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Risk of Mortality Subsequent to Umbilical Cord Infection Among Newborns of Southern Nepal:

Cord Infection and Mortality

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Abstract

Background—Neonatal sepsis may stem from local umbilical cord infections. Signs of cord infection are common in low-resource settings, yet the risk of mortality subsequent to these signs has not been quantified in either developed or developing countries. We compared the risk of mortality between infants with and without signs of umbilical cord infection during a community-based trial of chlorhexidine interventions in southern Nepal.

Methods—Newborns were evaluated for signs of umbilical cord infection (pus, redness, swelling). A nested case-control approach was used to estimate the odds of mortality between infants with and without umbilical cord infection as defined by various levels of severity. For each death in the parent trial, 10 controls were selected, matched on sex, treatment group, and number of cord assessments. The main outcome measures were all-cause and sepsis-specific mortality.

Results—Among 23,246 assessed infants, there were 392 deaths. Odds of all-cause mortality were 46% (8–98%) higher among infants with redness extending onto the abdominal skin. A nonsignificant increased odds of mortality [odds ratio (OR): 2.31; 95% confidence interval (CI): 0.66–8.10] was observed among infants with severe redness and pus. Infections occurring after the third day of life were associated with subsequent risk of all-cause (OR: 3.11; 95% CI: 1.68–5.74) and sepsis-specific (OR: 4.63; 95% CI: 2.15–9.96) mortality.

Conclusions—This study provides evidence that common local signs of cord infection are associated with increased risk of mortality. Where exposure of the umbilical cord to potentially invasive pathogens is high, interventions to increase hygienic care of the cord should be promoted and including hand washing, avoiding harmful topical applications, and topical cord antisepsis.

Keywords

omphalitis; neonatal infection; umbilical cord infection; Nepal; neonatal mortality

Approximately 99% of the 4 million annual neonatal deaths occur in low and middle income countries, and 36% are attributed to serious infections; in high mortality settings this proportion may approach 50%.¹ The overall proportion of mortality related to local umbilical cord

infections that become systemic^{2–4} is unknown, but exposure to pathogens, with or without the development of local signs of omphalitis is thought to be an important proximal event in the pathway to sepsis and death in newborns. Observational data from Papua New Guinea indicated that probable sepsis and fever were 9.4 and 6.7 times less likely among newborns exposed to acriflavine spirit cord cleansing compared with unexposed historical controls.⁵ Recently, the first community-based, randomized trial of topical chlorhexidine cord cleansing showed that application of 4.0% chlorhexidine within 24 hours could reduce neonatal mortality by 34%.⁶ Such data support, but do not directly address the hypothesis that local signs of cord infection indicate increased subsequent risk of mortality.

Clinical sign-based algorithms, such as in Integrated Management of Childhood Illness, which are used to identify neonates with cord infections are poorly defined. Understanding the associated risk of these signs progressing toward systemic infection and death is essential to guide case management, yet such risk has not been quantified. Although such signs are common in the community and can be prevented through topical chlorhexidine,⁶ most cord care programs promote dry cord care, as per current World Health Organization guidelines.² Such guidelines have been made in the absence of specific data linking signs of infection with risk for mortality.^{3,4} To provide improved guidelines for both prevention programs and community-based identification and management of umbilical cord infections, further information on the consequences of umbilical cord infection is required.

We analyzed data from our large, community-based, randomized trial in Sarlahi, Nepal⁶ to gain insight into the consequences of umbilical cord infection as typically in low-resource communities of developing countries. In-home assessments of clinical signs of cord infection and population-based follow-up allowed us to estimate the subsequent risk of all-cause mortality associated with umbilical cord infections.

MATERIALS AND METHODS

Data Collection

The analysis presented here is a nested case-control study of data previously collected within a community-based, cluster-randomized trial of the impact of newborn skin and umbilical cord cleansing with chlorhexidine on neonatal morbidity and mortality, conducted by the Nepal Nutrition Intervention Project–Sarlahi (NNIPS). Details of the study population, recruitment, assessment of infection signs, and other procedures have been provided previously.^{6–8} Briefly, infants were randomized within clusters to 1 of 2 full-body wiping regimens (1-time wipe with either 0.25% chlorhexidine or placebo as soon as possible after birth) and 3 cord care regimens (umbilical stump cleansing with 4.0% chlorhexidine, cleansing with soap and water, or dry cord care only). Live-born infants from the parent trial were included in the current analysis of cord infection and mortality risk if the mother provided verbal consent for the infant's participation in the trial and the infant's umbilical cord was assessed one or more times at home by project workers.

