Effect of a Sepsis Screening Algorithm on Care of Children with False-Positive Sepsis Alerts

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Objectives To determine if implementation of an automated sepsis screening algorithm with low positive predictive value led to inappropriate resource utilization in emergency department (ED) patients as evidenced by an increased proportion of children with false-positive sepsis screens receiving intravenous (IV) antibiotics.

Study design Retrospective cohort study comparing children <18 years of age presenting to an ED who triggered a false-positive sepsis alert during 2 different 5-month time periods: a silent alert period when alerts were generated but not visible to clinicians and an active alert period when alerts were visible. Primary outcome was the proportion of patients who received IV antibiotics. Secondary outcomes included proportion receiving IV fluid boluses, proportion admitted to the hospital, and ED length of stay (LOS).

Results Of 1457 patients, 1277 triggered a false-positive sepsis alert in the silent and active alert periods, respectively. In multivariable models, there were no changes in the proportion administered IV antibiotics (27.0% vs 27.6%, aOR 1.1 [0.9,1.3]) or IV fluid boluses (29.7% vs 29.1%, aOR 1.0 [0.8,1.2]). Differences in ED LOS and proportion admitted to the hospital were not significant when controlling for similar changes seen across all ED encounters.

Conclusions An automated sepsis screening algorithm did not lead to changes in the proportion receiving IV antibiotics or IV fluid boluses, department LOS, or the proportion admitted to the hospital for patients with false-positive sepsis alerts. *(J Pediatr 2021;231:193-9)*.

Severe sepsis and septic shock are leading causes of morbidity and mortality in the pediatric population with over 75 000 children treated yearly in the US and mortality rates as high as 20%.[1,2] Although early initiation of fluids and antibiotics improves outcomes of children with septic shock, timely therapy first requires clinician recognition of sepsis.[3-5] This task is particularly difficult in children because of the overlap in abnormal vital signs such as fever, tachycardia, and tachypnea between children with infections who will progress to life-threatening sepsis and those who will not.[6]

In an attempt to improve early recognition, many emergency departments (EDs) have employed sepsis screening tools that seek to identify children at increased risk for developing sepsis based on vital signs, laboratory values, and patient characteristics.[7,8] Pediatric sepsis screening is rapidly becoming the standard of care for children presenting to the ED, with the implementation of a systematic screen suggested by the recently published Surviving Sepsis Campaign International Guidelines.[9] Three states have even mandated the use of pediatric sepsis screening in the ED, and several other states and regulatory bodies are considering similar regulations.[4,10]

Despite the growing adoption of sepsis screening tools, there are limited data on their effectiveness. In adults, sepsis screening tools have been shown to decrease hospital length of stay (LOS) and time to antibiotic administration in those with severe sepsis,[11] though these findings are not universal, and no mortality benefit has been demonstrated.[12] In children, Balamuth et al showed that a pediatric sepsis-screening tool improved recognition of severe sepsis among clinicians and decreased missed cases of sepsis in the study ED.[8]

Currently, pediatric sepsis screening tools have a positive predictive value that ranges between 2.5% and 25%,[7,8,13] raising the concern that this high false-positive rate may potentially lead to unnecessary treatments including the administration of antibiotics and intravenous (IV) fluids, as well as hospital admission.[14,15] The downstream results of this may include hospital or ED overcrowding, increased antibiotic resistance,[16] medication side effects, and cost. This pattern of false positive screens leading to

aMD	Adjusted median difference
ED	Emergency department
EMS	Emergency medical services
EHR	Electronic health record
ICU	Intensive care unit
IV	Intravenous
LOS	Length of stay

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unnecessary resource utilization has previously been reported with certain cancer screens, electrocardiograms administered during routine physical examination, and other medical screening tests.[17-19]

The objective of this study is to determine whether the introduction of an automated sepsis-screening algorithm embedded in the electronic health record (EHR) resulted in increased antibiotic exposure for children with false-positive sepsis alerts in the ED.

Methods

This was a retrospective cohort study of patients presenting to a pediatric ED who met criteria for a sepsis alert before and after "go-live" of an automated, EHR-embedded sepsis-screening algorithm.

