subphenotypes.

Subphenotypes of sepsis defined by biomarker panels were first described in paediatric sepsis by Wong and colleagues.[25] Genome-wide expression of whole blood-derived RNA was used in a prospective cohort of 98 children with septic shock.[25] Data was then subjected to unsupervised hierarchical clustering to identify three subphenotypes (A, B, and C). Patients in subclass A were younger, had higher illness severity, higher degrees of organ failure, and higher mortality. Furthermore, subclass A differed from subclasses B and C in that genes associated with adaptive immunity, glucocorticoid receptor signalling, and zinc biology were repressed.[25] Subsequently, investigators described a 100-gene signature model to distinguish subphenotypes.[26,27] This model was developed into a multiplex messenger RNA quantification platform that was prospectively tested in another cohort.[30] Mosaics representing expression patterns of the 100 subphenotype-defining genes for each patient were compared with reference mosaics and the group was assigned by least difference. In this cohort, no patients met the criteria for subclass C. Children from subclass A had worsened mortality when prescribed corticosteroids compared with subclass B, although allocation was non-randomised.[30] This work on paediatric sepsis subphenotypes has been translated into a protein biomarker-based classification and regression tree model for mortality risk that has been used in children and adults.[28,29]

Alternative biomarker-derived sepsis subphenotypes have been described in adults. In a series of studies, investigators identified distinct transcriptomic subphenotypes by cluster analysis of peripheral blood leucocyte genome-wide transcription profiles in a prospective cohort of 265 adults with sepsis secondary to community-acquired pneumonia.[33] These findings were validated in a second independent cohort[34] and tested for differential treatment response in a secondary analysis of an RCT.[35] The first subphenotype, SRS1, had gene expression patterns indicative of an immunosuppressed pattern, suggesting endotoxin tolerance, T-cell exhaustion, and HLA class II downregulation. Mortality was higher among those with the SRS1 subphenotype compared with SRS2.[33,34] Furthermore, in a secondary analysis of an RCT, in which a simplified model was used consisting of seven genes, investigators again identified the two subphenotypes and corticosteroid therapy was associated with increased mortality in the SRS2 subphenotype.[35] This evidence suggests not only a clinical application for identified subphenotypes, but also a model that could feasibly be used at the bedside.

Research from a Dutch group used machine learning and cluster analysis of whole blood genome-wide expression profiles to identify four sepsis subphenotypes, termed Mars1–4.[36] These subphenotypes were derived in a prospective cohort and subsequently validated in an adult and paediatric retrospective cohort. The Mars1 subphenotype was associated with poor prognosis and downregulation of genes associated with the innate and adaptive immune system. Mars2, which had intermediate mortality risk, was associated with increased expression of genes involved in pattern recognition (recognition of pattern-associated and damage-associated molecular patterns) and cytokine, cell growth, and mobility pathways (eg, NF-κB, IL-6, and inducible nitric oxide synthase). The Mars3 subphenotype was associated with upregulation of adaptive immune function, upregulation of T-cell function, and lower risk of mortality. Mars4, similarly to Mars2, was associated with intermediate mortality and increased expression of genes involved in pattern recognition and cytokine pathways, although different specific pathways were implicated (eg, interferon signalling and antiviral innate immune response receptor RIG-I [DDX58] signalling).

Elsewhere, Sweeney and colleagues[59] used a novel clustering algorithm to derive subphenotypes in sepsis on the basis of whole blood genome-wide expression profile data retrieved retrospectively from a composite of multiple small studies in adult and paediatric populations.[37] Investigators identified three subphenotypic clusters,[37] termed the inflammopathic (innate immune activation; higher mortality), adaptive (adaptive immune activation; lower mortality), and coagulopathic (gene expression suggestive of platelet degranulation and coagulation dysfunction; higher mortality and older) groups. Of note, 16% of patients in the discovery cohort were not clustered to a subphenotype. Through analysis of clinical data, investigators suggested that patients with the adaptive subphenotype are less ill, whereas the inflammopathic and coagulopathic subphenotypes split the more severe sepsis cohort into younger and older groups, respectively. These findings should be interpreted with caution, however, as age and severity data were available for only 36% of patients.