Workers assessed the cord for signs of infection (pus, redness, swelling) during in-home visits throughout the neonatal period. “Mild” redness (or swelling) was limited to the cord stump while “moderate” or “severe” was defined as inflammation extending to the skin at the base of the stump (ie, <2 cm extension onto the abdominal skin) or affecting an area 2 cm or more from the cord, respectively.⁷ Workers were instructed to refer infants with redness or swelling at the moderate or severe level to the nearest health post.

Analysis—The exposure of interest for this analysis was umbilical cord infection. Daily umbilical cord assessment data on pus, redness, and swelling collected at each household visit for each child were combined into visit-specific infection status, with infection defined using

3 algorithms based on a validation exercise described previously⁷: (1) Infection 1: moderate or severe redness; (2) Infection 2: presence of pus with either moderate or severe redness, or presence of severe redness with or without pus; (3) Infection 3: severe redness with pus. These definitions are progressively more restrictive, with Infection 3 including infants with the most definitive infection criteria.

The outcome for this analysis was all-cause mortality; all deaths among the infants available were included as cases. A naive comparison of mortality risk between those with and without infection would likely under-estimate the association between local signs of infection and death, for 2 reasons. First, the mortality risk of newborns during the first 24 hours greatly exceeds the risk during subsequent days of the neonatal period¹ and many of these early deaths are known to be because of causes unrelated to cord infection (ie, birth asphyxia, prematurity, and congenital anomalies). Second, infants must be visited alive to have their cord assessed and the number of visits is directly related to the probability of one or more visits meeting the criteria for infection. Thus, a nested case-control analysis that allows for adjustment for these variables was adopted as a more appropriate analytic strategy to assess the relationship between cord infection and mortality risk.

For each death (case) that occurred, the time of death, number of cord assessments before death, sex, and trial cord cleansing group was noted. Ten controls for each case were then randomly selected from among the entire cohort of infants who: (1) survived to this age and (2) received the same number of cord assessments before this age, were of the same sex, and had been allocated to the same treatment group. Exposure for both cases and controls was then defined as one or more of the cord assessments (ie, cord infection noted on any one of the days the child was visited for assessment) meeting the definitions of cord infection before selection as a case or control.

The crude association between mortality and infection adjusted for the matched variables, sex, trial treatment, and number of cord assessments, was estimated using conditional logistic regression. Additional variables known to be related to mortality in this population were examined for confounding and were included in multivariate conditional logistic models. Timing of onset of infection was examined by sequentially restricting the exposure definition to that occurring after 1, 2, and 3 days since birth. The case-control analyses were repeated with cases that were redefined as probable sepsis deaths. Sepsis mortality was defined using an algorithmic approach to analysis of verbal autopsy data as reported previously, except that cord infection was removed as a potential sign of sepsis.^{8,9} Sepsis deaths were defined by the presence of 2 or more of the following signs or symptoms: (a) caretaker's report of fever, (b) vomiting more than half of feeds, (c) unconsciousness, (d) bulging fontanelle, (e) feeding difficulty (not able to suck before death or feeding less than normal), (f) jaundice, and (g) difficulty breathing and either rapid breathing or chest indrawing. All analyses were conducted in parallel using the 3 different definitions of cord infection ranging from most inclusive to most exclusive (definitive) local signs of infection.

Analyses were conducted using Stata 9.2 (Stata Corp, College Station, TX). The Nepal Health Research Council (Kathmandu, Nepal) and the Committee on Human Research of the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD) approved the protocol. This trial is registered at Clinicaltrials.gov (NCT00109616).

