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WHAT'S IN A DEFINITION? A SIMULATION FRAMEWORK FOR MODELING SEPSIS INTERVENTIONS USING ELECTRONIC HEALTH RECORDS

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ABSTRACT

Sepsis, the body's inflammatory response to infection, is a serious complication and leading cause of in-hospital mortality. Timely intervention is both difficult and critical since sepsis can rapidly worsen to organ dysfunction and septic shock. However, the lack of a gold-standard definition renders the lines between these transitions unclear, complicating medical decision-making. Using electronic health records, we build a simulation framework to study the evolution of dynamic physiological and cellular responses to therapeutic interventions in septic patients. Since sepsis trajectories can manifest differently depending on patient characteristics, we incorporate patient heterogeneity through comorbidity, age, race, and gender. Under therapeutic interventions recommended by the Centers for Medicare and Medicaid Services (CMS), we illustrate the framework on patient trajectories using the CMS criteria for sepsis definition. The framework is designed to support the comparison and quantification of the impact of clinical definitions and recommended interventions on the timely identification of sepsis states.

1 INTRODUCTION

Sepsis may be broadly described as a complication associated with an infection that can manifest as systemic inflammation. Sepsis is one of the leading causes of mortality as well as the most expensive condition to treat in hospitals (Liu et al. 2014; Torio and Andrews 2013). The lack of a gold-standard diagnostic test makes diagnosis difficult and subjective. There has been a recent spotlight on the disease, in part due to new guidelines and definitions, and an overall increase in awareness (Singer et al. 2016; Seymour et al. 2016).

The burden of sepsis management is increased by the complexity of diagnosis and treatment. There is significant heterogeneity in both disease manifestation as well the affected population (Marshall 2005), while pre-existing conditions can confound diagnosis due to variations in response (Iskander et al. 2013). Timely intervention and monitoring are critical, as patients can deteriorate rapidly. Unfortunately, there is significant subjectivity involved in the diagnosis of sepsis due to the lack of a well-defined patho-physiological feature

associated with sepsis and, subsequently, tests with adequate sensitivity and specificity (Rhee et al. 2014). This results in poor diagnostic accuracy, with many true sepsis cases being missed. The lack of a specific anti-sepsis treatment means that therapeutic and source-control interventions are the only options physicians have (Cohen et al. 2015).

1.1 Defining Patient Trajectories

Patient deteriorations vary without clear transitions from one health state to the next. Traditionally, sepsis, is defined as the presence of two or more Systemic Inflammatory Response Syndrome (SIRS) criteria, including changes in heart rate, respiratory rate, temperature and white blood cell count, along with suspected infection. Sepsis is thought to progress to severe sepsis (sepsis plus acute organ dysfunction) and then septic shock (severe sepsis plus hypotension that cannot be reversed with fluid administration) (Levy et al. 2003). However, the SIRS criteria are far too broad and not specific enough to distinguish between individuals with sepsis or another cause of clinical deterioration (e.g., myocardial infarction, hemorrhage, etc.) (Vincent et al. 2013; Kaukonen et al. 2015). The nonspecific transitions along the clinical trajectory, combined with the fact that the identification depends heavily on frequency of monitoring, further complicate clinical decision-making. Consequently, a significant focus of the international community has been on addressing the challenge of defining sepsis (Czura 2011; Vincent et al. 2013; Singer et al. 2016).

The subjective nature of disease diagnosis has led to difficulties in identifying a cohort of sepsis patients using structured, retrospective Electronic Health Record (EHR) data. Identifying individuals with sepsis using the International Classification of Diseases (ICD) diagnoses codes is an option that is often widely used (Yang et al. 2010; Esper et al. 2006; Beck et al. 2016), despite these diagnoses codes being primarily designed for reimbursement purposes and the potential suboptimal quality of the codes in identifying true sepsis cases. This is in part because ICD codes are easy to access. More importantly in our context however, the rigor involved with the process of coding ICD sepsis ensures that all patients with a diagnosis of sepsis can be reliably assumed to have had the condition. Patients identified through these codes are often considered the next best alternative to the gold standard of chart review for a correct identification of sepsis (Jolley et al. 2015).

The Centers for Medicare and Medicaid Services (CMS) defines sepsis as the presence of two or more SIRS criteria, as shown in Figure 1. The CMS definition of severe sepsis requires the prior presence of sepsis, in addition to one or more signs of organ dysfunction. Finally, septic shock is defined by severe sepsis in addition to hypo-perfusion despite adequate fluid resuscitation or high lactate levels. Based on these definitions, CMS also provides the SEP-1 guidelines for interventions (Faust and Weingart 2017). The time-sensitive therapeutic recommendations that determine compliance include (i) administration of antibiotics within 3 hours of presentation of severe sepsis as defined above, (ii) administration of adequate fluids within 3 hours of presentation of septic shock, (iii) administration of vasopressors within 6 hours of presentation of septic shock, if hypotension persists after fluid resuscitation. No therapeutic recommendations exist for the sepsis state under the SEP-1 therapeutic guidelines.

