

Sepsis Subclasses: A Framework for Development and Interpretation*

Abstract: Sepsis is defined as a dysregulated host response to infection that leads to life-threatening acute organ dysfunction. It afflicts approximately 50 million people worldwide annually and is often deadly, even when evidence-based guidelines are applied promptly. Many randomized trials tested therapies for sepsis over the past 2 decades, but most have not proven beneficial. This may be because sepsis is a heterogeneous syndrome, characterized by a vast set of clinical and biologic features. Combinations of these features, however, may identify previously unrecognized groups, or “subclasses” with different risks of outcome and response to a given treatment. As efforts to identify sepsis subclasses become more common, many unanswered questions and challenges arise. These include: 1) the semantic underpinning of sepsis subclasses, 2) the conceptual goal of subclasses, 3) considerations about study design, data sources, and statistical methods, 4) the role of emerging data types, and 5) how to determine whether subclasses represent “truth.” We discuss these challenges and present a framework for the broader study of sepsis subclasses. This framework is intended to aid in the understanding and interpretation of sepsis subclasses, provide a mechanism for explaining subclasses generated by different methodologic approaches, and guide clinicians in how to consider subclasses in bedside care.

KEY WORDS: heterogeneity; phenotype; sepsis; subclass

Sepsis is a widely heterogeneous syndrome, recently defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection (1). Every year, sepsis afflicts nearly 50 million patients worldwide, and case fatality rates vary from 5% to 40% (2, 3). There is increasing pressure to reduce avoidable deaths and poor outcomes. However, trials of supportive care and novel therapeutics have been consistently disappointing, suggesting that the inherent complexity of clinical sepsis requires more sophisticated approaches to patient stratification (4). Recent efforts to identify groups within the broader sepsis syndrome give hope that treatments targeted to subclasses, or patients in whom there are shared features, will result in positive treatment effects. These treatments can be informed by the pathophysiology in question and thus targeted more toward the individual.

Archetypes of sepsis for which treatments are precise may exist in the mind of clinicians, such as the multimorbid elder with pneumococcal pneumonia. Yet, these cases are a minority of the larger septic population (5, 6). As a result, various approaches are proposed to group patients into subclasses of sepsis, often with different goals (Table 1). There may be room for many approaches to subclasses that do not make another right or wrong. We suggest, however, that the subclasses of sepsis derived in different study designs and for different purposes may be complementary to patient care, as long as their relationship is transparent

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*See also p. 861.

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DOI: 10.1097/CCM.0000000000004842

TABLE 1.
Conceptual and Scientific Considerations for Sepsis Subclasses

Framework Steps	Purpose/Detail	Caveats	Example of Areas of Tension for Sepsis Subclasses
Conceptual issues			
Epistemology	A philosophic view regarding whether sepsis is an entity that subclasses exist	Disagreement may exist over whether subclasses represent new knowledge and are unique to sepsis, as opposed to overlapping with other conditions	Hyperinflammatory subclasses are identified in sepsis and ARDS but may also be found in pancreatitis or hemorrhagic shock
Semantics	Define all relevant terms that frame the problem, such as phenotype, subphenotype, endotype, subclass, or subgroup	Not all terms are consistently used between investigators in sepsis or in other fields	Use of “endotype” in sepsis corresponds to a shared underlying biologic mechanism for grouped patients, but does this imply a single affected gene/pathway? Can multiple affected pathways exist in an endotype?
Goals and priorities	Setting of priorities that balance tradeoffs for clinicians, researchers, funders, and quality improvement specialists	Alternative subclass schemes have different merits (e.g., cost and pragmatism) and can be prognostic, predictive, or both	Blood leukocyte gene-expression subclasses may be prognostic and describe biologic mechanism but may be difficult to incorporate into clinical care
Scientific considerations			
Domains for subclasses	Multiple domains could inform how patients are grouped into subclasses	Domains could be informed by existing constructs, conceptual models of inflammation (e.g., Medzhitov) (46), crude patterns of organ dysfunction, or by data availability	Pathogen/infection site is a clinically important domain for subclasses but not always known at the time of sepsis diagnosis
Data source(s)	Subclasses can be determined from widely variable data sources (e.g., existing cohorts, prospective cohort studies, and randomized trials)	Clinical trial datasets sponsored by industry partners may not always be available for secondary analyses. Prospective observational cohort studies are difficult to fund	Clinical trials allow for testing of predictive subclasses but themselves may not be generalizable to the larger sepsis population for subclass derivation
Data preparation	Statistical methods to derive subclasses may be difficult after data processing from raw, noncurated data (“noisy data”) to “clean data”	Multiple issues should be investigated regarding candidate variables, including distribution, correlation, missingness, and limits of detection for biomarkers	Sepsis electronic health record data for subclasses commonly have high degree of nonrandom missing data