There are some unexpected data points around sepsis subphenotypes that require further examination. In addition to counterintuitive results with regard to responsiveness to recombinant IL-1RA,[24] a retrospective analysis of the VANISH trial cohort[60] showed increased mortality in SRS2 patients randomised to receive corticosteroids (odds ratio 7·9, 95% CI 1·6–39·9), but no treatment effect for SRS1.[35] Although hypotheses are presented in the primary sources to explain these results, the unexpected findings highlight our insufficient understanding of sepsis biology.

There are overlaps and conflicts between existing biomarker-driven approaches to sepsis classification. Of note, both paediatric subclass A and adult subphenotype

SRS1 have gene expression patterns suggestive of immunosuppression when compared with their counterpart subphenotypes, but appear to exhibit disparate responses to corticosteroids. When given corticosteroids, children in subclass A showed increased mortality;[30] a similar effect was not observed in SRS1 adults. In fact, patients with the relatively immunocompetent SRS2 subphenotype showed increased mortality in response to steroids.[35] In other comparisons, investigators noted that the Mars3 subphenotype was correlated with the SRS2 subphenotype, with both groups showing heightened expression of genes involved in adaptive immunity.[36] Similarly, Sweeney and colleagues[37] observed that their inflammopathic subphenotype corresponded most closely to SRS1 and paediatric subclass B, whereas the adaptive subphenotype corresponded to SRS2. Although the proposed similarities are encouraging, there were also substantial discordances between subphenotype allocations for all comparisons. The interactions between existing subphenotypes raise several fundamental questions about sepsis pathophysiology, and further study is needed to provide insights into underlying mechanisms.

Subphenotypes of AKI

AKI is another heterogeneous critical care syndrome. Current definitions[61,62] do not provide information on the biology of AKI. AKI stages do not accurately represent renal pathophysiology, which could potentially offer pharmacological targets.[63] An overview of AKI subphenotyping studies is provided in table 1 and the appendix (p 13).

In 2016, Bhatraju and colleagues[38] identified subphenotypes of AKI on the basis of the creatinine trajectory. In a secondary analysis of two prospective trials, patients with AKI were classified as resolving or non-resolving on the basis of the creatinine trajectory in the first 72 h after study enrolment. Non-resolving patients had 68% higher mortality (relative risk 1·68, 95% CI 1·15–2·44), even after adjustment for stage of AKI severity.[38] The same research group, using latent class analysis of clinical data and serum biomarkers, then identified AKI subphenotypes in a retrospective analysis of two clinical trials.[39] Compared with AKI-SP1, AKI-SP2 was characterised by poorer renal function, higher vasopressor use, and higher concurrence of sepsis with ARDS.[39] AKI-SP2 also showed more endothelial activation, lower serum bicarbonate, and higher concentrations of IL-6 and IL-8.[39] In a post-hoc analysis of the VASST trial,[64] patients with AKI-SP1 had improved mortality with vasopressin as opposed to noradrenaline (27% *vs* 46%, p=0·02), but no benefit was observed for patients with AKI-SP2 (45% *vs* 49%, p=0·99).[39]

As in ARDS, some distinguishing biomarkers for AKI subphenotypes are IL-6, IL-8, and bicarbonate. This finding raises the question of parallels between critical illness syndromes and could suggest shared mechanisms that transcend syndromic definitions.

Subphenotypes of acute pancreatitis

Neyton and colleagues[65] used unsupervised clustering of proteomic, transcriptomic, and metabolomic data to describe four subphenotypes of acute pancreatitis, referred to as hypermetabolic, hepatopancreaticobiliary, catabolic, and innate immune. The hypermetabolic subphenotype had increased markers of glutathione synthesis, gastrointestinal metabolism of dopamine, the tricarboxylic acid cycle, and sphingolipid biosynthesis (eg, GGT2, citrulline, and SPTSSB); the hepatopancreaticobiliary subphenotype was associated with bilirubin glucuronidation and bile transporters; the catabolic subphenotype with proteolysis and apoptosis; and the innate immune subphenotype with complement regulation and immune cell adherence.[65] Pancreatitis is a late entry to the field of critical care subphenotyping, and although these results are interesting, the findings are based on small sample sizes and have not yet been subject to peer review. Whether or not these groupings are robust and clinically meaningful remains to be seen. Proposed pancreatitis subphenotypes are summarised in the appendix (p 14).