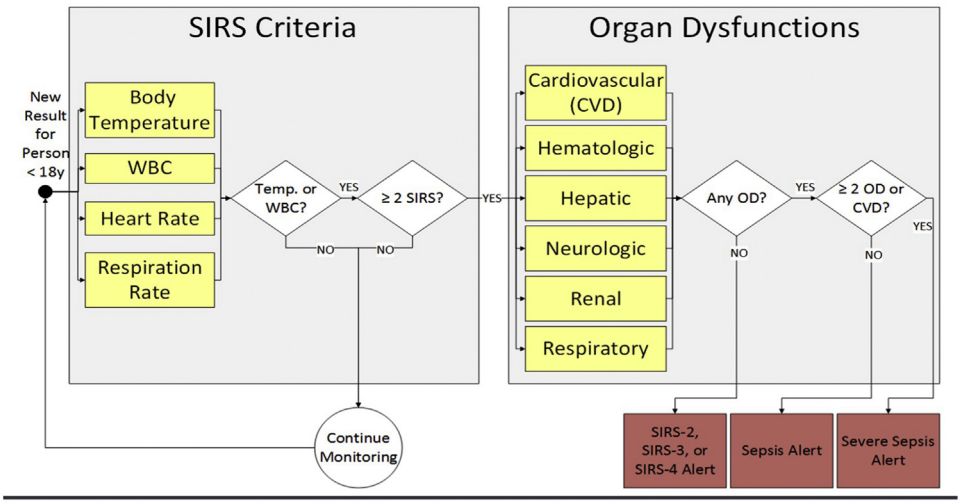
Setting

ED of a free-standing quaternary care, children's hospital with approximately 60 000 annual visits. The ED is staffed full-time with pediatric emergency medicine-trained physicians, and approximately 70% of patients are also seen by a trainee, physician assistant, or nurse practitioner prior to the attending. The baseline prevalence of severe sepsis or septic shock in the study ED is approximately 1.8 per 1000 encounters. The study was approved by the institutional review board with a waiver of informed consent.

Sepsis Alerting in the ED

An EHR-embedded real-time sepsis detection algorithm was designed to alert clinicians when patients met 1 of 3 alert criteria based on a modified version of the International Pediatric Sepsis Conference Consensus definitions for the systemic inflammatory response syndrome, sepsis, and severe sepsis[13] (**Figure 1**).

The algorithm was initially implemented in silent mode over a consecutive 5-month period in 2016. During that time, alerts were tracked by the study investigators but were not visible to the clinical team. Starting in 2018, the alerts were presented to physicians and nurses caring for patients in real-time with an EHR pop-up message and an indicator icon appearing on the ED-tracking board (**Figure 2**, *A*;



Cardiovascular Dysfunction
- Low systolic blood pressure
- Vasoactive drug administration
- Two of the following:
  - Low arterial bicarbonate
  - High arterial lactate
  - Prolonged capillary refill (>3 seconds)*
  - High core to peripheral temperature gap
  - Abnormal pulse quality*
  - Abnormal skin assessment*

Respiratory Dysfunction
- Low PaO_2/FIO_2 in absence of cyanotic heart disease
- High or large increase in $PaCO_2$
- High FIO_2

Neurologic Dysfunction
- Low or large decrease in Glasgow Coma Score
- Documentation indicating low mental status*

Hematologic Dysfunction
- Low or large decrease in platelet count
- High international normalized ratio (INR)
- Low absolute neutrophil count (ANC < 0.5 × $10^3/mm^3$)*

Renal Dysfunction
- High or large increase in serum creatinine

Hepatic Dysfunction
- High bilirubin
- High alanine transaminase (ALT)

Figure 1. Sepsis screen algorithm logic used in EHR-embedded alert. Sepsis screening algorithm logic.[13] Additions and changes to Goldstein et al definitions are marked with an asterisk (*); removals are oliguria and need for mechanical ventilation. *FiO_2*, fraction of inhaled oxygen; *OD*, organ dysfunction; *$PaCO_2$*, partial arterial pressure of carbon dioxide; *PaO_2*, partial arterial pressure of oxygen; *SIRS*, systemic inflammatory response syndrome.

available at www.jpeds.com) when alert criteria were met. There were no changes in alert criteria between the 2 time periods.

For the 2 lower level alerts (with no or only 1 noncardiac organ dysfunction, respectively), nurses would complete a secondary screening form to determine if the patient was immunocompromised or had altered mental status or altered perfusion (**Figure 2**, *B*). Patients who had one of the lower level alerts and a negative secondary screen were not considered to be at high risk of sepsis and subsequently received routine care–though the clinician was still forced to acknowledge the pop-up message by closing it and the indicator icon still remained on the tracking board. For patients with a positive secondary screen, or with the highest-level alert (indicating cardiac or 2 other organ dysfunctions), staff were instructed to perform a sepsis huddle, in which members of the care team convened at the patient's bedside to determine if the patient required treatment for severe sepsis and initiate this treatment when appropriate.

