Machine Learning Used to Compare the Diagnostic Accuracy of Risk Factors, Clinical Signs and Biomarkers and to Develop a New Prediction Model for Neonatal Early-onset Sepsis

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Background: Current strategies for risk stratification and prediction of neonatal early-onset sepsis (EOS) are inefficient and lack diagnostic performance. The aim of this study was to use machine learning to analyze the diagnostic accuracy of risk factors (RFs), clinical signs and biomarkers and to develop a prediction model for culture-proven EOS. We hypothesized that the contribution to diagnostic accuracy of biomarkers is higher than of RFs or clinical signs.

Study Design: Secondary analysis of the prospective international multicenter NeoPInS study. Neonates born after completed 34 weeks of gestation with antibiotic therapy due to suspected EOS within the first 72 hours of life participated. Primary outcome was defined as predictive performance for culture-proven EOS with variables known at the start of antibiotic therapy. Machine learning was used in form of a random forest classifier.

Results: One thousand six hundred eighty-five neonates treated for suspected infection were analyzed. Biomarkers were superior to clinical signs and RFs for prediction of culture-proven EOS. C-reactive protein and white blood cells were most important for the prediction of the culture result. Our full model achieved an area-under-the-receiver-operating-characteristic-curve of 83.41% (±8.8%) and an area-under-the-precision-recall-curve of 28.42% (±11.5%). The predictive performance of the model with RFs alone was comparable with random.

Conclusions: Biomarkers have to be considered in algorithms for the management of neonates suspected of EOS. A 2-step approach with a screening tool for all neonates in combination with our model in the preselected population with an increased risk for EOS may have the potential to reduce the start of unnecessary antibiotics.

Key Words: early-onset sepsis, risk factors, clinical signs, biomarkers, antibiotic therapy

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Suspected early-onset sepsis (EOS) represents the main reason to start antibiotic therapy in late-preterm and term neonates within the first 3 days of life. A low threshold regarding start of therapy for suspected EOS traditionally has been justified by the higher mortality and morbidity associated with delayed initiation of antibiotic therapy.[1,2] In high-income countries, the incidence of culture-proven EOS and sepsis-related mortality in late-preterm and term neonates have significantly decreased.[3,4] Strategies for risk stratification and prediction of EOS remain inefficient and recent publications report up to over 100 neonates started on antibiotic therapy to capture one neonate with culture-proven EOS.[3,5] Evidence is growing that each day on antibiotics at the start of life may lead to perturbations of the individual microbiome with potential consequences for future health.[6,7] Currently, the sepsis calculator published by investigators

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of the Kaiser Permanente group in California is the most prominent algorithm using risk factors (RSs) and clinical signs (CSs) for prediction of EOS.[8]

In recent years, machine learning has started transforming diagnostics and decision making in medical sciences. The spectrum of machine learning goes from strongly human-guided methods to completely data-driven analyses.[9] In recent medical literature, there is a debate if machine learning methods compared with more traditional statistical methods, such as linear regression models, may achieve stronger predictive results.[10–14]

In 2017, we published NeoPInS, an investigator-initiated, multicenter randomized intervention study analyzing the impact of a procalcitonin (PCT)-guided algorithm regarding duration of antibiotic therapy for suspected EOS.[15] The database of NeoPInS includes 1710 neonates with antibiotic therapy. The aim of this article was to leverage the predictive power of machine learning methods to compare the predictive value of RFs, CSs and biomarkers and to develop a first version of a multivariable prediction model for culture-proven EOS. We hypothesized that the contribution to diagnostic accuracy of biomarkers is higher than of RFs or CSs.

