# Redefining Critical Illness

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**Abstract**

Both research and practice in critical care medicine have long been defined by syndromes. Though clinically recognizable entities, these are in fact loose amalgams of heterogeneous states, within which responses to therapy may vary. Mounting translational evidence suggests the current syndrome-based framework of critical illness should be reconsidered. Moreover, research conducted during the COVID-19 pandemic illustrates how the study of a more biologically homogeneous condition – respiratory failure due to SARS-CoV-2 infection – can increase the efficiency with which actionable results are generated. We discuss recent findings from basic science and clinical research in critical care, and explore how these might inform a new conceptual model of critical illness. De-emphasizing syndromes, we focus instead on the underlying biological changes that underpin critical illness states, and that may be amenable to treatment. We hypothesize that such an approach will accelerate translational critical care research, leading to a richer understanding of the pathobiology of critical illness and of the proximate determinants of ICU outcomes. The specificity and granularity gained will support the design of more effective clinical trials, and inform a more precise, effective practice at the bedside.

A 66 year-old woman is admitted to the intensive care unit (ICU) with fever, cough, and difficulty breathing. She is diagnosed with pneumonia, intubated, and placed on mechanical ventilation. The following day, her chest x-ray reveals bilateral infiltrates, and arterial blood gas analysis shows severe hypoxemia. Her treating clinicians consider what to do next.

Were this patient admitted in 2019, her management might have been beset by more questions than answers. She has both sepsis – a syndrome of life-threatening organ dysfunction in the face of infection – and acute respiratory distress syndrome (ARDS) – a syndrome of respiratory failure associated with lung injury and impaired gas exchange. Both of these syndromes have been the subject of numerous epidemiological and interventional studies, yet little of the resulting evidence is clinically actionable; there are no specific treatments for her sepsis beyond antmicrobials[1], and the ventilation strategies used to treat ARDS might reasonably be applied to any patient in the ICU[2].

Were she admitted today – and depending on geography and time of year – her condition might well be the result of critical COVID-19. She would still meet diagnostic criteria for both sepsis and ARDS, and would ostensibly face a similar degree of therapeutic uncertainty. But in the last few years, a number of large randomized trials have provided a wellspring of evidence, suggesting that a patient in her condition was likely to benefit from corticosteroids[3] and interleukin-6 receptor antagonists[4,5], but that treatments for milder disease – including remdesivir[6] and systemic anticoagulation[7] – were unlikely to provide significant benefit. To the great relief of many, the once arid landscape of clinical evidence in critical care had begun to germinate.

In what follows, we examine how advances in translational critical care brought us to this inflection point in our field, and how these advances stand to fundamentally alter the way we conceptualize and classify critical illness.

**A new era in translational critical care research**

The field of critical care medicine can be described by three stages of development (Figure 1). In the first stage (“Foundations”, c. 1955 – 1980s), mechanical ventilation and continuous monitoring of physiological parameters were introduced to the care of the critically ill, along

with higher nurse-to-patient ratios, standardized practices, and an emerging recognition of critical care as a standalone medical specialty. These technological advances provided the basis for a physiology-based understanding of the host response to injury, and saved the lives of patients who were otherwise destined to die. Critical illness was defined as organ-level pathophysiology (e.g. shock, respiratory failure), and the delivery of intensive care services was centred on maintaining organ-level homeostasis (e.g. assisted breathing, circulatory support).

A second stage ("Acceleration", c. 1980s – 2020) arose alongside advances in translational critical care research that proffered an improved understanding of the pathophysiology of the host response. In this era, the field acquired structure, with the advent of quantitative scoring systems and standardized syndrome definitions. These included the APACHE score[8], as well as definitions for the systemic inflammatory response syndrome (SIRS), sepsis[9], and ARDS[10]. Together, these laid the groundwork for rigorous clinical and translational studies, which in combination with better organization and inter-disciplinary collaboration, led to tremendous improvements in outcomes for critically ill patients.

From the late 2000's, emerging evidence has begun to suggest that while initially useful in research and practice, current disease concepts do not sufficiently capture the full complexity of critical illness[11,12]. Advances in -omics science, data science, and machine learning have generated evidence of heterogeneity in common ICU syndromes. Gene expression data from the blood of both pediatric and adult patients with sepsis have been used with hierarchical clustering algorithms to discover and validate distinct subsets of patients with shared transcriptomic responses to severe infection[13-19]. Similarly, latent class analysis has been used with clinical and biomarker data from patients with ARDS, to reveal hypo- and hyper-inflammatory subtypes[20-22]. These findings clearly resonate with the day-to-day experience of clinicians caring for critically ill patients, whom despite sharing common diagnoses nonetheless exhibit substantial variability in clinical course and outcome [19,20,22-25]. There is an increasingly compelling need to reconsider the prevailing approach to the classification of critical illness[26-28].

Critical care medicine is on the cusp of a sea change – a third phase of development ("Precision" - Figure 1), defined by advances in translational science. This phase stands to be more disruptive than those preceding, and will require a wholesale reconfiguration of existing classification frameworks.

