Journal of Critical Care 35 (2016) 90–95

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Actuating critical care therapeutics

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ARTICLE INFO

Keywords:
Predictive monitoring
Risk analysis
Risk stratification
Systemic inflammation
Therapeutic load

ABSTRACT

Viewing the intensive care unit (ICU) as a control system with inputs (patients) and outputs (outcomes), we focus on actuation (therapies) of the system and how to enhance our understanding of status of patients and their trajectory in the ICU. To incorporate the results of these analytics meaningfully, we feel that a reassessment of predictive scoring systems and of ways to optimally characterize and display the patient's "state space" to clinicians is important. Advances in sensing (diagnostics) and computation have not yet led to significantly better actuation, and so we focus on ways that data can be used to improve actuation in the ICU, in particular by following therapeutic burden along with disease severity. This article is meant to encourage discussion about how the critical care community can best deal with the data they see each day, and prepare for recommendations that will inevitably arise from application of major federal and state initiatives in big data analytics and precision medicine.

1. Introduction

Critical care medicine has done a commendable job supporting patients with life-critical processes but has not advanced significant intensive care unit (ICU)–specific therapeutics in an era when other specialties, such as oncology, have made notable advances based on molecular technologies [1,2]. Certainly, elimination of minimally useful, unnecessary, or even harmful interventions such as the pulmonary artery catheter, unsubstantiated blood transfusion trigger thresholds, and high tidal volume ventilation represents an achievement, as is revisiting initially promising interventions (tight glycemic control, activated protein C) with larger studies. Although we are better at administering humane care in futile situations, we are still delivering a tremendously costly product that often results in painful temporary prolongation of "life" with a kind of chronic critical care [3,4,5]. The current status of critical care justifies a modified perspective: We need to find new approaches identifying effective therapeutics as well as identifying what are effectively palliative situations. Here we suggest an approach to monitoring disease severity that captures well-described heterogeneities in ICU patient populations, and their response to therapy, in an attempt to address these needs. With the expected onslaught of big data into critical care medicine through predictive medicine initiatives, we feel that methods to quantify responses to interventions along with disease trajectory are needed.

1.1. Heterogeneity

Some elements of care are very much alike across very different ICU patients and settings. Examples emerging from generally accepted best practices include venous thromboembolism (VTE) prevention, low tidal volume ventilation, and adequate (but not excessive) sedation and analgesia. Nonetheless, ICU care is also heterogeneous, highlighting the gap for evidence-based standards that transcend geography, institutional milieus, and individual caregiver preferences. VTE prophylaxis is a good example of the difficulty in promoting homogeneous best practices in the ICU. The American College of Surgeons National Surgical Quality Improvement Program database shows how varied application of VTE prophylaxis is, even with good best-practices recommendations. This example also points to how hard it will be to develop specialized therapies for managing complex systemic inflammation, organ injury, and organ/systems failure [6].

Heterogeneity starts with the patient. The grouping of patients into as homogeneous a group as possible (similar to disease phenotyping in biology) is important for developing predictive tools in the ICU. Success in validating scoring systems by studying only cardiac surgical patients [7,8] underscore this point. But as well described by Vincent and Singer [1], ICU patients are particularly heterogeneous. Reasons for admission are widely variable, as are genetic background, comorbidities, prior therapies, and of course age. These heterogeneities in the context of sepsis are particularly notable [5]. In addition, heterogeneities in local medical cultures; clinician backgrounds, experience, and performance; and type of ICU are challenges for improving ICU outcomes.

Here we attempt to identify, capture, and leverage detectable heterogeneity in *severity* as a potential guide for targeting therapeutic

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http://dx.doi.org/10.1016/j.jcrc.2016.05.002
0883-9441/

efforts. In critical care medicine, we have done a reasonable job of assigning prognosis and severity scores. Here we suggest that these scoring systems would benefit greatly by combining measures of the state of the patient with the state of the therapeutic response for optimal utilization of data we generate and follow in the ICU. The therapeutic score or load index, would be constructed analogously to sequential organ failure assessment (SOFA) on a systems basis with scores from 0–4 for 6 systems based on the intensity of the intervention. For example, the respiratory system might be scored on a four point basis assigned to the following in sequence- "oxygen by mask or nasal prongs; non-invasive ventilation; conventional mechanical ventilation; special ventilatory mode." We suggest the therapeutic equivalent of a scoring system and a possible graphic display. This application of a score to therapeutics begins to address the level of quantification required to define effectiveness and assigns the therapeutic side of the equation more weight than in previous scoring systems. This suggestion arises from viewing the ICU as a system in the way an engineer would view a "plant" subject to engineered controls and responses to interventions.