Translation of subphenotypes into clinical practice

In critical care, the question of whether to treat syndromes, subphenotypes, or some combination of the two needs to be resolved. How to address this question to improve outcomes for critically ill patients is not entirely clear and will undoubtedly require a larger body of evidence and further discussion. To this end, there has been a rapid growth in critical care subphenotyping studies, with several recruiting worldwide (table 2). As the scientific community moves towards the era of precision medicine in critical care, numerous barriers will need to be overcome to translate our current knowledge into clinical practice. We present an overview of challenges and potential solutions in table 3.

Understanding of pathophysiology

Knowledge of the pathophysiological mechanisms of critical illnesses is superficial, hindering their study. Differences between subphenotypes in terms of biomarkers can be identified with unbiased analytical approaches, but these differences are difficult to interpret without insights into how the biomarkers interact and are regulated. This knowledge gap is apparent in the counterintuitive results involving IL-1RA responsiveness in sepsis,[24] and in the divergent response to corticosteroids between paediatric subclass A[30] and SRS1.[35] Very little is known about the mechanisms of critical care illnesses in general, let alone the mechanisms of the proposed subtypes. Although the biomarkers used to identify subphenotypes in humans might be useful to guide future study, no evidence exists to confirm that they are mediators rather than simply markers.

	Solutions
Understanding of pathophysiology: knowledge of pathophysiological mechanisms of critical illnesses is insufficient	Design mechanistic studies targeted at biomarkers identified by unbiased, bottom-up approaches to syndrome classification (eg, by latent class analysis); start with transcriptomic analysis of subphenotypes, followed by studies to identify candidate protein mediators, then causal studies in model systems; develop novel animal models or appropriate existing animal models (eg, identify existing model with transcriptomal changes similar to an identified human subphenotype)
Comparison of subphenotypes: overlap and correlation between existing subphenotypes is unclear	Validate similar subphenotypes in large, prospective cohorts (eg, with Mars and hypoinflammatory–hyperinflammatory ARDS subphenotypes in one cohort)
Stability of subphenotypes: the extent to which subphenotypes are stable over time, in response to treatment, and across sampling sites and methods is not known	Repeat prospective cohort studies to validate subphenotypes that differ by disease stage and severity; repeat subphenotype assignment at multiple timepoints in prospective cohorts; compare subphenotype-defining biomarker panels across varying tissue types (eg, blood *vs* lungs in ARDS)
Multimorbidity: complex multimorbidity in critical care is a challenge for precision medicine	Validate subphenotypes in large, prospective cohorts with few exclusion criteria
Diminishing returns with increasing subdivision: a limit for the subdivision of syndromes needs to be established	Focus on clinically useful subphenotypes, with a strong biological rationale and plausible heterogeneity of treatment effect
Speed of subphenotype assignment: real-time diagnostic assays are needed to make subphenotypes clinically viable	Develop and validate parsimonious subphenotype assignment algorithms; develop and validate point-of-care biomarker assays
Large prospective studies and global cooperation: well designed, prospective studies, and sharing of datasets and discriminant algorithms, will be needed to develop and validate subphenotyping strategies	Undertake prospective studies in large, heterogeneous patient cohorts; decentralise patient data away from hospitals and towards collaborative databanks; establish international consortiums on critical care subphenotyping

ARDS=acute respiratory distress syndrome.

Table 3: **Challenges in the clinical implementation of subphenotypes in critical care**

To translate critical care subphenotypes into endotypes, studies that employ discovery approaches will need to be done, followed by the establishment of causality in model systems. Our proposed approach first involves collecting cell isolates of interest (eg, peripheral leucocytes, alveolar macrophages, or glomerular cells) from patients who are subphenotyped, and comparing whole-genome expression profiles to identify differentially expressed genes that might represent candidate mechanistic pathways. Studies that include protein quantification and characterisation methods should follow to link this transcriptomic data to proteomic differences between subphenotypes. The use of selective inhibitors to some of these identified proteins in vitro and in vivo might then establish causality. Such an approach would require the concomitant development of in vitro and animal subphenotype models, which do not exist at present.