When this sepsis alerting system was independently studied for its ability to detect severe sepsis and septic shock in the study ED, it was found to alert in 5.0% of patient encounters with a positive predictive value of 8.1% for an episode of severe sepsis.[13]

Selection of Participants

The hospital's data warehouse was queried for all encounters of patients less than 18 years of age presenting to the ED who triggered an automated sepsis alert over 2 distinct time periods: August 1-December 28, 2016, when the alerts ran silently in the background and were visible only to study personnel, not ED clinicians, and August 1-December 28, 2018, when clinicians received the sepsis alerts as part of their normal workflow in the EHR. Encounters were excluded if the patient met criteria for severe sepsis as defined by the International Pediatric Sepsis Consensus Conference definitions of severe sepsis or septic shock between ED arrival and ED disposition (true positive cases).[14] The excluded cases of severe sepsis were identified by manual chart review of all encounters in which the patient was admitted to the intensive care unit (ICU), was given an *International Classification of Disease, 10th Revision* code for severe sepsis or septic shock (R65.20 and R65.21), was transferred within 72 hours of ED disposition from a general floor to an ICU, died within 72 hours of presentation, or in whom a physician utilized the septic shock order set. Patients who received a sepsis or severe sepsis alert in the ED were not excluded from the study unless they were found on chart review to meet consensus criteria. Although these populations were similar, there were several groups of patients who met alert criteria for severe sepsis but were not included as sepsis cases after manual chart review (eg, those with baseline organ dysfunction that was not worse during the ED stay or those who had vital signs consistent with sepsis but did not have suspected infection). Patients who were treated for sepsis by the clinician and never went on to meet consensus criteria were also not excluded from the study, as it cannot be known how the child would have progressed without the interventions.

Outcomes

The primary outcome was the proportion of encounters in which an IV antibiotic was administered between the time the sepsis alert fired (either silently or actively) and when the patient was discharged from the ED. Because the goal of this study was to determine if the alerting system influenced provider behavior, encounters in which an antibiotic was given during the ED stay prior to the alert firing were excluded from analysis of the primary outcome, as the decision to give antibiotics could not have been influenced by an alert occurring after the antibiotic was administered. Secondary outcomes included (1) the proportion of encounters in which the patient received at least one IV fluid bolus between time of the sepsis alert and ED discharge; (2) the proportion of encounters where the patient was admitted to the hospital; and (3) ED LOS. We additionally compared the proportion of encounters in the 2 time periods where the patient returned to the ED within 72 hours and required admission, proportion where the patient returned to the ED within 72 hours and was discharged home from the ED, proportion of encounters where a blood culture was sent, mortality rate, and ICU-free days for those admitted to the ICU. Data were extracted from the EHR and when data were missing, charts were manually reviewed.

Statistical Analyses

Proportions of encounters in which the patient received IV antibiotics, IV fluids, blood cultures, was admitted to the hospital, returned to the ED within 72 hours, and died within 30 days of ED arrival were compared between time periods using a multivariable logistic regression model with aORs and 95% CIs. Continuous outcomes of ED LOS, hospital LOS, and ICU-free days were analyzed with a multivariable quantile regression model; effect estimates were expressed as adjusted median differences (aMDs) and 95% CIs. The models controlled for the following variables judged to be relevant based on prior literature and clinician experience: age, sex, race, ethnicity, proportion of complex care patients (as defined by Feudtner codes[20]), emergency severity index, arrival by transfer, and triage vitals.[6,21,22] Triage vitals were classified as tachycardia, tachypnea, and hypotension based on published age-adjusted cut-offs also used in the study sepsis-alerting system.[13] Respiratory chief complaint was also controlled for in the model, given that children presenting with asthma, bronchiolitis, or other primary respiratory illnesses often meet systemic inflammatory response syndrome criteria in the absence of sepsis and may skew the results.

The overall patient volume of the study hospital increased throughout the study period, resulting in higher rates of patients being kept in the ED for observation who would have otherwise been admitted because of limitations in hospital capacity. This translates to longer ED stays and lower admission rates between the 2 study periods for the ED population

as a whole. To adjust the admission outcome for fluctuations in ED-wide disposition patterns, we re-estimated the multivariable quantile regression model with hospital admission rate as the dependent variable and time period (silent vs active) and the daily ED-wide admission rate as the independent variables. Similarly, to adjust the LOS outcome for fluctuations in ED-wide LOS, we re-estimated the multivariable quantile regression model with LOS as the dependent variable and time period (silent vs active) and the daily ED-wide median LOS as the independent variables.