## Critical illness syndromes

Most of the illnesses treated in the ICU are syndromic in nature. Conditions like sepsis, ARDS, acute kidney injury, delirium, and even chronic critical illness are characterized not by any particular biopsy feature, genetic mutation, microbial culture, or serologic test, but rather by collections of signs and symptoms that together paint the picture of a clinically recognizable entity. As a result, critical illness syndromes are heterogeneous by nature. For instance, sepsis can arise from a multitude of infections, caused by numerous different pathogens, and resulting in different patterns of organ injury. ARDS may arise from either pulmonary or non-pulmonary triggers, and delirium may manifest as both agitation and somnolence. There is temporal heterogeneity as well. A patient meeting diagnostic criteria for one syndrome may progress through different, often disparate phases. Added to this is the tremendous heterogeneity in host response from one individual to the next.

The outward manifestations of critical illness syndromes are often codified into formal diagnostic criteria. Syndromes enable the objective and reproducible assembly of patient cohorts, and as such are useful in research and quality improvement. Syndromes can also be *prognostic*, meaning they can be used to estimate the likelihood of an outcomes. For example, the current clinical criteria for septic shock are associated with a risk of death in excess of 40%[29]. These criteria do not, however, identify which patients are likely to respond to any specific treatment. Classifiers that exhibit this latter function are often called *predictive*. For example, coagulopathy due to thrombocytopenia is likely to improve with platelet transfusion, whereas that which is due to dysfibrinogenemia is not. This inherent limitation in the syndrome-based classification of critical illness arises because current criteria are based on clinical findings, rather than the underlying biological processes that give rise to them. An important question therefore is whether our current syndrome-based classification schema is fit for purpose, and whether a new approach is needed.

## A translational classification of critical illness

Illness classifications have been proposed and revised since antiquity, but for the most part, the essential components have changed very little. An early taxonomy developed by Linnaeus in the 18th century bears striking resemblance to modern schemas such as the International

Classification of Diseases (ICD) system; individual diseases are specified on the basis of signs and symptoms, and the relationships between them are delineated, often as a nested hierarchy.

Important conceptual advances have nonetheless been made. The TNM staging system in oncology has been useful in framing cancer not as a single disease, but as a collection of related conditions whose optimal treatment depends on the extent of their progression. Adapting this concept to the ICU, the PIRO model (predisposition, insult, response, organ dysfunction) was proposed to underscore the notion that response to treatment is impacted by more than whether certain syndromic criteria are met; any given patient's outcome will also be strongly influenced by their baseline physiology, the nature of the precipitating insult, and the way in which various organ systems respond[30].

The PIRO model was an important early step towards acknowledging heterogeneity in critical illness. But translational and clinical evidence accrued in the last decade has deepened our understanding of the complexity of critical illness and its biological determinants, compelling us to revisit the nosology of critical care. To best capitalize, a new framework must accommodate complexity and heterogeneity, and must also establish a closer correspondence between diagnosis and treatment. In other words, critical illness classification should be not only prognostic – as syndromes are – but predictive as well, allowing researchers and practitioners to focus on measures that stand to improve outcomes.

Conceptually, a new classification system should encompass the inciting illness event, the physiologic disturbances produced, and the treatments that could return the overall system to a state of health. We advance a new concept here that begins with **insults** – events that instigate an acute departure from some baseline level of homeostasis, with the potential to elicit critical illness. Insults are myriad and diverse. Infection, trauma, stroke, haemorrhage, overdose, major surgery – all of these represent an abrupt change in baseline physiology, and all are common reasons for ICU admission. Insults in turn give rise to perturbations in bodily systems that in turn lead to disease states, organ dysfunction, and clinically overt morbidity.

The basis of this model is a more direct correspondence between insults, and the pathophysiologic states they engender. This is achieved by placing the insult, along with treatments and their consequences, in a causal pathway. Causality is a key feature here, and an important change from current syndromic classifications; while we know that in general fluids will be helpful in septic shock, and low driving pressures during mechanical ventilation will be helpful in ARDS, the heterogeneity of these conditions limits the causal inferences than

can be made, thereby hindering the clinical actionability of these principles in the treatment of any individual patient.

To enhance the precision of diagnosis in critical care, we invoke the concept of a **treatable trait** – a specific physiologic derangement characterized by biomarkers that portend a predictable response to a particular therapy[31]. Though biomarkers are often understood to refer to specialized laboratory tests – usually from blood or tissue – our use of the term here is more broadly construed. Biomarkers are any observable trait that corresponds with the biological abnormality of interest, and that underpins a prediction around how a patient will respond to a specific therapy. As such, biomarkers may include transcriptomic features derived from RNA sequencing, virulence factors identified by pathogen genomics, features seen on advanced imaging studies, or even imbalances in the autonomic nervous system identified by millisecond-scale changes in heart rate variability. They may also include simple and routinely measured clinical variables such as oxygen saturation, haemoglobin levels, and glucose concentrations, which currently serve a similar role by enabling predictions about the effects of oxygen titration, transfusion, and insulin therapy, respectively. The particular modality used is of secondary importance; what matters is that the feature can be measured, that it corresponds with the physiological process causing harm, and that it can be linked to treatment response.

Recent evidence suggests that disparate insults may give rise to shared molecular patterns of injury. Influential work by the Inflammation and the Host Response to Injury Program (NCT00257231) replicated clinical observations of pathophysiological similarities across critical illness syndromes, by showing that molecular signatures in trauma and burn injuries include activation of some of the same pathways implicated in severe infection and inflammation[32]. This work has since been extended, revealing molecular similarities between bacterial sepsis and COVID-19 viral sepsis[33], as well as between ARDS and pancreatitis[34]. These observations suggest that some subgrouping signals might be generalizable across different forms of critical illness, precipitated by very different insults.