An example comes from Bos and colleagues,[16] who note that the reactive subphenotype of ARDS shows up-regulation of genes associated with neutrophil activation, oxidative phosphorylation, and mitochondrial dysfunction compared with the uninflamed subphenotype. One could hypothesise that alveolar damage in this subphenotype is dependent on neutrophil serine proteases, such as neutrophil elastase, and fluorescence resonance energy transfer and a specific inhibitor (eg, sivelestat) could be used to test this hypothesis.[16]

An alternative approach to the identification of candidate mechanisms is evidenced by Jones and colleagues,[66] who used an application of Mendelian randomisation in the context of an observational study to suggest that there is a causal role for sRAGE in ARDS. This study follows from previous work that similarly suggested a causative role for ANG-2.[67] Although this approach requires genomic data and needs further replication, it could be co-opted for subphenotype studies in which causal inference methods are used to identify genes that might be linked to mechanisms of critical illness. This information could then inform in vitro or in vivo studies of selective inhibitors. Although such studies are exciting, mechanistic differences between critical care endotypes are likely to be more complex than single targets and mediators.

Comparison of subphenotypes

Within syndromes, overlap between identified subphenotypes remains unclear because of differences between the patient populations studied, clinical characteristics and biomarkers used, and methods of analysis. Some studies that have identified critical care subphenotypes used small discovery cohorts and have yet to be replicated. Furthermore, the various cluster analysis methods that have been used to identify critical care subphenotypes tend to generate different results depending on the variables chosen for analysis and the method of clustering.[68] A number of different clustering methods have been used to identify critical care subphenotypes. It is therefore possible that some described subphenotypes are spurious findings.

Disparities between identified subphenotypes are evidenced in sepsis. Of particular note is the conceptual analogy between paediatric subclass A and adult subphenotype SRS1. Both subphenotypes have characteristics suggesting immunosuppression relative to their

counterpart phenotypes, but they appear to show disparate responses to treatment with steroids.[30,35]

There are also notable disparities within ARDS subphenotyping systems. In a retrospective analysis of the HARP-2 study,[55] a treatment interaction was found, with the hyperinflammatory group showing improved survival with simvastatin.[9] Conversely, in an analysis of the SAILS study,[56] no treatment effect was found for rosuvastatin.[10] This discrepancy might be related to differential drug concentrations, differential ARDS causes in the two trials (sepsis-related *vs* all-cause), differential ARDS severity, or differential hydrophilicity of the two statins used. Nonetheless, these data emphasise our insufficient knowledge of critical care subphenotypes and show that trial recruitment methods could directly influence the results of retrospective biomarker analyses. Hence, in the future, methods used to define subphenotypes should be reported in detail to facilitate comparisons and analysis.

Stability of subphenotypes

A major remaining question is whether or not subphenotypes are stable over time, in response to treatment, and across multiple sampling sites and methods. Different subphenotypes could possibly represent different temporal stages in the evolution of the syndrome in question. Since some subphenotypic definitions of ARDS are based on inflammatory biomarkers, changes in inflammation in response to disease course could affect the reliability of subphenotype allocation. Latent transition analysis, a clustering approach used to determine movement between subgroups over time, showed stability of the hypoinflammatory and hyperinflammatory groups retrospectively at day 0 and day 3 in the ARMA[51] and ALVEOLI[52] clinical cohorts.[69] Most patients assigned to a class at day 0 remained assigned to the same class at day 3 (>94%).[69] Stability will be required for recruitment to future clinical trials targeting specific ARDS subphenotypes. However, the stability of ARDS subphenotypes past study day 3 or in response to specific treatments remains unknown.

The temporal stability of sepsis subphenotypes over time and across age demographics is even more unclear. Wong and colleagues[31] showed that subphenotypes derived in children might not be clinically useful in older adults, as evidenced by the weak correlation between paediatric subphenotype and SRS. These findings suggest that the sepsis subphenotype could be age dependent and response to corticosteroids might change accordingly, implying complex changes in the immune landscape with host age. Age will undoubtedly need to be accounted for in future assessment of the host immune transcriptome in sepsis and other syndromes, and further study of its role in subphenotype determination could provide insights into the underlying pathophysiology of these syndromes.