METHODS

This is a secondary analysis of the NeoPInS study, a randomized controlled intervention study in 17 centers in The Netherlands, Canada, Czech Republic and Switzerland.[15] The local institutional review boards and the national ethical committees of each site approved the study. Written informed consent was obtained from all parents or caregivers. The trial was registered at Clinicaltrials.gov (NCT00854932). The report of the current study is according to the TRIPOD statement for transparent reporting of a multivariable prediction model for individual prognosis or diagnosis.[16]

Participants and Definition of Proven EOS

Neonates born after 34 completed weeks of gestation with antibiotic therapy due to suspected EOS within the first 72 hours of life participated. Suspicion of sepsis was defined as neonates with RFs, and/or CSs, and/or biomarker measurements possibly related to EOS. Of note, biomarker measurements without RFs or CSs were not part of the standard procedure in any of the participating units. The group of proven sepsis was defined as neonates with positive blood cultures and with duration of antibiotic therapy of at least 3 days or until death, whichever occurred first. Positive blood cultures with growth of skin flora or very atypical microbes for EOS and a shorter duration of antibiotic therapy than 3 days were included among the group without proven sepsis. RFs, CSs, biomarker measurements at start of antibiotic therapy and blood culture results were defined as key variables. Neonates with missing all key variables or unknown blood culture result were excluded.

Predictive Variables

RFs, CSs and biomarkers around the time-point start of antibiotic therapy were defined as primary predictive variables. RFs were defined as positive maternal group B streptococci (GBS) status, CSs of chorioamnionitis, premature rupture of membranes longer than 18 hours and gestational age <37 0/7 weeks. These RFs were used as dichotomized data (present/absent). CSs possibly related to infection included signs of respiratory distress, apnea, tachycardia or bradycardia, arterial hypotension or tissue hypoperfusion, hypothermia or hyperthermia, neurologic signs and abdominal signs. Assessed biomarkers were C-reactive protein (CRP), total white blood cell count (WBC) and thrombocyte count (TC). According to the protocol, PCT was not part of the measurement around the time-point start of antibiotic therapy. Nevertheless, in some study centers, PCT was measured at that time-point and the obtained PCT values were included in the prediction analysis. All biomarkers were measured in central laboratories and were included if the results were known within 6 hours from the time-point start of antibiotic therapy.

All variables were assessed as single variables and as subsets of variables regarding RSs, CSs and biomarkers. Other variables related to birth and generalizable for the total cohort were assessed in addition (ie, mode of delivery, Apgar scores). See Table 1 for a list of all variables.

Outcome

The outcome was defined as the predictive performance for culture-proven EOS with variables known around the start of antibiotic therapy; predictive importance was defined for both single variables and grouped variables (RFs, CSs and/or biomarkers). There are different definitions of culture-negative sepsis and most of them are using RFs, CSs and abnormal biomarker results.[17] These were the analyzed predictive variables and we wanted to use clear cases with a strict definition. Therefore, we focused just on culture-positive EOS.

Machine Learning

Machine learning was used to predict the result of the culture test based on the variables known at the start of antibiotic therapy. As input to the classifier, we have investigated several subsets of variables, grouped as follows: (1) all variables; (2) all variables excluding biomarkers; (3) biomarkers only; (4) RFs only; and (5) CSs only. Figure 1 provides an overview of these groups of variables as well as the outcome variable and ablations used for this study. Machine learning was used in form of a random forest classifier to predict the probability that a culture test will be positive or negative.[18] The random forest is a type of nonlinear classifier that consists of an ensemble of decision trees, each of which is a classifier that is trained on a different subset of data. Every tree is trained by maximizing the Gini impurity, an entropy measure that is used to decide which variable to split on in each step of building the tree. The predicted probability computed by the random forest is the average over the predictions of all decision trees that comprise the forest. Such a majority vote of classifiers trades off the bias, that is, the overspecialization of each tree, against the variance across the trees' predictions. As such, the random forest is an established machine learning method known for its strong predictive performance (especially on tabular data) and its robustness to overfitting.[18] The choice to use the random forest model for our analysis was affirmed in a recent publication comparing 4 different models (logistic regression, random forest, support vector machine and a single-hidden layer neural network) to predict serious bacterial infections in young febrile infants showing that the random forest model showed the highest accuracy.[13]

To assess the relative effect of a variable on the prediction, the variable importance was computed. For a decision tree, variable importance measures the relative effect of a variable as the Gini importance, that is, the total decrease in node impurity weighted by the fraction of samples the variable contributes to. For the random forest, variable importance is defined as the average over the variable importance of all trees. All machine learning methods have hyperparameters, that is, control knobs that can be adjusted to tune the performance of the system for the task at hand. For the random forest, we used the default configuration provided by the scikit-learn library (v0.21.3) and increased the number of trees to 300, to reduce the variance of the estimation.

