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Patient and Population-Level Approaches to Persistent Critical Illness and Prolonged ICU Stays

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Synopsis:

The differential diagnosis of prolonged ICU stays includes: Intrinsic patient and admitting diagnostic characteristics; things that happen during the course of critical illness; and, system failures. Among these, existing (albeit fragmentary) data suggest that the development of new cascading problems in the ICU is the most common experience of patients with prolonged ICU stay. Such patients with persistent critical illness have been defined as those patients whose "reason for being in ICU is now more related to their ongoing critical illness than their original reason for admission to the ICU". There are urgent research needs for such patients, but accepting the dynamism inherent in such a clinical course has implications for contemporary clinical care.

Keywords

prolonged length of stay; prolonged mechanical ventilation; chronic critical illness; persistent critical illness; ICU

Consider taking over a clinical service in an ICU. As you receive hand-off of the patients, you are told it is ICU day 11 for the patient in bed 06. What differential diagnosis will allow you to appropriately move forward with this patient? We suggest Table 1 as one approach to the differential for such a patient. Broadly, this differential diagnosis can be organized into 3 categories:

- Intrinsic patient and admitting diagnostic characteristics;
- Things that happen during the course of critical illness; and,

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- System failures.

In this chapter, we will develop an approach to patients with prolonged ICU stays. First, we will briefly sketch the system issues that make these rare patients—those with an ICU stay of more than 10 days—worthy of consideration. Second, we will consider the patient-level differential diagnosis of these patients, surveying the explanations that have been proffered for them. Third, we will review the existing epidemiologic evidence asking: at a population-level, what can we say about the relative commonness of the various individual-level processes to generate the system issues? Finally, we will speculate—and we want to be clear, these will be frank speculations—on the potential clinical and research implications of this line of work.

The Epidemiology of Long Stays in the ICU

Prolonged intensive care unit (ICU) stays while not common are costly, increasing in prevalence, and results in long term morbidity.[1–3] In 2009, in the United States, it was estimated that 380,000 cases remained in the ICU for at least 8 days with an estimated $25 billion in hospital-related costs.[1] With an aging population and advancements in critical care, more people are surviving their admitting diagnosis only to remain in the intensive care unit for prolonged periods of time being subjected to the complications and problems which can occur while being hospitalized.[4] However, once the patient is discharged, the sequale of the problems from the prolonged ICU hospitalization continue to impact the patient and their caregivers. The mortality is higher than most malignancies in the subsequent year (48–73%).[3,5] Of those who survive, many have functional and cognitive disabilities.[3,6] Only 20% are discharged directly home from their prolonged ICU stay, with the majority being discharged to long term acute care facilities (LTACS) or subacute care rehabilitation (SAR) facilities.[5]

Diverse definitions of "prolonged" have been used across studies. A metaanalysis of 124 studies with prolonged mechanical ventilation provides an illustrative example. Inclusion criteria for studies were: "(1) mechanical ventilation for 14 days or more; (2) mechanical ventilation with admission to a specialised ventilator weaning unit in either an acute care hospital or a post-acute care hospital; or (3) mechanical ventilation for 96 h or more plus a tracheostomy procedure (ie, diagnosis-related group [DRG] for tracheostomy for acute respiratory failure)."[5] In general, these definitions of "prolonged" have been based on an expert opinion and/or the exigencies of data availability.

Despite these variations in important details of the definition, a coherent picture emerges: there are a modest number of patients who nonetheless require vast resources. The math of prolonged ICU stays is ineluctable—the number of bed-days required by these patients will be at least an order magnitude higher than the number of patients. Providers' experiences and hospital-systems' budgets are driven by the number of bed-days.

As an example, Iwashyna *et al* used a population-based and statistical definition to identify a group of patients with prolonged ICU length of stay they termed "persistent critical illness".[7] Such persistent critical illness patients accounted for only 5.0% of all ICU patients in Australia and New Zealand—yet also 32.8% of all ICU bed-days and 14.6% of all hospital-bed-days by ICU patients.