1.2 Research Objectives

While some recent models study sepsis progression in patients using EHR data (Beck et al. 2016; Amland and Hahn-Cover 2016), to the best of our knowledge, there are no models at present that determine the change in vitals (i.e., physiological responses) and labs (i.e., cellular responses) in patients with sepsis over time. Amland and Hahn-Cover (2016) used a cloud based clinical decision support system to study the timing of alerts compared with the timing of interventions in patients with sepsis, defined using the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition (Levy et al. 2003). The authors used a retrospective multi-center cohort study to help assess the performance of the system, and found that it was helpful in identifying patients that physicians did not expect to show signs of SIRS. Beck et al. (2016) used ICD 10 diagnoses of sepsis from Danish electronic health records (EHR)

STATE	CRITERIA
SEPSIS	**Suspected infection** *and* ***at least*** 2 SIRS criteria: • Temperature ≥ 38.3˚C (101˚F) *or* Temperature < 36˚C (96.8˚F) • Heart Rate ≥ 90 bpm • Respiratory Rate ≥ 20 breaths/min • White blood cell count (WBC) > 12,000 cells/μL *or* WBC < 4,000 cells/μL • Bandemia of white blood cells > 10%
SEVERE SEPSIS	**Sepsis *plus*** any organ dysfunction (OD) *or* lactate > 2 mmol/L. ***Any* evidence of OD:** • Systolic blood pressure (SBP) < 90 mmHg • Mean arterial pressure (MAP) < 70 mmHg • Decrease in SBP > 40 mmHg from baseline • Creatinine > 2.0 mg/dL • International Normalized Ratio >1.5 or Clotting Time < 60 sec* • Bilirubin > 2 mg/dL • Platelets < 100,000 cells/μL • Altered Mental Status • Lactate > 2.0 mmol/L • Urine output < 0.5 mL/kg/hr for >2 hrs*
SEPTIC SHOCK	**Severe sepsis *plus*** hypoperfusion despite adequate fluids *or* lactate > 4. **Hypoperfusion:** • (SBP < 90 mmHg, *or* MAP < 65 mmHg, *or* SBP ≥ 40 mmHg below baseline) *and* Fluids

Time windows: Vitals & fluids valid for 8-hours, labs for 24-hours; * Data unavailable in EHR data used

Figure 1: CMS definition of states along the sepsis trajectory. Suspected infection is undefined. Darker shades for states are indicative of a worsening health state.

to quantify mortality risk in multi-morbid patients with sepsis based on their previous-disease-diagnoses trajectories. However, in both cases, the entirety of the patient trajectories came directly from the EHR data.

We present a comprehensive framework for a Discrete-Event Simulation (DES) model at a patient level to understand the impact of definition and associated treatment guidelines on sepsis trajectories. The framework consists of a cluster analysis component to identify important comorbidities in septic patients, a distribution fitting component to understand how dynamic clinical attributes change after an intervention, and a DES component that simulates the impact of interventions on patient trajectories sampled from EHR data. Using EHR data, this research aims to understand and quantify the impact of definitions and recommended guidelines on the timely identification of sepsis states. We attempt to address the significant heterogeneity in the population by studying sub-populations based on gender, race, age, and type of comorbidity. We use the framework to help answer the following research questions under a specified treatment guideline: (i) How do dynamic physiological and cellular attributes evolve over time after a therapeutic intervention, given static patient attributes such as age, gender, race, and the types of comorbidities that are present? (ii) What impact does this evolution of attributes have on a patient's subsequent health state?

We illustrate the framework using the CMS guidelines for therapeutic interventions utilizing the CMS definitions of sepsis. We limit our study to therapeutic interventions (i.e., anti-infectives and fluids) that are designed to improve patients' physiological and cellular conditions. However, we note that the framework can be extended to study the observational interventions (e.g., shift to ICU) and diagnostic interventions (e.g., culture orders and lab measurements) on a patient's trajectory if the features affected by these interventions are known and specified.

The remainder of this paper is structured as follows – we first introduce the features of the EHR used, followed by an overview of the simulation framework including the patient cohort. We then present results pertaining to the impact of the simulated interventions. Finally, we discuss the implications of our findings and scope for future work.