TABLE 1. Baseline Characteristics and List of All Variables Used in Analysis for All Patients Included and Culture-proven Sepsis Cases

	All Included Neonates	Sepsis-proven	Used as Variable for ML
	n = 1685	n = 28	
Sex			
Male	989 (58.7%)	15 (53.6%)	Yes
Female	696 (41.3%)	13 (46.4%)	
Gestational age, wks	39.6 (37.3–40.6)	39.9 (37.7–40.9)	Yes
Birth weight, kg	3.4 (2.9–3.8)	3.4 (3.0–3.7)	Yes
Mode of delivery			
Spontaneous vaginal	802 (47.6%)	17 (60.7%)	Yes
Vacuum or forceps	262 (15.6%)	4 (14.3%)	Yes
Primary cesarean section	141 (8.4%)	2 (7.1%)	Yes
Secondary cesarean section	477 (28.3%)	5 (17.9%)	Yes
Epidural anesthesia	695 (41.25%)	5 (17.9%)	Yes
Meconium stained fluids	461 (27.4%)	10 (35.7%)	Yes
Intrapartum antibiotics	802 (47.6%)	4 (14.3%)	Yes
Arterial cord pH	7.23 (7.16–7.29)	7.25 (7.19–7.33)	Yes
APGAR score			
1-min postpartum	8 (6–9)	8 (7–9)	Yes
5-min postpartum	9 (8–10)	9 (8–10)	Yes
10-min postpartum	9 (8–10)	9 (8–10)	Yes
RFs			
Group B streptococcus carriage	243 (14.4%)	7 (25.0%)	Yes
Chorioamnionitis	324 (19.2%)	4 (14.3%)	Yes
PROM > 18 h	393 (23.3%)	4 (14.3%)	Yes
Gestational age < 37 wks	347 (20.6%)	6 (21.4%)	Yes
Clinical signs			
Respiratory distress/apnea	1012 (60.1%)	24 (85.7%)	Yes
Tachycardia or bradycardia	177 (10.5%)	11 (39.3%)	Yes
Arterial hypotension/poor perfusion	156 (9.3%)	12 (42.9%)	Yes
Hypothermia or hyperthermia	278 (16.5%)	11 (39.3%)	Yes
Seizure/floppy infant/irritability/lethargy	165 (9.8%)	8 (28.6%)	Yes
Vomiting/feeding intolerance/ileus	114 (6.8%)	1 (3.6%)	Yes
Duration of antibiotic therapy, h	60 (45–144)	192 (160–300)	
Biomarker values at start of antibiotic therapy			
WBC, n	1571 (93.2%)	24 (85.7%)	
WBC, 10^9/L	18.3 (13.3–23.2)	8.0 (4.5–12.4)	Yes
CRP, n	1519	24 (85.7%)	
CRP, mg/L	1.0 (1.0–6.0)	24.4 (5.6–44.4)	Yes
PCT, n	292	2 (0.7%)	
PCT, ng/L	0.29 (0.15–1.33)	16.3 (9.1–23.4)	Yes
Platelets, n	1539 (91.3%)	25 (89.3%)	
Platelets, 10^9/L	229 (183–274)	180 (125–223)	Yes
Blood culture positive	30 (1.8%)	28 (100%)	
Group B streptococcus	21 (1.2%)	21 (75%)	
Escherichia coli	3 (0.2%)	3 (10.7%)	
Other bacteria	4 (0.2%)	4 (14.3%)	
Contamination*	2 (0.1%)	0	

All values are shown as n (%) or median (IQR).

*Contamination: Positive blood cultures with growth of skin flora or very atypical microbes for EOS and a duration of antibiotic therapy of <3 days.

