**A Bioinformatics Approach to Identify Pediatric Sepsis**

**Episodes Using Electronic Clinical Data**

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**KEY POINTS**

***Question:*** Can a bioinformatics algorithm identify episodes of pediatric sepsis using routine clinical data?

***Findings:*** In this single-center retrospective study, a bioinformatics algorithm to identify pediatric sepsis episodes was derived and validated using routine clinical data for infection with concurrent organ dysfunction. Among 832,550 emergency and inpatient encounters over eight years, the incidence of pediatric sepsis increased over time without bias from changing diagnosis or coding practices. Mortality was 6.7% and did not vary over time.

***Meaning:*** A bioinformatics algorithm using routine clinical data to identify episodes of pediatric sepsis demonstrated an unbiased increase in sepsis incidence and stable mortality.

**ABSTRACT**

***Importance:*** An objective, efficient, and reliable method to identify pediatric sepsis episodes that is not prone to variability in diagnosis and claims-based codes does not exist.

***Objective:*** To derive and validate a bioinformatics algorithm to identify episodes of pediatric sepsis using routine clinical data and apply the algorithm to study longitudinal trends in sepsis epidemiology.

***Design:*** Retrospective observational study.

***Setting:***Single academic children’s hospital.

***Participants:*** All emergency and hospital encounters from January 2011 to January 2019, excluding the neonatal intensive care unit and cardiac center.

***Exposures:*** Sepsis episodes were identified by a bioinformatics algorithm using routine clinical data to identify infection and concurrent organ dysfunction.

***Main Outcomes and Measures:*** Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of the bioinformatics algorithm to identify sepsis episodes in derivation and validation cohorts were determined by comparison to an adjudicated sepsis database. Longitudinal trends in incidence and mortality of pediatric sepsis were calculated.

***Results:*** Among 93,987 hospital encounters in the derivation period, 1065 episodes of suspected sepsis were adjudicated. The bioinformatics algorithm yielded sensitivity 78% (95% CI 72, 84%), specificity 76% (95% CI 74, 79%), PPV 41% (95% CI 36, 46%), and NPV 94% (95% CI 92, 96%). Among 64,388 hospital encounters in the validation period, 361 episodes of suspected sepsis were adjudicated. The bioinformatics algorithm yielded sensitivity 84% (95% CI 77, 92%), specificity 65% (95% CI 59, 70%), PPV 43% (95% CI 35, 50%), and NPV 93% (95% CI 90, 97%). Notably, 98% of the bioinformatics algorithm “false-positives” were deemed true sepsis cases after manual review. The hospital-wide incidence of sepsis was 0.69% (95% CI 0.67, 0.71%) over eight years. Among 207,368 admissions, the inpatient incidence of sepsis was 2.8% (2.8%, 95% CI 2.7, 2.9%). Risk-adjusted sepsis incidence, free from changing diagnosis or coding practices, increased over time (p<0.001). Mortality was 6.7% and did not change over time (adjusted OR per year 1.01, 95% CI 0.96, 1.06; p=0.81).

***Conclusions and Relevance:*** A bioinformatics algorithm using routine clinical data provided an objective, efficient, and reliable method for pediatric sepsis surveillance. An unbiased increase in sepsis incidence and stable mortality was evident.

**INTRODUCTION**

Sepsis, a life-threatening organ dysfunction caused by a systemic infection,1 is a leading cause of morbidity, mortality, and health care costs.2,3 Consensus criteria are used to standardize the presence of sepsis and level of illness severity. Until recently, adult and pediatric sepsis was defined as a systemic inflammatory response syndrome to infection, with severe sepsis indicating organ dysfunction using arbitrary thresholds and septic shock indicating cardiovascular dysfunction.4 In 2016, Sepsis-3 reframed adult sepsis as an infection causing an acute increase of ≥2 points on the Sequential Organ Failure Assessment (SOFA) organ dysfunction score and septic shock as sepsis requiring vasopressor therapy and hyperlactatemia.1 A similar framework for pediatric sepsis has been proposed, but not yet established.5-7

Despite the availability of consensus criteria for adult and pediatric sepsis, their practical application across clinical, research, quality improvement, and epidemiologic efforts has been inconsistent and unreliable. For example, tracking cases of sepsis within and across hospitals for research or quality improvement initiatives often requires laborious chart reviews, with variable interrater reliability. Other data sources, particularly large administrative datasets commonly leveraged for research or epidemiologic surveillance, do not contain sufficient clinical data to identify cases of sepsis using consensus criteria. As a result, reliance on claims data has become standard. However, numerous studies have shown that claims data are neither reliable nor accurate in identifying episodes of adult and pediatric sepsis.8,9