Patient-Level Differential Diagnosis

Given the generality of the motivating problem—a "long" stay in the ICU—there is no basis for assuming that there will be a single unitary cause. As such, a broad differential diagnosis must be considered. (Table 1)

Intrinsic patient and admitting diagnostic characteristics

The most obvious reason for a patient to have a long stay in the ICU is that there are some admitting diagnoses that (a) take a long time from which to recover; (b) are not immediately highly lethal if provided contemporary supportive care; and (c) for which we lack efficacious therapies. No list is likely to be complete, but common diseass with a long intrinsic recovery time include:

- Neurologic disorders: Guillan-Barre and other acute paralysis; myasthenia gravis; traumatic brain injury; certain encephalitides and acute demyelinating conditions
- Pulmonary: COPD exacerbations in patients with baseline poor lung function, acute exacerbations of interstitial lung disease
- Inflammatory: severe acute pancreatitis, undrainable infections (e.g. pulmonary abscess)
- Complex nursing needs: burns and complex wound care, prolonged withdrawal syndromes
- Patients with unrecoverable illness: whether chronically from frailty, or acutely, as from a relapsed liquid tumor despite multiple transplant attempts.

Things that happen during the course of critical illness.

The above aspects of the differential diagnosis largely emphasize factors that are true of the patient on admission. They draw from mental models that emphasize a single discrete critical injury, and a progressive (although sometimes slow) playing out of the recovery (or not) from that injury.

In contrast, the lived experience of ICU clinicians often involves patients who acquire new problems in the ICU. Two classes of explanations can be usefully distinguished: those that place the blame in the acquisition of single organ system's persistent failure to emphasize a largely static state; and those that emphasize a continued dynamic development of new failures over time.

A major focus of attention has been prolonged mechanical ventilation.[5] This is most commonly attributed to muscle weakness and diaphragmatic failure, leading to hypercarbic respiratory failure—although the empirical basis for such attribution may be weaker than is commonly assumed. More recently, the role of persistent delirium in limiting weaning from mechanical ventilation has received attention. Nelson *et al's* influential work on chronic critical illness placed prolonged mechanical ventilation at the center of its definition.[3]

Others have emphasized distinctive pathways into prolonged ICU stays.[8] Van den Berge's work in the 1990's suggested a potentially important role for an acquired endocrinopathy.[9] Others have hypothesized poor attention to the early nutritional needs of ICU patients is a driver of—not just consequence of—prolonged ICU stays. The effector arms of such iatrogenic malnutrition may be hypothesized to be poor protein intake.[10] A growing body of work suggests that immune-suppression (or "immunoparalysis") is common after sepsis, trauma, and other severe illnesses, and this work implies a causal role for such immune dysfunction in patients stuck in the ICU.[11]

A contrasting possibility is that patients in the ICU are not dominated by a single fixed lesion, either present on admission or acquired shortly thereafter. Instead, there are patients with seemingly new problems every day. Patients with persistent critical illness have been defined as those patients whose "reason for being in ICU is now more related to their ongoing critical illness than their original reason for admission to the ICU". A survey of Australian and New Zealand critical care practitioners suggested that such patients were common in their ICUs and were a source of substantial stress to such clinicians.[12] It is possible that such cascading critical illness could be caused by repeated new insults and injuries from the lack of homeostasis, from simple bad luck, or that such cascades could be caused by repeated errors or poor judgment by the care teams—what Hofer *et al* have termed "cascade iatrogenesis".[13]

System failures

A third class of reasons for patients to have long stays in the ICU are frank system failures. For example, one reason for patients to have prolonged stays in the ICU is that the system lacks the ability to move them out of the ICU once their critical illness is resolved. The incidence of such "bed block" varies across systems and in its duration. Nonetheless, patients who are merely boarding in an ICU awaiting the availability of lower intensity care should be usefully distinguished from those truly still needing the high-level nursing and physician care that define the ICU. Such differentiation rarely presents a challenge for the bedside clinician—but such patients can be difficult to differentiate for the epidemiologist and health services researcher.

The provision of ICU care to patients with unrealistic expectations is a second form of system failure. The general problem is that there are patients who will die regardless of the care they receive. Some may be admitted to the ICU for high-intensity palliative care, in the absence of formal units specializing in acute care of the dying. It is our opinion that such is an entirely appropriate use of ICU. In contrast, there are systems that routinely fail to detect patients who have no realistic chance of surviving critical illness despite best care. Such patients are offered critical care under illusions about its potential benefit. And such care directed to an outcome that cannot be achieved will mandate prolonged periods of care.

