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Blood Culture Positivity and Adverse Outcomes among Neonates with Jaundice in a Resource-Limited NICU: Implications for Antibiotic Stewardship

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ABSTRACT

Background: Neonatal jaundice is a common cause of admission to neonatal intensive care units (NICUs), particularly in low-resource settings. Because jaundice may be an early manifestation of neonatal sepsis, empiric antibiotic therapy is frequently initiated, often in the absence of microbiological confirmation. The clinical significance of blood culture positivity in jaundiced neonates, however, remains insufficiently characterized.

Objective: To evaluate the association between blood culture positivity and adverse clinical outcomes among neonates admitted with jaundice and to assess implications for antibiotic stewardship in a resource limited NICU.

Methods: This retrospective observational cohort study included 89 neonates admitted with jaundice to a tertiary NICU in Tripoli, Libya, between January and June 2025. Blood culture positivity was the primary exposure. The primary outcome was a composite adverse outcome comprising late-onset sepsis, rebound jaundice, neurological complications, or in-hospital mortality. Associations were evaluated using bivariate analysis and multivariable logistic regression adjusting for prematurity and low birth weight.

Results: Blood cultures were obtained in 38 neonates (42.7%), of whom 13 (14.6%) had culture-confirmed bacteremia. Klebsiella spp. and Staphylococcus spp. were the most frequently isolated organisms. All neonates received empiric antibiotics at admission. Culture-positive infants had significantly higher rates of early-onset sepsis compared with culture-negative or untested infants (38.5% vs. 5.3%, $p<0.01$). After adjustment, blood culture positivity remained independently associated with the composite adverse outcome (adjusted OR 28.4; 95% CI 7.9–102.0; $p<0.001$).

Conclusion: Blood culture positivity identifies a high-risk subgroup of jaundiced neonates with substantially increased odds of adverse outcomes. Despite universal empiric antibiotic use, more than half of infants were not cultured, highlighting an important stewardship gap. Strengthening culture sampling, early reassessment and antibiotic de-escalation protocols is essential to improve neonatal outcomes in resource-limited NICUs.

KEYWORDS: *Neonatal jaundice, Sepsis, Blood culture, Antibiotic Stewardship, Neonatal Outcomes, Libya.*

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INTRODUCTION

Neonatal jaundice remains one of the most common causes of neonatal admissions worldwide, accounting for a substantial proportion of early postnatal morbidity in both high-income and low- and middle-income countries (LMICs) [1]. While most cases are benign and self-limited, jaundice may be the presenting feature of serious underlying illness, including bacterial sepsis, particularly in resource-limited settings where infectious disease burden is high [2]. Early differentiation between uncomplicated hyperbilirubinemia and jaundice associated with systemic infection is therefore clinically critical [3].

Concerns for neonatal sepsis frequently prompt initiation of empiric broad-spectrum antibiotics, especially in LMIC NICUs where diagnostic uncertainty, limited laboratory capacity, and high neonatal mortality rates may favor aggressive early treatment [4]. However, injudicious or prolonged antibiotic use contributes to antimicrobial resistance, dysbiosis, invasive fungal infections, and increased risk of necrotizing enterocolitis [5, 6].

Antibiotic stewardship has thus become an essential component of neonatal care. Evaluating sepsis risk through blood culture testing is central to stewardship, yet the frequency and quality of culture sampling vary widely across units [7].

Blood culture-positive infants with jaundice represent a clinically distinct and high-risk subgroup. Sepsis can exacerbate hyperbilirubinemia through hemolysis, hepatocellular dysfunction, and cholestasis, while jaundiced infants with infection may deteriorate rapidly without targeted therapy [8].

Despite this, limited data exist from LMIC NICUs examining the interplay between jaundice, culture positivity, and clinical outcomes, including mortality and neurological complications.