Such findings hint at a previously uncharacterized richness in the biological determinants of critical illness. Rather than a one-to-one correspondence between insult and disease state, a one-to-many, or even many-to-many relationship is likely more appropriate. As traditional hierarchical models of classification cannot easily represent such a system, we offer the circular model shown in Figure 2 to depict the precise biological processes that characterize a disease mechanism shared between different illness states, irrespective of the insult from which they

arise. This configuration better accommodates the complexity of critical illness by acknowledging that certain states may be reached through different causal paths, and that while the insult itself is important, it is the resultant physiologic state that may better characterize a patient's current status.

To illustrate the potential utility of a model thus construed, consider the role of toll-like receptor (TLR) signalling in critical illness. TLR pathways contribute to the inflammatory response, and are known to be activated by various triggers, both exogenous (eg., bacterial endotoxin), and endogenous (eg. heme, hyaluronic acid) [35]. Upregulation of TLR pathways has in fact been identified through gene expression profiling in the settings of both trauma [32], and sepsis[36]. However, given the heterogeneity of these clinical syndromes – as well as differences in the genetic determinants of the immune response to TLR activation[37] – the extent of TLR-mediated inflammation likely varies among patients. This biological heterogeneity may in part explain why inhibiting TLR-mediated inflammation does not appear to be an effective treatment for cohorts defined by diagnostic criteria for severe sepsis[38]. We might, however, hypothesize that this approach will be helpful in a subset of sepsis patients with more pronounced dysregulation of TLR signaling. What's more, we might also hypothesize that a subset of trauma patients who manifest maladaptive TLR pathway upregulation will benefit from this approach as well, even though their illness state arose from a different insult. Answering this question would require a clinical trial in which patients are enrolled based on a treatable trait – in this case TLR upregulation – rather than a clinical syndrome such as sepsis or trauma.

TLR signaling may also play an important role in the host response to SARS-CoV-2. Rapid whole-exome sequencing of probands with COVID-19 have identified deletions in the *TLR7* gene that were associated with an extreme critical illness phenotype[39]. Although TLR signaling is implicated here as well, the nature of the derangement is different; loss of function variants led to an impaired interferon-mediated response to the virus. Rather than a TLR antagonist, a TLR agonist such as imiquimod might therefore be effective in these cases. This would be a different treatable trait, one that might be shared by other conditions, including certain skin cancers[40].

The conceptual model we here describe has yet to be validated in prospective clinical trials. However, early evidence for the feasibility and efficacy of this approach is mounting. In oncology, the I-SPY platform uses molecular profiling of breast tumours to identify specific subtypes most likely to respond to certain treatments, such as the tyrosine kinase inhibitor

neratinib[41]. This approach – often called predictive enrichment – is coupled with adaptive randomization to evaluate a number of breast cancer subtypes derived from tumour gene expression data, adjusting the treatment allocation strategy according to interim results. The I-SPY consortium has recently expanded to launch I-SPY COVID, a phase 2 clinical trial platform designed to use adaptive randomization to rapidly evaluate the viability of new COVID-19 therapies, with those deemed potentially viable graduated to larger definitive trials[42].

Within critical care, randomized trials are beginning to explore the use of predictive enrichment to reduce the heterogeneity of treatment effect seen when recruitment is based strictly on syndromic criteria. One example is the EUPHRATES study, which examined the use of polymyxin B hemoperfusion in patients with septic shock[43]. This therapy is designed to remove bacterial endotoxin from the circulation, and so rather than enrolling all patients meeting syndrome criteria for septic shock, the investigators randomized only those patients with high baseline levels of circulating endotoxin. The EUPHRATES experience demonstrates the feasibility of using a biomarker to rapidly identify a specific subgroup of patients expected to be most treatment-responsive. It also illustrates the challenges in identifying treatable traits. With no difference in mortality seen between the treatment and placebo arms, this study highlights the importance of defining appropriate subgroups, developing predictive biomarkers, and devising realistic measures of treatment response.

In many ways, recent COVID-19 clinical trials have also demonstrated the potential viability of using a treatable trait concept to disambiguate critical illness syndromes, and increase the yield of actionable evidence. The role of corticosteroids in treating ARDS remains uncertain, but many patients with ARDS arising from COVID-19 appear to respond favourably to this treatment. Here, a positive PCR test for the SARS-CoV-2 virus might be seen as a biomarker for a subtype of ARDS with a greater likelihood than average of responding favourably to corticosteroid therapy. Adding further nuance still are the predictive importance of dynamic patient factors, such as timing with respect to the initial insult, and the severity of resultant illness state; corticosteroids for COVID-19 appear most effective in those who are sickest, and when given at the rate phase of illness. With the success of the RECOVERY[3] and REMAP-CAP[4] studies, COVID-19 research also increased our familiarity with adaptive randomization.

In proposing this modernized conceptual model of critical illness, we hasten to add some potential limitations. First, though the model has direct implications for treatment, it leaves prognosis largely unchanged. Age, for example, may not be a treatable trait (because it is not

"treatable"), but it is prognostic in most conditions. That said, critical care has no shortage of prognostic models – both general and disease-specific – that fulfil this function well.

