



Predictors of Neonatal Sepsis in Resource-Limited Intensive Care Settings

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Abstract

Neonatal sepsis remains disproportionately common and disproportionately fatal in resource-limited intensive care settings, with a recent 49-study African meta-analysis placing overall prevalence near 41%. This short communication synthesizes recent literature on the predictors of neonatal sepsis in these settings, spanning maternal, perinatal, neonatal, and iatrogenic risk factors as well as the diagnostic and microbiological context in which those predictors must be applied. Prolonged rupture of membranes, inadequate antenatal care, foul-smelling amniotic fluid, and maternal genitourinary infection carry pooled and adjusted odds ratios in the range of 3 to 10 for neonatal sepsis, while low birth weight, prematurity, low Apgar score, and escalating exposure to invasive devices such as mechanical ventilation and umbilical catheters carry similarly elevated, and in some cohorts markedly higher, odds. Diagnostic prediction models validated in low- and middle-income countries report reasonable pooled accuracy, but the great majority have not been tested in the lowest-resource settings, and the biomarker combinations with the strongest documented performance are frequently unavailable where sepsis burden is highest. Compounding this gap, the gram-negative organisms that dominate resource-limited NICUs are increasingly resistant to first-line empirical antibiotics. Interventions that act directly on modifiable predictors, including hand hygiene, infection-prevention bundles, and kangaroo mother care, have documented benefit and do not depend on laboratory capacity many units lack, positioning them as the most immediately actionable response to the predictor evidence reviewed here.

Keywords: neonatal sepsis; resource-limited settings; risk factors; neonatal intensive care; low- and middle-income countries

1. Introduction

Neonatal sepsis remains one of the most consequential and most preventable causes of newborn death in low-resource intensive care settings, precisely because so much of what predicts it is knowable at the bedside before a blood culture ever returns. A recent meta-analysis pooling 49 African studies and nearly 88,000 neonates put the overall burden of neonatal sepsis on the continent at 40.98% (95% CI 30.50-51.46%), a figure that would be considered a crisis-level attack rate in almost any other clinical domain [1]. That number is not simply a reflection of how sick African newborns are; it also reflects how much of neonatal intensive care in resource-limited settings still runs on clinical suspicion rather than confirmed diagnosis, because the laboratory infrastructure needed to rule sepsis in or out quickly and reliably is frequently unavailable [2].

This short communication synthesizes what the recent literature says about the predictors of neonatal sepsis specifically in resource-limited intensive care settings — the maternal, perinatal, neonatal, and iatrogenic factors that raise pretest probability enough to justify empirical treatment, and the diagnostic and microbiological realities that shape how those predictors actually get used. We do not report new data; we bring together case-control, cohort, and meta-analytic findings published largely in the past five years to outline where the predictive signal is strongest, where diagnostic support is weakest, and what that combination means for a NICU that cannot simply order more tests.

2. Burden and Epidemiology in Resource-Limited Settings

The epidemiological picture in low-resource NICUs differs from that in high-income settings in ways that matter for prediction. Gram-negative organisms, rather than group B streptococcus, dominate the pathogen profile in many low- and middle-income country (LMIC) units, and a substantial share of those organisms are already multidrug-resistant by the time a neonate is enrolled in a study [3]. An editorial summarizing a multi-site Indian NICU cohort reported early-onset bloodstream infection in 1.7% of neonates and late-onset infection in 5.5%, with mortality roughly three times higher among infected infants than uninfected ones in both periods (29% versus 10% early, 24% versus 7% late) [4]. Resistance in that same cohort was severe:

82% of gram-negative isolates were resistant to third-generation cephalosporins and 58% were carbapenem-resistant, numbers that reframe "predictors of sepsis" as inseparable from "predictors of a sepsis that first-line antibiotics will not touch" [4]. A seven-country characterization of gram-negative isolates causing neonatal sepsis across Ethiopia, Nigeria, Rwanda, South Africa, Bangladesh, India, and Pakistan found that 95% of isolates were resistant to ampicillin and 60% were resistant to both first-line empirical agents, ampicillin and gentamicin, together [3]. Epidemiologically, then, a resource-limited NICU is not simply a smaller or less-equipped version of a high-income unit; it is a setting where the baseline probability of sepsis is higher, the dominant organisms are different, and the first-line treatment is more likely to fail outright.