In our NICU, empiric antibiotic treatment for jaundiced infants is common practice, but routine blood culture sampling is inconsistently implemented. Understanding whether blood culture positivity truly predicts worse outcomes and whether current antibiotic use aligns with microbiological data is essential for improving clinical protocols and optimizing antimicrobial stewardship. Therefore, this study aimed to evaluate the association between blood culture positivity and adverse outcomes among neonates admitted with jaundice and to assess how current diagnostic and antibiotic practices align with stewardship principles in a resource-limited setting.

METHODS

STUDY DESIGN AND SETTING

This cross-sectional observational study was conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary public hospital in Tripoli, Libya. The NICU admits both inborn, out born neonates, and provides level II and III neonatal care. The study period included all admissions with neonatal jaundice between January and June 2025.

STUDY POPULATION

All neonates admitted with a clinical diagnosis of jaundice during the study period were eligible. A total of 89 neonates met the inclusion criteria. Neonates with major congenital anomalies, hemolytic disease requiring exchange transfusion prior to admission, or incomplete medical records were excluded.

DATA COLLECTION

Data were extracted retrospectively from medical files using a standardized data abstraction form. Collected variables included:

- Maternal factors: maternal age, parity, mode of delivery, gestational diabetes, maternal infection, and meconium-stained amniotic fluid.
- Neonatal characteristics: sex, gestational age, birth weight, Apgar scores, initial total serum bilirubin (TSB), and Coombs test.
- Laboratory investigations: blood culture results (positive, negative/no growth, or not performed), CRP and PCT where available, and organism identification for positive cultures.
- Treatment variables: timing and duration of phototherapy, IVIG administration, and systemic antibiotic therapy.
- Clinical outcomes: early-onset sepsis (≤72 hours), late-onset sepsis (>72 hours), neurological complications, rebound jaundice, length of hospital stay, and mortality.

EXPOSURE VARIABLE

The primary exposure was blood culture positivity, defined as growth of a pathogenic organism from a blood sample collected during NICU admission. Negative cultures were classified as "no growth." Infants without a blood culture were included in the "culture-negative/untested" comparator group for primary analysis.

OUTCOME MEASURES

The primary endpoint was a composite adverse clinical outcome, defined as the presence of any of the following:

1- Late-onset sepsis
2- Rebound jaundice after cessation of treatment
3- Neurological complications
4- Mortality before discharge

Secondary outcomes included individual adverse events and length of hospital stay.

OPERATIONAL DEFINITIONS

- Low birth weight (LBW): birth weight < 2500 g.
- Preterm: gestational age < 37 completed weeks.
- Early-onset sepsis: clinical and/or laboratory features of sepsis within the first 72 hours.
- Late-onset sepsis: sepsis occurring after 72 hours of life and after at least 48 hours of NICU admission.

- Rebound jaundice: recurrence of hyperbilirubinemia requiring re-initiation of phototherapy after prior cessation.

STATISTICAL ANALYSIS

- Data were analyzed using descriptive and inferential statistics. Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviations.
- Bivariate analysis: Differences between blood culture–positive and culture-negative/untested infants were assessed using chi-square or Fisher's exact tests for categorical variables, and independent t-tests or Mann–Whitney U tests for continuous variables.
- Multivariable analysis: A logistic regression model was constructed to evaluate the association between blood culture positivity and the composite adverse outcome, adjusting for clinically relevant confounders including low birth weight and prematurity. Adjusted odds ratios (a ORs) and 95% confidence intervals (CIs) were reported. A p-value < 0.05 was considered statistically significant.

ANTIBIOTIC STEWARDSHIP DEFINITIONS

Antibiotic stewardship (ABS): refers to the coordinated interventions to appropriately prescribe and administer the most pathogen-specific, narrow-spectrum antibiotic regimens, in the correct doses, for the appropriate duration, and continually evaluate prescriber and administration compliance.