Second, while we emphasize some of the key molecular findings that have shown promise in critical care, the critical illness concept proposed herein by no means requires that a treatable trait be a molecular or genomic trait. Despite an increasing emphasis on molecular techniques in translational critical care research, there are no guarantees that increasing granularity will lead to tangible gains. Any feature that distinguishes a specific pathophysiologic process with causal links to treatment effects can serve this function.

Third, the discussion of a new conceptual model of critical illness surfaces some questions related to the fate of the critical illness syndromes that for decades have steered the field through a period of remarkable advancement. These are bedrock concepts in the modern ICU, and they are deeply ingrained in our systems of prognostication, record keeping, disease surveillance, epidemiology, administration, quality improvement, and research. It remains to be seen whether the field is ready for a wholesale shift away from syndromes, or whether they will be retained in some capacity.

Lastly, the model proposed here is but one among many possible ways forward. While we believe the principles outlined above address many of the challenges facing critical care, our overarching objective is to bring these challenges to light, and suggest how progress might be made in addressing them.

**The next phase of critical care**

Upon arrival in the ICU, our patient is found to have a PCR-positive nasopharyngeal swab for the SARS-CoV-2 virus, worsening hypoxemia, decreased urine output, and confusion. An echocardiogram reveals mild left ventricular dysfunction, and her D-dimer levels are markedly elevated. By current standards, we would diagnose a number of syndromes – ARDS, sepsis, acute kidney injury, delirium, disseminated intravascular coagulation – each of which may be treated with different types of supportive care. These treatments may conflict with one another, and the lack of precision in our diagnoses makes it difficult to predict how she will respond to any of them.

A new conceptual model developed on the principles described above would support a more efficient approach in which syndrome labels are de-emphasized in favour of more precise

biological descriptors. Genome sequencing may reveal that she has an allelic variant that puts her at much higher risk of severe lung inflammation than age- and sex-matched counterparts with the same presentation[44,45]. Transcriptome profiling could reveal her organ dysfunction to be largely the result of TNF/IL-1-mediated inflammation[46], with little contribution from microvascular thrombosis. Heart rate variability analysis may reveal changes in autonomic function that portend delirium[47]. What's more, these pathophysiologic features might not be confined to COVID-19 alone, and may be seen in critical illness states arising from entirely different insults. These features will be understood as treatable traits, evoking a specific therapeutic course; the genetic polymorphism may be targeted with a known pharmacologic agent, she may be more likely to benefit from the inhibition of certain inflammatory pathways, and a sympatholytic medication may prove better than an antipsychotic at preventing and treating agitation.

**How do we get there?**

The gulf between aspiration and achievement is wide. Many share the conviction that we need to move beyond syndromic characterization of the diseases of critical illness, and to develop disease models based on shared biology[48-51]. Position papers and consensus conferences will be useful in cultivating and refining key concepts. But meaningful progress will also require concerted effort directed towards technical considerations as well. An overall approach to addressing the challenges arising is shown in Figure 3, and must focus on theoretical and practical considerations across a range of key domains:

**Basic science -** The concept of a "treatable trait" generally implies that the underlying mechanism is understood and that the treatment relates to the mechanism. Thus, detailed preclinical work aimed at mechanistic understanding of putative treatable traits must be undertaken in earnest.

**Biomarker development -** On a practical level, operationalizing the treatable trait concept will in some cases necessitate the development of novel biomarkers that can be used in the ICU environment. This will require close collaboration with clinical chemists and laboratory experts to create validated assays that can be run in a clinical lab, respecting both the multifocal nature of critical care, and the rapid turnaround times needed to inform decision making. Assays run on readily available samples like blood, urine, exhaled gases, or even physiologic signals, are

more likely to be adopted than tissue biopsies. Similarly, tests based on faster modalities such as PCR or molecular barcoding platforms will see greater uptake than more cumbersome sequencing technologies. Developing viable biomarker assays will involve addressing numerous hurdles including identifying physiologically important disease states, describing the appropriate clinical interpretation of test results, and satisfying regulatory requirements. Entirely new technologies will undoubtedly be explored to meet the exigencies of finding treatable traits in the ICU.

**Outcome measures –** Clinicians and scientists will also have to work diligently to link biomarkers with underlying disease states, and to potential treatments[52]. Outcomes must be devised that can readily determine whether treatment has been effective. Current outcomes like mortality, organ support-free days, and coarse measures of neurologic function may lack the necessary specificity to adjudicate the success of a given treatment. For instance, a patient with COVID-19 may respond favourably to corticosteroids, only to succumb later to a pulmonary embolism or bacterial coinfection. We must consider the relative importance of intermediate outcomes, as well as outcomes that may not be considered patient-important by current standards.

**Data integration** – The noise resulting from large numbers of variables, the confounding effects of differing approaches to treatment and health care delivery, and the diminishing realistic size of individual effects all argue for the integration of data on a grand scale, and over a sustained period of time. Data from electronic health records, next-generation sequencing, and multi-omics biology provide the substrate, while data science and enhanced statistical and analytic approaches provide the methods. The precedents of the Framingham Heart Study[53], the Human Genome Project[54], or the insights in particle physics generated by the large Hadron collider all speak to the power of the creation, curation, and sharing of large amounts of data.