Within adult populations, temporal instability is evident. In the study of faecal peritonitis by Burnham and colleagues,[34] 46% of patients with serial samples moved between SRS groups over time, with changing gene expression profiles. This result indicates that SRS grouping might be an indicator of host immune state rather than representing endotypes of sepsis.

The potential influence of time on sepsis subphenotypes is shown in a study of myeloid-derived suppressor cells in persistent organ dysfunction after sepsis.[70] Myeloid-derived suppressor cells are a heterogeneous group of immature myeloid cells that have been implicated in sepsis pathobiology.[71] Expansion and infiltration of myeloid-derived suppressor cells after sepsis is thought to induce persistent organ dysfunction through host immunosuppression and inhibition of lymphocyte proliferation. Surprisingly, Hollen and colleagues[70] showed that myeloid-derived suppressor cell function evolves over time, with myeloid-derived suppressor cells being stimulatory toward T cells 4 days after sepsis. This finding suggests that future precision medicine approaches in sepsis will need to consider temporal instability in immune states, and might indicate that sepsis subphenotypes that are defined by immune function are in fact different points on a temporal continuum.

There is a further possibility that biomarker and transcriptomic signatures will vary with the cell or tissue type sampled, reducing the generalisability of many subphenotyping strategies. In ARDS, we do not know how accurately subphenotypes defined by blood biomarker panels reflect what is happening in the lung. In sepsis, since contemporary transcriptome analysis strategies use heterogeneous cell populations (whole blood or peripheral blood leucocytes), biomarkers and subphenotypes based on this analysis could be subject to instability with disease course. If mRNAs that are used to quantify differential gene expression are expressed specifically or preferentially by one or more leucocyte subtypes, changes in differential cell count that occur with disease progression could affect the stability of subphenotype allocation.

Much is left to be understood about the stability of biomarkers in critical illness and, consequently, subphenotype stability. Fluctuations in group allocation might reduce the applicability of subphenotypes in recruitment to future clinical trials, although these fluctuations could also be productively harnessed for other purposes. Perhaps, in future, changes in subphenotype allocation could be used to monitor syndrome progression or to monitor response to treatment.

Multimorbidity

The problem of multimorbidity in critical care will present a challenge to precision medicine.[72] Many trials in which subphenotypes have been identified exclude

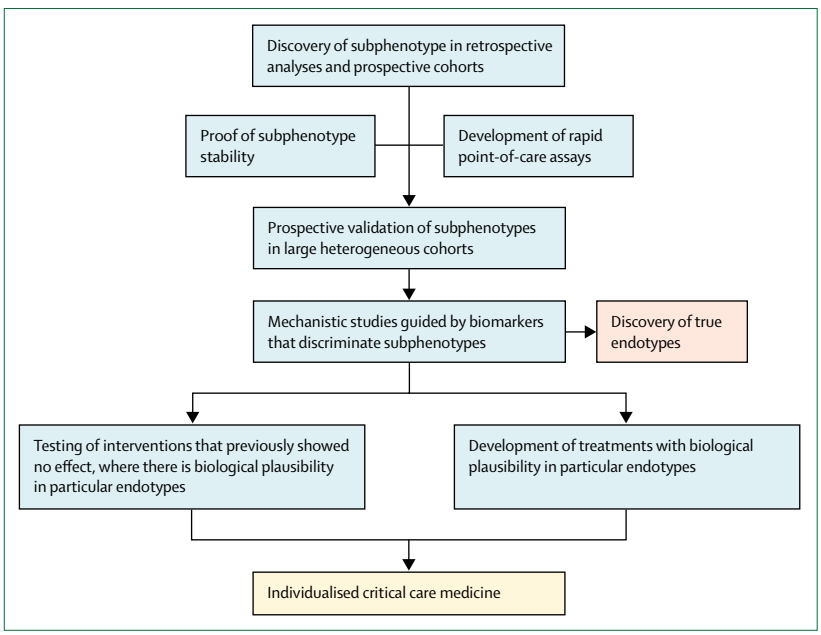

Figure 2: **An approach to precision medicine in critical care**
Patients could be screened rapidly for multiple subphenotype assignments at intensive care unit admission and then directed to endotype-specific therapies. Many more subphenotype assignments and treatment options than those shown will probably be available in the future.