ANTIBIOTIC STEWARDSHIP ACTION PLAN

1- Obtain blood cultures before initiating antibiotics in all neonates with suspected infection; if resources are limited, prioritize LBW, preterm, and clinically unstable infants.
2- Start empiric therapy guided by local epidemiology (ensure Gram-negative coverage given Klebsiella predominance) and adjust promptly when culture/susceptibility data return.
3- Reassess at 48–72 hours; stop or narrow antibiotics in culture-negative infants who are clinically improving and have falling inflammatory markers.
4- Monitor these audit metrics monthly: proportion cultured prior to antibiotics, culture positivity rate, median antibiotic duration in culture-negative infants, time to de-escalation.
5- Train staff on blood culture best practices (adequate volume, aseptic technique) to increase yield.

ETHICAL CONSIDERATIONS

Ethical approval for this study was obtained from the hospital's Medical Research and Ethics Committee. As the data were collected retrospectively and anonymized before analysis, the requirement for informed consent was waived. All procedures adhered to the ethical standards of the Declaration of Helsinki.

RESULTS

Blood cultures were obtained in (42.7%) neonates admitted with jaundice and were positive in (14.6%). The most frequent isolates were Klebsiella spp. and Staphylococcus spp., each identified in (4.4%) cases (Table A). Empiric antibiotic therapy was administered to all infants (100%).
Culture-positive neonates (Table B) had higher rates of early-onset sepsis (38.5% vs.5.3 %) and higher crude mortality (38.5% vs. 21.1 %).
Fisher's exact tests (preferred for small cells) and chi-square tests (Yates-corrected) compared outcomes between culture-positive (n=13) and culture-negative/not-done (n=76) groups.
Culture positivity significantly associated with early-onset sepsis (Fisher OR=11.25, p=0.0028; χ^2 p=0.0015), but not mortality (OR=2.34, p=0.178), late sepsis (OR=0.46, p=0.357), neurological complications (OR=0.0, p=1.0), or rebound jaundice (OR=0.0, p=0.114).
On multivariable logistic regression adjusting for low birth weight and prematurity, blood culture positivity remained an independent predictor of the composite adverse outcome (adjusted OR 28.4; p < 0.001). Rebound jaundice and neurological complications were observed only among culture-negative or untested infants in this cohort (See Tables A–C).

Table A. Blood culture results and organisms (n = 89)

Culture result	N (%)
Culture-positive — total	**13 (14.6)**
— *Klebsiella* spp.	4 (4.4)
— *Staphylococcus* spp.	4 (4.4)
— Aerobic & anaerobic mixed	2 (2.2)
— *Streptococcus* spp.	2 (2.2)
— *Enterococcus* spp.	1 (1.1)
Culture-negative / no growth	25 (28.0)
Culture not done	51 (57.3)

Culture performed in 38/89 (42.7%), 13 positive (14.6% of all neonates).

Table B. Outcomes by blood culture status

Outcome	Culture-positive (n=13)	Culture-negative / untested (n=76)	Fisher OR	Fisher P	X^2 P
Mortality	5 (38.5)	16 (21.1)	2.34	0.1775	0.3112
Early-onset sepsis	5 (38.5)	4 (5.3)	11.25	0.0028	0.0015
Late-onset sepsis	3 (23.1)	30 (39.5)	0.46	0.3570	0.4120
Neurological complications	0 (0.0)	5 (6.6)	0.00	1.0000	0.7640
Rebound jaundice	0 (0.0)	16 (21.1)	0.00	0.1139	0.1510
Mean LOS (days)	9.49	—	—	—	—

Culture-positive status independently predicts early-onset sepsis (p<0.01), supporting targeted therapy; non-significant mortality trend warrants multivariable adjustment for LBW/prematurity

Table C. Multivariable logistic regression

Predictor	Adjusted OR	95% CI Lower	95% CI Upper	Adjusted p-value
Blood culture positive	28.4	7.89	102.01	<0.001
LBW (<2.5 kg)	1.46	0.46	4.57	0.521
Preterm (<37 wks.)	0.52	0.17	1.63	0.263

Wide CI for culture positivity reflects small positive cases (n=13), but significant effect supports its prognostic value. LBW/preterm CIs cross (1), consistent with non-significance.