**Novel trial designs** – Causal inference is challenged by confounding. Randomization provides the most reliable means of reducing confounding, thereby establishing causality. Large randomized clinical trials, therefore, provide powerful but under-used opportunities for causal inference, while emerging methods such as Mendelian randomization enable more robust inferences of causality from random biologic variability. The use of platform trials to study a disease state, rather than a particular treatment, has shown promise in efficiently weighing the effectiveness of multiple different treatments, and can accommodate heterogeneity in the study population.[55] This design was deployed to great effect during the COVID-19 pandemic, with

platforms such as RECOVERY and REMAP-CAP generating important clinical evidence for patients with critical illness due to SARS-CoV-2 infection[3,7].

**National and international collaboration of investigator-led research consortia** – Large scale, multinational and multi-institutional collaborations such as CERN, LIGO, or the Human Genome Project are becoming more common. The increasing embrace of open science, and the creation of shared data repositories emphasize the will, and provide the platforms for collaboration. Collaboration between national clinical research groups is increasing in areas such as emerging infectious diseases, cancer, stroke, and thrombosis. In critical care, the International Forum for Acute Care Trialists (InFACT) has provided a forum for early discussions on the staging and stratification of critical illness. Collaboration at the scale needed to address the challenge is becoming possible.

## Conclusion

The management of patients with cancer was transformed by the creation of the Union for International Cancer Control (UICC) in 1933, and by the development of the TNM staging system, first proposed by Pierre Denoix in the 1940s [56,57]. The treatment of cardiovascular disease has been shaped by the Framingham Heart Study, with its comprehensive characterization of the natural history of a disease over time [58]. A similar approach will be needed to reframe critical illness. Owing to the rapid changes and multi-organ manifestations seen in critical illness, it is likely to be more complicated, and to take a correspondingly greater effort than the precedents of oncology and cardiology. It is achievable, but will require collaboration at a global scale – in reaching agreement on terminology and approaches to taxonomy, in creating shared data repositories to test and validate models, and in incorporating models into randomized trials to evaluate causal inference. For all the upheaval it has created, COVID-19 has shown that such an aspiration in global research collaboration is not only desirable, but possible.

**Box 1 – Precision in Diagnosis and Treatment**

When first diagnosed in the mid-19th century, Hodgkin lymphoma was identified as a painless enlargement of the lymph nodes. Around the turn of the 20th century, histologic examination revealed the presence of pathognomonic Reed-Sternberg cells within the affected nodes. Towards the end of that century, new techniques revealed that some cases were characterized by a specific translocation in the transcription factor BCL6[59]. At each stage in its evolution, the diagnosis of Hodgkin lymphoma has evolved further from the general to the specific, and from its physical manifestations, to its biological underpinnings. This march toward greater precision has changed diagnosis from an exercise driven by clinical signs and symptoms, to one that is anchored in the underlying mechanisms of disease.

By contrast, diagnosis in critical care is still largely a clinical undertaking. Syndromes are identified and defined on the basis of derangements in vital signs, along with basic laboratory investigations. These abnormalities paint a picture of organ system dysfunction, with only inferences to link them to the underlying biology. The approach is inherently imprecise; pulmonary embolism, viremia, and gastrointestinal haemorrhage all culminate in tachycardia, but tachycardia on its own provides no insight into the underlying cause. These conditions have vastly different treatments, none of which is to treat the tachycardia itself. A contemporary model of critical illness must address this limitation and provide greater precision in diagnosis. This will allow clinicians to disambiguate clinical syndromes that under current frameworks encompass disparate disease states, and more importantly, to target therapies to specific physiological derangements.

The modern management of myelodysplastic syndromes (MDS) is a useful example of precision in treatment. Long characterized as a group of related conditions characterized by low blood counts and a hypercellular, dysplastic bone marrow, advances in cytogenetics have allowed haematologists to better parse this syndrome, identifying a more precise subtype arising from a deletion of the long arm of chromosome 5 (del(5q)). All forms of MDS might be treated supportively with transfusion, but only del(5q) responds to lenalinomide. This molecular characterization of disease has been widely touted as the basis of precision medicine, and provides an illustrative example of how the deconstructing of heterogeneous syndromes into biologically distinct subtypes can improve treatment.

Subtype discovery has recently become a major focus of critical care research as well. Different subtypes of sepsis have been identified using clinical data[60], but also on the basis of gene expression profiling[19,36,61-63]. Subtypes of ARDS have been identified in clinical profiling studies[20,61] and even found in patients deemed to be merely at risk for this syndrome[64]. Importantly, some of these subtypes have implications for treatment. Certain gene expression patterns in sepsis have been associated with a favourable response to glucocorticoids[65], while others have been associated with harm from this same treatment[66-68]. Different ARDS subtypes may respond differently to fluids[22]. These subtypes begin to hint at ways we might connect diagnostics and therapeutics on a much deeper level.

## Figure legends

**Figure 1 — Three eras of critical care medicine**. The first era, *Foundations*, spans from the founding of the discipline in the 1950's and '60's, to roughly the mid-1980's. In the second era, *Acceleration*, critical illness was better characterized through formal syndrome definitions, and quantitative descriptions of illness severity. Improvements in outcomes were achieved, although few clinical studies yielded actionable results. A third era, *Precision*, is now emerging, based on a growing body of translational findings that reveal substantial biological heterogeneity within current critical care disease concepts. Parsing this heterogeneity to identify precise mechanisms of disease — along with ways to identify these clinically — will lead to more precise treatments, and greater efficiency of care. Delineating these mechanisms and translating them to practice will be central tasks in critical care research in the coming decades.