patients with considerable comorbidity. Through studying subphenotypes in retrospective analyses of RCTs, investigators are eliminating the complexity introduced by chronic disease and multimorbidity, potentially reducing the applicability of subphenotypes at the bedside. This issue is most pronounced in those subphenotypes that are based on retrospective analyses of highly selected clinical trial cohorts. It is also possible that biomarker-based subphenotypes are representative of differing multimorbidity states. In a study published in 2019, multimorbidity subphenotypes of sepsis were recognised and assigned by latent class analysis.[22] This approach could provide interesting insights if compared with biomarker-based classification approaches.

Diminishing returns with increasing subdivision

Deciding whether or not to further subdivide syndromes will be another challenge. As more data are incorporated, there is the potential to subdivide syndromes into a large number of subphenotypes. Although this increased resolution represents a closer approximation of truly individualised medicine, health-care economics and clinical utility might necessitate a threshold beyond which further subdivision is not deemed to be useful. As an extreme example, at some level every patient represents an individual subphenotype, and unique treatments for individual patients are unlikely to be feasible. Some generalisability will be required, at least in the foreseeable future of medicine, and the optimum way in which to subdivide syndromic conditions could depend on the treatment in question.

Speed of subphenotype assignment

For subphenotypes to become clinically viable, real-time diagnostic assays must be available. At present, sepsis typing is limited by the time required to perform transcriptomic analysis. In paediatric sepsis, Wong and colleagues[30] initially attempted to address this issue by rationalising their microarray data into an assay for 100 genes that can classify subphenotypes in 8–12 h, and then further simplifying the approach to a decision tree involving four genes, which is probably more feasible in clinical practice.[32]

In ARDS, there has been considerable interest in the hypoinflammatory and hyperinflammatory subphenotypes seen across five RCTs, and their apparent interaction with treatment effect to simvastatin, PEEP, and fluid-management strategies.[6,8,9] However, the latent class analysis models used in these cohorts require multiple predictor variables, making them impractical for clinical use. A simplified parsimonious model that can prospectively identify ARDS subphenotypes has been reported.[11] To bring prospective ARDS classification to fruition in the clinical setting, these data will have to be combined with real-time testing for associated biomarkers. Unfortunately, at present, no such commercially available test exists, although candidate point-of-care assays are in development and could bring subphenotyping to the bedside.

Large prospective studies and global cooperation

In the future, the research community needs to determine which subphenotypes are reproducible, which are spurious, and which overlap, and establish their stability across patient demographics (ie, are they the same in children and adults?). To answer these questions, the most compelling dataset would involve prospective validation of multiple subphenotyping strategies in large, heterogeneous patient cohorts. A single such study would allow comparisons between subphenotyping strategies and would help to delineate their overlap, interactions, and clinical applicability. Reproducing these results in other cohorts would then help to determine subphenotype stability. Our ongoing study, clinical evaluation of a point-of-care assay to identify phenotypes in ARDS (PHIND; NCT04009330), is one initiative that aims to allow such comparisons. In addition, the REALISM project[46] aims to immunophenotypically characterise a large cohort of critically ill patients, and the subsequent IMPACCT study aims to prospectively allocate subphenotypes of sepsis identified in REALISM and allocate them at the bedside.

Prospective validation of subphenotyping strategies will require sharing of datasets and discriminant algorithms between investigators. International databanks could be used to identify generalisable subphenotypes. The ideal solution would be a decentralised open-access databank akin to tumour registries in oncology. However, there are potential issues with data sharing, including those of

international transferability and differences in patient privacy law. Decentralisation of health records and greater levels of cybersecurity are needed before this strategy can be fully realised.

A further issue impeding global collaboration is the reluctance of some investigators to openly share subphenotype-defining algorithms. Although understandable, such competition is counterproductive. A useful approach to overcoming this barrier would be the establishment of collaborative organisations for critical care subphenotyping, in which many investigators contribute to all publications (akin to the ARDSnet group), facilitating recognition of authors and investigators.