2 SIMULATION FRAMEWORK

A DES framework was developed to study the evolution of and the impact of clinical definitions on sepsis patient trajectories. This framework may be used under different clinical definitions of sepsis to compare hospital policies and therapeutic recommendations for sepsis in patients given their comorbidities. DES is advantageous in this setting since it provides the flexibility to model complex interactions between model elements such as dynamic clinical attributes, disease progression, and stochastic treatment impact, as well as incorporate patient heterogeneity. Since this framework does not incorporate the dynamics of infection spread, but rather focuses on the trajectory of sepsis within individuals who have already acquired an infection, DES is selected to allow us to focus on a patient's trajectory at discrete points in time as per the EHR data. Finally, a simulation framework will also allow us to easily layer additional complexities in the future, such as patient movements across healthcare delivery locations.

Figure 2 presents an overview of the comprehensive simulation framework used to personalize interventions in septic patients with comorbidity. Inputs to the framework consist of (i) a dataset of patients with infection, derived from EHR data, (ii) definitions for sepsis identification, and (iii) guidelines for interventions. The EHR dataset is central to the framework and can be used to identify which comorbidities are most related within gender, race, and age subpopulations via variable cluster analysis. Simulated patients at the visit-level are obtained directly from the EHR data by sampling patients and their static and dynamic clinical, demographic, and comorbidity-related attributes in their entirety. The EHR data is also used to obtain percent changes in vitals and labs after an intervention, based on their demographic and comorbidity-related features, that can be fit to distributions. The simulated patients, comorbidity clusters and fitted distributions then become inputs to the simulation model. Using dynamic clinical attributes obtained from the EHR datasets, the simulation model (i) tracks the trajectory of patients over time, as categorized into states by any definition specified; (ii) simulates the impact of an intervention (determined by the specified guidelines) on vitals and labs by generating a random number from the fitted distributions; and (iii) determines the new post-intervention state using the specified definitions. This allows us to study outcomes related to state change in patients at an episode-level. We define an episode to represent a portion of a patient's visit defined by hospital location, within a single hospital unit such as ED or ICU. A patient's visit may be comprised of multiple episodes. We distinguish episodes from one another in order to address the challenge of reduced visibility to the ICU vitals in our EHR data. We note however, that this framework can be used at the visit-level as well.

We illustrate the use of this framework by employing the CMS definition to identify sepsis and the CMS SEP-1 therapeutic guidelines (Faust and Weingart 2017) to determine the state at which to intervene. We do not take into account the other recommendations by CMS that cover examination and diagnostic interventions.

2.1 Data

We use retrospective, de-identified Electronic Health Records (EHR) data from Christiana Care Health System in Newark, Delaware. Christiana Care Health System, headquartered in Wilmington, Delaware is a health care provider with 1,100 in-hospital patient beds and over 53,000 hospital admissions annually. The data consists of 119,968 adult inpatients over 210,289 visits between July 1, 2013 and December 31, 2015. The data includes all inpatient visits for individuals over the age of 18 at the time of admission. Visits without subsequent hospitalizations (outpatient visits) are excluded. The data consists of demographic, diagnosis- and visit-event-related attributes. Patient demographics include gender, age, race, and ethnicity. Diagnosis-level information comprises admitting, primary, and up-to -sixty secondary diagnoses codes, as well as certain history flags. Visit events consist of any time-stamped change in vitals recorded, administered therapies and interventions, lab results, assessment scores, change in hospital unit, discharge disposition, etc., that can occur during a patient's visit. In this study, we exclude 40,874 visits with unknown gender, surgical visits, and visits with diagnoses coded with the ICD 10 classification system (implemented in