The wide availability of electronically recorded clinical data provides an opportunity to apply a bioinformatics algorithm to identify episodes of sepsis within and across health care systems. Using electronic health record (EHR) data from 409 hospitals, Rhee et al adapted clinical criteria from Sepsis-3 and the SOFA score to estimate the incidence of adult sepsis in the United States.10 Their bioinformatics approach yielded 69.7% sensitivity and 98.1% specificity and was overall more accurate than claims data. A similar algorithm has not been developed for pediatric sepsis. Therefore, our objectives were a) to derive and validate a bioinformatics algorithm to identify episodes of pediatric sepsis using routine clinical data available within the EHR and b) apply the algorithm to study longitudinal trends in sepsis epidemiology.

**METHODS**

*Study Design and Population:* We performed a retrospective observational study using routine clinical data recorded in the EHR at a single academic children’s hospital. Patients treated in the emergency department or admitted to an inpatient ward at the Children’s Hospital of Philadelphia (CHOP) between January 1, 2011 and January 31, 2019 were eligible. Because we sought an algorithm inclusive of the entire population cared for within the scope of pediatrics, we did not apply an upper age limit. We excluded patients admitted to or discharged from the neonatal intensive care unit and cardiac center (including general cardiology ward and cardiac intensive care unit) because these populations were anticipated to have unique physiology that may require a more tailored bioinformatics approach. However, infants and children with cardiac conditions treated in other hospital locations were included. This study was approved by the CHOP Institutional Review Board (IRB) with a waiver of informed consent and assent.

*Bioinformatics Algorithm:* A team of bioinformatics experts in the Arcus program at CHOP worked with clinical sepsis experts to develop the clinical criteria used to identify episodes of sepsis. The Arcus program is a strategic initiative of the CHOP Research Institute created to link clinical and research data and offers secure data archives, patient privacy protection, and access to clinical data on over 2 million patients.  Although the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) defines pediatric severe sepsis as 1) ≥2 age-based systemic inflammatory response syndrome (SIRS) criteria, 2) suspected or confirmed invasive infection, and 3) cardiovascular dysfunction, acute respiratory distress syndrome, or ≥2 other organ dysfunctions,4 we focused on the updated Sepsis-3 framework for sepsis as serious infection with acute organ dysfunction without the qualifying term “severe sepsis” or the need to include SIRS criteria. This approach is consistent with calls for a revised definition of pediatric sepsis to align with Sepsis-3.11

For our bioinformatics algorithm, we defined suspected infection as a blood culture (ordered or collected) and sustained administration of new antibiotics, similar to Rhee et al.10 In order to also capture patients for whom a blood culture may have been obtained during initial resuscitation at a referring facility, we allowed for transfer to CHOP from a referring facility to substitute for a blood culture. Patients were required to receive at least four consecutive days of antibiotics (though not necessarily the same antibiotics on all days), staring within ±2 calendar days of the blood culture or transfer and at least one dose of a parental antibiotic. The first antibiotic was required to be “new”, defined as that antibiotic not having been administered within the prior seven days. Four days of antibiotics were required in order to exclude patients for whom bacterial infection was suspected but not confirmed. Fewer than four days of antibiotics was allowed for patients who died or were discharged to hospice before four days.

We modeled organ dysfunction based on criteria from the pediatric SOFA (pSOFA) score reported by Matics et al,5 with modifications derived from the adult sepsis surveillance criteria,10 another well-validated pediatric organ dysfunction score (Pediatric Logistic Organ Dysfunction Score [PELOD]-2),12,13 and three iterative revisions among our local sepsis experts. Sepsis-3 requires an increase in SOFA of ≥2 points, which equates to moderate dysfunction in a single organ system or mild dysfunction in two or more organ systems.1 The pSFOA score evaluates cardiovascular, respiratory, coagulation, hepatic, renal, and neurologic dysfunction. Similar to Rhee et al,10 we required at least one moderate organ dysfunction within ±2 calendar days of blood culture or transfer to identify sepsis in our bioinformatics algorithm, and selected criteria readily available within the EHR that corresponded to pSOFA ≥2 points in each organ system (except renal, see Table 1). We defined acute organ dysfunction as >60 mL/kg bolus fluid resuscitation within a seven-hour period, new/increased vasoactive infusion, hyperlactatemia ≥2 mmol/L, new invasive or new/expanded non-invasive mechanical ventilation, or changes from baseline in platelet count or serum creatinine (Table 1). Although not in SOFA or pSOFA, we included elevated lactate because it is a common manifestation of cardiovascular dysfunction in septic shock, associated with mortality, and demonstrated utility in the adult sepsis surveillance definition.10,14,15 We also included fluid resuscitation >60 mL/kg to capture children with fluid-responsive shock.16 On iterative reviews, we excluded bilirubin from the final algorithm because isolated hyperbilirubinemia as the defining organ dysfunction is rare in pediatric sepsis,17,18 and this criteria led to substantial false-positives from non-septic hepatic dysfunction.

