Original Article

Diagnostic value of superficial cultures for late-onset sepsis

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ABSTRACT

Background: Late-onset sepsis (LOS) is associated with poor outcome and one of the prevalent causes of death in preterm population; hence, there is always a need for early prediction of sepsis. The performance of routine superficial swab culture is one of the strategies for the early prediction and may help in the selection of appropriate empirical antibiotics. **Objective:** The purpose of the study is to evaluate the diagnostic value of superficial swab cultures for LOS. **Methods:** We conducted a retrospective cohort study (November 2015-October 2016) in a tertiary neonatal intensive care. Inclusion criteria were preterm infants with gestational age ≤34 weeks with a diagnosis of sepsis (culture-positive and culture-negative clinical sepsis). In our unit, weekly surveillance swab cultures (skin swab, mouth swab, nasopharyngeal aspirate, and umbilical surface swab) are taken from all admitted neonates, and usually, no interventions are carried out based on these culture results. We excluded infants with surgical diagnosis/congenital anomalies and infants with early-onset sepsis. **Results:** After exclusion, there were 38 preterm infants fulfilling our inclusion criteria; among them, there were 108 LOS episodes. Blood culture was positive in 33 episodes, and Staphylococcus epidermidis (21%) was the most common organism cultured. In our study, superficial swab cultures had a very low diagnostic value, as sensitivity (42.9%), specificity (28.7%), predictive values, and likelihood ratio that all the estimations were low. **Conclusions:** Superficial swab cultures are associated with low diagnostic value for LOS. Superficial swab culture may be used surveillance of colonizing organism in the neonatal unit and provides antibiotic sensitivity pattern.

Key words: *Neonates, Sepsis, Superficial culture*

Globally, sepsis is one of the prevalent causes of death in neonates, particularly in the preterm population [1-5]. With advances of neonatal intensive care and improvement in respiratory care, there is a significant reduction in respiratory mortality, but there is no significant change in mortality due to sepsis [6]. Apart from the increasing mortality, sepsis is also associated with adverse neurodevelopmental outcome [7,8]. With rapidity of progression of the clinical picture and associated poor outcome, there is always a need for early prediction and intervention of sepsis. The performance of routine superficial swab culture is one of the strategies for the early prediction and may help in selection of appropriate empirical antibiotics [9-10]. This is based on the hypothesis that superficial colonization precedes invasive infection. The purpose of the study is to evaluate the diagnostic value of superficial cultures for neonatal sepsis.

METHODS

We conducted a retrospective study in a tertiary neonatal intensive care unit (NICU) for 1 year (November 2015-October 2016). We used combined neonatal national database and microbiology database for identification of potential subjects. Inclusion criteria were preterm infants with gestational age ≤34 weeks with a diagnosis of late-onset sepsis (LOS) (>72 h of birth); both culture-positive bacterial sepsis and culture-negative clinically suspected LOS (any episode of sepsis requiring blood culture with clinical features suggestive of sepsis). We defined early-onset sepsis with the onset of sepsis within 3 days of life, and we excluded these infants, as it will reflect perinatal transmission. We excluded preterm infants with a surgical diagnosis and congenital anomalies, as these infants are higher baseline risk for sepsis. Superficial culture is defined as cultures taken from any surface (skin swab, throat/mouth swab, nasopharyngeal aspirate, nasogastric, umbilical surface swab, ear swab, and endotracheal aspirate [intubated infants]) and not from invasive sites (blood, urine, cerebrospinal fluid, pleural, and ascitic fluid). For the purpose of the study, these swab cultures are classified as "Superficial swab cultures". If the blood culture has more than one organism, then based on clinical discretion, it was labeled as "contaminant" and excluded from the analysis. This project was started as an audit, and the approval was obtained from the hospital audit committee.