3. Maternal and Perinatal Predictors

The strongest and most consistently reported predictors of neonatal sepsis in resource-limited settings originate before birth. In the Africa-wide meta-analysis, prolonged rupture of membranes carried a pooled odds ratio of 4.11 (95% CI 2.81-5.41) for neonatal sepsis, a history of maternal urinary tract or sexually transmitted infection carried an odds ratio of 3.28 (95% CI 1.97-4.58), and neonatal resuscitation at birth — itself often a marker of a difficult, potentially contaminated delivery — carried an odds ratio of 3.26 (95% CI 1.96-4.56) [1]. A separate systematic review focused specifically on maternal and neonatal sepsis across sub-Saharan Africa found broadly convergent signals: prolonged membrane rupture beyond 12 hours (odds ratio 2.8), meconium-stained amniotic fluid (odds ratio 2.9), and maternal intrapartum fever (odds ratio 2.4) were each independently associated with neonatal sepsis, alongside a pooled neonatal sepsis prevalence of 36.02% (95% CI 26.68-45.36%) across the included studies [5].

A case-control study conducted explicitly in a resource-limited NICU setting sharpened these associations further and added detail that pooled meta-analyses tend to average away: foul-smelling amniotic fluid carried an adjusted odds ratio of 10.3 (95% CI 1.9-56.4), unclear vaginal examinations during labor carried an adjusted odds ratio of 4.2 (95% CI 1.6-11), prolonged labor beyond 24 hours carried an adjusted odds ratio of 6.2 (95% CI 2.8-17), and fewer than four antenatal care visits carried an adjusted odds

ratio of 2.9 (95% CI 1.4-6.5) [6]. Read together, these findings describe a coherent obstetric pathway: inadequate antenatal surveillance increases the chance that an ascending or intrapartum infection goes undetected and unmanaged, prolonged labor and ruptured membranes extend the window during which that infection can reach the fetus, and infection-control lapses during vaginal examination add an iatrogenic layer on top of an already elevated baseline risk.

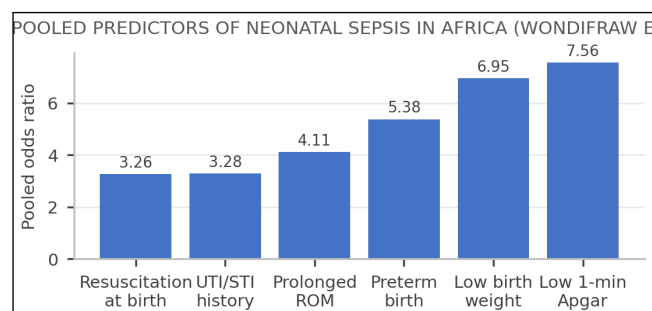


Figure 1: Pooled odds ratios for the strongest maternal, perinatal, and neonatal predictors of neonatal sepsis identified in a 49-study, 87,548-neonate meta-analysis across Africa [1].

4. Neonatal and Iatrogenic Predictors

On the neonatal side, low birth weight and prematurity are, unsurprisingly, the dominant predictors, but the magnitude reported in resource-limited settings is striking. The Africa-wide meta-analysis reported a pooled odds ratio of 6.95 (95% CI 3.00-10.89) for birth weight under 2500 g and 5.38 (95% CI 3.23-7.52) for preterm birth, with a one-minute Apgar score below 7 carrying the single largest odds ratio in the analysis, 7.56 (95% CI 3.39-11.73) [1]. The resource-limited case-control study found a similar pattern for prematurity (adjusted odds ratio 4.3, 95% CI 2.8-6.6) and low birth weight under 1500 g specifically (adjusted odds ratio 3.6, 95% CI 2.2-5.7), but its most notable contribution is quantifying how sharply risk escalates with level of intensive-care support: continuous positive airway pressure carried an adjusted odds ratio of 15.4 (95% CI 9.4-25.1), and invasive mechanical ventilation carried an adjusted odds ratio of 53 (95% CI 12.7-89) [6].