(Continued)

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Conceptual and Scientific Considerations for Sepsis Subclasses

Framework Steps	Purpose/Detail	Caveats	Example of Areas of Tension for Sepsis Subclasses
Variable selection	Study design must choose variables to include in subclass models	Different methods proposed to select and/or reduce the number of variables	Even “unsupervised” approaches using machine learning methods on “all” the data are still supervised in the choice of candidate variables
Statistical method	Multiple machine learning methods to derive subclasses are available	Results derived from different statistical models may classify patients differently	Both the optimal number of classes (<i>k</i>) and the members may be different using clustering or partitioning methods on the same dataset
Reproducibility	Subclasses derived in a single study need validation	Reproducibility may be impacted by data type, case mix, geography, missing data, and setting, among others	Is a subclass considered “real” if not reproduced in different patients in a different setting?
Biologic mechanism	Different subclasses may have fundamentally distinct, underlying biologic processes	Characterization of biologic underpinning of subclass may increase validity, and potential for differential treatment response	The current understanding of sepsis biology is incomplete and will evolve
Treatment heterogeneity	Subclasses may have a differential treatment effect compared with another subclass, and are termed “predictive”	Require assignment of patients in a clinical trial to subclasses, using data prior to randomization. Testing of treatment effects by subclass in observational data requires advanced causal modeling and multivariable adjustment for indication bias	Favorable treatment effects for a subclass in one trial are not necessarily reproducible in other trials
Uncertainty	Approaches to derive and test subclasses will have error and uncertainty	Multiple steps in this framework include subjective choices during design and will impact subclass uncertainty or error in results. Many variables in models are measured with some degree of uncertainty	There is no truth or gold standard for sepsis subclasses

and understood. Here, we discuss challenges for clinicians, researchers, trialists, and health policy makers relating to both adult and pediatric sepsis subclasses.

WHY IS CREATING SEPSIS SUBCLASSES DIFFICULT?

Disease classification is an inherent step in everyday clinical practice, especially in critical illness (7). We

often consider a disease to be present or absent, preferring to make binary decisions to support treatments (e.g., initiating antibiotics for infection). Such discrete, unambiguous determinations are beyond reach for most conditions. Although the “truth” behind classifications can be complex, it remains a motivation to understand biological mechanisms and treatment responses and is a key to communication and decision-making. A challenge for the derivation