Unit Practice

Our NICU is a perinatal center in the west of Scotland region with approximately 8000 deliveries every year. We have approximately 600 intensive care admissions per year, and the common diagnosis for admission includes prematurity, sepsis, hypoglycemia, cardiac malformation, and infants with surgical pathologies. Our unit is staffed by junior level trainees, senior trainees, neonatal nurse PR actioners, neonatal nurses, neonatal midwives, and consultants. Weekly, surveillance swab cultures are taken from all admitted neonates, and usually, no intervention is carried out based on these culture results. In our unit, we use vancomycin and gentamicin as the first line of empirical antibiotics for the episodes of LOS.

Data Collection and Analysis

We collected the following data: demographics including sex, birth weight, gestational age, corrected gestational age at the time of sepsis episode, blood culture organism, and superficial swab culture results. We used descriptive statistics for the population characteristics. Categorical variables are presented as proportions, whereas numerical variables are presented as mean (standard deviation) for normally distributed data or median (interquartile range) for skewed data as appropriate. Superficial swab cultures taken at the week of sepsis episode (date of blood culture taken) is used for analysis. We calculated sensitivity, specificity, predictive value, and likelihood ratio of superficial culture for LOS (R Commander Version 2.2-4). True positive (TP) is defined as both blood culture and superficial swab culture growing the same organism. False positive is defined, when the superficial culture is positive with negative blood culture or when the organism is different from both cultures. False negative is defined when blood culture is positive and superficial culture is negative. True negative (TN) is defined when both cultures are negative. Patient identifiers were removed from all data before analysis. We used STROBE checklist for the observational studies for reporting.

RESULTS

During the study period, we had a total of 1427 admissions. After exclusion of surgical diagnosis/congenital anomalies, term admissions, and early-onset sepsis, there were a total of 38 preterm infants (gestational age 34 weeks) with a diagnosis of LOS. Among these 38 infants, there were a total of 108 LOS episodes. Study demographics are shown in Table 1. Blood culture was positive in 33 episodes. Staphylococcus epidermidis (21%) was the most common organism cultured, followed by Staphylococcus capitis (18%) and Coagulase-negative Staphylococci (not identified to species level) (15%). In our study, superficial swab cultures had a very low diagnostic value, as sensitivity, specificity, predictive values, and likelihood ratio that all the estimations were low (Table 2). In the TP cases (n=9), swab cultures were obtained from endotracheal aspirate (n=4), mouth/throat swab (n=4), and gastric aspirate (n=1). In all these episodes, vancomycin and gentamicin were used, as the initial choice of antibiotics and the swab cultures did not influence the choice of antibiotics.

Table 1: Baseline characteristics of the study population (GA ≤34 weeks)

Characteristic	Results (n=38)
Mean gestational age at birth (±SD*)	29.5 weeks (±2.3)
Mean corrected gestational age at the time of sepsis (±SD)	31.5 weeks (±3.3)
Mean birth weight (±SD)	1124 g (±162)
Male sex	18 (47.36)
Blood culture positive	33 out of 108 late onset sepsis episodes (30.5%)

*SD: Standard Deviation

Table 2: Diagnostic value of superficial cultures

Parameter	Estimation (%)	95% (lower CI-upper CI)
Sensitivity	42.9	21.8-66
Specificity	28.7	19.5-39.4
PPV	12.7	6.0-22.7
Diagnostic accuracy	0.31	0.23-0.41
Negative predictive value	67.6	50.0-82
Likelihood ratio of a positive test	0.60	0.36-1.0
Likelihood ratio of a negative test	1.98	1.21-3.26

CI: Confidence interval, PPV: Positive predictive value

DISCUSSION

In a large study of 99,796 very low body weight infants with suspected LOS, blood culture was positive only in 8.9% of the cases [5]. New evidences are emerging regarding non-bacterial causes of sepsis. In a prospective study by Ronchi et al., 8% had respiratory virus detected out of 100 infants evaluated for LOS [11]. In the NICU setting, fungal infections, most commonly involving *Candida* spp., are more frequently associated with LOS, with an incidence inversely proportional to the estimated gestational age and birth weight. The incidence of *Candida* species early-onset neonatal sepsis in NICUs has been reported to be 1.4% [1]. In our study, it is possible that some sepsis episodes could be due to non-bacterial reasons. Even though predictive values are dependent on the disease prevalence in a setting, sensitivity, specificity, and likelihood ratios, all the estimations are independent of disease prevalence and should be applicable to other settings.