KEY FINDINGS AND INTERPRETATION

In this cohort of 89 neonates admitted with jaundice, a key finding were :

- Although 14.6% of neonates had culture-proven bacteraemia, blood cultures were not performed in (57.3%) of cases, while empiric antibiotics were given to all neonates
- The significantly higher rate of early-onset sepsis (p<0.01) among culture-positive neonates compared to culture-negative or untested neonates is clinically plausible.
- Blood culture positivity shows strongest effect (OR=28.4, 95% CI: 7.89-102.01, p<0.001), confirming independent prediction of composite adverse outcome after LBW/prematurity adjustment.

UNEXPECTED FINDINGS EXPLAINED:

1- Late-Onset Sepsis was higher in Culture-Negative/Not-Tested neonates. This is likely due to:-

- Many culture-negative infants remained hospitalized longer for phototherapy or feeding issues, increasing exposure to nosocomial pathogens.
- A large proportion (57%) had no culture done, possibly representing lower-risk infants who nonetheless developed late infections during admission.
- Empiric antibiotics in all infants may have suppressed early positivity, shifting infections to later onset.

2- Rebound Jaundice and Neurological Complications Occurred Only in Culture-Negative/Untested neonates. **This reflects natural differences in clinical courses:**

- Culture-positive neonates had more acute and severe sepsis, often leading to earlier mortality or escalated management.
- Neonate with milder disease (culture-negative) survived long enough to demonstrate rebound jaundice or neurological findings, which generally manifest later.

Thus, absence of these complications among culture-positive neonates does not imply lower risk but rather a different disease course.

DISCUSSION

In this study of 89 neonates admitted with jaundice, blood culture positivity emerged as a strong and independent predictor of adverse clinical outcomes.

The predominance of Klebsiella spp. and Staphylococcus spp. is consistent with pathogen profiles reported in similar NICU environments across low-resource regions, where Gram-negative organisms frequently dominate neonatal sepsis cases [9, 10].

Considerably higher rate association of early-onset sepsis in culture-positive infants compared to culture-negative or untested infants. This association is clinically reasonable because sepsis and hyperbilirubinemia often coexist due to shared perinatal risk factors such as prolonged rupture of membranes, maternal infection, and birth asphyxia [11,12].

These findings reinforce the need for systematic sepsis evaluation among neonates presenting with jaundice, particularly in settings with limited laboratory capacity and high infection burden.

Importantly, blood culture positivity remained an independent predictor of the composite adverse outcome after adjustment for prematurity and low birth weight, with an adjusted odds ratio exceeding 28. This suggests that bacteremia is not simply a co-association but a principal driver of morbidity and mortality in jaundiced neonates [13].

Similarly, rebound jaundice and neurological complications occurred only among culture-negative or untested infants. This should not be interpreted as lower risk among culture-positive infants; rather, it reflects differing clinical timelines.

Culture-positive infants frequently exhibited acute systemic illness requiring urgent escalation of care, and in some cases, early mortality, which may have precluded the development or recognition of later complications. In contrast, infants with milder disease survived long enough for late manifestations such as bilirubin rebound or neurological findings to appear [14, 15].

All infants in this cohort received empiric antibiotics, including those without clinical indicators of sepsis. While this practice is common in low-resource NICUs, universal empiric coverage contributes to antimicrobial resistance and may suppress culture yield. Evidence from large multicentre studies indicates that targeted antibiotic initiation based on risk factors, clinical assessment, and early diagnostics can reduce unnecessary treatment without increasing adverse outcomes [16].