RESULTS

There were 23,662 live births eligible for enrollment between September 2002 and January 2006, and 23,246 (98.2%) were enrolled and received one or more home visits. The total number of in-home cord assessments was 214,756; the mean (SD) number of visits per child

was 9.2 (2.1). Visits were missed during periods of uncertain security, military curfews, nationwide strikes, religious holidays, and late arrival at the home after the birth or death of the infant. Ninety percent of infants were born in the home, 51.5% were male, 29.8% were low birth weight (<2500 g), and 76.0% of newborns' mothers had received no formal education. Additional details on the characteristics of the study population were reported previously.⁶

In the entire sample there were 759 neonatal deaths (neonatal mortality rate = 32.2/1000). Within the analytic data set the risk of mortality (392 deaths, 17.1/1000) was lower because of excluding deaths that occurred before the first in-home cord assessment visit. Estimates of the odds ratio (OR) for all-cause mortality comparing infected and noninfected infants for each definition of infection are shown in Table 1 (upper). Mortality risk was 46% [95% confidence interval (CI): 8–98%] higher among infants with redness extending to the abdominal skin around the stump compared with those without. Estimated risk was slightly elevated (OR: 1.27) for the moderately restrictive definition of infection (redness with pus or severe redness) and more than twice as high (OR: 2.31) among infants with the most severe infections (severe redness with pus); these comparisons did not reach statistical significance.

There were 217 probable sepsis deaths (9.3/1000; 95% CI: 8.2–10.8) among infants included in the analysis, as determined by verbal autopsy. Odds ratios for sepsis mortality for each cord infection definition are shown in Table 1 (lower), and follow the same general pattern as for all-cause mortality. The risk of sepsis mortality was 43% (95% CI: 7–126%; $P = 0.09$) greater among those with infection defined broadly (redness extending to the abdominal skin), and 3.52 times greater (95% CI: 0.67–18.4) for those with severe infection (severe redness with pus).

Exposure was sequentially restricted to that occurring after the first, second, and third days of life to examine timing of infection (Table 2), and recognizing that early signs of pus and redness may reflect inflammation after cord cutting rather than true infection. By definition, this also restricts deaths (cases) to those occurring after these time points. Restricting exposure to that occurring after 1 day led to minimal changes in the estimates of the mortality and infection relationship [eg, under the broadest definition, the comparative risk estimate for all-cause mortality changed from 1.46 (Table 1) to 1.38 (Table 2)]. However, the estimated odds ratio for all-cause mortality under the broad definition of omphalitis increased substantially to 2.04 (95% CI: 1.27–3.27) when restricted to infections occurring after day 2 and to 3.11 (95% CI: 1.68–5.74) for those after day 3. Odds of sepsis-specific mortality was increased 4.63 (95% CI: 2.15–9.96) times among infants with redness extending to the skin. For severe infections, the odds of all-cause and sepsis-specific mortality were 5.00 (95% CI: 1.25–20.0) and 6.67 (95% CI: 1.11–39.9) times greater, respectively.

After adjustment for low birth weight, ethnic group, maternal education, and maternal age, estimates of the association were either unchanged or increased (data not shown). For example, under the primary definition of infection, the adjusted odds ratio for mortality was 1.40 (compared with 1.46), whereas for severe infections the odds ratio increased to 3.38 (compared with 2.31). Interaction terms for chlorhexidine cleansing were added to conditional logistic models; for all definitions, the interaction term was close to unity and nonsignificant (Infection 1: 0.81, $P = 0.52$; Infection 2: 0.69, $P = 0.53$; Infection 3: 1.13, $P = 0.93$).

DISCUSSION

These data provide some supportive evidence for an increased risk of mortality associated with common signs of umbilical cord infections and suggest that risk depends on timing of infection onset. The odds of all-cause mortality were increased 46% among those with infection compared with matched controls without infection. As the definition of infection was restricted

to include more specific criteria, the estimate of associated risk increased for both all-cause (OR: 2.31) and sepsis-specific (OR: 3.52) mortality, but statistical evidence was weaker. After restricting the analysis to infections that occurred 2 or 3 days after cord cutting to remove the confounding influence of cases of cord inflammation after cord cutting and to focus more specifically on cases with clinical signs attributable to infection, the associated risk of all-cause and sepsis-specific mortality increased substantially and was statistically significant.