To examine the potential effect of pre-existing secular trends and potential confounders on each of the outcomes, interrupted time series analysis was performed to assess for differences in slope and intercept in rate of IV antibiotic administration, IV fluid bolus administration, ED LOS, and admission rate to the hospital during the pre- and post-implementation periods.

Sample Size Calculation

To detect a difference in the proportion of encounters receiving IV antibiotics of 10%, (ie, from 30% in the silent alert period to 40% in the active alert period), with alpha level of .05 and power held at 80%, we required 356 encounters in each group.

Results

Characteristics of Study Subjects

Between August and December 2016, there was a sepsis alert in 1293 of 23 056 (5.6%) of all ED encounters. In 16 encounters in which an alert fired, the patient met study criteria for severe sepsis or septic shock within 24 hours of ED discharge, leaving 1277 false positive sepsis alerts. After the alert went live, between August and December 2018, there was a sepsis alert in 1480 of 23 265 (6.4%) of all ED encounters. From these, 23 encounters were excluded because the patient met study criteria for severe sepsis or septic shock, leaving 1457 false positive alerts.

There were no differences in demographics between the 2 populations with the exception of triage emergency severity index, proportion with tachypnea at triage, and proportion who arrived via emergency medical services (EMS) (**Table I**).

Main Results

In the adjusted multivariable model, there was no change between the study periods in the proportion of encounters in which the patient was administered an IV antibiotic (27.0% vs 27.6%, aOR 1.1 [0.9, 1.3]) or IV fluid bolus (29.7% vs 29.1%, aOR 1.0 [0.8, 1.2]) for children with false-positive sepsis alerts.

After the sepsis alerts went live, the median ED LOS for patients with false-positive alerts increased by 18 minutes (median 4.6 hours vs 4.9 hours, aMD 0.4 [0.2, 0.6]) and the proportion of patients admitted to the hospital decreased by 5% (48.4% vs 43.4%, aOR 0.8 [0.7, 0.9]). No difference was found in the proportion admitted to an ICU (6.9% vs 6.7%, aOR 1.0 [.7, 1.4]). Notably, ED LOS also increased and admission rate decreased for all ED patients between the 2 time periods because of hospital capacity issues, decreased bed availability, and more frequent use of ED observation status. When we adjusted for these larger trends among all ED patients, the changes in ED LOS (aMD 0.05 [-0.2,0.3]) and proportion admitted to the hospital (aOR 0.9 [0.7, 1.0]) among patients with a false-positive sepsis alert were no longer significant.

Finally, there were no differences between the study periods in the proportion of encounters in which the patient had a positive blood culture, required transfer from the floor to the ICU within 24 hours of admission, returned to the ED within 72 hours (whether or not they required subsequent admission), or died within 30 days (**Table II**). Nor were there any differences between study periods in the length of overall hospital stay or ICU-free days.

In the interrupted time series analysis, there was no change between the study periods in either the slope or the intercept for the proportion receiving an IV antibiotic or an IV fluid bolus, ED LOS, or hospital admission rate (**Figure 3**; available at www.jpeds.com).

Discussion

Despite concerns that sepsis screening may lead to unnecessary interventions for patients who receive alerts but do not have sepsis, in this population of children with false-positive sepsis alerts we saw no increase in use of IV antibiotics or IV fluid boluses after an alert went from silent to clinician-facing. Though small differences in ED LOS and proportion admitted to the hospital were found, neither was significant when controlling for changes in ED-wide LOS and admission rate during these time periods. Importantly, these 2 populations of patients with false-positive sepsis alerts were equally ill with the same proportion of positive blood cultures, admissions and transfers to the ICU, and 72-hour rates of returning to ED care.

Although mandated sepsis screening tools have become increasingly popular and may improve the care of patients who meet criteria for severe sepsis,[8] there is a dearth of evidence for how they impact the care of other children in the ED. The high false positive rate of published pediatric sepsis screens makes examination of the unintended effects of sepsis screening on children without sepsis critical to assessing the effect of these screening tools on care for children in the ED.