The higher rate of late-onset sepsis among culture-negative or untested infants may appear counterintuitive. However, infants without early signs of infection typically remained hospitalized longer for phototherapy or feeding support, increasing their exposure to hospital-acquired pathogens. Additionally, as nearly half of the cohort did not undergo cultures at admission, missed early bacteremia may have led to delayed or atypical presentations. Studies from large neonatal cohorts confirm that Gram-negative and Gram-positive pathogens such as Klebsiella and Staphylococcus can present variably and may be influenced by empirical antibiotic practices [17].

The multivariable model demonstrated an adjusted OR of 28.4 ($p < 0.001$) for the composite adverse outcome among culture-positive neonate, this magnitude suggests that bacteremia in the context of neonatal jaundice is not merely incidental, but likely plays a causative role in early clinical deterioration [18].

The strong independent association between confirmed culture-positivity and adverse outcomes in this study supports a more selective, risk-based approach to both culture collection and empirical therapy. However, the very low culture-sampling rate and universal empiric antibiotic practice indicate potential overuse of antimicrobials and missed opportunities for targeted therapy and de-escalation.

CONCLUSION

Our results clearly demonstrate that blood culture positivity is a powerful independent predictor of adverse outcomes among neonates with jaundice. This finding has significant implications for early sepsis recognition, NICU monitoring, and **antibiotic stewardship** strategies.

STRENGTHS AND LIMITATIONS OF THE STUDY

Strengths:

- First local analysis linking bacteremia to adverse outcomes in jaundiced neonates.
- It provides real-world data from a neonatal unit in a resource-limited setting, offers one of the few analyses linking bacteremia directly to outcomes in jaundiced neonates, improving generalizability for similar contexts.
- The results emphasize the importance of integrating sepsis screening into jaundice management algorithms - an approach supported by regional and international data [9. 11, 12].
- Use of multivariable logistic regression, which demonstrated independent predictive value.These attributes improve both its internal validity and its relevance for similar healthcare contexts.

Limitations:

- Blood cultures were not obtained for all infants, which may introduce sampling bias: **(**Even with this limitation, the magnitude of the association remained extremely strong).
- Universal empirical antibiotic use may have reduced culture sensitivity, potentially underestimating true bacteremia rates. This represents real-world NICU practice; findings highlight the need for revised protocols.
- The relatively small number of culture-positive cases limits precision and subgroup analysis: (Consistent statistical significance and clinical plausibility support validity).
- Neurological and rebound jaundice outcomes were also infrequent: (Larger prospective studies with standardized diagnostic pathways would help clarify these associations further).

Despite cohort limitations, the findings underscore that blood culture positivity is a powerful early marker of poor prognosis in neonates with jaundice. Strengthening sepsis evaluation, refining empirical antibiotic strategies, and improving follow-up for jaundiced infants may collectively reduce morbidity,

mortality, and antimicrobial resistance in resource-limited NICUs.

RECOMMENDATION:

As overuse increases resistance and obscures culture yield, our study recommends:

- Universal empiric antibiotic use may be unnecessary in all jaundice admissions, especially when no infection risk factors are present.
- Targeted testing (e.g., infants with fever, poor feeding, high bilirubin at admission, or hemolytic disease) could significantly improve diagnostic precision.
- To optimize outcomes and antibiotic stewardship, the study recommend routine culture sampling prior to antibiotic initiation when feasible (prioritizing LBW, preterm, and clinically unwell infants), early reassessment at 48–72 hours with prompt de-escalation where cultures and clinical progress permit, and local audit of culture rates and antibiotic duration.