PROM indicates premature rupture of membranes.

Statistics

We evaluated the prediction of culture-proven EOS with a repeated, stratified 5-fold cross-validation, with 10 different splits to reduce the variance due to outliers given the relatively small number of culture-positive patients.[19] Stratification was used to match the frequency of culture-positive cases in the overall population. Cross-validation is a default model validation method to compute averages and SDs over different partitions of the cohort. In our case, each partition or fold represents a split into 80% training data used to fit the model and 20% test data for evaluation. The predictive performance of the random forest was measured in area-under-the-receiver-operating-curve (AUROC) and area-under-the-precision-recall-curve (AUPRC). Precision is equal to the positive predictive value, whereas recall is equal to sensitivity. To study the effect of individual variables for the prediction, we computed the variable importance and performed a backward variable selection for each group of variables.

RESULTS

Sixteen hundred eighty-five neonates treated for suspected infection with key variables available were analyzed. Twenty-five neonates from the original cohort of the NeoPInS cohort had to be excluded due to missing key variables. Twenty-eight (1.7%) neonates had a proven infection. Table 1 gives an overview of baseline characteristics of all included patients and all variables used for analysis. The predictive performance of the random forest achieved 83.4% (±8.8%) AUROC and 28.4% (±11.5%) AUPRC compared with the random classification baselines of 50% AUROC and 1.5%

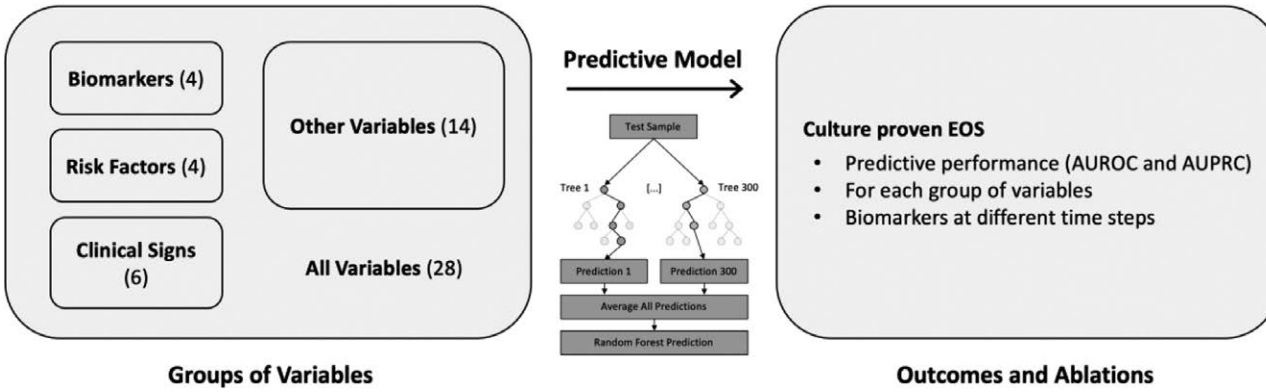

FIGURE 1. Overview of analysis using machine learning (random forest) to develop a model for the early prediction of culture-proven EOS. In parentheses, we report the number of variables in the respective group; all 28 variables are listed in Table 1. Note that all predictive variables were measured before the result of the culture test was known at the start of the antibiotic therapy. Apart from the primary outcome (predictive performance of the model for culture-proven EOS) analyses without a specific variable investigated the predictive performance for each clinically relevant group of variables.

AUPRC, respectively (Fig. 2). Biomarkers contributed significantly to the predictive performance, as a model without biomarkers resulted in an AUROC of 73.3% (±10.3%) and an AUPRC of 15.7% (±10.1%). The assessed predictive value of the subsets of variables RFs, CSs and biomarkers showed AUROC of 43.9%, 61.5% and 73.2%, respectively. In terms of AUPRC, the scores were 1.7% for RFs, 12.7% for CSs and 17.6% for biomarkers, respectively (Fig. 2).