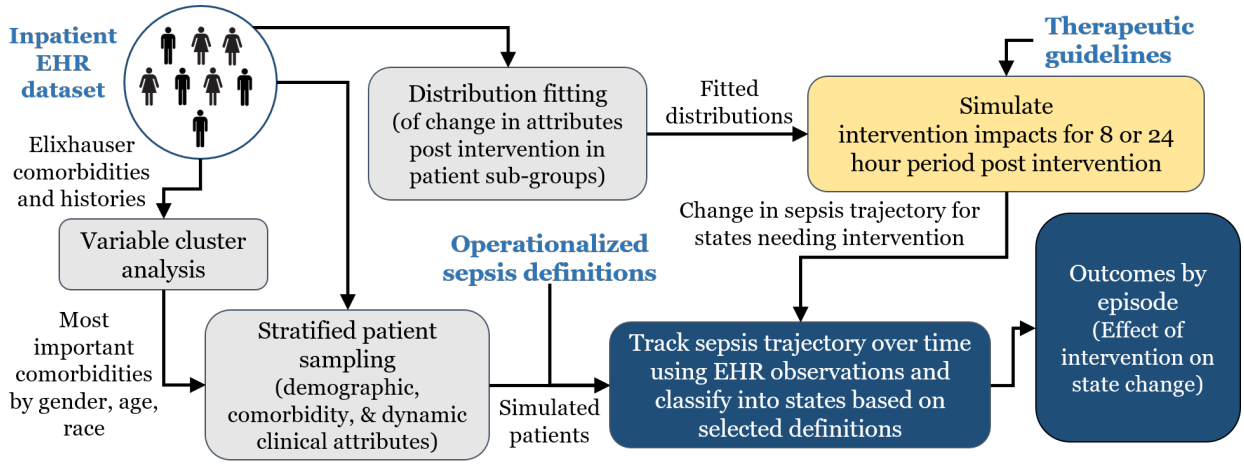

Figure 2: Overview of comprehensive DES framework modeling the impact of definition and sepsis interventional guidelines on patient trajectories. Gray boxes represent inputs to the framework, blue boxes are model components, and the yellow box is the simulation component (detailed further in Figure 3).

October 2015). We exclude the ICD 10 coded visits because of possible discrepancies that may have arisen in coding during the initial transition period. These are of particular concern since the ICD 10 system categorizes sepsis differently than the ICD 9 system. Of the remaining visits, we restricted our attention to visits with any ICD 9 code associated with sepsis (present anywhere in their records), resulting in a final sample size of 6,137 unique visits during the study period.

2.2 Cohort Definition

In order to avoid the drawbacks of using either the ICD 9 diagnoses or clinical definitions of sepsis alone, we initially selected our cohort using ICD 9 diagnoses for sepsis to ensure that everyone in our population had some form of confirmed sepsis at some point during their stay. We define individuals in the retrospectively collected EHR dataset as having sepsis based on ICD 9 codes in any of their admitting, primary or up to sixty secondary diagnoses. The ICD 9 codes pertaining to sepsis and its various stages are one or more of the following - septicemia (038), sepsis without acute organ dysfunction (995.91), puerperal sepsis (670.2), severe sepsis with organ dysfunction (995.92), and septic shock (785.52).

To study the actual evolution of confirmed sepsis in patients, we used the CMS definition of sepsis for state identification. However, the flexibility of the framework allows for the cohort to be defined in other ways (such as individuals with infection or other clinical sepsis definitions) depending on the trajectories of interest. We note that patients without suspected infection (i.e., any administration of anti-infectives or positive Polymerase-Chain-Reaction culture) and patients who had surgery were excluded from our study population. Surgical patients were excluded from our study because sepsis is thought to manifest and progress differently in this population, who are at a greater risk for infection post-surgery (Moore and Moore 2012).

2.3 Variable Cluster Analysis

Comorbidities can complicate the trajectory of sepsis and increase the risk of poorer outcomes and hospital resource use (Yang et al. 2010; Oltean et al. 2012). Beck et al. (2016) found that the risk of mortality significantly increased when diabetes, anemia and alcohol abuse were part of the temporal trajectories of multimorbidity in sepsis. Esper et al. (2006) found gender and racial disparities of comorbidities in septic populations – sepsis was more prevalent in male and black patients. The most common comorbidities in white patients were Coronary Obstructive Pulmonary Disease (COPD) and cancer, while black patients

were often found to have renal failure, diabetes, HIV and alcohol abuse. This suggests that quantification of the impact of comorbidities on sepsis trajectories can possibly assist in personalized treatment.

We use hierarchical variable cluster analysis models to characterize pre-existing conditions and understand which conditions are most similar in patients with sepsis. Hierarchical clustering produces nested clusters represented in the form of a dendrogram (i.e., tree), allowing us to "prune" the tree at different levels to obtain clusters that are most relevant in a given setting.

An individual may have a history of an Elixhauser condition (1998) from a previous visit, or a comorbidity present on their current visit diagnosis (indicating that they currently have the condition, even if it was not diagnosed during the visit), both or neither. ICD 9 diagnosis codes were used to identify the presence of any of the Elixhauser comorbidities. Corresponding histories were directly available in the dataset for patients with a previous visit. To determine the distance between two clusters, we used the S2 asymmetrical coefficient (Gower and Legendre 1986). The S2 coefficient is defined as, $a/(a+b+c+d)$, where, the number of data points with, (1) both conditions 1 and 2 is a, (2) condition 1 absent and condition 2 present is b, (3) condition 1 present and condition 2 absent is c, and (4) neither condition1 nor 2 is d. In our context, given the heterogeneity of the population, the simultaneous presence of two conditions is more informative than the simultaneous absence. To address the significant heterogeneity in comorbidity in individuals with sepsis (Esper et al. 2006), we further split the population into subpopulations determined by gender, race, and age.