A third class of system failure are hospital policies that mandate the provision of certain therapies in an ICU setting when such care is more typically safely provided in the ward settings. For example, the authors have worked in hospitals that would only allow use of non-invasive ventilation on the wards in patients who had undergone an outpatient sleep study. As such, all other non-invasive ventilation needed to be provided in the ICU setting.

Differentiating such patients from the persistently critically ill rarely presents a challenge for the bedside clinician.

Population-Impact

One might imagine a vast longitudinal cohort study, where patients are assessed in standardized ways by omniscient, highly reliable experts. On each day, each patients' reason for being in the ICU is unambiguously arbitrated into one of a series of mutually exclusive categories. In the context of such an all-seeing apparatus, one might readily count the contribution of each of the aspects of Table 1 to the total population burden of prolonged ICU use.

Such a vast cohort study does not exist.

As such, we must consider the existing fragmentary data. In 2016, Iwashyna and colleagues examined 1,028,235 critically ill patients from 182 ICUs across Australia and New Zealand, hospitalized from 2000 to 2014, as discussed above. Their core population-based findings have been replicated in analyses—unpublished as of the time of this writing but presented at the 2017 American Thoracic Society International Conference[14]—from both the Veterans Affairs system of 120 hospitals in the United States, and in a Scotland-wide database.

Complimenting these population-based data are three detailed single-center studies of patients with prolonged ICU lengths of stay. Elizabeth Viglianti *et al* examined 50 consecutive patients who spent at least 14 days in the ICUs of the University of Michigan Medical Center.[15] Toby Jeffcote *et al* examined 100 patients who spent at least 10 days in the ICU of the Austin Hospital (Melbourne, Australia), and 100 age, sex, acute physiology and chronic health score (APACHE III) and Charlson co-morbidity score matched controls.[16] Jai N Darvall *et al* examined 72 adult patients admitted to the ICU and who spent more than 10 days in the ICU of the Royal Melbourne Hospital, matched on diagnostic code, gender, age within 10%, and Acute Physiology and Chronic Health Evaluation (APACHE) III risk of death within 10%.[17]

From this admittedly fragmentary evidence, certain tentative conclusions can be drawn about the relative importance of processes leading to prolonged ICU stay. The first is that long-stayers do not appear to be concentrated in a subset of diagnoses. Similarly, Viglianti found that characteristics of the patients present on admission had little capacity to distinguish those who would go on to develop prolonged ICU length of stay from those who were discharged alive or died earlier. Taken together, these argue against intrinsic patient characteristics and admitting diagnoses being the major driver of prolonged ICU length of stay.

In all of the detailed single site studies, there were surprisingly high rates of successful extubation among patients who remained in the ICU for prolonged periods of time. In the U.S., this might be attributed to selective referral of patients with simple prolonged mechanical ventilation to long term acute care hospitals—although Viglianti argue against this as a major source of bias. Australia has no such long-term acute care hospitals, but showed similarly high rates of successful extubation but continued ICU use. Furthermore, among those patients in the Viglianti series who were still intubated, the vast majority remained hypoxic—defined as a P/F ratio of 200 or less—arguing further against simple muscle weakness as the major driver of prolonged mechanical ventilation.

Other population data argue against system failure alone as a major reason for prolonged mechanical ventilation. In particular, if the major reasons for prolonged ICU length of stay were simply continuing to provide care to patients with unsurvivable illness, we would expect their short-term mortality to be quite high—perhaps 75% or more within 90 days of hospital admission. In contrast, if patients remained in the ICU merely because of bedblock, we would expect little difference in their mortality compared to shorter-stay patients. The population-based data showed neither extreme.

Instead, the population-based data show 2 key features. The first is a substantial post-ICU discharge mortality, but nothing that would rise to the level of “futile” care or inevitable death. The second feature of the population-based data is a point, in the second week of the ICU stay, when characteristics of the patient present on admission (e.g. diagnosis, severity of illness) become no better able to discriminate hospital death than simple patient demographics and comorbidities.

We interpret this “loss of discrimination” to mean that, by around day 10, ICU patients have undergone a diverse set of intercurrent events. These new ICU events are sufficiently common and variable that they become major determinants of mortality, rather than whatever brought the patients to the ICU in the first place.