Analysis of the individual variable importance is shown in Figure 3. The biomarker CRP had the highest impact regarding prediction of culture-proven EOS followed by WBC. RFs were not in the top 15 predictor variables. Within the subset of CSs, cardiovascular signs showed the highest contribution to diagnostic accuracy.

DISCUSSION

Using machine learning allowed us to analyze the predictive accuracy of RFs, CSs and biomarkers in a large dataset of a high-quality international prospective trial. With help of this analysis, we developed a first version of a new prediction tool for early detection of culture-proven EOS in a preselected population of late-preterm and term neonates suspected for EOS and therefore started on antibiotic therapy. Our full model achieved an AUROC of 83% and an AUPRC of 28% and identified biomarkers as superior to CSs and RFs for prediction of culture-proven EOS around the time-point of start of antibiotic therapy. CRP and WBC were most important for the prediction of the culture result. The predictive performance of the model with RFs alone was comparable with random.

Overall, clinicians are valuing biomarkers as very limited in their performance and timely availability regarding the decision to start antibiotic treatment for suspected EOS.[20] Newman reported in a huge retrospective cross-sectional study that the positive likelihood ratio of leukocytopenia regarding culture-proven EOS increased within the first hours of life to over 80 after 4 hours.[21]

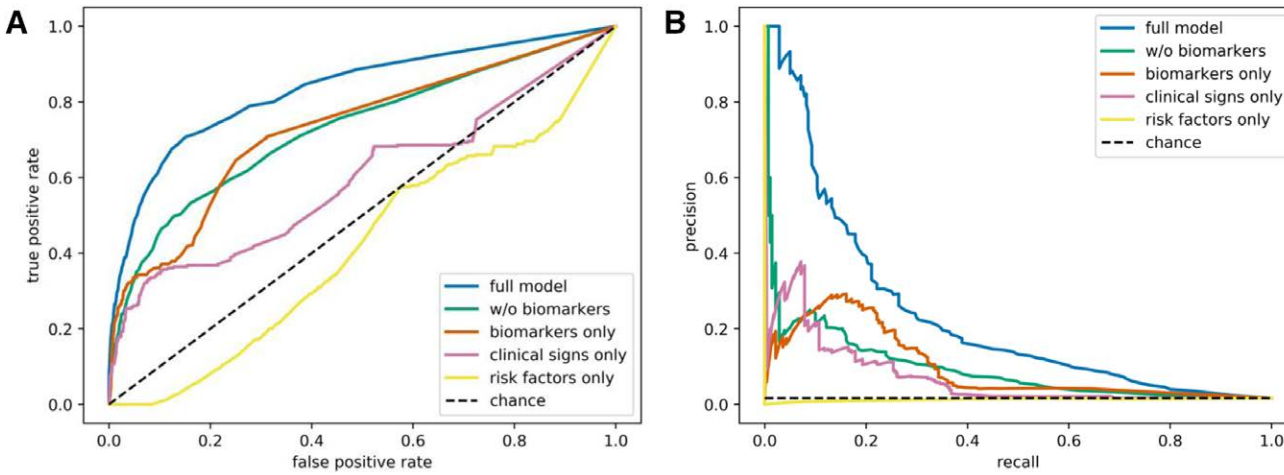

FIGURE 2. Predictive performance of the random forest. Receiver operating characteristic curve (A) and precision-recall curve (B) for the full model, the full model without biomarkers, and the respective subsets of variables. AUC values in %. While biomarkers contribute significantly to the prediction of culture-positive EOS, the predictive performance of clinical signs and especially RFs are not significantly better than chance. The provided ROC- and PR-curves are showing the tradeoff between various metrics for different decision thresholds and allow to answer, for instance, the question "what sensitivity can be achieved for a specific PPV." Precision indicates positive predictive value; recall, sensitivity.