Hierarchical variable cluster analysis was conducted on the Elixhauser comorbidities and histories in ICD-9-coded sepsis patients, corresponding to 6,207 visits (after excluding non-White/non-Black races, and those who had missing values in any clustering field), in R. Visits were grouped by gender (Male, Female), race (White, Black/African-American), and age (< 60, $\geqslant 60$). Clustering suggested that comorbidities and histories of hypertension, anemia, and electrolyte and fluid disorders were most frequently seen in patients diagnosed with ICD 9 sepsis. Further, the clusters also revealed that histories of a condition and present comorbidity behaved similarly. Therefore, we created a binary variable (*comorbidity flag*) to represent the presence of current or history of hypertension, anemia, or fluid and electrolyte disorders, and, thereby, take into account the impact that major comorbidities have on the change in vitals and labs after an intervention.

2.4 Simulating Interventions

To simulate interventions, we must be able to capture the impact of therapeutic interventions such as anti-infectives and fluids on the vitals and labs in individuals with sepsis. In the absence of any models suggesting what these impacts may be in individuals with sepsis, we fit distributions to the percent change in specific labs or vitals after an intervention of a given type. The interventions considered include anti-infectives (defined as the administration of any dose of antibiotics, antivirals, or antifungals) and fluids (any dose). Since interventions likely impact different patient subpopulations very differently, we categorized the isolated population of ICD 9 diagnosed sepsis into gender, race, age, and comorbidity subpopulations. In order to focus on the most important comorbidities in the sepsis population, we used the comorbidity flag derived from the cluster analysis.

To accurately capture the impact of interventions, we created look-back 'time windows' to establish the worst value of the vital or lab in question prior to the administration of a given intervention. Similarly, look-forward time windows were used to determine the average value of the vital or lab after an intervention. As with the sepsis state definitions, based on clinical opinion, the look-back and look-forward time windows for vitals were considered to be 8 hours (since they are more frequently measured) versus 24 hours for labs. Each time an intervention under consideration was administered to patients within a subpopulation, a percentage change in the value of the attribute post-intervention was recorded. This allowed us to estimate the impact of an intervention on a patient's clinical attributes within each subpopulation.

A given intervention is assumed to only directly impact certain vitals and labs in patients. The clinical attributes impacted by each intervention are listed in Table 1. We do not include vasopressors in our illustration due to concerns regarding vasopressors serving both an intervention as well as a state definition

Table 1: Interventions considered and corresponding effects on cellular and physiological state markers.

Intervention	Impact Category	Attributes	Effect Type
Anti-infectives	Cellular	Bandemia, C-Reactive Protein, Sed Rate, Procalcitonin, White Blood Cell count	Direct
	Physiological	Heart Rate (HR), Respiratory Rate, Shock Index, Temperature*	Direct
Fluids	Physiological	Heart Rate, Systolic Blood Pressure (SBP)**	Direct
		MAP (i.e. HR/SBP), SBP Drop	Indirect

Worst value is the maximum; * Worst value is dependent on mean; ** Worst value is the minimum

for septic shock. Additionally, the SEP-1 guidelines recommend vasopressors be administered when fluids alone are insufficient for resuscitation, requiring that the impact of vasopressors be distinguished from those of fluids, which is difficult in the EHR data.

We use the 'worst' value of an attribute prior to an intervention because it suggests that something about the patient's health state prompted the provider to take action. However, the continued use of the worst value after the intervention would be misleading, because it might represent the value of the attribute just after the intervention, before any possible improvement has had time to take effect. If any time window was missing values entirely, those observations were not included in our analysis. Worst values for all vitals and labs, with the exception of temperature, were defined as minimum or maximum values depending on whether abnormality is defined as being less than or greater than the cut-off values listed in any given definition, respectively. Because temperature is considered to be abnormal outside of a range (36°C – 38°C), we used the mean to determine whether the maximum or the minimum value was worse for a given set of observations corresponding to a patient. Since a patient is more likely to have a fever as compared to hypothermia, if the mean temperature in the look-back window is $\geqslant$ 36°C, we defined the worst value to be the maximum temperature; if not, we used the minimum temperature as the worst value.

The files containing the intervention effects for each given subpopulation, intervention, and vital or lab were then used as inputs to a distribution fitting function in Matlab, *AllFitDist*. Limited visits for certain subpopulations and infrequent recording of certain labs in the EHR resulted in some intervention-attribute combinations with a few or no observations. For these instances, we aggregated the subpopulations, starting first by aggregating age-groups, followed by gender, and then race.

