The value of routine empiric antibiotic use in neonates born to mothers with prolonged rupture of membranes

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Background. The routine use of empiric antibiotics in neonates born to mothers with prolonged rupture of membranes (PROM) is controversial.

Objectives. To determine the incidence of probable and proven sepsis in such neonates and identify risk factors for sepsis and their outcomes.

Methods. This was a retrospective chart review conducted at King Edward VIII Hospital over two years. Study participants included 200 neonates and 181 mothers. Data were captured onto Microsoft Excel, collated and analysed using descriptive statistics and comparative data utilising the R Core Team's R Statistical Computing Software, 2020.

Results. Seven neonates (3.5%) had proven sepsis, 58 (29%) had probable sepsis, and 135 (67.5%) were without sepsis. Two (1.0%) neonates died and 188 (94.0%) received antibiotics. White cell count was normal in all cases without sepsis and abnormal in 65.5% and 28.6% of cases with probable and proven sepsis, respectively. A raised C-reactive protein was observed in only 22.4% and 14.3% of neonates with probable and proven sepsis, respectively. One hundred and sixty-seven (83.5%) mothers had no Group B Streptococcus (GBS) screening. Of those screened, three had GBS infection, but two did not receive antibiotics.

Conclusions. The incidence of sepsis following PROM is low. Identifying neonates at risk is challenging, but the absence of clinical features and normal rapidly obtained supportive laboratory markers of sepsis provides reassurance that antibiotics could be temporarily withheld. Better GBS screening programmes and appropriate antibiotic responses for pregnant women should be implemented rigorously.

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Prolonged rupture of membranes (PROM) is defined as rupture of membranes for more than 18 hours prior to delivery. It is a relatively common complication of pregnancy, occurring in approximately 8 - 10% of mothers.[1,2] PROM may occur at preterm or term gestation. Premature rupture of membranes (ROM) leads to one-third of preterm deliveries, and complications in 3 - 8% of preterm pregnancies, as well as a 1 - 2% risk of fetal death.[3]

The maternal factors that increase the risk of neonatal sepsis include chorioamnionitis, Group B Streptococcus (GBS) colonisation, preterm delivery and PROM >18 hours.[4] The risk for neonatal sepsis doubles with an increased duration of PROM >24 hours.[5] In term neonates with PROM, the incidence of chorioamnionitis has been reported to be <10%, with a delayed delivery beyond 24 hours of PROM increasing this risk to 40%.[3]

The management of neonates with PROM varies between and within countries. In England, United Kingdom, an approach of observing newborns with prolonged ROM without administering antibiotics has been adopted.[6] Asymptomatic neonates born to well mothers with PROM remain in hospital and are monitored closely for the first 12 hours of life. If signs of early neonatal sepsis, viz. grunting, subcostal recessions, nasal flare, central cyanosis, poor perfusion, poor feeding and floppiness develop, antibiotics are initiated. Symptomatic neonates, including those born through offensive smelling liquor, are subjected to a full septic screen and immediate intravenous antibiotics. Babies born to symptomatic mothers with chorioamnionitis, viz. temperature >37.8˚C, white cell count (WCC) >20 000, GBS carriage, a previous child infected with GBS, offensive lochia and PROM require a full septic screen and a course of broad-spectrum antibiotics, irrespective of the culture results.[6]

In some developing countries, a policy of immediate commencement of antibiotics to all neonates born of mothers with PROM and laboratory testing is employed. This policy increases the number of days of admission as it usually takes 48 hours before culture results are obtained. This policy may contribute to adverse outcomes by changing the human microbiome and associated antibiotic resistance owing to inappropriate antibiotic use. Antimicrobial resistance increases the cost of health.