**Figure 2 — Schematic of a proposed conceptual model for critical illness based on biological features learned from translational research**. Individual insults and biological abnormalities are combined in a circular model that accommodates connections between entities. In this example, four insults are portrayed (infection, trauma, surgery, pancreatitis). The same biological abnormality (represented by interconnecting bands) can arise from multiple different insults, for example, inflammation-mediated pathways underpin infection, trauma and surgery.

**Figure 3 — Operationalizing a new conceptual model of critical illness.** At the top of the figure, the new conceptual model shows how different insults can give rise to shared biological abnormalities (see Figure 2). To illustrate how such a schema might be implemented, the grey triangles on the circle each represent a patient with a specific insult. In order to characterize the patient response to injury, samples are collected at various times (blue dots) and used to generate biological characteristics. These may include clinical blood tests, physiologic waveforms, imaging studies, as well as genomic, transcriptomic, and proteomic data, among other modalities, and may be added to existing data on characteristics such as age, comorbidities, environmental factors, and functional status. The heatmap depicts the clustering of these data to identify physiologic states of interest, which may be used to place patients into cohorts, or to describe any single patient along a temporal trajectory of injury response. Note that each subject, when assessed at multiple points, may remain in an unchanged physiological state, or move to another physiological state. Unsupervised machine learning and other statistical techniques are used for subtype discovery, with supervised machine learning deployed to identify potential biomarkers. These are developed into tests that can be used at the point of care, including as an enrichment strategy for recruitment into prospective trials. Novel trial designs such as platform trials allow for the testing of numerous interventions using adaptive randomization. Endpoints that directly reflect the response of the treatment are defined, and may include more proximal outcomes that can be located in a causal pathway with the treatment. A physiologic state of interest and its corresponding predictive biomarker constitute a treatable trait.

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**Author Contributions:**

B. Tang and J. Marshall conceived of the idea, with all authors making important conceptual contributions, and refining the writing of the manuscript. D. Maslove, B. Tang, M. Shankar-Hari, P. Lawler, and J. Marshall formed the primary writing group.

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**Competing Interests**

Dr. Baron reports having served on advisory boards for Merck and Genentech. Dr. Bauer is stock-holder of SmartDyeLivery, Jena, Germany, a company developing nanodrugs for sepsis. Dr. Buchman has no direct conflict of interest. His employer, Emory University, collects a stipend for his service as Editor-in-Chief of Critical Care Medicine from the Society of Critical Care Medicine. Emory University also collects a stipend for his service as senior advisor to the Biomedical Advanced Research and Development Authority from the United States Government. Outside the submitted work, Dr. McAuley reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis, Sobi, and Eli Lilly, and from sitting on a DMEC for trials undertaken by Vir Biotechnology and Faron Pharmaceuticals. In addition his institution has received funds from grants from the NIHR, Wellcome Trust, Innovate-UK, MRC and Northern Ireland HSC R&D Division. In addition, he holds a patent for an anti-inflammatory treatment issued to Queen's University Belfast. Dr. McAuley was a Director of Research for the UK Intensive Care Society (term ended in June 2021) and is NIHR/MRC Efficacy and Mechanism Evaluation Programme Director. Dr. Menon reports: grants from the

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Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to (1) the use of PCSK9 inhibitor(s) in sepsis, (2) the use of vasopressin in septic shock and (3) a patent owned by Ferring for use of selepressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell was a founder, Director and shareholder in Cyon Therapeutics Inc. and is a shareholder in Molecular You Corp. Dr. Russell is no longer actively consulting for any industry. Dr. Russell reports receiving consulting fees in the last 3 years from: (1) SIB Therapeutics LLC (developing a sepsis drug); (2) Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin); (3) Dr. Russell was a funded member of the Data and Safety Monitoring Board (DSMB) of an NIH-sponsored trial of plasma in COVID-19 (PASS-IT-ON) (2020-2021); (4) PAR Pharma (sells prepared bags of vasopressin). Dr. Russell reports having received an investigator-initiated grant from Grifols (entitled “Is HBP a mechanism of albumin’s efficacy in human septic shock?”) that was provided to and administered by UBC. Dr. Russell has received 4 grants for COVID-19 research from the Canadian Institutes of Health Research (CIHR) and 2 grants from the St. Paul’s Foundation (SPF). Dr. Russell was a non-funded Science Advisor and member, Government of Canada COVID-19 Therapeutics Task Force (June 2020 – 2021). Dr. Shapiro reports Research funding from the National Institutes of Health, Luminos, Inflammatix, and Google, and is a consultant for Diagnostic Robotics. Dr. Sweeney is stockholder in, and employee of, Inflammatix, Inc., which is developing a rapid test for sepsis endotypes.