*Derivation and Validation Cohorts:* Our sepsis quality improvement program uses an electronic flag to identify cases of suspected sepsis. This flag included a new antibiotic order in proximity to a blood culture or new fever (see eTable1). Starting September 1, 2017, all patients flagged for suspected sepsis were manually adjudicated through chart review by trained clinicians to confirm or reject the presence of severe sepsis or septic shock based on criteria slightly modified from the IPSCC (see eTable 2). Patients with non-bacterial causes of infection-mediated organ dysfunction (i.e., viral and fungal sepsis) were included as having severe sepsis or septic shock, as were patients in whom infection was suspected and treated by the clinical team in the absence of a definitive source of infection.

Adjudicated patients between September 1, 2017 and June 30, 2018 served as the “gold-standard” for the derivation cohort. A temporally distinct validation cohort included adjudicated patients between July 1, 2018 and January 31, 2019. All adjudicated cases confirmed to have sepsis that were not identified by the bioinformatics algorithm (false-negatives) and a random subset of false-positives were manually reviewed to determine the cause of misclassification.

*Data Collection:* Data were collected about sepsis and non-sepsis episodes, including demographics, chronic comorbid conditions (CCC),19 admission to the pediatric intensive care unit (PICU), and mortality. The onset of sepsis was identified as the earliest of either the blood culture order or collection time, time of hospital arrival (for transfers), or first new qualifying antibiotic order. Sepsis was considered community-acquired if onset occurred within two days of initial hospitalization or hospital-acquired if onset occurred on or after day three. A patient could account for more than sepsis episode, either within the same or across different hospital encounters. However, to differentiate clinical decompensation from a new episode of sepsis, we required that at least 14 days to elapse from sepsis onset before classifying a new sepsis episode.

*Statistical Analyses:* Analyses were performed using *R* *Version* 3.3.3 (R Foundation) and STATA 12.1 (College Station, TX). Descriptive data are summarized as medians (interquartile range, IQR) or percentages. Test characteristics of the bioinformatics algorithm were calculated for the derivation and validation cohorts, including sensitivity, specificity, and positive and negative predictive values (with 95% confidence intervals [CI] using Wald estimates). As a sensitivity analysis, we recalculated test characteristics of the bioinformatics algorithm after correcting misclassification errors within the adjudicated gold-standard. Finally, we determined the incidence of pediatric sepsis episodes across the entire eight-year study period using the bioinformatics algorithm, along with characteristics and mortality from these episodes. We used multivariable Poisson and logistic regression models to assess for longitudinal changes in the incidence and mortality of sepsis over time, respectively, adjusting for patient-level characteristics. Statistical significance was defined as a p-value <0.05.

**RESULTS**

Across the entire eight-year study period, derivation period, and validation period, there were 832,550, 93,897, and 64,388 eligible hospital encounters, respectively. The characteristics for the entire study population and derivation and validation periods were similar (eTable 3). The derivation cohort included 1065 episodes and the validation cohort included 361 episodes flagged as suspected sepsis using the quality improvement electronic criteria (eFigure 1).

Within the derivation period, there were 1065 suspected sepsis episodes flagged by the quality improvement electronic criteria, of which 187 were confirmed sepsis episodes after manual adjudication. Using the 1065 flagged/adjudicated episodes as the “gold-standard”, the bioinformatics algorithm yielded a sensitivity of 78% (95% CI 72, 84%), specificity of 76% (95% CI 74, 79%), positive predictive value (PPV) of 41% (95% CI 36, 46%), and negative predictive value (NPV) of 94% (95% CI 92, 96%) (eFigure 2a).

Within the validation period, there were 361 suspected sepsis episodes flagged by the quality improvement electronic criteria, of which 85 were confirmed sepsis episodes after manual adjudication. Using the 361 flagged/adjudicated episodes as the “gold-standard”, the bioinformatics algorithm was validated to have a sensitivity of 84% (95% CI 77, 92%), specificity of 65% (95% CI 59, 70%), PPV of 43% (95% CI 35, 50%), and NPV of 93% (95% CI 90, 97%) (eFigure 2b).