The best-fit distribution within *allfitdist* was chosen based on the Bayesian Information Criteria (BIC) value for each fit modeling the distribution of physiological and cellular responses after an intervention, A chi-square goodness of fit test was then performed to determine the quality of fit, since the BIC is only useful when comparing between fits, but cannot be used as an absolute measure of fit appropriateness. For intervention effects with the number of observations greater than 200, we used a stricter α value of 0.01 for the goodness of fit test. For those between 50 and 200, a less strict α of 0.05 was used. Finally, for instances where the chi-square goodness-of-fit test failed, or where the number of observations were less than 50, we used the empirical distribution.

2.5 Patient Sampling

Given the large size of the EHR data, we limited our study to a randomly-selected 10% sample of the 6,137 unique visits with any ICD 9 diagnosis of sepsis, stratified by gender, race, age and the comorbidity flag. The number of visits without the comorbidity flag represent roughly only 5% of the entire population, underscoring the prevalence and importance of these comorbidities in the septic population. Consequently, some subpopulations such as those representing Black women under the age of 60 with no comorbidities are represented by only a few visits in the sample. The benefit of tracking patients' trajectories by episode is that episodes result in larger sample sizes. For each sampled visit, we retained the patient's entire visit-event information, including static and dynamic clinical attributes, to track their movement along the

sepsis trajectory over time. We note that the sampled patients may be anywhere along the sepsis spectrum depending on their clinical attributes.

2.6 Simulation Patient Trajectories

As described previously, the simulation model consists of three primary components, detailed below. The first component tracks a patient's sepsis trajectory over time using clinical attributes available in the sampled EHR dataset. The second simulates the impact of a first intervention of a given type (anti-infective or fluid) using the fitted distributions. The final component determines a patient's new state after an intervention and records statistics. We restrict our attention to the first intervention alone, since subsequent interventions may have cumulative effects on the attributes.

At any given time, the patient's static and dynamic attributes are used to flag whether or not they can be identified on the sepsis trajectory either through one or more considered definitions. Because the EHR data was sparse with a significant amount of missingness, we used the previously-defined look-back windows to identify if any of the past attributes within the window have an abnormal value. Thus, at any given point in time, we can determine whether or not the patient meets the criteria for one of the three following CMS states - sepsis, severe sepsis, or septic shock.

In the discussion that follows, we introduce the assumptions used to operationalize the CMS definition. First, based on expert opinion, we assume that since hypo-perfusion is undefined in the CMS septic shock criteria, it can be defined as an abnormal Systolic Blood Pressure (SBP), MAP (Mean Arterial Pressure, defined in Table 1), or a significant drop in SBP compared to a known baseline. Second, we treat any missing location information (that represents the unit a patient is in, e.g., ICU or Step-down) at the end of a visit as a separate episode. This can occur in the EHR data because lab results can be received even once an individual has been discharged, resulting in a missing location code with lab results that are time-stamped. Third, fluids and assessment events do not have care delivery location information available in the EHR data. However, since these events are time-stamped, we can infer the location information using the previous location carried forward for these events. Finally, we assume that altered mental status can be determined if an individual's Glasgow Coma Score is less than 15.

Figure 3 depicts the three components of the simulation model. We study a patient's trajectory over time until it reaches a trigger state for a given intervention type, defined by the CMS guidelines. For anti-infectives, the trigger state is organ dysfunction or CMS severe sepsis. For fluids, the trigger state is septic shock. For each patient and each episode, we track a patient's initial state trajectory by categorizing them into one of three definition states (CMS sepsis, CMS severe sepsis, CMS septic shock) at every time-stamped point in the data using dynamic attributes from the sampled EHR dataset. Then, for the *first* time in the episode that any of the states that would elicit an intervention are flagged to be true (i.e., the triggering state), we intervene immediately with the corresponding intervention (anti-infectives or fluids). The intervention triggers a randomly generated impact (as percent change) from either the fitted distributions or the empirical CDF, as described previously. We note that the new value of the attribute is subsequently bound in order to make sure that is physiologically possible (e.g., an individual's temperature may not be over 45°C). Physiological attributes have both lower and upper feasibility limits, while cellular attributes (from lab results) only have lower limits. For vitals, the new value is assumed to apply 8 hours after an intervention, and 24 hours after an intervention for labs. As a reminder, the intervention only impacts the relevant attributes listed in Table 1. Consequently, a new set of vitals and labs are generated, as described below, that can be used to redefine the health state the patient is in, that is then assumed to be retained till the end of an episode (i.e., resulting health state).

Let A_0 represent the value of the attribute (vital or lab), A, prior to the intervention, S. Let A_{upper} and A_{lower} represent any upper and lower bounds for possible values of the attribute. The function $w(A,t)$ determines the worst value of the attribute A within a time-window, t. Finally, let R represent the random number generated from either the best-fitted or empirical distribution of the percentage change in A due to S. Then, we have the post-intervention value, A_1, as determined by Equation 1.