Conclusions and future directions

Substantial progress has been made in the identification of subphenotypes of critical care syndromes, with important implications for the future of critical care, but many barriers need to be overcome to translate subphenotypes into clinical practice and realise the potential of precision medicine. Undoubtedly, to bring the promise of precision medicine to fruition, a large body of research and international cooperation will be needed.

We propose an approach for precision medicine in critical care (figure 2). Establishing the existence of subphenotypes is only the first part of the puzzle. Opportunities are arising to streamline subphenotyping strategies, compare them, and prospectively validate them in real time with parsimonious assays and algorithms. To progress from subphenotypes to endotypes, and from endotypes to clinically valuable, treatable traits, basic science studies need to be designed to establish mechanistic differences between subphenotypes and to develop treatments targeted to plausible mechanisms of disease pathology. This strategy will require the development of new in vitro and in vivo models. Targeted interventions will then need to be tested prospectively to attribute clinical value to subphenotypes and endotypes.

Pursuing subphenotypes might lead to the development of beneficial new treatments, provide insights into pathophysiology, and provide opportunities to identify commonalities across syndromes, leading to the redefinition of critical illness by biological similarity rather than clinical symptomatology. Since critical illness syndromes are often multisystem insults, there is a possibility that subphenotypes could transcend current disease definitions and describe multisystem inflammatory states, changing how we understand critical illness. This is an exciting time for critical care research and clinical practice, and we can expect a strong focus on subphenotypes in the coming years.

To translate subphenotypes for clinical application at the bedside, there is a need to develop rapid real-time assays for subphenotype assignment and to compare disparate subphenotyping strategies prospectively in heterogeneous patient cohorts.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed (MEDLINE) for articles published before Jan 27, 2020, with the terms "critical care", "intensive care", "ARDS", "AKI", "pancreatitis", "sepsis", "phenotype", "sub-phenotype", and "endotype". Primary research and reviews resulting from this search, and relevant references cited in those articles, were selected on the basis of relevance to the topics covered in this Review; papers published in English were considered. The initial search was done on May 28, 2019, and updated on Nov 10, 2019, and on Jan 27, 2020. Planned and ongoing studies of subphenotypes presented in table 2 were identified from a search of ClinicalTrials.gov and included on the basis of novelty.

Global cooperation between critical care researchers, with free sharing of data and determinant algorithms, will be needed to validate subphenotypes and realise the potential of precision medicine.

Contributors

KR prepared the first draft and subsequent revisions of the manuscript. PS, CMO'K, ACG, CSC, and DFM contributed to the writing of the manuscript, reviewed and edited the manuscript, and approved the final version of the manuscript.

Declaration of Interests

CMO'K reports grants from Innovate UK in collaboration with Randox for the PHIND trial, and grants from the UK National Institute for Health Research (NIHR), Wellcome Trust, and other funders for studies investigating treatments for ARDS; her spouse has received personal fees from GlaxoSmithKline, Boehringer Ingelheim, Bayer, Quench Bio, and GEn1E Lifesciences for consultancy on ARDS, outside of the submitted work. ACG reports an NIHR Research Professorship grant; personal fees and non-financial support from Orion Corporation (Orion Pharma); grants and other support from Tenax Therapeutics; and support from Bristol-Meyers Squibb and GlaxoSmithKline, outside of the submitted work. CSC reports grants from the US National Institutes of Health; grants and personal fees from Bayer; grants from GlaxoSmithKline; and personal fees from Roche (Genentech), Prometic, CSL Behring, and Quark, outside of the submitted work. DFM reports a grant from Innovate UK in collaboration with Randox for the PHIND trial; and personal fees for consultancy from GlaxoSmithKline, Boehringer Ingelheim, Bayer, Quench Bio, and GEn1E Lifesciences, outside of the submitted work. His institution, Queen's University Belfast, has received funds through grants from the NIHR, Wellcome Trust, Innovate UK, and other sources. He is one of four named inventors on a patent covering the use of sialic acid-bearing nanoparticles as anti-inflammatory agents issued to his institution (US8962032), which had no direct bearing on the content of this Review. DFM is a director of research for the Intensive Care Society and a director for the NIHR Efficacy and Mechanism Programme. All other authors declare no competing interests.

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