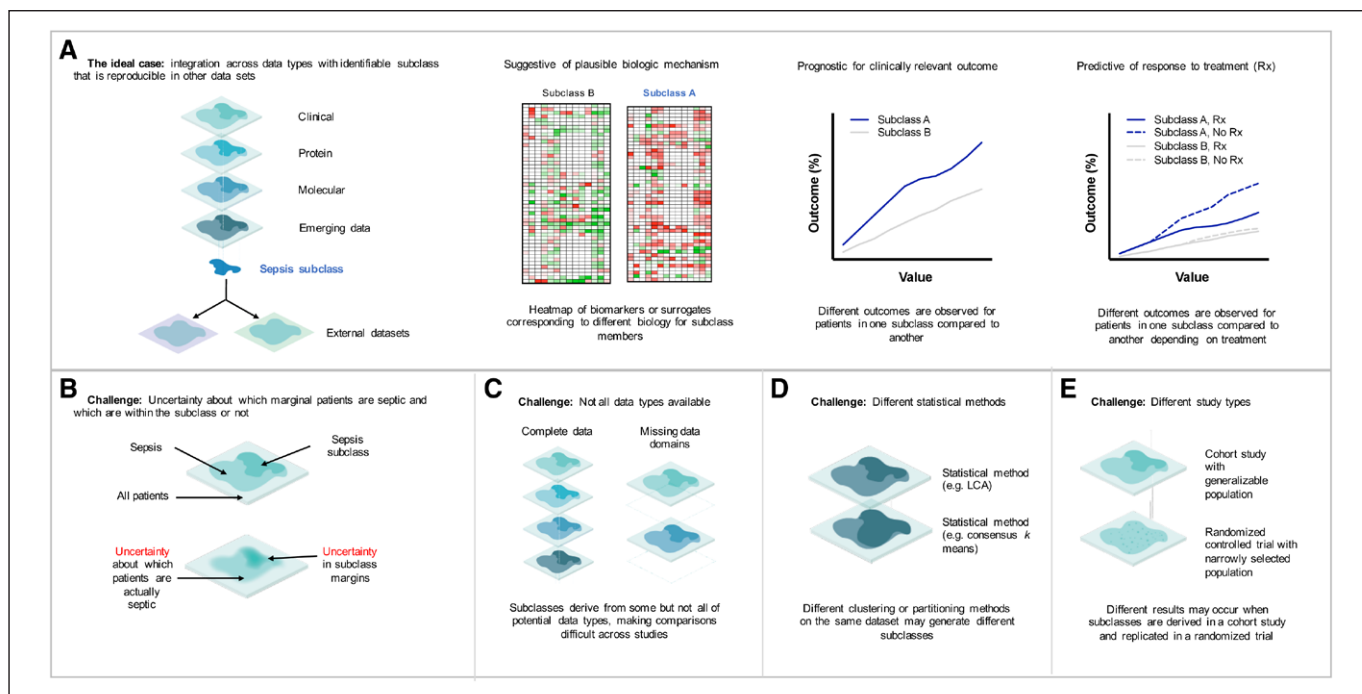


Figure 1. The ideal case in sepsis subclasses involves the integration across different compartments that is; **A**, (i) suggestive of biologic mechanism, (ii) prognostic of outcome, and/or (iii) predictive of treatment response. However, there are challenges in sepsis subclasses, including: uncertainty (**B**), missing data (**C**), different statistical methods (**D**), and different study types (**E**).

of sepsis subclasses arises when the classification of the overarching condition, sepsis, itself is changing and uncertain (**Fig. 1**) (1). Prior work shows clinicians do not agree (8), and revised criteria for sepsis identify patients differently from those labeled as septic in prior iterations (e.g., “Sepsis-2”) (9–11).

More complexity arises where there is lack of agreement about terms or semantics. For example, traditional approaches to sepsis classification often stratify by illness severity without differentiation by pathophysiology. Future subclasses might consider a combination of these features. More uncertainty arises when the components of sepsis, infection, and acute organ dysfunction, themselves have unclear “boundaries” (12). The chronicity of organ dysfunction, such as kidney disease, challenges both clinicians and researchers to tease apart whether new changes are causally related to infection, the trajectory of chronic disease, or a combination of both (13). The fuzzy boundaries around these decisions affect the credibility and reproducibility of proposed subclasses.

The open questions are as follows:

- 1) How do we consider uncertainty and marginal patients when defining subclasses?
- 2) Are subclasses discrete?

WHAT ARE THE GOALS WHEN STRATIFYING SEPSIS INTO SUBCLASSES?

Sepsis outcomes remain dismal (14). New innovations in sepsis care should reduce avoidable deaths and improve life after sepsis among survivors. However, do we know which groups will “matter” for patients and why? One approach is to identify groups based on prognosis, an approach that stratifies patients’ risk on their likelihood of death from sepsis or another targetable adverse outcome (15). For example, differentiating patients based on pre-existing comorbid disease or presence of multiple organ dysfunction may distinguish a group of patients with high risk of death from the disease under investigation (13). In addition, yet, because of the complex interplay of factors that together contribute to mortality in sepsis, clinical trials using prognostic enrichment have not proven successful in identifying effective treatments (15, 16).

Another approach is to identify groups based on prediction, in which patients are grouped based on their likelihood of responding to a specific therapy based on an underlying biological mechanism, irrespective of prognosis. Predictive enrichment should not be conflated with prognostic enrichment, although there are scenarios where there is overlap (17). One example is