A prospective NICU cohort from Nepal converted this same intuition — that intensity of intervention predicts sepsis — into per-day exposure estimates that are directly actionable for bedside surveillance: each additional day of an indwelling IV cannula raised the odds of sepsis by a factor of 1.15 (95% CI 1.04-1.27), each additional day of mechanical ventilation by a factor of 1.09 (95% CI 1.01-1.17), and each additional day with an

umbilical arterial catheter by a factor of 1.38 (95% CI 1.05-1.80); each blood transfusion event carried an odds ratio of 3.08 (95% CI 1.41-6.76), and failure to breastfeed carried an odds ratio of 1.13 per day (95% CI 1.06-1.21) [7]. Table 1 places the strongest predictors from these studies side by side. The consistent thread across the neonatal and iatrogenic predictors is that invasive devices and prolonged NICU stay are not incidental to resource-limited care, they are close to unavoidable given the acuity of admitted infants, and each device-day is itself measurable, cumulative risk rather than a fixed one-time exposure.

Table 1: Selected predictors of neonatal sepsis reported in recent resource-limited-setting studies, with the reported effect estimate and source. [1,6,7].

Predictor	Source	Population	Reported Effect
Low birth weight (<2500 g)	Wondifraw et al. [1]	Africa, 49-study meta-analysis	Pooled OR 6.95 (95% CI 3.00-10.89)
Preterm birth	Wondifraw et al. [1]	Africa, 49-study meta-analysis	Pooled OR 5.38 (95% CI 3.23-7.52)
1-minute Apgar score <7	Wondifraw et al. [1]	Africa, 49-study meta-analysis	Pooled OR 7.56 (95% CI 3.39-11.73)
Invasive mechanical ventilation	Qureshi et al. [6]	Resource-limited NICU case-control	Adjusted OR 53 (95% CI 12.7-89)
CPAP requirement	Qureshi et al. [6]	Resource-limited NICU case-control	Adjusted OR 15.4 (95% CI 9.4-25.1)
Each additional day of umbilical arterial catheter	Manandhar et al. [7]	Nepal tertiary NICU cohort	OR 1.38 per day (95% CI 1.05-1.80)
Each additional day of mechanical ventilation	Manandhar et al. [7]	Nepal tertiary NICU cohort	OR 1.09 per day (95% CI 1.01-1.17)

5. Diagnostic Constraints and Biomarker-Based Prediction

Predictors are only clinically useful if they can be acted on quickly, and this is where resource-limited settings diverge most sharply from the settings in which most sepsis biomarker research is validated. A scoping review of 82 studies validating 44 distinct clinical prediction models for neonatal sepsis across LMICs, covering more than 24,000 neonates, found a median sensitivity of 81% and median specificity of 83% across 109 model evaluations, but two-thirds of the validated models required laboratory testing, 99% of the included studies were conducted in middle-income rather than low-income countries, and only 5% were conducted in the WHO African Region [2]. That distribution means the

models with the best-documented performance are, by construction, the ones least likely to have been tested in the settings with the least laboratory capacity — precisely where a low-cost, minimal-infrastructure predictor would matter most.

Among the biomarkers that are available in better-resourced units, a meta-analysis of 28 studies and 2,661 participants found procalcitonin outperformed C-reactive protein alone (pooled sensitivity 0.85 versus 0.71, pooled specificity 0.84 versus 0.88, area under the curve 0.91 versus 0.85), while combining the two markers improved discrimination further, to a pooled sensitivity of 0.91, specificity of 0.89, and area under the curve of 0.96 [8]. Procalcitonin assays remain considerably less available than C-reactive protein in resource-limited NICUs, however, which means the diagnostic combination with the best-documented accuracy is frequently the one least likely to be accessible where sepsis prevalence, and therefore diagnostic need, is highest.