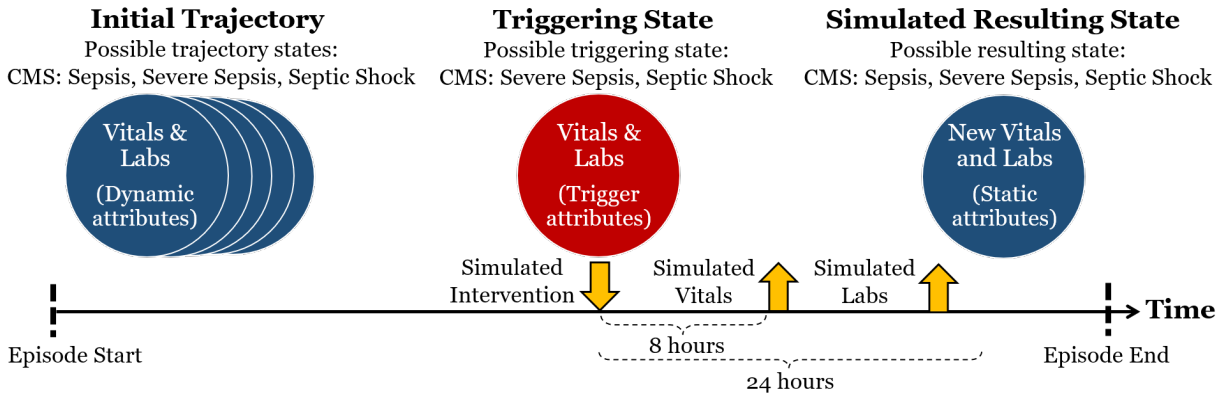

Figure 3: Simulating the impact of interventions on state definitions for a given episode within a visit.

$$A_1 = \begin{cases} \max\{\min\{(1-R/100)*w(A,t), A_{\text{upper}}\}, A_{\text{lower}}\}, & \text{if } A \text{ has upper and lower bounds} \\ \max\{(1-R/100)*w(A,t), A_{\text{lower}}\}, & \text{if } A \text{ only has lower bounds} \end{cases} \quad (1)$$

The resulting state can then either show improvement (i.e., the patient is no longer in the state post-intervention and the flag indicating the presence of the state has changed from 1 to 0), deterioration (i.e., the patient is now in the state post-intervention and the state flag has changed from 0 to 1), or no change. In circumstances where the patient shows no change, it can be either due to the state still persisting (state flag stays at 1 post-intervention) or because the patient was never in the state to begin with (state flag stays at 0 post-intervention).

3 RESULTS

Across the subpopulations, post-aggregation, there were a total of 135 fitted distributions corresponding to the impacts of anti-infectives on physiological responses (39 distributions), cellular responses (64 distributions), and fluids on physiological responses (32 distributions). The most common distribution used was the empirical (58 instances), followed by the t Location-Scale distribution (40 instances). The distribution fits results are not included in this manuscript due to space constraints.

While the simulation framework can be used to look at other metrics, in this study we limit our discussion to an illustration of summary comparisons of state change before and after an intervention. We evaluated the impact of simulated interventions as specified by the CMS guidelines on state change in all patients over 20 replications. The number of replications was restricted due to computational time limits. We studied two simulated interventions - anti-infectives in individuals with severe sepsis and fluids in individuals with septic shock. Table 2 shows the percent of cases with improvements, deterioration, and those with no state change after an anti-infective was administered.

The simulated impact of anti-infectives was designed to directly or indirectly affect cellular and physiological markers of inflammation (Table 1). There were improvements in approximately 1 in 5 episodes of CMS severe sepsis (21%). Every improvement in severe sepsis states was due to the resolution of the underlying sepsis and corresponding inflammatory markers. This is because anti-infectives only impact these inflammatory markers, and have no effect on CMS severe sepsis (i.e., OD) attributes. A few cases of CMS shock were resolved as well (6%), because these definitions required underlying sepsis, whose criteria were affected by anti-infectives. Most frequently, however, the patient tended to stay in the state they were in, as seen in the always-in-state and never-in-state rows in Table 2.

The administration of fluids directly impacted heart rate and systolic blood pressure, while indirectly impacting MAP and the drop in blood pressure (Table 1). Consequently, intervening with fluids can

Table 2: Mean post-intervention state changes ($\bar{N}$) across 20 replications (State absence: 0, presence: 1).