Identification of risk factors for neonatal sepsis would be useful to decide on safe withholding of antibiotic therapy. In a study by Linder *et al.*,[8] neonatal sepsis occurred in 11 (8.1%) of 135 births with PROM; 10 were premature births, and 1 was a term small-for-gestational-age newborn. In another study by Alam *et al.*,[14] the incidence of PROM was 27/1 000 live births, with only 17 (4%) having blood culture-proven bacterial sepsis. Statistically significant independent risk factors for sepsis included maternal fever, PROM >48 hours, neonatal prematurity <34 weeks and low birthweight (LBW) <1 500g.[9] A Cochrane review by Kenyon *et al.*[7] found that the administration of antibiotics to women with PROM was associated with a significant reduction in neonatal sepsis (risk ratio (RR) 0.67, 95% confidence interval (CI) 0.52 - 0.85) and a significant reduction in chorioamnionitis (average RR 0.66, 95% CI 0.46 - 0.96).

In a study by Olita'a *et al.*,[10] a simplified management protocol for the term neonate with PROM was devised. The incidence of sepsis was yet again low and, in this study, antibiotics were withheld in neonates who had no risk factors for sepsis. In the South African

context, there have been no set guidelines to date.[10] Some local, regional and tertiary hospitals in KwaZulu-Natal Province have adopted an approach of routine empiric antibiotic use in all cases of PROM based on their prevalence of neonatal sepsis and clinical outcomes in their respective units. This practice is of concern as the incidence of culture-proven or probable sepsis among neonates born to mothers with PROM has not been documented in the South African context. The present study aimed to look at the incidence of proven and probable sepsis and identify factors that would allow early detection of sepsis.

Methods

A retrospective chart review was conducted of all neonates with PROM at the neonatal unit, King Edward VIII Hospital (KEH), eThekwini region, South Africa. Admission book records were used to screen cases for enrollment. Medical records of screened neonates from 1 January 2017 to 31 December 2018 were reviewed. Inclusion criteria included all neonates born after 18 hours of ROM, while exclusion criteria were neonates in whom the duration of ROM was not documented or delivered within 18 hours following ROM. Obstetric files of mothers of enrolled cases were retrieved from the KEH Medical Records Department, and the relevant maternal risk factors for PROM were extracted. Data were captured onto Microsoft Excel and were collated and analysed with the help of a statistician, using descriptive statistics and comparative data utilising the R Statistical Computing Software of the R Core Team (2020).

Neonatal data collected included neonatal demographics (gender, gestational age), risk factors which included booked or unbooked pregnancy, mode of delivery, syphilis exposure, HIV status, clinical features of sepsis (temperature instability, hypotension, tachycardia, bradycardia, apnoea, and offensive smell from neonate, sclerema, and respiratory distress) and laboratory markers of sepsis (full blood count, C-reactive protein and blood cultures) and relevant radiology. In addition, antibiotic courses, duration of antibiotics, duration of hospital stay, and outcomes were also captured. The neonatal categories included term neonates (born at ≥37 weeks' gestation) and preterm neonates (born before 37 completed weeks of gestation). The premature neonates were further sub-categorised into early premature (born before 32 weeks of gestation) and late premature (born after 32 weeks of gestation but before 37 weeks).[11] Extreme low birthweight neonates were defined as weighing <1 000 g (up to and including 999 g). Very low birthweight neonates were defined as weighing <1 500 g (up to and including 1 499 g), and low birthweight neonates were those weighing <2 500 g (up to and including 2 499 g).[12]

Maternal data collected included the age, gestation, documented signs of chorioamnionitis such as maternal fever, duration of PROM, organisms cultured and site of culture, HIV status, the number of documented vaginal examinations, invasive procedures, the use of antibiotics, duration and type of antibiotics, GBS status (current or previous), the severity of illness and maternal outcome.

Permission to conduct the study was granted by the University of KwaZulu-Natal Biomedical Research Ethics Committee (ref. no. BE/548A8). Informed consent from the participants was not required because of the retrospective nature of the study.