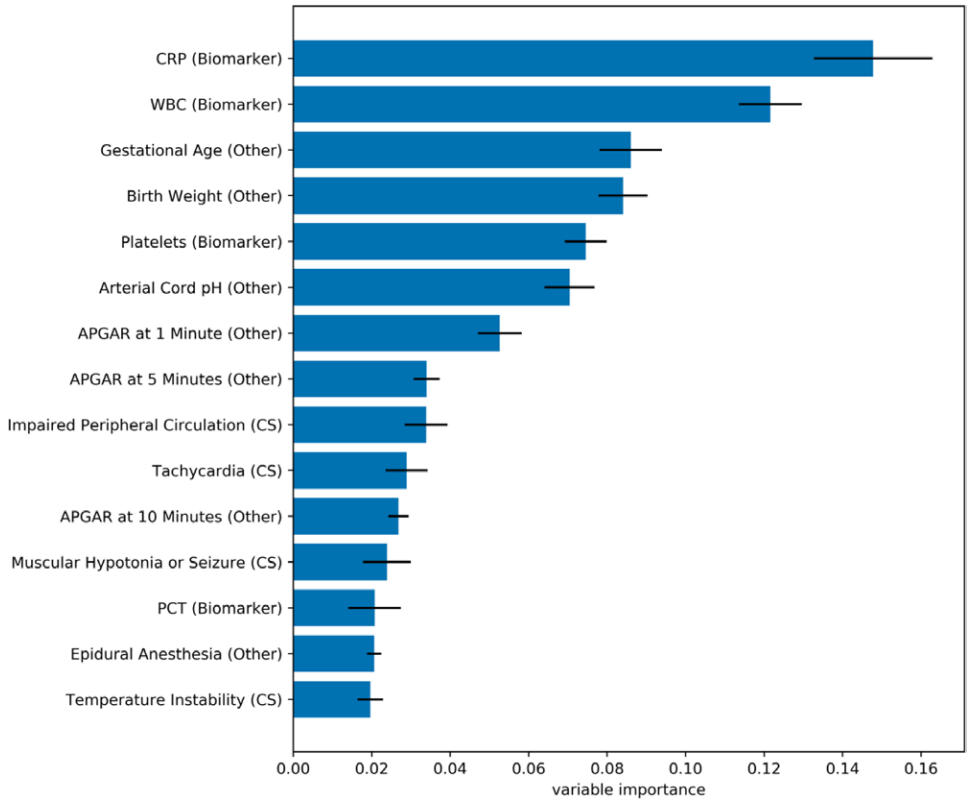

FIGURE 3. The 15 variables with largest variable importance (larger is better), normalized such that values sum to 1 over all variables. Bars depict variable importance values averaged over 5 cross-validation folds, whereas lines depict 1SD, respectively. In parentheses, it is denoted if the variable belongs to the group of biomarkers (Biomarker), CSs, RFs or other variables (other). full color online

This is in line with our findings. Nevertheless, the overall literature is in line with the clinician's assessment and a recently published review reported a moderate accuracy between 80% and 90% for CRP and PCT for diagnosis of neonatal sepsis.[22] But biomarkers performed best in our model. One potential explanation for this discrepancy would be an overfitted model. However, we have taken serious precautions against overfitting by evaluating the model on data that was not used for training the model. In particular, we used stratified cross-validation and we reported the variance across folds for each model. The lower granularity of our dichotomized data regarding RFs and CSs (present/absent) compared with the biomarker data may result in lower predictive performance and may give another potential explanation. But additionally, all neonates were suspected to have EOS because of RFs, and/or CSs, and/or abnormal biomarkers. Therefore, our cohort was preselected and CSs were most prominent. Nevertheless, we may ask what is the overall predictive value of RFs and clinical signs regarding diagnostic accuracy for EOS? Whereas biomarkers were far from being perfect predictors, we have to compare them with the diagnostic accuracy of RFs and CSs.

In a large case-control study, the highest maternal intrapartum temperature showed the highest predictive value of all RFs in a continuous temperature-dependent fashion for culture-proven EOS.[23] Maternal GBS status, duration of rupture of membranes and prematurity of 34–36 weeks of gestational age showed ORs between 1 and 5, which is moderate in a setting with a low incidence of culture-proven EOS. Various networks of perinatal care changed their practice and studies implementing the strategy to use RFs as guidance in which neonates have to be observed closely, but not as guidance regarding antibiotic treatment showed promising results with a very low rate of morbidity and mortality.[24–27] This is in line with our results that a model with RFs alone was comparable with random. But further studies are needed to prove the safety of this approach.