As skeptics of pediatric sepsis screening have noted, these false-positive alerts may expose children to unnecessary antibiotics and the ensuing risks of antibiotic toxicity, disruption of the microbiome, and the development of antibiotic resistance.[23,24] In this study, however, we did not observe an increase in exposure to antibiotics among study patients once the automated sepsis alert system went live. Notably, there are a proportion of false-positive patients who will appropriately require antibiotics even if they do not meet criteria for sepsis. These patients include those with infections (eg, pneumonia, osteomyelitis), patients with underlying

Table I. Demographic characteristics of false positive alerts for sepsis during the silent alert and active alert

	Silent alert August-December 2016 n = 1277	Active alert August-December 2018 n = 1457	Risk difference (95% CI)
Age in y (mean, IQR)	3.7 (1.6, 8.5)	3.6 (1.8, 8.6)	−0.05 (−0.48, 0.38)
Male	674 (52.8%)	745 (51.1%)	−1.6% (−5.4, 2.1)
White	511 (40.0%)	541 (37.1%)	−2.9% (−6.5, 0.7)
Hispanic	128 (10.0%)	163 (11.2%)	1.2% (−1.1, 3.5)
Complex care patient*	312 (24.4%)	379 (26.0%)	1.5% (−1.7, 4.8)
Emergency severity index†			
1	30 (2.4%)	22 (1.5%)	−0.8% (−1.9, 0.2)
2	540 (42.3%)	634 (43.5%)	1.2% (−2.5, 4.9)
3	509 (39.9%)	507 (34.8%)	−5.1% (−8.7, −1.4)
4/5	191 (15.0%)	291 (20.0%)	5.0% (2.2, 7.9)
Triage vitals			
Temp ≥38.5	605 (47.4%)	663 (45.5%)	−1.8% (−5.9, 1.9)
Tachycardia for age‡	511 (40.0%)	635 (43.6%)	3.6% (−0.1, 7.3)
Tachypnea for age‡	743 (58.2%)	790 (54.3%)	−4.0% (−7.7, −0.2)
Hypotension for age‡	23 (1.8%)	20 (1.4%)	−0.4% (−1.4, 0.5)
ED chief complaint			
Fever	717 (56.1%)	812 (55.7%)	−0.4% (−4.1 3.3)
Respiratory	254 (19.9%)	305 (20.9%)	1.0% (−2.0, 4.1)
Gastrointestinal	199 (15.6%)	221 (15.2%)	−0.4% (−3.1, 2.3)
Neurologic	80 (6.3%)	98 (6.7%)	−0.5% (−1.4, 2.3)
Other	168 (13.2%)	187 (12.8%)	−0.3% (−2.8, 2.2)
Mode of arrival			
Walk in	1071 (83.9%)	1257 (86.3%)	2.4% (−0.3, 5.1)
EMS	115 (9.0%)	99 (6.8%)	−2.2% (−4.2, −0.2)
Transfer	62 (4.9%)	75 (5.2%)	2.9% (−1.3, 1.9)
Positive blood culture§	18/505 (3.6%)	16/563 (2.8%)	−0.7% (−2.8, 1.4)
Alert type received¶			
ED SIRS alert	1154 (90.4%)	1360 (93.3%)	3.0% (0.9, 5.0)
ED sepsis alert	139 (10.9%)	139 (9.5%)	−1.3% (−3.6, 0.9)
ED severe sepsis alert	52 (4.1%)	53 (3.6%)	−0.4% (−1.9, 1.0)

SIRS, systemic inflammatory response syndrome; *EMS*, emergency medical services.
*As defined by Feudtner complex care codes.[20]
†Gilboy N, Tanabe T, Travers D, Rosenau AM. Emergency Severity Index (ESI): A Triage Tool for Emergency Department Care, Version 4. Implementation Handbook 2012 Edition, 2011.
‡As defined by sepsis screen algorithm used at this institution, Eisenberg et al. Performance of an Automated Screening Algorithm for Early Detection of Pediatric Severe Sepsis.
§Percentages calculated from total number of blood cultures sent.
¶Patient may receive more than 1 alert.

comorbidities that require antibiotics with every fever (eg, neutropenia, sickle cell disease), and patients who may have developed sepsis had they not received early antibiotics.

Antibiotic exposure is just one of the potential risks of false positive sepsis screens. Concerns have also been raised that patients who may have required little more than an antipyretic will now have higher rates of IV placement and IV fluid administration if they are flagged as potentially having sepsis. Our study, however, observed no increase in administration of IV fluid boluses after the alerts went live. Further supporting the idea that the sepsis screens did not lead to inappropriate resource utilization, neither ED LOS nor proportion of patients admitted to the hospital increased after introduction of the alert when adjusted for overall ED LOS and admission rate.