All 42 episodes adjudicated as sepsis in the derivation cohort that were missed by the bioinformatics algorithm (“false-negatives”) and a random selection of 50 (24%) of the 207 episodes adjudicated as not sepsis that were identified as having sepsis by the bioinformatics algorithm (“false-positives”) were manually reviewed (Table 2). The most common reasons for bioinformatics algorithm “false-negatives” were <4 days of antibiotics (usually due to viral etiology), slow fluid administration over >7 hours, and incorrect adjudication. The reasons for “false-positives” were largely due to single-organ dysfunction that met the more inclusive bioinformatics criteria. In our sensitivity analysis, the four patients incorrectly adjudicated as having sepsis were re-coded as “not sepsis”. In addition, 49 of the 50 “false-positives” were deemed appropriately classified as sepsis by the bioinformatics algorithm, including those with single-organ dysfunction and misclassification errors. We extrapolated these findings to recode 203 of the 207 “false-positives” as true sepsis. After these adjustments, the test characteristics of the bioinformatics algorithm were sensitivity 90% (95% CI 87, 93%), specificity 99% (95% CI 99, 100%), PPV 99% (95% CI 98, 100%), and NPV 95% (95% CI 93, 96%).

The hospital-wide incidence of pediatric sepsis episodes across the entire eight-year study period using the final bioinformatics algorithm was 6.9 episodes per 1000 hospital encounters (0.69%, 95% CI 0.67, 0.71%). Among the 207,368 hospital admissions (excluding ED visits that did not result in admission), the incidence of sepsis was 27.8 episodes per 1000 hospital admissions (2.8%, 95% CI 2.7, 2.9%). The incidence of sepsis among all hospital encounters increased over time after controlling for age, sex, race, and number of CCC (p<0.001). Although there were efforts to increase lactate measurement as part of our sepsis quality improvement program during the study period, there was no change in the proportion of sepsis episodes identified by the hyperlactatemia criterion over time (eFigure 3). Patient characteristics for all sepsis episodes are shown in Table 4 (patient characteristics for sepsis episodes in the derivation and validation periods shown in eTable 4).

Overall mortality was 6.7% (95% CI 6.1, 7.3%). Mortality did not change over time after accounting for age, sex, race, community- versus hospital-acquired onset of sepsis, presence of CCC, or number of organ dysfunctions (adjusted OR per year 1.01, 95% CI 0.96, 1.06; p=0.81). The distribution and number of organ dysfunctions, along with associated hospital mortality, among sepsis episodes identified using the bioinformatics algorithm are shown in Figure 2.

**DISCUSSION**

We successfully developed a bioinformatics algorithm to identify episodes of pediatric sepsis using routine clinical data available within the EHR. In both derivation and temporally distinct validation cohorts, the bioinformatics algorithm achieved acceptable sensitivity and specificity relative to an adjudicated “gold-standard” and comparable results to a recent electronic surveillance definition for adult sepsis. The bioinformatics algorithm was easily applied retrospectively to generate eight years of epidemiological data about pediatric sepsis episodes using consistent clinical criteria without having to rely on laborious and expensive manual chart review or claims data that suffer from variability across providers and time.

A reliable method to identify episodes of pediatric sepsis has been elusive to date. We, and others, have historically relied on a combination of clinician self-report, medical record review, “home-grown” electronic flags, and billing codes to identify children with sepsis.3,20-22 Unfortunately, none of these methods provides an objective, efficient, and reliable approach, making epidemiologic comparisons across time and location difficult. For example, a recent review of 94 studies involving children with severe sepsis and septic shock noted substantial variability in patient characteristics between studies.23 The extent to which patient-level variability reflects true differences in the local case-mix versus heterogeneity in the criteria used to identify sepsis cases is unclear. Moreover, there is a well-documented disconnect between clinician diagnosis, fulfillment of consensus criteria, and assignment of billing codes for pediatric sepsis such that none of these methods provides a clear standard.8,9,24