CS possibly related to neonatal EOS are very nonspecific.[1] Respiratory distress may have many different reasons of which EOS is seldom the only one.[8] Ohlin et al[28] reported in a prospective cohort study no impact of oxygen requirement or tachypnea on the positive likelihood ratio for culture-proven EOS. Only arterial hypotension or impaired peripheral circulation had a small, but significant impact. This is in line with our findings showing cardiovascular instability as the best predictor among the CSs studied. In summary, the literature regarding CSs and neonatal EOS shows that the negative predictive value is very high when neonates exhibit no CSs, whereas the positive predictive value in the presence of CSs for culture-proven EOS is limited.[29,30] In a recently published quality improvement study, Capin et al[31] reported no missed EOS cases after introduction of a new management protocol requesting not to start antibiotic therapy just based on respiratory distress. The high incidence of respiratory distress with a low predictive performance for EOS may be the main cause for low predictive performance of CSs in our model.

The sepsis calculator is the most validated algorithm using RFs and CSs of neonates.[8] Various studies reported a benefit in terms of reduced exposure to antibiotics within the first week of life.[32] However, in a recently published individual patient meta-analysis,

only around 40% of neonates with culture-proven EOS were initially assigned (strong consideration) for antibiotic treatment. This proportion increased to 61% at the age of 12 hours of life. The reported sensitivity of the sepsis calculator for culture-proven EOS is dependent on a priori EOS incidence rate and treatment thresholds.[33] This is true as well for our model: Sensitivity will go up if we accept a higher proportion of treated neonates without culture-proven EOS (Fig. 2). If we accept a treatment of 50 neonates to capture one neonate with culture-proven EOS (precision of 2%), the sensitivity of our model is around 80%. It is important to realize that an initial delay in treatment does not equal a worse clinical outcome. However, it makes clear that vigilance is required for all infants, despite the risk estimate—probably true for every neonatal sepsis prediction tool in the future.

In contrast to the sepsis calculator, our new model is applied in a preselected population at the moment of start of antibiotics, and does include biomarkers. Our analysis demonstrates in that particular clinical phase, biomarkers may carry the most additional value. It also shows that using machine learning, further discrimination between high- and low-risk infants is possible, and therefore, further reduction of overtreatment may be possible. Therefore, a combined application of the sepsis calculator with our new model has to be considered. As the sepsis calculator is highly dependent on clinical observation, it is similar to a population preselected by healthcare workers using serial examinations.[33] Studies of approaches using serial examinations are increasingly conducted, with promising results.[24,25,27] This approach may be combined with our new model as well.

The relatively small number of positive blood cultures represents the main limitation of this study. It leads to a high variability in the classification of performance. Second, we analyzed the predictive performance only for culture-proven EOS. Culture-negative EOS is highly contradictory within the literature.[17,34] Nevertheless, culture-negative EOS may exist and antibiotic treatment may be beneficial for some neonates.[35] Besides, the dataset was limited to the variables collected for NeoPInS with RFs and CSs known only as dichotomized data (present/absent), with biomarkers limited to CRP, WBC and TC and only a small number of PCT measurements around the starting point of antibiotic therapy. RFs used as continuous data such as exact duration of prolonged rupture of the membranes in hours as applied by the group of Kaiser Permanente may result in better predictive performance.[8] Similarly, CSs including severity or duration of CSs may result in better predictive performance as well. Therefore, our current model is just the first step in the development of a new prediction tool. It needs to be validated and refined in an iterative process.[11,14] Our results cannot be transferred to a setting with a high burden of EOS or with a high sepsis-related mortality. In addition, for implementation into clinical practice an easy-to-use and data safe human–machine interface is required.[10,11] The time delay to get biomarker results back limits the use of our model and the development of point-of-care measurements with availability of accurate biomarker results within a short timeframe is mandatory for implementation. Neonates presenting with evident clinical sepsis always have to be started immediately on antibiotic treatment and biomarker results should have no impact on this decision.