There are several limitations to this study. First, this is a single-center study of an academic pediatric ED using one available pediatric sepsis screening algorithm. The sepsis screening tool used in the study ED was also quite complex with EHR integration and real-time tracking of vital signs and laboratory results, as well as a 2-tiered alert system with a nursing screen. These results, therefore, may not be generalizable to other clinical settings or sepsis screening tools.

Second, in this study, 98.6% of all sepsis alerts were false positives, even higher than previously reported studies and higher than the previous published false positive rate for this particular sepsis tool at the study institution.[13] This is likely due to our strict definition of sepsis, as we used only encounters in which the clinician entered *the International Classification of Disease, Tenth Revision*, code for severe sepsis or septic shock or when the patient met formal criteria as set out by the International Pediatric Sepsis Consensus Conference. As a result, among our "false positives" may be children who were suspected of having sepsis but never met these strict criteria, children who would have developed severe sepsis if not for early recognition and treatment, or children who developed organ dysfunction after leaving the ED. In addition, this study did not address other potential adverse effects of an automated sepsis screening tool, such as alert fatigue or the possibility that clinicians may have lowered their clinical suspicion for sepsis when an alert did not fire and, therefore, paradoxically increased the risk of missing sepsis cases. Lastly, even though the 18-month gap period between the study groups was unavoidable based on when the alert system was initially tested and when it went live, it introduces the possibility that other unmeasured trends in sepsis care may

Table II. Association between silent and active alert on resource utilization in children with false positive sepsis alerts

	Silent alert August-December 2016 n = 1277	Active alert August-December 2018 n = 1457	aOR (95% CI)*
Received antibiotics after alert†	311/1152 (27.0%)	366/1328 (27.6%)	1.1 (0.9, 1.3)
Received IVF bolus after alert‡	294/989 (29.7%)	345/1184 (29.1%)	1.0 (0.8, 1.2)
Blood culture obtained after alert§	248/1020 (24.3%)	269/1163 (23.1%)	1.0 (0.8, 1.3)
Admitted to hospital	618 (48.4%)	632 (43.4%)	0.8 (0.7, 0.9)
Admitted to ICU	88 (6.9%)	98 (6.7%)	1.0 (0.7, 1.4)
Floor to ICU transfer within 24 h¶	14/477 (2.9%)	9/534 (1.7%)	0.5 (0.2, 1.2)
72-h ED discharge to representation**	55/659 (8.4%)	66/825 (8.0%)	0.9 (0.6, 1.4)
72-h ED discharge to admission**	18/659 (2.7%)	25/825 (3.0%)	1.1 (0.6, 2.1)
Mortality within 30 d	3 (0.23%)	4 (0.27%)	1.5 (0.3, 7.4)
			Median Difference (95% CI)
ED LOS (h)	4.6 (3.2-6.2)	4.9 (3.4-7.0)	0.4 (0.2, 0.6)
Hospital LOS for admitted patients (h)	70.6 (42.1-141.7)	70.3 (44.0-144.0)	−1.7 (−11.2,7.8)
Alive ICU-free d††	27.6 (24.0-28.7)	26.9 (22.1-28.5)	−0.6 (−2.0, 0.9)

*Controlling for age, sex, race, ethnicity, proportion of complex care patients, emergency severity index, arrival by transfer, triage vitals, and proportion with respiratory chief complaint.
†Patients who received antibiotics prior to the alert were excluded from these calculations.
‡Patients who received intravenous fluid prior to the alert were excluded from these calculations.
§Patients who received a blood culture prior to the alert were excluded from these calculations.
¶Only patients admitted to the floor were included in these calculations.
**Only patients discharged from the ED were included in these calculations.
††Number of days out of 30 days that a patient admitted to the ICU was not in the ICU.

have occurred during that time period that influenced our outcomes.

It will be important to assess if our study findings are replicated in other settings, such as general EDs, with other groups of clinicians, and with other sepsis screening algorithms. In addition, given the low positive predictive value of this and other sepsis screening algorithms, it will be crucial to continue to refine screening tools and processes to improve their specificity while maintaining or even increasing their sensitivity. Given the substantial overlap in vital signs and common laboratory tests such as white blood cell count between children with sepsis and those with nonlife-threatening infections, this likely means utilization of sepsis-specific biomarkers that are available at the point of care.

In summary, in this study of over 2700 pediatric ED encounters with false positive sepsis alerts, we found that the proportions of IV antibiotic and IV fluid bolus administration, department LOS, and the proportion of hospital admission did not change with the implementation of an automated, EHR-embedded sepsis screening tool. For ED clinicians, it seems the sepsis alert was one of many factors that influenced clinical decision making and the concerns for overtreating may not be founded. ■

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50 Years Ago in *The Journal of Pediatrics*

Advances in Neonatal Thyrotoxicosis

Wilroy RS, Etteldorf JN. Familial hyperthyroidism including two siblings with neonatal Graves' disease. J Pediatr 1971;78:625-32.