The probability of superficial culture in diagnosing/ruling out LOS is extremely low as likelihood ratio of a positive test <1 and likelihood ratio of a negative test >1. Another measure of diagnostic effectiveness is "diagnostic accuracy," expressed as a proportion of correctly classified subjects (TP+TN) among the total number of subjects, and it is dependent on the disease

prevalence. In our study, 34 (TP+TN) were correctly classified among 108 sepsis episodes providing a low diagnostic accuracy. In our study, for all the suspected episodes, vancomycin and gentamicin were used, which would cover adequately both coagulase-negative Staphylococci and/or Gram-negative organisms.

Berrington et al. had contrary findings, and they reported that superficial cultures had high sensitivity (74%), low specificity (38%), and low negative predictive value (47%). However, in their study, the prevalence of sepsis was high (46%), and they included all the cultures taken within the first 2 weeks [6]. Shenoy et al., in a study to determine the value of superficial cultures in the diagnosis of neonatal sepsis, reviewed 63 babies who were admitted with suspected sepsis. A total of 369 cultures were obtained from these babies, 252 (68.29%) superficial and 171 (31.70%) deep cultures. Of the 369 cultures, 225 (60.97%) were positive for pathogens, which included *Staphylococcus aureus*, *Klebsiella* sp., *Escherichia coli*, Group B *Streptococcus,* and *Enterococcus faecalis*. All superficial cultures obtained during the study on each patient were simultaneously compared with the deep cultures by antimicrobial sensitivity method. They posited that the practice of superficial cultures could be useful to predict the pathogenic organisms causing invasive disease [9].

In another study, analyzing the cost benefit analysis of the superficial cultures, Isabel et al. reported that cost of surface culture was high and only in 25% of the time did it influence a therapeutic decision [12]. Zuerlein et al. in a review of 66 neonates with early-onset sepsis also concluded that superficial cultures did not influence antimicrobial decision-making [13]. With poor diagnostic value and high cost involved with superficial swab cultures in diagnosing/predicting LOS, this practice is of very low-cost benefit value. This might lead to the inadvertent use of antibiotics just based on swab cultures. In an Egyptian study of high-risk neonates (predominantly preterm), Badawy et al. reported sepsis in 70 of 101 neonates developed sepsis (69.3%). The incidence of LOS was 19.8%, and the most prevalent organism recovered from blood culture was *Klebsiella* (40%), followed by CONS (20%), *S. aureus* (15.7%), and Enterobacter (15.7%). Throat and ear swabs correlated with the cultures in 20% of sepsis cases. They also concluded that superficial swabs were of limited value in diagnosing neonatal sepsis [14].

Choi et al. evaluated 497 preterm infants <33 weeks gestational age and within 72 h of chronological age, and the sensitivity, specificity, and Positive predictive value (PPV) of skin cultures were analyzed among 3,765 blood-skin culture pairs. The overall sensitivity, specificity, and PPV were 16%, 38%, and 5%, respectively. While their study population was similar to ours, they were assessing early-onset sepsis [15]. Another important aspect of superficial swab culture is for surveillance of colonizing organism in the neonatal unit. Positive superficial culture swab results can represent colonization, provides antibiotic sensitivity and resistance pattern, and may aid in strategies for infection control in the unit.

Drawbacks of our study are its retrospective method, and we have not included clinically presumed sepsis (based on clinical features alone)**.** We did not perform typing or molecular testing to verify whether the organism isolated from swab culture and the blood cultures were of the same strain of species. Another inherent problem with blood culture is the technique of blood sampling, volume of the blood, and culturing method. Even with the best technique, blood cultures are positive only in the certain percentage of neonates.

CONCLUSION

Superficial swab cultures are associated with low sensitivity, predictive value, and lower likelihood ratio, and it did not influence the choice of antibiotics for LOS.

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