6. Predictors of Treatment Failure: Resistance as a Downstream Risk

Because first-line empirical regimens fail so often against the gram-negative organisms that dominate resource-limited NICUs, antimicrobial susceptibility functions as a second-order predictor of outcome once sepsis is already suspected. A multi-country trial assessing alternative antibiotic combinations against gram-negative isolates from neonatal sepsis cases found that flomoxef-amikacin, fosfomycin-amikacin, and flomoxef-fosfomycin covered 71%, 79%, and 76% of tested isolates respectively, compared with only 31% coverage for ampicillin-gentamicin and 22% for cefotaxime, the regimens most widely used as first-line therapy under current WHO guidance [9]. Against extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli* specifically, flomoxef-amikacin and flomoxef-fosfomycin achieved complete coverage of tested isolates [9]. In a setting where the first antibiotic dose is typically chosen before any culture result exists, local resistance surveillance is, functionally, part of the predictor set that determines whether an infant who already has every clinical and obstetric risk factor for sepsis will also survive its empirical treatment.

7. Predictors as Levers for Prevention

Several of the strongest predictors identified above are also, encouragingly, modifiable through interventions with directly reported effects on infection outcomes. A Cochrane review of hand hygiene interventions for neonates, while noting that the certainty of the underlying evidence varies across included trials, situates hand hygiene compliance as the foundational, lowest-cost intervention against the device-associated and contact-transmitted infections that the Nepal cohort's per-day catheter and ventilation odds ratios describe [10]. A review of healthcare-associated infection prevention bundles in resource-limited neonatal units reported concrete effects from several deployed interventions: an infection-control bundle in Zambia was associated with a drop in hospital-associated mortality from 23.6% to 18.0%, a multimodal cleaning intervention in South Africa reduced bloodstream infection incidence from 6.7 to 3.9 per 1,000 patient-days, and an antibiotic stewardship bundle in Chile reduced late-onset sepsis incidence from 14.3 to 8.5 per 1,000 live births [11]. On the maternal-neonatal contact side, a systematic review and meta-analysis of 31 trials and more than 15,500 infants found kangaroo mother care reduced mortality relative to conventional care (relative risk 0.68, 95% CI 0.53-0.86) and reduced severe infection through latest follow-up (relative risk 0.85, 95% CI 0.79-0.92), with early initiation within 24 hours of birth showing a further mortality reduction over later initiation (relative risk 0.77, 95% CI 0.66-0.91) [12]. None of these interventions require the laboratory infrastructure that the diagnostic prediction models above were found to be missing; they act directly on the predictor variables themselves.

8. Conclusion

The predictors of neonatal sepsis in resource-limited intensive care settings are, at this point, reasonably well characterized: prolonged rupture of membranes, inadequate antenatal care, foul-smelling amniotic fluid, and intrapartum infection on the maternal side; low birth weight, prematurity, low Apgar score, and escalating device exposure on the neonatal side [1,5,6,7]. What remains far less developed is the infrastructure to translate that predictive knowledge into fast, locally validated action — most clinical prediction models with strong reported accuracy have not been tested in the lowest-resource settings where they would be most valuable, and the biomarker combination with the best diagnostic performance is frequently unavailable where

sepsis prevalence is highest [2,8]. Meanwhile, the organisms actually causing sepsis in these units are increasingly resistant to the antibiotics recommended as first-line therapy, which means a correct clinical prediction does not guarantee a successful outcome [3,9,4]. The interventions with the clearest documented benefit — hand hygiene, infection-prevention bundles, and kangaroo mother care — are also the ones that act directly on modifiable predictors without depending on laboratory capacity that many resource-limited NICUs do not have [10,11,12]. Closing the gap between what predicts neonatal sepsis in these settings and what can actually be measured and acted on at the bedside is, in our reading of this literature, the more pressing unmet need relative to identifying further predictors themselves.

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Conflict of Interest

The authors declare no competing interests relevant to the content of this article.

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Ethical Approval

Not applicable. This article synthesizes previously published literature and did not involve human participants, animal subjects, or the collection of primary clinical data by the authors.

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