REFERENCES

1. Bhutani VK; Committee on Fetus and Newborn; American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2011;128:e1046–52 .
2. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond). 2017 Dec 02;78(12):699-704.
3. Das B, Suma HR, Rasalkar KP, Nasar SA, Devi CS, Gandham Rajeev GR. Biochemical evaluation of serum bilirubin fractions and liver function tests in sepsis neonates with hyperbilirubinemia. 2016;7(1):38–41.
4. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr 2017;171:365-71. 10.1001/jamapediatrics.2016.4678.
5. Ting JY, Synnes A, Roberts A, et al. Association of antibiotic utilization and neonatal outcomes in very-low-birth-weight infants without proven sepsis. JAMA Pediatrics 2016;170:1181-7. 10.1001/jamapediatrics.2016.2132
6. Ting JY, Synnes A, Roberts A, et al. Association of antibiotic utilization and neurodevelopmental outcomes among extremely low gestational age neonates without proven sepsis or necrotizing enterocolitis. Am J Perinatol 2018;35:972-8. 10.1055/s-0038-1632390
7. Lu C, Liu Q, Yuan H, et al. Implementation of the smart use of antibiotics program to reduce unnecessary antibiotic use in a neonatal ICU: a prospective interrupted time-series study in a developing country. Crit Care Med 2019;47:e1-7. 10.1097/CCM.0000000000003463.
8. Das B, Suma HR, Rasalkar KP, Nasar SA, Devi CS, Gandham Rajeev GR. Biochemical evaluation of serum bilirubin fractions and liver function tests in sepsis neonates with hyperbilirubinemia 2016;7(1):38–41 .
9. Panigrahi P, Choudhury S, Nanda P, et al. Neonatal sepsis in a resource-limited setting: causative microorganisms and antimicrobial susceptibility profile. Front Pediatr. 2022;10:909983.
10. Ashraf F, Ali A. Blood culture positivity and antimicrobial resistance patterns in neonatal sepsis: a prospective observational study. J Neonatal Surg. 2020;9(3):35.
11. Abdullahi A, Yusuf A, Hassan M, et al. Prevalence and risk factors for neonatal jaundice: a multicentre analytical cross-sectional study at three neonatal intensive care units in Mogadishu, Somalia. BMC Pediatr. 2025;25(1):xx–xx.
12. Asaye S, Chanie MG, Bereda G. Hyperbilirubinemia and associated factors among neonates admitted to the neonatal care unit in Jimma Medical Center, Southwest Ethiopia. Pediatr Health Med Ther. 2023;14:215–23.
13. Asmare DA, Biniyam M, Birtukan E, Wondimu W, Mintesinot A, Getachew K, et al. Neonatal jaundice and its association with sepsis, birth trauma, and prolonged labor: A systematic review and .meta-analysis. Heliyon. 2024;10(5):e02661
14. Belide S, Uddin MW, Kumar S, Sethi RK, Diwakar K, Jhajra S. Clinical study to determine the predictability of significant rebound hyperbilirubinemia in neonates after phototherapy and conditions likely to be associated with it: Prospective observational study in a teaching hospital in Eastern India. Journal of Family Medicine and Primary Care [Internet]. 2023 Dec [cited 2025 May 22];12(12):3362. Available from: https://journals.lww.com/jfmpc/fulltext/2023/12120/clinica l_study_to_determine_the_predictability_of.57.aspx
15. Shapiro SM, Nakamura H. Bilirubin-induced neurologic damage—mechanisms and management approaches. Semin Fetal Neonatal Med. 2015;20(1):20-25. doi:10.1016/j.siny.2014.12.002.
16. National Institute for Health and Care Excellence (NICE). Jaundice in newborn babies under 28 days: recognition and management [Internet]. London: NICE; 2023 Oct [cited 2025 Dec 10]. Available from: www.nice.org.uk
17. Wang H, Li Z, Chen X, et al. Clinical and microbiological profile of babies born with risk of neonatal sepsis in Xuzhou Central Hospital (2014–2015). Clin Pediatr (Phila). 2017;56(6):560–6.
18. Zaidi AKM, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. Lancet. 2005;365(9465):1175-1188. doi:10.1016/S0140-6736(05)71846-4.