Definitions

Proven sepsis is defined as a significant blood culture with clinical and/or laboratory indices of infection.[13] Our study defined a significant pathogen as an infectious agent known to cause disease in a susceptible host. A contaminant was defined as a micro-organism not associated with a pathogenic role for the patient. Contaminants are attributed to the transfer of micro-organisms from the patient's immediate environment or from healthcare workers' hands, more rarely.[13]

Probable clinical sepsis was defined as a combination of risk factors for sepsis, clinical signs, and/or biochemical evidence of sepsis, with negative blood cultures. Clinical features of sepsis included respiratory distress, apnoea, mottled appearance, foul-smelling neonate, suppurative conjunctivitis, temperature instability, hypotension, bradycardia, tachycardia and hypoglycaemia. The biochemical markers that we used were an elevated C-reactive protein (CRP) >10 mg/L, leukopaenia <5^9/L in all neonates or a leukocytosis >20^9/L in preterm neonates and more than 25^9 in term neonates.[6]

Antibiotic policy

The protocol at the KEH neonatal unit for managing neonates with a history of PROM was screening them for sepsis (FBC, CRP and blood culture) and routinely commencing antibiotics (ampicillin) while awaiting culture results. Antibiotics are discontinued if the culture result and markers of infection are negative. Positive markers of infection without a positive culture are regarded as probable sepsis, and antibiotics are continued.

Results

Overall demographic variables and presentation

Two hundred of 306 neonates screened with PROM admission were enrolled in the study (Fig. 1). There was a total of 134 term, 35 late premature and 31 early premature neonates. The main reasons for screening failures were missing files and lack of PROM duration documentation (*n*=106). Records of only 181 (90.5%) mothers of these neonates were identified and reviewed.

It can be seen in Fig. 1 that 135 neonates (67.5%) did not have sepsis, 58 (29%) had probable sepsis, and 7 had proven sepsis (3.5%). The median PROM duration in the three groups was 26 hours (range 21.0 - 39.5 hours), 26.5 hours (range 23.0 - 42.8 hours) and 28 hours (range 23 - 30 hours), respectively. Sixty-six (33.0%) neonates were born prematurely, and 63 (33.5%) were LBW (Table 1).

Clinical features of sepsis included respiratory distress in 10 (5%) and single

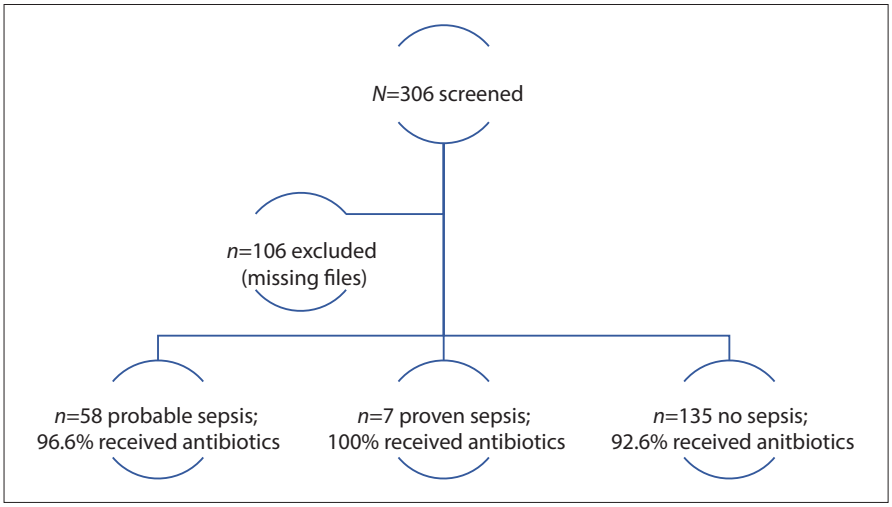

Fig. 1. Study profile of trial participants.

cases of mottled skin, hypoglycaemia, suppurative conjunctivitis and offensive smell. Forty newborns (20.0%) had abnormal WCC, and 14 (7.0%) had abnormal CRP tests.