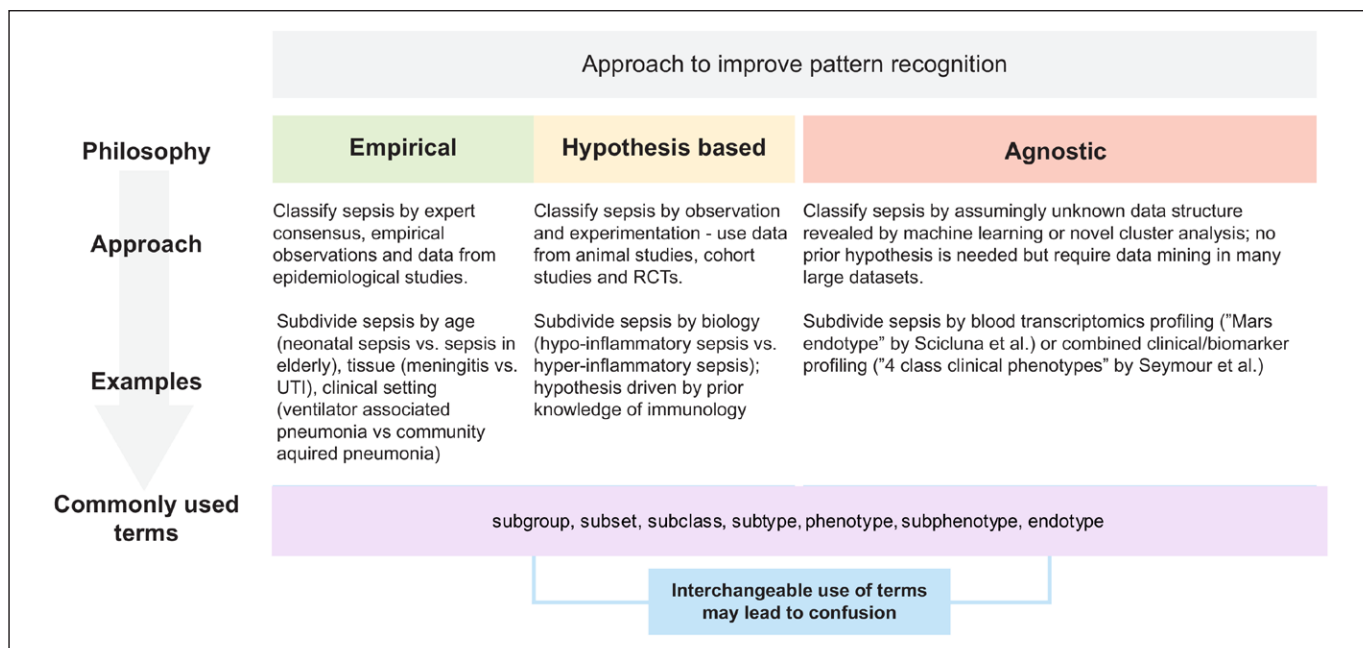


Figure 2. Proposed nomenclature for sepsis subclasses. RCT = randomized clinical trial, UTI = urinary tract infection.

severe hypoxemia in acute respiratory distress syndrome (ARDS). Severe hypoxemia can be both predictive and prognostic in that it can be associated with greater odds of death and greater likelihood of benefit from proning, for example (17).

Despite the promise of guiding treatment based on biologically plausible pathways, to date, these approaches have also yet yielded effective treatments in sepsis, nor have they been fully tested in randomized controlled trials (RCTs) (18). Moving forward, we expect novel computational approaches will inform subclasses using integrated clinical, molecular, and omic data from a variety of harmonized datasets. Prospective validation in randomized trials, for prognosis and/or predictive enrichment (19, 20), will be key to ensuring they are practical, uncover a distinct pathobiology, and achieve the goal for different scenarios.

The open question is as follows:

- 1) Should all contemporary randomized trials include prognostic or predictive enrichment?

WHAT ARE THE WORDS WE WILL USE?

Words matter. Choosing the right language to classify sepsis enables clinicians to stratify (high-risk patients), inform (what is the underlying cause), and prompt (therapeutic action). Sepsis epistemology is confusing and made worse by the diverse pattern recognition techniques used to derive sepsis subclasses. When

investigators employ techniques ranging from empirical methods to machine learning, new terms are inevitably introduced, which are infrequently reconciled with prior work (Fig. 2). For the past 2 decades, terms such as "subgroup" have been used to align patients by source of infection (e.g., community-acquired pneumonia vs ventilator-associated pneumonia), organ/tissue (meningitis vs urinary tract infection), or biology (hyperinflammatory vs hypoinflammatory sepsis). Now, data-driven methods classify sepsis in different ways (e.g., "Molecular diagnosis and Risk stratification of Sepsis [MARS2]" or "δ clinical phenotype") (6, 19, 21) and refer to these groups as subtypes, endotypes, clinical phenotypes, or subphenotypes. Terms are used interchangeably and inconsistently, and researchers lack consensus. The debate on terminology has been discussed and summarized in the literature (17). In this piece, we use "subclass" to denote a grouping of patients regardless of underlying approach to grouping.

The open questions are as follows:

- 1) Is there a unifying term, other than "subclass" in which to describe sepsis subgroups?
- 2) What steps will reduce semantic vandalism amongst clinicians and researchers?

WHAT DATA SOURCE SHOULD WE USE?