Supporting this “new cascading events” interpretation are several items from the hospital case series. Viglianti showed that only 22% of patients did *not* develop a new organ failure on day 4 or later—and the median patient experienced 2 new organ failures between days 4 and 14. Darvall used structured criteria to define why the patient was still in the ICU; they report that the original illness was no longer a cause for continued ICU stay after a median (IQR) of 10 (7 – 16) days.

In sum, we have support for the persistent critical illness hypothesis—that a major driver at the population-level of why patients remain in the ICU is cascading new critical illnesses, rather than simple prolonged mechanical ventilation from hypercarbic respiratory failure, failure of presenting complaints to heal, or system failures.

Implications of a Persistent Critical Illness Framework

These data suggest that many patients experience persistent critical illness, defined in the sense of experiencing multiple new and cascading problems. This has certain implications for both research and the practicing clinician.

In regards to research, a crucial question is whether these cascades are patterned in specific ways. The alternative hypothesis is that such cascades are simply a random aggregation of unlucky events—formally, a Markovian process. If there are specific patterns across organs over time, empirically identifying these regularities might offer deep insights into the structure of multi-organ interdependencies. These would be of prognostic value, and might suggest specific sub-sequences ("motifs") that are highly predictive of adverse events. Such motifs might prove key to a reliable bedside definition of persistent critical illness—and to identifying patients at the cusp of such cascades who would benefit from intensive salvage therapy.

Until such research is done, clinicians must nonetheless care for these patients. A survey suggested that there are a wide-range of feasible interventions that clinicians may already be attempting at the bedside.[12] These include: aggressive sepsis prevention and control efforts; integrated communication and continuity of care programs; and, early mobilization and delirium reduction.

Yet perhaps the most important clinical implication of this work is to remember the dynamism of critically ill patients. As a field, we have come to love the metaphor of the "golden hour". When this metaphor motivates prompt early recognition and lifesaving intervention, it is valuable. However, an unintended consequence of the focus on early resuscitation can be to imagine that only the first hours are interesting and dynamic—that the rest of the course of critical illness is only playing out of problems established in that early period. Such a focus exclusively on early resuscitation can lead to inappropriate anchoring, and premature diagnostic closure. The persistent critical illness framework reminds us that patients can have new golden hours each day, and constant vigilance is indicated.[18,19]

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Key Points:

- The differential diagnosis of prolonged ICU stays includes: Intrinsic patient and admitting diagnostic characteristics; things that happen during the course of critical illness; and, system failures.
- Existing data suggest that dynamic development of cascading new problems (so called "persistent critical illness") is a major driver at the population-level.
- Many patients with prolonged ICU stays do not have persistent respiratory failure; prolonged mechanical ventilation is only a subset of chronic critical illness.

Table 1:

Differential Diagnosis of Patients with Prolonged ICU Stays

Differential Diagnosis	Testable Implications in Existing Data
Intrinsic Patient Characteristics	
Diseases with long intrinsic recovery time	
• Neurologic	Long-stayers concentrated in a few discrete diagnoses
• Pulmonary	
• Inflammatory	
• Complex nursing needs	
Frailty	Very high mortality, older age, more comorbidity predictive of persistent critical illness
Acute unrecoverable illness	Very high mortality
Things that happen in the ICU	
Acquired single-organ problems	
Failure to wean from ventilator / Muscle & diaphragmatic weakness / Prolonged mechanical ventilation	Long stayers mostly ventilated, predominantly hypercarbic respiratory failure
Van den Beghe Endocrinopathy	Unclear population-level implications
Malnutrition / Protein Wasting	Unclear population-level implications
Immune-paralysis	Predominance of sepsis among later organ failures
Dynamic cascades in multiple organs	
Cascading critical illness	Increasing irrelevance of admitting diagnosis to prognosis with longer time in ICU
Cascade iatrogenesis	Increasing irrelevance of admitting diagnosis to prognosis, plus measureable errors
System Failures	
Bedblock	Little difference in mortality
Admitting patients with unrealistic expectations or lack of palliative care involvement	Very high mortality
Idiosyncratic requirements for ICU care for certain types of care	Little difference in mortality