PROM newborns without sepsis

Of the 135 neonates (67.5%) without sepsis, 17 (12.6%) were early premature, 26 (19.3%) were late premature and 92 (68.1%) were term neonates. Forty-two (31.1%) were LBW, and 93 (68.9%) were normal birthweight. Two neonates in this group (1.5%) were HIV infected. As seen in Fig. 1, a total of 135 neonates (92.6%) received antibiotics. However, 10 neonates (7.4%) in this group did not receive antibiotics owing to individualised decisions made, given that the neonates did not have any signs of sepsis. The median hospital stay was 3 days (range 2 - 4 days), 128 (94.8%) neonates were discharged home, *n*=6 (4.4%) were transferred to other units, and 1 (0.7%) extremely LBW premature neonate died.

PROM neonates with probable sepsis

Of the 58 (29.0%) neonates with probable sepsis, 11 (19.0%) were early premature, 8 (13.8%) late premature and 39 (67.2%) were term. Eighteen (30.9%) neonates were LBW, 39 (67.2%) were normal birthweight, and 1 (1.7%) was large for gestational age. Thirty-five (60.3%) neonates were HIV unexposed, 22 (37.9%) were HIV exposed but negative, and 1 (1.7%) tested HIV positive (DNA PCR). A total of 14 (7.0%) neonates had an abnormal CRP, 13 (22.4%) were in the group with probable sepsis, and 1 (14.3%) was in the group with sepsis. Overall, *n*=40 (20.0%) neonates had an abnormal WCC, of whom 38 (65.5%) were in the group with probable sepsis and 2 were in the group of patients with sepsis. Fifty-six (96.6%) neonates received antibiotics. One (1.7%) neonate with extremely LBW and unexplained preterm labour died. Forty-seven (81.0%) neonates were discharged home, and *n*=10 (17.2%) were transferred to other units to continue care.

Table 1. Demographic data of neonates born to mothers with PROM according to sepsis status

Neonatal variable	No sepsis (*n*=135)	Probable sepsis (*n*=58)	Proven sepsis (*n*=7)	Overall (*n*=200)	*p*-value
Gestational age					**0.200**
<34 weeks	17 (12.6%)	11 (19.0%)	3 (42.9%)	31 (15.5)	
34-<37 weeks	26 (19.3%)	8 (13.8 %)	1 (14.3%)	35 (17.5%)	
>37 weeks	92 (68.1%)	39 (67.2%)	3 (42.9%)	134 (67.0%)	
Birthweight					**0.841**
NBW/LGA	93 (68.9%)	40 (69.0 %)	4 (57.1%)	137 (68.5%)	
LBW	42 (31.1 %)	18 (31.0%)	3 (42.9%)	63 (31.5%)	
White cell count					**<0.001**
Normal	135 (100%	36 (62.1)	5 (71.4%)	160 (80.0%)	
Abnormal	0 (0%)	22 (37.9)	2 (28.6%)	40 (20.0%)	
CRP					**<0.001**
Normal	135 (100%)	45 (77.6%)	6 (85.7%)	186 (93.0%)	
Raised	0 (0%)	13 (22.4%)	1 (14.3%)	14 (7.0%)	
Neonatal antibiotics					**0.688**
No	10 (7.4%)	2 (3.4%)	0 (0%)	12 (6.0%)	
Yes	125 (92.5%)	56 (96.6%)	7 (100%)	188 (94.0%)	
Duration of hospital stay					**<0.001**
<3 days	53 (39.3%)	17 (29.3%)	0 (0%)	70 (35.0%)	
3 - 4 days	59 (43.7%)	19 (32.8%)	1 (14.3%)	79 (39.5%)	
>5 days	23 (17.0%)	22 (37.9%)	6 (85.7%)	51 (25.5%)	

PROM = prolonged rupture of membranes; NBW = normal birthweight; LGA = large for gestational age; LBW = low birthweight; CRP = C-reactive protein.