To determine sepsis subclasses, researchers could use many data sources (Fig. 2). The choice of dataset in

which to derive, reproduce, or explore new subclasses of sepsis may affect results. For example, multicenter, RCT data may come from a diverse geographic enrollment across many centers, have high internal validity, and can establish a causal relationship by leveraging randomization. Missing data are less common in case report forms from RCTs, and these datasets will have high confidence in treatment allocation and adherence (16, 22). However, most RCTs in sepsis have exclusions that may limit external validity of subclasses, such as comorbid illness, life expectancy, or illness severity.

Observational cohorts can be explored for sepsis subclasses. Cohorts that use electronic health record (EHR) data are flexible to different sepsis criteria, time of onset, a diverse range of pathogens, and typically include multiple data points per day (6). Observational cohort studies can also be expanded at large scale to low- and middle-income countries (3). Sample size may be many-fold higher than RCTs, affording more power to statistical algorithms. Although observational cohort studies are often generalizable at the patient, hospital, or system level, they may also contain missing data, outlier values, variations in clinical practice over time, and confounded by unknown variables (5). More rigorous prospective cohort studies can overcome some of these problems, but are historically difficult to fund and lack internal validity for evaluating causal effects.

In the end, the most knowledge can be gleaned combining cohort and RCT data. For example, the Sepsis ENdotyping in Emergency CAre (SENECA) study reported on sepsis phenotypes derived from multiple EHR cohorts that accrued patient encounters from 12 centers over 5 years (19). Then, the phenotypes were reproduced in historical cohorts with different sepsis types and applied to three RCTs (16, 22, 23). Conceptually, this approach “starts broad” to maximize the heterogeneity over which to subclass sepsis and then sought to “validate” or reproduce the findings in more highly curated data. In the end, if subclasses are proposed to reflect real differences in sepsis biology across subclasses, findings would be robust to different data sources, definitions of sepsis, treatment, and geography.

The open questions are as follows:

1) Can observational data and trial data be used to better model subclass treatment effects together rather than separately?

2) Is a subclass treatment effect relevant to clinicians if reported from an analysis of one trial alone?

DEFINING SEPSIS SUBCLASSES FROM CLINICAL OR TRANSCRIPTOMIC DATA

There are many data types to study when searching for sepsis subclasses (Fig. 2). Among the most commonly used are clinical, protein, and/or transcriptomic data. Clinical sepsis subclasses have distinct patterns of laboratory abnormalities, have organ dysfunction, and are prognostic of clinical outcomes (**eTable 1**, <http://links.lww.com/CCM/G108>) (19). Clinical data alone, however, provides limited information on a biologic mechanism, but measured host biomarkers can suggest a potential biologic mechanism driving clinical phenotypes (19). Clinical data in EHRs can be relatively sparse, found as free text, difficult to analyze, and restricted to readily available measurements such as vital signs, medications, and laboratory testing (6). However, the ability to aggregate these data for millions of patients may allow discovery of robust sepsis subclasses (19).

An alternative approach is to characterize sepsis subclasses using metabolomics, proteomics, and most commonly, transcriptomics (**eTable 1**, <http://links.lww.com/CCM/G108>). Key to this approach is technological advances that have led to a detailed understanding of the whole-blood genome expression and leukocyte transcriptome (24, 25). For example, the Genomic Advances in Sepsis consortium and the MARS consortium used whole blood gene expression to identify subclasses in community-acquired pneumonia, fecal peritonitis, and all cause sepsis, respectively (21, 26, 27). Although the exact number and composition of these subclasses varied, common elements persisted such as the association with disease severity and 28-day mortality. Whether these signatures are unique to sepsis or have relevance outside of sepsis remains unknown. Recent evidence, however, suggest that there may indeed be a fundamentally similar response to different types of stress. In a study by Xiao et al. (28), different injury mechanisms, trauma, burns, and endotoxemia yielded similarities in gene-expression patterns. Additionally, subclasses in acute pancreatitis may show similarities to those with ARDS (29). It is, therefore, likely that at least some of the molecular

subclasses in sepsis will reflect general features of the host response to critical systemic injury.

The promise of molecular subtypes applied in the clinical setting cannot be realized without considering the hurdles. Techniques must be performed in near real-time, at reasonable cost, and at low-complexity, and be reproducible. Fortunately, real-time RNA, protein, or metabolite quantification is now more affordable and accessible.

The open questions are as follows:

- 1) How can molecular subclasses be scaled from research studies to clinical practice?
- 2) What computational techniques will allow subclasses to be derived from integrated data, including clinical and omic sources?