We chose an approach that paralleled the Sepsis-3 framework rather than the 2005 IPSCC to ensure relevance to forthcoming pediatric sepsis updates11 and, for consistency, to mirror the recently published adult sepsis surveillance algorithm.10 However, the only “gold-standard” reference available was based on the 2005 IPSCC criteria.4 Key differences are that the IPSCC criteria include a) clinician suspicion of infection (with or without antibiotics), b) ≥2 SIRS criteria, and c) a complex set of criteria that can fulfill dysfunction among six organ systems. The 2005 IPSCC were developed primarily to identify “definitive sepsis” for clinical trials, and these criteria have not been advocated for use in the early identification of clinical sepsis.16 Our bioinformatics algorithm was designed for retrospective surveillance of pediatric sepsis episodes requiring high reliability, specificity, and efficiency.25 Because we compared a novel bioinformatics approach based on Sepsis-3 to an IPSCC-based “gold standard” with a different framework, we expected differences in the patients identified with sepsis. After adjusting the “gold-standard” to account for these differences (as well as adjudication errors), the bioinformatics algorithm yielded favorable test characteristics, with near-perfect specificity.

Ours is not the first attempt at a bioinformatics approach to identify pediatric sepsis episodes. Matics et al also applied the Sepsis-3 framework to 8711 PICU encounters from a single institution, substituting age-based values into a pSOFA score.5 However, their pSOFA score was not developed or validated in children prior to utilization; rather, it simply adopted the same criteria used in adults. We, and others, have shown that some features of SOFA may not be as useful in children. For example, Glasgow coma score is less reliably scored and recorded in pediatric hospitalizations,26 and hepatic dysfunction is a rare as the only organ dysfunction in pediatric sepsis.17,18 Moreover, Matics et al required hyperlactatemia to define septic shock—similar to Sepsis-3—but lactate is not always measured. Finally, it is not clear how accurately pSOFA would identify sepsis outside of the PICU, such as those with fluid-responsive septic shock. Our efforts expanded work by Matics et al to derive and validate a bioinformatics algorithm applicable to children in emergency, inpatient, and intensive care settings.

Applying our bioinformatics algorithm to eight years of available EHR data revealed an increase in the incidence of sepsis over time that could not be attributable to changes in diagnosis or billing practices. This distinction is critical because, to this point, it has not been possible to disentangle the extent to which the reported rise in pediatric sepsis reflects increased sepsis recognition/diagnosis, changes to coding practices, or a true increase in disease.3,20,21 In addition, the 2.8% incidence of sepsis among hospital admissions was in the middle of prior estimates that have ranged from 0.45% to 3.1% based on different claims-based strategies to identify sepsis.20,27 Because claims-based strategies that combine codes for infection plus organ dysfunction lack specificity while sepsis-specific codes lack sensitivity,8,28 our “in-between” estimate has face validity for achieving better balance in sensitivity and specificity.

There are several limitations of this study. First, the bioinformatics algorithm excluded children not treated with at least four days of inpatient antibiotics, such as viral sepsis. Given that children with viral sepsis without bacterial co-infection have a low risk of death,29 we felt this omission to be acceptable. Second, additional study is needed to determine the applicability of this algorithm to the neonatal intensive care unit and cardiac center. Third, we did not include hepatic or neurologic dysfunction. Hepatic dysfunction was excluded because a) inclusion of hepatic dysfunction decreased specificity by picking up many children with acute or chronic primary liver disease treated for mild infections and b) most children with sepsis-associated hepatic dysfunction had other qualifying organ dysfunctions. Neurologic dysfunction was excluded because a reliable indicator was not ascertainable from the EHR. Fourth, because our bioinformatics algorithm was based on Sepsis-3 but compared 2005 IPSCC criteria, we performed *post-hoc* re-categorization that is prone to potential bias. For this reason, an independent validation of our algorithm is needed. Fifth, this algorithm is not intended to assist in real-time clinical recognition of children with sepsis. Finally, the epidemiologic estimates reflect the experience at a single institution. However, broader application of this should provide an objective, efficient, and reliable method for epidemiologic surveillance of pediatric sepsis.

**CONCLUSIONS**

A bioinformatics algorithm that uses routine clinical data available within the EHR can provide an objective, efficient, and reliable method for pediatric sepsis surveillance across emergency and inpatient hospital settings. Applying this algorithm to eight years of data from a single-center demonstrated an unbiased increase in sepsis incidence and stable mortality.

**ACKNOWLEDGMENTS**

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**FIGURE LENGENDS**

**Figure 1: Sepsis Incidence and Mortality, 2011-2018**

**Figure 2: Organ Dysfunction and Associated Mortality in Sepsis Episodes**

**eFigure 1: Patient Flow Diagram**

**eFigure 2: Test Characteristics using Derivation and Validation Cohorts**

**eFigure 3: Hyperlactatemia As Organ Dysfunction Over Time**