In some ways, our suggested scoring system is similar to Model for End-Stage Liver Disease (MELD), a prognostic score for short-term survival originally developed for patients with primary biliary cirrhosis. MELD uses only objective data (international normalized ratio, creatinine, bilirubin), which was considered an improvement over the Child-Turcotte-Pugh (CTP) score used to stratify patients awaiting liver transplantation. (CTP included grading of ascites and encephalopathy, both prone to subjectivity, and the old scoring system for liver allocation gave credit to patients for long waiting times on the list.) MELD was used starting in 2002 to prioritize patients for liver grafts so that the most critically ill patients would be transplanted first; MELD was superior to CTP in defining disease severity pretransplant [9]. Use of MELD resulted in reduced mortality on the liver transplant waiting list [10], but MELD may not accurately predict posttransplant survival [11] in part because of necessary modifications to the system to accommodate patients with hepatocellular carcinomas and acute liver disease. Nonetheless, there are important lessons here for critical care: Rigorous evaluation of MELD by mathematicians was possible because the organ procurement system is networked for sharing information. MELD was evaluated in the background by mathematicians, comparing it against the CPT-based system using data from real patients, before it was rolled out. Finally, the system accommodates optimization, and MELD scoring may change over time [12], which may be particularly important because transplant recipient populations change (less hepatitis C, less futile retransplantation).

As in our prior publications, we emphasize the need to capture and use the data generated in critical care more effectively [13–19]. We need to know elements of the current armamentarium that work and do not work, and the best practices to follow in given clinical contexts in a truly data-driven fashion. This latter, contextually driven clinical decision support has to include the complex, unpredictable situations of everyday care in the ICU, as well as predictable core practices such as VTE prophylaxis. Although there are a variety of critical care–specific electronic data systems currently in use, these systems will need to be honed and optimized by feedback with clinicians to provide these functions.

1.2. The ICU as a system

Here we adopt the framework of treating the ICU as a system that accepts inputs (ie, admitted patients) and produces outputs (ie, clinical outcomes) [20]. A system is "robust" when its outputs can be controlled for stable performance despite heterogeneous components and inputs [21]. "Personalized medicine" can be thought of as an attempt to improve robustness, keeping the patient stable with optimal, individualized therapy. Improving ICU care can involve any component of the ICU system. For example, tele-ICU may improve care by improving the sensor component and shorten delays via improved monitoring and embedded algorithms that alert physicians to changes they cannot "see." Actuation may be improved by arming the system with timelier and better evidence-based best-practice advisories [22,23]. Although all system elements should be continuously optimized, *actuation* is the key to improving outcomes. Isolated improvements in diagnostic testing, for example, appear to have minimal effect on outcomes [24]. Together, improved tests themselves (ie, improved sensing) and resultant improved management decisions (ie, computation) do not automatically produce better actuation, so our focus is on actuation. In the ICU, actuation or intervention falls into 2 general groups: Most are those intended to support and maintain the current condition, and depend a lot on endogenous recovery and repair mechanisms, for example, ventilator and blood pressure support. The minority of actuations are targeted on reversing injurious processes: Examples are antimicrobials and curative surgical and interventional radiologic procedures [1].

1.3. Prognostic classification

Leveraging vast experience with the Acute Physiology and Chronic Health Evaluation (APACHE) scoring, Breslow and Badawi categorized ICU patients into 3 prognostic classes "to provide insight into heterogeneity in performance across risk groups" using less than 10% (low), 10% to 50% (medium), and greater than 50% (high) predicted mortality groupings. Across their ICU population, the incidence of low-risk patients was approximately two thirds of patients [25,26]. Even large, tertiary care hospital ICUs tend to have populations consisting more than half of low-risk patients [27]. In the study of Dahl et al [26] representing a large hospital system, the incidence of low-risk patients was 69.4%; medium risk, 26.6%; and high risk, 4%. So, a useful heuristic is that low-risk patients represent about two thirds of the ICU population in the United States with about 4% to 6% high risk and the rest medium risk. The corresponding therapeutic themes are "prevention (low risk), control (medium risk), and repair (high risk)." We recognize that these are simplifications and omit many possible selection and filtering processing for ICU admission and the determination of discharge readiness.

1.4. Low-risk patients: prevention

The majority of patients in US ICUs fall into this category. APACHE further stratifies the low-risk group by labeling those patients who have not received a specific "active treatment" (from a long list) as "low risk, monitored"; these patients represent a somewhat lower-acuity population not yet exposed to a therapeutic "perturbation," receiving only intense monitoring and nursing care. In a large benchmarking study, 40% of the overall ICU population fit the "low risk, monitored" category [27]. Therefore, of the approximately two thirds of patients at low risk, about 40% (60% of total low risk ~67%) are of even lower acuity and do not (yet) require ICU treatment. One might wonder if we have almost twice as many ICU beds as we need, but Dahl et al [26] reported that half of long-stay outliers were originally low-risk patients.

Our prediction tools are imperfect, as the trajectory of these low-risk patients (with much shorter predicted ICU stays and mortalities) into sicker ones is currently not predictable. Although caring for the low-mortality subset does not seem as heroic as other parts of ICU care, the beneficial impact of quality care of this group on the overall health care system is likely high because survivors from this category are likely discharged in good condition. And because the 16.7% of patients who represented ICU length of stay outliers accounted for 56.7% of total ICU costs in the study of Dahl et al [26], with 47% of these outliers low risk, the impact of this population on costs is also an important consideration. From such studies, we cannot know whether conversion of the low-risk patient to a higher risk is a function of having been in the ICU, an adverse event unrelated to critical care per se, or some other brewing factor(s) boding near-term deterioration. (These factors may be "sensed" by the experienced clinician who admitted the patient to ICU, but an automated sensing system is certainly the goal of next-generation data analysis.) So within a presumably more heterogeneous population are those who might have benefitted from never entering the ICU and those who may have deteriorated in a less intensely monitored and actuation-ready