EMERGING DATA TYPES TO INFORM SEPSIS SUBCLASSES

Modern molecular techniques have greatly expanded. A single patient specimen, at a single time point, can yield hundreds of thousands of measurements, informing us about host genomics, gene expression, protein synthesis, metabolic activity, microbial identity and function, and effects of therapeutic interventions (17). Therefore, when measured at multiple time points and potentially multiple locations, the information set expands substantially to measuring the host response to both infection and treatment. This wealth of data presents us with opportunities for advancing sepsis subclasses but also introduces unresolved methodological and analytical challenges.

Fundamentally, new technologies provide additional numerical observations about patients. These observations are not conceptually different from other tests such as WBC count or creatinine, and each observation is a marker for a biological process that may, or may not, be clinically important.

One example of emerging data for sepsis subclasses is the microbiome: the 1.5 kg of bacteria, fungi, archaea, and viruses found in a patient. The microbiome has multiple potential roles in the pathophysiology of sepsis (30): 1) a reservoir of potential pathogens, 2) a metabolic/endocrine organ (turning gut contents into systemically active small molecules), 3) a direct mediator of local and systemic inflammation, or 4) a source of systemically translocated bacteria and bacterial products (31, 32). Both gut and respiratory

microbiota are profoundly altered in patients being treated for sepsis compared to healthy subjects (31, 33, 34). In critically ill humans, variation in lung microbiota correlates with variation both in systemic and alveolar inflammation (31, 35), whereas a decreased diversity of gut bacteria has been shown to predict bacteremia and mortality in patients at risk for sepsis (36–38).

The open questions are as follows:

- 1) How will emerging data types like the microbiome inform sepsis subclasses caused by different pathogens?
- 2) Do emerging data types such as the dysbiosis of critical illness play a causal role in sepsis biology or merely reflect an epiphenomenon?

WHAT ABOUT SUBCLASSES IN CHILDREN?

Sepsis subclasses are also proposed in pediatric patients. These studies use a variety of conceptual approaches, either supervised, knowledge-based subclasses, or discovery work using gene expression. For example, Carcillo et al (39) found that features from rheumatologic diseases identified pediatric subclasses that were prognostic and predictive of response to interleukin receptor antagonist therapy (e.g., macrophage activation syndrome) (40). An alternative is to be agnostic to existing knowledge and determine data-derived subclasses. Among PICU patients, Wong et al used gene-expression profiling to find transcriptionally distinct subclasses that may explain heterogeneity in pediatric sepsis (41). The distinct profiles translate into clinically meaningful protein biomarkers that both predict high mortality in pediatric patients (40). Subclasses were present, with some similarities in gene expression in adult patients (42) and may interact with steroid treatment for shock (43).

Age presents a unique challenge to deriving and interpreting pediatric sepsis subclasses. The broad age range in children encompasses a variable immune response, vaccine exposure, different pathogens, and vital signs that may be normal for one age but abnormal for another. These data are challenging for the clinical interpretation of subclasses, as it may be unclear if the biology informing the subclass is linked to age or independent of age.

The open questions are as follows:

- 1) Are sepsis subclasses treatment responsive in children?
- 2) Will pediatric sepsis subclasses be similar comparing adolescents to younger children?

THE IMPORTANCE OF TIMING

There is debate about how time relates to sepsis subclasses. Some may view subclasses as assigned for a lifetime, due to a patient's underlying genotype such as Trisomy 21. Others may consider subclasses to be bounded by a specific episode of illness, episode of care, or single moment. For example, the SENECA study in adult sepsis derived subclasses over a 6-hr window in the emergency department (19). These data included clinical moments that may influence both treatment and eligibility for randomized trials.

However, a narrow view of "time" has many drawbacks. First, it is limited to data that are observable in a specified time window and may miss informative data from other moments. Second, patients assigned to subclasses derived at a single moment may change over the disease course (27, 44). Although not unexpected, evolving membership from one subclass to another

may confuse clinicians, reduce confidence in the biologic underpinnings of such subclasses, or even make targeted therapy difficult to achieve. A change in subclass membership over time, however, may also reflect treatment response or even consequence or harm (44). Evaluation at early time points does not reflect the effect of subsequent treatments, whereas evaluation at later time points reflects a net consequence of both the original insult and the impact on host response, all of which may be modified by actions of the clinician. The use of repeated data or treating time as a continuous variable when determining subclasses could help address some of these challenges.

The open questions are as follows:

- 1) How frequently do sepsis subclasses change?
- 2) Does a changing subclass assignment reflect prognosis, treatment response, biology, or all three?