Neonatal thyrotoxicosis is a rare, potentially life-threatening condition if not treated early. In 1971, Wilroy et al reported a multigenerational family with hyperthyroidism, including multiple infants born with thyrotoxicosis.

The past medical history included the maternal grandmother's death during removal of a toxic goiter; her daughter had also developed a goiter and exophthalmos as a teen requiring propylthiouracil, Lugol's solution, and subtotal thyroidectomy. Subsequently, she was euthyroid when she delivered a premature infant who died in the neonatal period and then a stillborn infant with a goiter with her second pregnancy.

Her next 2 pregnancies resulted in premature infants, both with microcephaly, a small anterior fontanelle, significant tachycardia, and advanced bone ages. One had exophthalmos and the other a significant goiter. Both children continued to have symptoms of hyperthyroidism, despite propylthiouracil treatment. Developmentally, 1 child was reported to have minimal intellectual disability, and the other had significant developmental delay as an adolescent. Long-acting thyroid stimulator assays were unavailable when they were neonates, but detectable at ages 8 and 9 years, respectively. At the time, it was hypothesized that maternal long-acting thyroid stimulator crossed the placenta and caused the hyperthyroidism. It was thought to be a brief condition that self-resolved and very little was known on the long-term effects of this condition.

Fifty years later, our understanding of the pathogenesis of neonatal thyrotoxicosis, its implications, prevention, and management has advanced significantly. Neonatal thyrotoxicosis continues to be rare and commonly caused by maternal Grave's disease. However, maternal Hashimoto thyroiditis, and nonautoimmune etiologies like genetic mutations that activate the thyroid stimulator hormone receptor and in the stimulatory G protein in McCune-Albright syndrome are described. Now, pregnant women with Grave's disease receive screening for thyroid receptor antibodies. If elevated, serial fetal ultrasound examination is performed to evaluate for fetal tachycardia, bone maturation, and the presence of a goiter.[1] Pregnant women are closely followed and receive therapy with antithyroid drugs to prevent fetal hyperthyroidism. Infants at risk are screened and monitored closely, and those born with thyrotoxicosis immediately start treatment with methimazole, instead of propylthiouracil given the risk of hepatic failure.[1]

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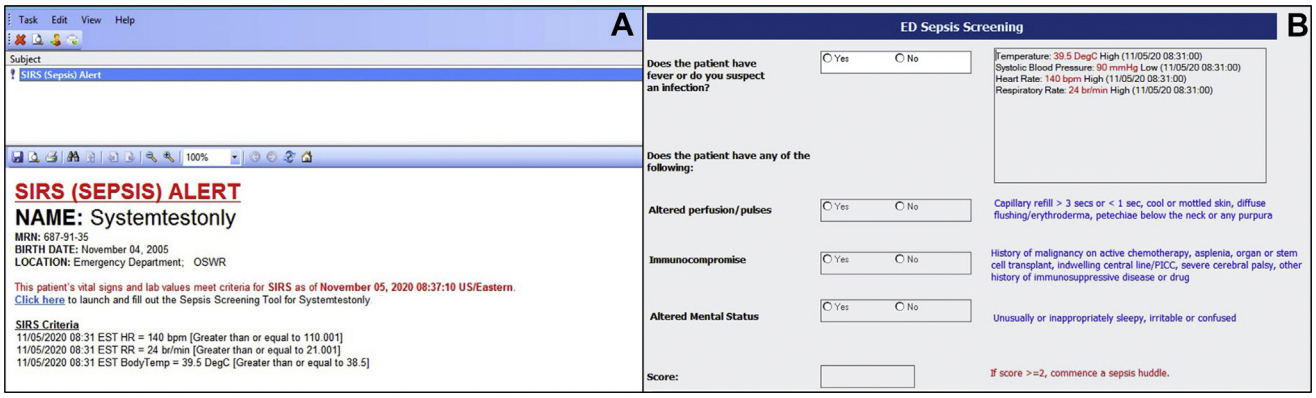

Figure 2. Screenshots of the **A,** pop-up alert and **B,** secondary screening form.