Intervention	**Triggering State**	**State Change**	**Sepsis** $\bar{N}$ **(SD), %**	**Severe Sepsis** $\bar{N}$ **(SD), %**	**Septic Shock** $\bar{N}$ **(SD), %**
Anti-infectives	CMS Severe Sepsis (N = 1,253)	Improved (1-0)	269 (15.3), 21%	269 (15.3), 21%	78 (7.8), 6%
		Always in state (1-1)	984 (15.3), 79%	984 (15.3), 79%	300 (7.8), 24%
		Never in state (0-0)	0 (0), 0%	0 (0), 0%	875 (0), 70%
		Deteriorate (0-1)	0 (0), 0%	0 (0), 0%	0 (0), 0%
Fluids	CMS Shock (N = 620)	Improved (1-0)	60 (6.7), 10%	170 (6.5), 27%	246 (7.7), 40%
		Always in state (1-1)	560 (6.7), 90%	450 (6.5), 73%	374 (7.7), 60%
		Never in state (0-0)	0 (0), 0%	0 (0), 0%	0 (0), 0%
		Deteriorate (0-1)	0 (0), 0%	0 (0), 0%	0 (0), 0%

potentially impact all states along the sepsis spectrum. Intervening with fluids had the largest positive effect across all interventions and states on septic shock (40% of episodes saw an improvement). The next highest improvement came with fluids on severe sepsis episodes (27% improvement). Finally, a few cases of sepsis were also resolved with fluids (10%). This improvement is much smaller since the only impact of fluids relevant to sepsis inflammatory markers is on heart rate. Our results suggest that fluids are more effective than anti-infectives in improving a patient's trajectory.

While the model allows for a patient to improve or deteriorate in response to an intervention, we note that in our illustration with the CMS definition, a patient does not deteriorate after any intervention (i.e., change from an absence of the state (0) to presence (1)). This is because the CMS definition requires sepsis in order to progress to severe sepsis, and severe sepsis to progress to septic shock. Therefore, according to the CMS guidelines, the administration of an anti-infective is triggered by severe sepsis and the patient must, by definition, have already had sepsis. A similar argument applies when intervening at septic shock with fluids. However, the model supports the possible negative impacts of interventions, since the fitted distributions come from the data directly. This may be possible in other definitions that may allow a patient to transition to worse states directly without requiring them to have been observed in the preceding state.

4 DISCUSSION

The recent spotlight on sepsis and the controversies surrounding the different definitions highlight the need for a better understanding and improved definition of the sepsis spectrum. We developed a simulation-based framework to study the evolution of the disease and determine the impact of sepsis clinical definitions and guidelines on outcomes in patients with sepsis using EHR data. We illustrated the use of this comprehensive framework, consisting of cluster analyses, distribution fitting and DES components, using the CMS definition of sepsis, under the CMS guidelines for intervention. Our flexible framework is designed to test other definitions and guidelines. It will enable both the improved identification of patients with sepsis and personalization of guidelines based on patient demographic and comorbidity-related features. It also offers the flexibility to support the comparison and quantification of the impact of multiple clinical definitions on the timely identification of sepsis states.

This framework facilitates a better understanding of both the recommended guidelines, as well as the definitions used to identify sepsis patients and their trajectories. The results from our illustration indicate that fluids are more effective than anti-infectives in improving a patient's progression along the sepsis trajectory. This may possibly be because even though anti-infectives are targeted at resolving the underlying infection, fluids are more important clinically from a resuscitation perspective. Our results also highlighted a common critique and major limitation of using the CMS definition – these criteria require underlying sepsis and severe sepsis in order to progress to severe sepsis and septic shock respectively, unlike some newer definitions (Singer et al. 2016). This can lead to missing patients who have clear signs of the onset of organ dysfunction and infection simply because the nonspecific SIRS criteria were not met, resulting in delayed or missed treatment. Conversely, this definition also has the potential to

mis-classify patients who meet the SIRS criteria who are not septic, causing the potential over-treatment of some patients.

The complex nature of sepsis and the difficulty associated with operationalizing EHR data for sepsis identification results in some limitations of the model. The high specificity but poor sensitivity of ICD-diagnosed sepsis might result in our results being biased toward those with a more severe or easily-diagnosable manifestation of sepsis (Jolley et al. 2015). The present study uses a relatively small sample and may not represent the entire patient population of interest. Finally, the granularity of the sub-populations studied resulted in a smaller number of observations for distribution-fitting and modeling for some groups. The former can be partially addressed by carrying out more replications, while the latter can be addressed by drawing a larger sample size and using additional EHR data.

This simulation framework establishes a structure for assessing the effect of sepsis definitions and intervention guidelines on patients' biological responses. Areas for future work include extending the model to differentiate between patients who have received anti-infectives or fluids prior to the CMS trigger from those who receive these interventions after the CMS trigger. In addition, the model could be extended to incorporate multiple interventions taken simultaneously. Next steps also involve identifying additional performance metrics such as length of stay and studying the changes in state after an intervention by comorbidity-based and demographic subpopulations.

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