STATISTICAL METHODS FOR DERIVING SEPSIS SUBCLASSES

The three main statistical objectives for subclasses (Fig. 2) are to group patients: 1) with similar variables, 2) by differences or similarities in outcomes, or 3) by

TABLE 2.
Commonly Used Statistical Approaches to Derive Subclasses in Sepsis

Model Type	Features	Caveats
Unsupervised cluster analysis (objective 1)	Designed to uncover hidden structure in a high-dimensional space of patient characteristics Naturally produces a set of subclasses with respect to similarity of patient characteristics	Does not take into account outcomes or treatment assignment, so should not be expected to generate optimal outcome and treatment effect predictions Biologic mechanisms can be learned from subclasses, but membership is dependent on the data available to the model
Supervised outcome modeling (objective 2)	Can be tuned to generate subclasses of patients within which expected outcomes are similar and between which outcomes are different	Degree of heterogeneity of expected outcomes across subclasses depends on the strength of association between available patient characteristics and the outcome Results may be sensitive to missing patient covariate data, number of highly correlated patient covariates
Treatment effect modeling (objective 3)	Interaction between treatment and predictor is the focus Can be used to generate subclasses with differential treatment effects	The same caveats as for supervised outcome modeling May exaggerate heterogeneity of treatment effects in the sample that was used to fit the model Model selection is difficult, because treatment effects are not observable at the patient level

differential treatment response. Different modeling strategies are suggested for each of these three objectives (Table 2). Objective 1 typically uses an unsupervised learning approach, as the primary goal does not involve prediction of a specific outcome (6). In contrast, when objective 2 or 3 is the focus, subclasses can be derived more directly using supervised models. A supervised outcome model is given a set of patient characteristics as inputs and is fit in such a way as to predict the measured outcome most accurately. These models can be used to develop risk-based groups from available covariates that are useful for prognostic enrichment. Supervised methods can also be used to find treatment by covariate interactions in order to find subclasses that may benefit or be harmed by a specific treatment. To avoid overfitting and ensure prediction accuracy, it is crucial to use the testing or validation set approach. Among these statistical approaches and many others, the choice of strategy should be primarily driven by the research objective, stated goals, and resources available, and ultimately, the model should be interpretable and plausible.

THE SEARCH FOR MEANING

When a sepsis subclass is proposed, how do we know if it is meaningful? The measurement of validity is the main challenge. The distinction between subclasses and cohesion among members may not be enough to convince the skeptic that a group of sepsis patients belongs together. A new subclass could be assessed in the following steps: 1) biologic plausibility, 2) the ability to predict treatment response, and 3) consistency and reproducibility in other datasets. One might also assess a subclass in terms of feasibility of implementation in clinical care and/or clinical trials; however, it is important to note that this may not affect the plausibility, predictability, consistency, or reproducibility of the proposed subclass.

It is also possible that a subclass proposed in one dataset lays fallow, unable to be tested in subsequent data due to the nature of the trial or biologic samples used in subclass models. The steps necessary to reject a proposed subclass are vaguer. One could find fatal flaws in a design or statistical method used to derive a subclass, issues with misclassification of the larger population under study, problems with the underlying dataset, or even nonreproducibility. The identification

of synonymous groups is perhaps easier. Datasets that include clinical, biologic, or molecular data necessary to define potentially overlapping classes are the key step, as demonstrated for gene-expression subclasses, for example, SRS and MARS, among others (21, 26, 45).

SUBCLASSES AT THE BEDSIDE?

The translation of sepsis subclasses to the bedside as a prognostic and/or treatment-guiding tool is a key step to achieving the goal of individualized or “precision” medicine. Integral to this transition is embedding of subclasses into routine clinical care—using the EHR. Such a process may require informatics solutions that: 1) model a set of clinical variables for subclass assignment and 2) prompt clinicians to measure laboratory tests or biospecimens (if not already obtained). It is unlikely that a single clinical trait, genetic, or protein biomarker will define a subclass, and the EHR could help manage the integration of data across many compartments (46). Beyond just subclass recognition and alerting, treatment-response subclasses could affect care at the bedside through targeted clinical decision support. Using reinforcement learning algorithms (47), treatments can be prompted when patients enter a subclass or state. Ultimately, in a “learning while doing” approach (48), subclasses can be refined at the same they are guiding improvements in sepsis care.

A PATH FORWARD

Before the broad use of sepsis subclasses at the bedside, it is helpful to consider the many issues related to purpose, statistical methods, data sources, timing, and assessment of truth. Is it enough to identify groups of patients in a single dataset, hitherto not recognized to cluster together, for prognosis or a precision treatment? Or is the goal a truly individualized strategy? Rather than “subclasses,” per se, perhaps we should be searching for “clinically relevant, nonsynonymous, biologically plausible, treatment-responsive, and reproducible” subgroups. Once tested in randomized trials with accompanying treatments, these subclasses would have the potential to inform not only the pathophysiology of sepsis, but future efforts to improve patient outcomes.