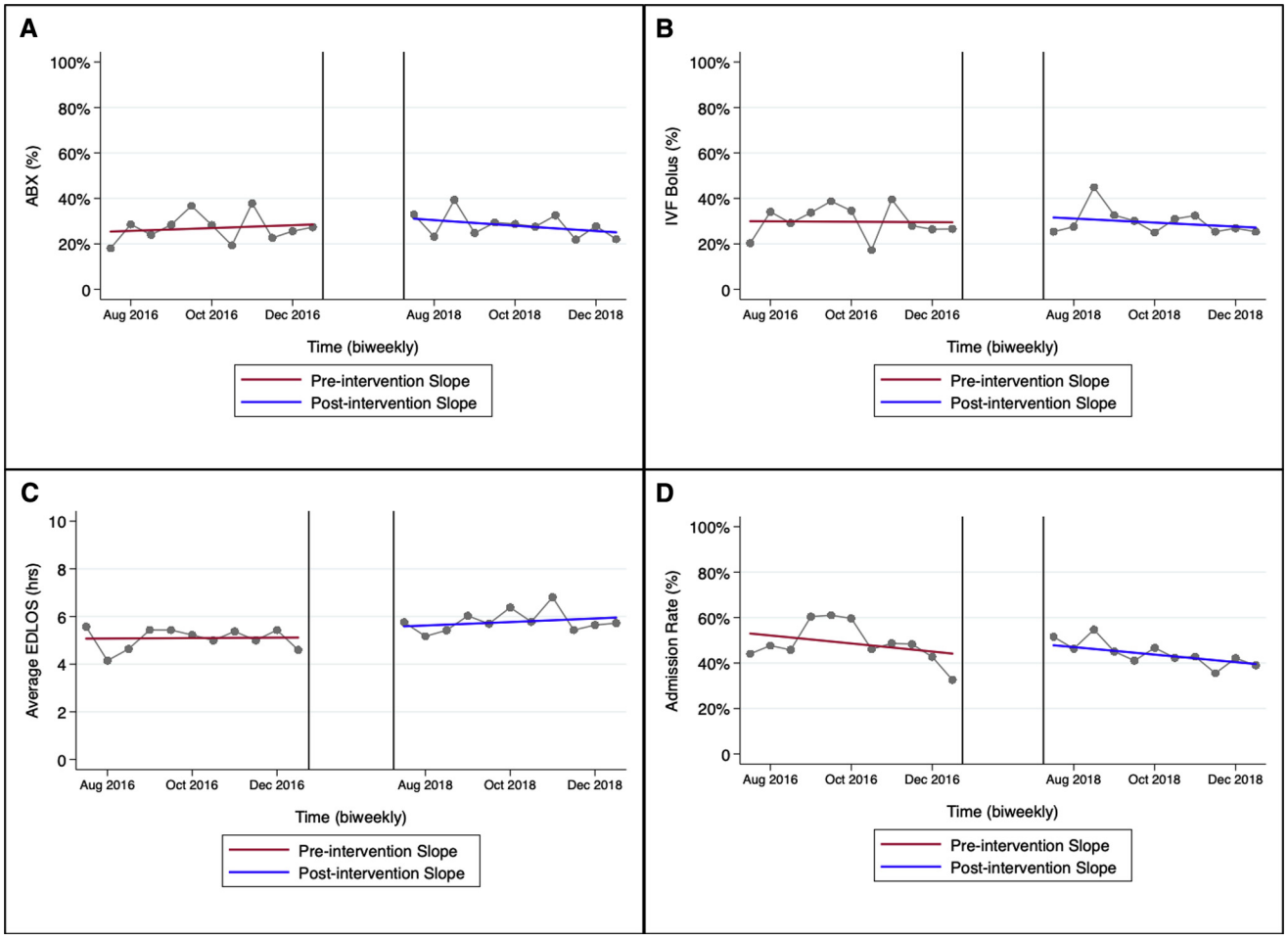

Figure 3. Interrupted time series analysis. **A,** Rate of IV antibiotic usage in 2-week intervals. Slope comparison OR 0.95 (0.9,1.0); Intercept comparison (level change) 0.7 (0.5, 1.0). **B,** Rate of IV fluid bolus usage in 2-week intervals. Slope comparison OR 1.0 (0.9,1.0); Intercept comparison (level change)1.1 (0.8, 1.7). **C,** Average ED LOS in 2-week intervals. Slope comparison OR 1.0 (1.0,1.0); Intercept comparison (level change) 0.9 (0.8, 1.0). **D,** Rate of hospital admission in 2-week intervals. Slope comparison OR 1.0 (0.9,1.1); Intercept comparison (level change) 0.8 (0.6, 1.2).