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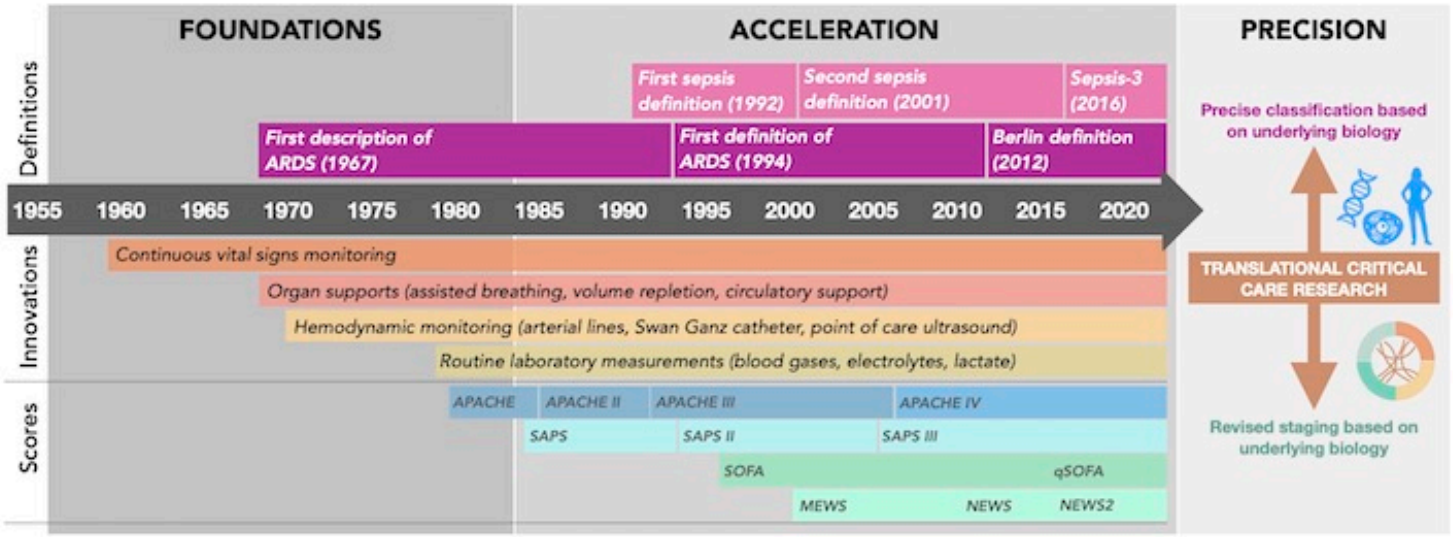
FOUNDATIONS
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First sepsis definition (1992)
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Sepsis-3 (2016)
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First definition of ARDS (1994)
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Continuous vital signs monitoring
Organ supports (assisted breathing, volume repletion, circulatory support)
Hemodynamic monitoring (arterial lines, Swan Ganz catheter, point of care ultrasound)
Routine laboratory measurements (blood gases, electrolytes, lactate)