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The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and social care. The funding source did not have any role in the design, conduct or interpretation of study results.

Dr. Seymour helped in designing the concept. Drs. DeMerle, Angus, and Seymour helped in designing. Drs. DeMerle, Baille, Brant, Calfee, Carcillo, Chang, Dickson, Evans, Gordon, Kennedy, Knight, Lindsell, Liu, Marshall, Randolph, Scicluna, Shankar-Hari, Shapiro, Sweeney, Talis, Tang, Thompson, Tsalik, van der Poll, van Vught, Wong, Yende, Zhao, and Seymour drafted the article and critically revised the article for important intellectual content.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjournal>).

Dr. DeMerle's institution received funding from R35 GM119519-03 and T32HL007820. Dr. Calfee is supported in part by grants from the National Institutes of Health (NIH; HL140026). Dr. Carcillo is supported in part by grants from the National Institutes of Health (R01GM108618). Dr. DeMerle is supported in part by grants from the National Institutes of Health (T32HL007820). Dr. Angus received funding from Ferring Pharmaceuticals, Bristol-Myers Squibb, Bayer AG, and Alung Technologies. Drs. Angus, Brant, Carcillo, Chang, Dickson, Kennedy, Lindsell, Liu, Randolph, Thompson, Tsalik, Wong, and Seymour received support for article research from the NIH. Dr. Baillie received support for article research from Wellcome Trust/Charity Open Access Fund (COAF), and Research Councils UK. Dr. Calfee's institution received funding from Roche/Genentech and Bayer, and she received funding from Roche/Genentech, Quark, CSL Behring, Bayer, Gen1e Life Sciences, and Vasomune. Drs. Carcillo's and Seymour's institutions received funding from the National Institute of General Medical Sciences. Drs. Chang's, Lindsell's, Liu's, Randolph's, Shapiro's, and Wong's institutions received funding from the NIH. Dr. Gordon's institution received funding from the National Institute for Health Research (NIHR) Research Professorship (RP-2015-06-18), NIHR Imperial Biomedical Research Centre, GlaxoSmithKline, and Bristol Myers Squibb. Dr. Knight received support for article research from Wellcome Trust/COAF. Dr. Lindsell's institution received funding from the Centers for Disease Control and Prevention (CDC), Department of Defense, Marcus Foundation, Entegriion, Endpoint Health, and bioMerieux, and he disclosed he is a coinventor on patents related to risk stratification in septic shock. Dr. Marshall received funding from AM Pharma, AKPA Pharma, and the Society of Critical Care Medicine (Critical Care Medicine Associate Editor). Dr. Randolph's institution received funding from the CDC, and she received funding from La Jolla Pharma. Dr. Shapiro's institution received funding from rapid pathogen screening, Baxter, and Inflammatrix, and he received funding from Diagnostic Robotics. Dr. Sweeney received funding from Inflammatrix. Dr. Thompson's institution received funding from the National Heart, Lung, and Blood Institute, and he received funding from Bayer and Thetis. Dr. Tsalik disclosed that he is a founder and holds equity in Predigen; he receives salary support from the Durham VA Healthcare System and Duke University; and he has received salary support and/or grant funding (paid to his university) from the NIH, DARPA, DTRA, Karius, and Sanofi US. Dr. Wong disclosed that he and his institutions hold U.S. patents for sepsis biomarkers. Dr. Yende received funding from serving as

consultant for expert testimony and he disclosed government work. Dr. Knight is supported by a Wellcome Trust Investigator Award (204969/Z/16/Z) and the NIHR Oxford Biomedical Research Centre. Dr. Lindsell was supported in part by grants from the National Institutes of Health (R35GM126943, R01HL149422), a research grant to VUMC from Endpoint Health, and is also listed as co-inventor on patents for endotyping and risk-stratification in pediatric septic shock. Dr. Liu is supported in part by grants from the National Institutes of Health (R35GM128672). Dr. Marshall is supported in part by grants from the Canadian Institutes of Health Research. Dr. Randolph is supported in part by grants from the National Institutes of Health (R21HD095228). Dr. Shankar-Hari is supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011). Dr. Wong is supported in part by grants from the National Institutes of Health (R35 GM126943). Dr. Sweeney is an employee of, and shareholder in, Inflammix. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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