Table 2. Maternal data of neonates born with PROM according to sepsis status

Maternal variable	No sepsis (*n*=127)	Probable sepsis (*n*=48)	Proven sepsis (*n*=6)	Overall (*n*=181)	*p*-value
Maternal antibiotics					**0.006**
No	83 (65.4%)	20 (41.7%)	2 (33.3%)	105 (58.0%)	
Yes	44 (34.6%)	28 (58.3%)	4 (66.7%)	76 (42.0%)	
Maternal GBS status					**0.073**
Negative	8 (5.9%)	2 (3.4%)	1 (14.3%)	11 (5.5%)	
Current infection	1 (0.7%)	1 (1.7%)	1 (14.3%)	3 (1.5%)	
Unknown	118 (87.4%)	45 (77.6%)	4 (14.3%)	167 (83.5%)	
Maternal infection					**0.023**
Yes	2 (1.4%)	2 (4.2%)	4 (5.8%)	8 (4.4%)	
No	125 (98.4%)	46 (95.8%)	2 (33.3%)	173 (95.5%)	

PROM = prolonged rupture of membranes; GBS = Group B Streptococcus.

PROM neonates with proven sepsis

Four of the 7 cases (57.2%) of proven neonatal sepsis were born premature (3 early and 1 late), and 3 (42.9%) were LBW. There were two cases of GBS and *Enterococcus faecalis* and one each of *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida albicans*. There were no HIV-infected neonates in this group. Two (28.6%) neonates each had clinical symptoms of sepsis (conjunctivitis and respiratory distress) and abnormal WCC, as shown in Fig. 2. All 7 (100%) patients received antibiotics with a median of 6 days (range 5 - 10 days), and the median duration for hospital stay was 5 days (range 5 - 8.5 days). There were no morbidities or mortalities, and 3 (42.9%) patients were transferred to other hospitals to continue kangaroo mother care while awaiting weight gain.

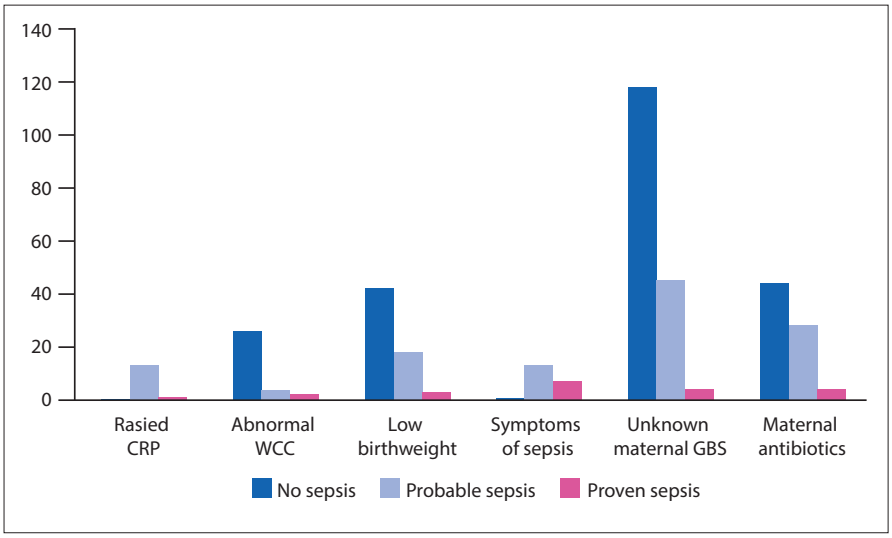

Fig. 2. Factors predictive of sepsis in neonates born with PROM. (CRP = C-reactive protein; WCC = white cell count; GBS = Group B Streptococcus.)

Maternal data

Of the 181 maternal records reviewed, 76 (42.0%) received antibiotics (Table 2). Forty-four of 127 (34.6%) mothers whose neonates did not have sepsis, 28 of the 48 mothers (58.3%) whose babies had probable sepsis and 4 of the 6 mothers (66.7%) whose babies had proven sepsis received antibiotics (Table 2). Maternal infection was noted in 8 cases (4.4%), highest in those neonates with proven sepsis (n=4) and 2 in the probable and no-sepsis groups, respectively. The most common infections were GBS (n=3), urinary tract infection (n=2), vaginal candidiasis (n=2) and maternal pyrexia with an unknown source. One hundred and sixty-seven mothers (92.3%) were of unknown GBS status. All mothers were well post discharge.