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APACHE IV
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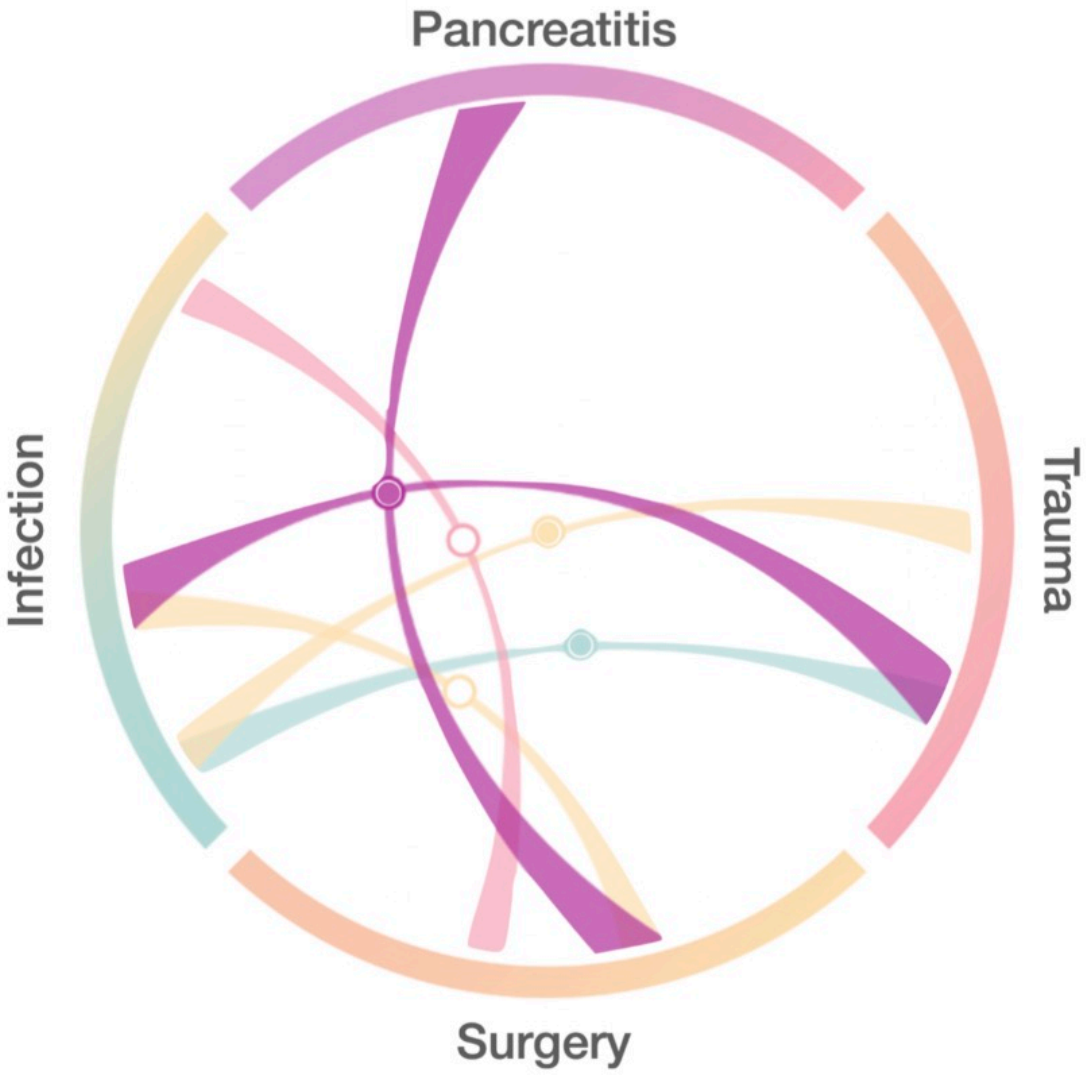
Revised staging based on underlying biology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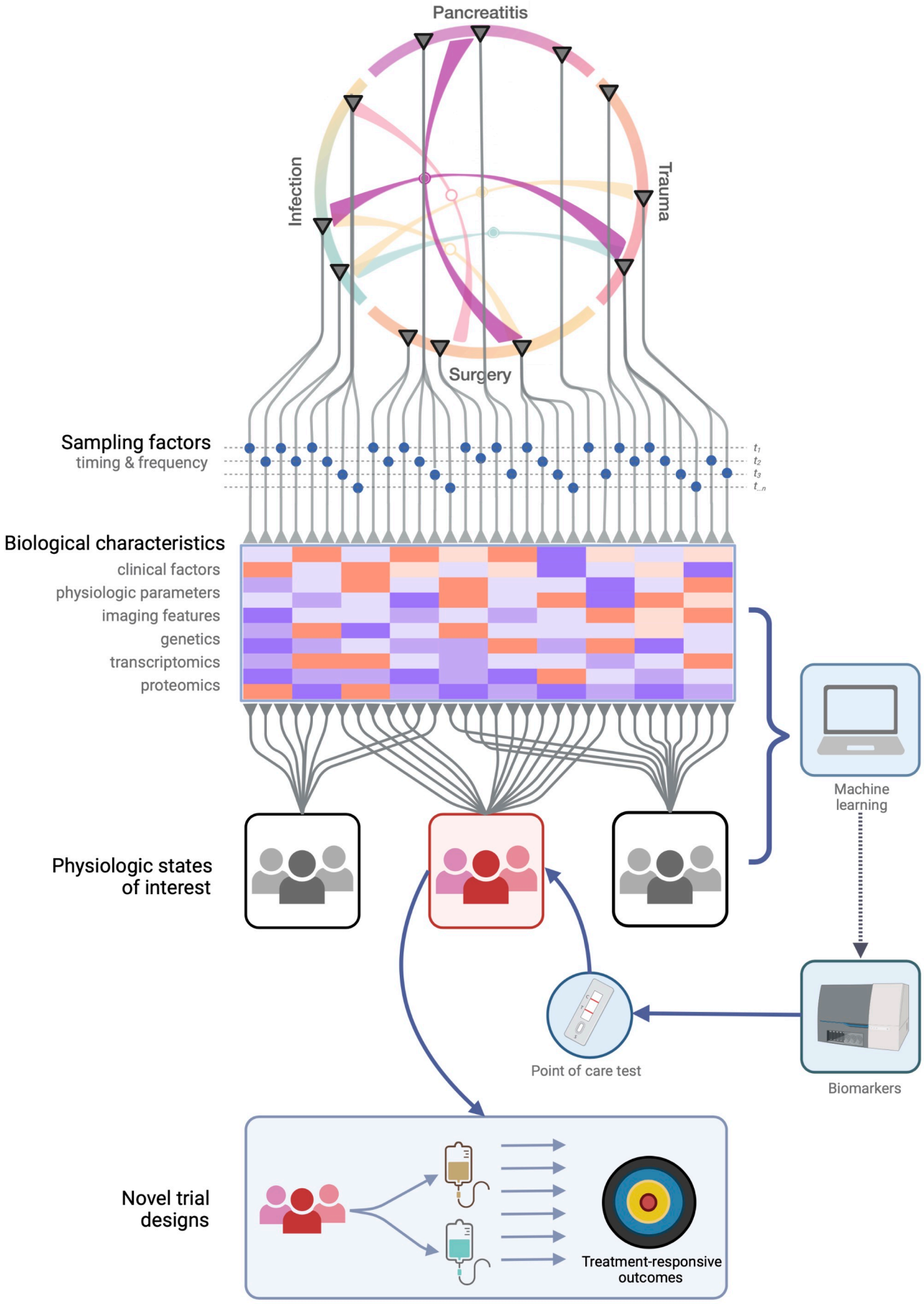
Pancreatitis
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clinical factors
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imaging features
genetics
transcriptomics
proteomics
Machine learning
Physiologic states of interest
Point of care test
Biomarkers
Novel trial designs
Treatment-responsive outcomes