We conclude that biomarkers have to be considered in future analyses and algorithms for management of late-preterm and term neonates suspected of EOS. A 2-step approach with a screening tool for all neonates (unselected population) in combination with our model in the preselected population of neonates with an increased risk for EOS may have the potential to reduce start of unnecessary antibiotics. Timely available biomarkers results are mandatory and development of point-of-care measurements are urgently needed. In addition, future studies are needed to validate and refine the first version of our model. Accurately defined CSs and new biomarkers have to be tested to get the highest possible prediction performance.

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Current Abstracts

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COVID-19-Associated Mucormycosis—Arkansas, July–September 2021

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During September 17–24, 2021, 3 clinicians independently notified the Arkansas Department of Health (ADH) of multiple patients with mucormycosis after a recent diagnosis of COVID-19. To provide data to guide clinical and public health practice, ADH coordinated a statewide call on October 11, 2021, to infection preventionists for COVID-19-associated mucormycosis cases. A case of mucormycosis was defined as laboratory identification of Mucorales by culture, histopathology, or polymerase chain reaction in a patient with a clinical diagnosis of invasive mucormycosis. Cases were considered COVID-19-associated if the patient received a positive reverse transcription-polymerase chain reaction or antigen test result for SARS-CoV-2 (the virus that causes COVID-19) during the 60 days preceding the mucormycosis diagnosis.

Ten COVID-19-associated mucormycosis cases that occurred during July 12–September 28, 2021, were reported to ADH by 6 hospitals. Nine patients lived in Arkansas, with patients representing each of the state's 5 public health unit regions; 1 patient lived in a neighboring state. Among all 10 patients, the median age was 57 years (range, 17–87 years). All patients were non-Hispanic White persons, 7 were male, 1 had a history of organ transplantation, and 1 had a history of traumatic injury at the body site where mucormycosis later developed.

Eight patients had diabetes; among these, the median hemoglobin $A1_c$ was 8.6% (range = 6.0%–14.3% [normal < 5.7%]). Mucormycosis clinical signs and symptoms included those that were rhino-orbital (4 patients, including 3 with cerebral involvement), pulmonary (3), disseminated (2), and gastrointestinal (1).

The median interval from COVID-19 diagnosis to the first positive test result for mucormycosis was 18.5 days (range = 6–52 days). None of the patients had been vaccinated against COVID-19. COVID-19 treatment included supplemental oxygen therapy (8 patients), invasive mechanical ventilation (5), corticosteroids (9), tocilizumab (2), and baricitinib (2). Five patients received surgical treatment to excise mucormycosis-affected tissue. Six of the 10 patients died during hospitalization or within 1 week of discharge.

Comment: Mucormycosis is an uncommon but severe invasive fungal infection caused by molds in the order Mucorales. Mucormycosis typically affects persons with immunocompromising conditions, such as hematologic malignancy, stem cell or solid organ transplantation, or uncontrolled diabetes. The emergence of COVID-19-associated mucormycosis has been described in other parts of the world, including India (Joshi S, et al *Emerg Infect Dis* 2022; 28: 1–8) and Honduras (Mejia-Santos H, et al *Morbid Mortal Wkly Rep* 2021; 70: 1747–1749) but has been infrequently reported in the United States. COVID-19 might increase mucormycosis risk because of COVID-19-induced immune dysregulation or associated treatments such as corticosteroids and immunomodulatory drugs (eg, tocilizumab or baricitinib) that impair host defenses against molds.

Because of the severity of mucormycosis, it is important that clinicians maintain a high index of suspicion for COVID-19-associated mucormycosis, including in patients without severe immunocompromising conditions. Mucormycosis treatment guidelines recommend prompt antifungal therapy and surgical intervention to improve outcomes. Maintenance of glycemic control in patients with diabetes, guideline-based use of corticosteroids for COVID-19 treatment, and vaccination against COVID-19 should be encouraged.