Discussion

The main finding of this study was the high routine empiric antibiotic utilisation rate at 94% in newborns with PROM despite over two-thirds of them not having sepsis. Antibiotic usage was high at 92.5% in neonates without sepsis, resulting in an extra three-day hospital stay. A third of neonates had probable or proven sepsis that could justify routine empiric antibiotic therapy, but these cases could be recognised timeously with clinical and laboratory markers of sepsis supporting a temporary delay in antibiotic initiation (Fig. 2). A combination of lack of maternal risk factors, absence of clinical features and normal WCC and CRP was associated with a significantly low risk of neonatal sepsis (Fig. 2). Good outcomes support this conservative approach of neonates with PROM with or without sepsis, and could assist in reducing the number of admissions to the nursery. However, it should be noted that the absence of clinical features for sepsis, or lack of an abnormal WCC or abnormal CRP, does not exclude a diagnosis of sepsis. A low threshold with the presence of any of these features should trigger the initiation of antibiotic therapy.

The incidence of proven and probable sepsis was low in our study. This finding is not dissimilar to a study of 176 neonates with PROM by Al-lawama *et al.*, where the incidence of culture-positive sepsis was 5%, and that of culture-negative sepsis was 13%.[14] In another study by Popowski *et al.*, neonatal sepsis occurred in 3.4% of all PROM cases.[15] Maternal risk factors for neonatal sepsis following PROM include duration of PROM >24 hours, fever, urinary tract infection, chorioamnionitis and an unknown maternal GBS status.[14] In our study, maternal infection was associated with an increased risk for proven neonatal sepsis, albeit in a small sample size. Even though the use of antibiotics in mothers with PROM may have contributed to an overall low neonatal sepsis rate, the erratic use of antibiotics in this group is of concern. The significant finding that the mothers on antibiotics had lower rates of sepsis than mothers who did not receive antibiotics could be artificial as indications for antibiotic use in mothers were not standardised. Less than half of all mothers with PROM had received antibiotics. In addition, we noted that some of the mothers without any additional risk factors for sepsis received prophylactic antibiotics prior to delivery while others did not. A major concern that we identified was the lack of maternal GBS screening (Table 2), with over 80% not having been screened. This deficiency was further highlighted by both mothers of neonates who were culture positive for GBS, being GBS infected.

Known neonatal risk factors for sepsis include LBW, prematurity, and PROM duration >24 hours.[15] However, expectant management of preterm pregnancies was uniformly well practised at our institution. Consequently, independent predictive risk factors for sepsis such as extreme prematurity and LBW (Fig. 2) were not seen, although this could also be due to the small sample size.

Study limitations

A limitation of our study was the retrospective nature that did not allow thorough or precise interrogation of the clinical features of sepsis for the neonate or the mother. Our institution does not utilise a standardised checklist for clerking neonates with PROM. The reason for antibiotic use in neonates and mothers was not specifically mentioned, and there were 10 neonates who did not receive antibiotics as per the current policy at KEH.

Conclusion

Our study showed that the incidence of proven sepsis in neonates of mothers with PROM was low. We have shown that maternal screening for GBS is inappropriately low, and especially that the yield was relatively high where testing was performed. The lack of standardised maternal management of PROM is concerning. We propose that in patients with no risk factors for sepsis and no clinical features of sepsis, a wait-and-watch approach to antibiotic use should be considered until the WCC and CRP results are obtained. If these are normal, no antibiotics should be commenced. If any risk features of sepsis are present or the WCC or

CRP are abnormal, antibiotics should be commenced. This policy will require further study in a randomised controlled fashion.

Declaration.

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