The estimates presented support the hypothesis that mortality risk associated with unhygienic umbilical cord care might be increased along 2 separate but potentially related pathways. Our earlier evaluation of topical chlorhexidine antiseptics suggested that the most important cause of umbilical cord related mortality was early exposure of the open vessels to pathogens, leading to systemic infection, even in the absence of clinical signs of omphalitis. The current data additionally suggest that local signs of cord infection are also associated with increased risk of mortality; the 2 processes may occur in consort, but cannot be distinguished from each other in the current study.

The Integrated Management of Childhood Illness algorithms for assessment and management of umbilical cord infections in the young infant categorizes an infant with either umbilical redness extending to the skin or the presence of pus draining from the umbilicus as having serious umbilical infection and recommends the administration of intramuscular antibiotics. Our data suggest that, although there is some increased risk for mortality associated with umbilical redness extending to the skin, this sign is substantially more ominous when pus discharge is also present or when redness radiates from the area immediately around the umbilical stump. The most recent Young Infant Study to define the clinical signs of illness, which signal the need for referral-level management (ie, severe illness) of the young infant presenting for care to a primary health facility found that neither of these signs of umbilical cord infection when taken alone was associated with severe illness.¹⁰ Taken together, these studies highlight the need to more precisely define management algorithms for omphalitis in developing country community settings.

Although World Health Organization guidelines acknowledge the potential role for topical antiseptics in cord care, the general recommendation is for dry cord care² and this is largely followed by programs promoting neonatal health. However, given recent results from Nepal demonstrating marked reductions in umbilical cord infections and mortality of neonates provided with cord cleansing with topical chlorhexidine,⁶ and the data presented here suggesting that commonly seen cord infection signs are associated with increased mortality, the role of routine umbilical cord antiseptics as part of essential newborn care, particularly in low-resource settings with high proportions of home births, needs to be reconsidered.

The most important limitation of this study centers on the specificity of the exposure measurement. Through an extensive validation exercise⁷ we tried to minimize this misclassification by choosing infection signs and definitions that had the best combination of intra and interworker agreement and sensitivity and specificity compared with a gold standard. However, residual misclassification may lead to an underestimate of the association between infection signs and mortality. Our data support this conclusion, with higher estimates of the odds ratio for mortality for infants with the more specific definition of severe umbilical cord infections. Similarly, increasing specificity of the outcome (deaths) by focusing on deaths more likely to be because of sepsis and thus directly associated with umbilical cord infections, also resulted in higher estimates of the relative odds. This relationship was more apparent after redefining the exposure on the basis of timing of onset of signs of infection; with sequential restrictions on exposure the magnitude and statistical strength of the association with mortality increased. Rather than indicating that later-onset infection are more serious, these estimates suggest that misclassification of exposure (especially redness of the cord stump, which can

result from inflammation associated with the birth and cord-cutting process) may be particularly acute within the first 48 hours after birth.

CONCLUSIONS

The overall contribution to neonatal mortality because of the associated risk between local signs of cord infection and death is difficult to define, and likely varies substantially across communities. Entry of pathogens into the bloodstream to cause death of the neonate seems to occur either directly, in the absence of local signs of umbilical cord infection (for example, shortly after cutting the cord when the umbilical vessels are patent, and before local signs of infection have developed), or via invasion into the bloodstream at a later date from infected umbilical tissue. The data presented here, although not conclusive, provide supportive evidence for continued risk of mortality as a result of the second pathway (ie, subsequent to local cord infections progressing to systemic infections). Importantly, this suggests that a single cleansing of the cord with a topical antiseptic at the time of cutting might be less effective than a more intensive continued follow-up of cord cleansing through the first week of life. Continued promotion of clean and hygienic cord care at birth and during the immediate postpartum period is necessary and emphasis should be placed on recognition of signs of cord infection by both caretakers and by neonatal and/or maternal health outreach workers.

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TABLE 1

Association of Umbilical Cord Infection and All-Cause Mortality

Cord Infection Definition	Cases	Controls	AOR* (95% CI)
All cause mortality			
Infection 1: redness extending onto the abdominal skin			1.46 (1.07–1.98)
No cord infection	336	3503	
Cord infection	56	407	
Infection 2: redness with pus or severe redness			1.27 (0.74–2.20)
No cord infection	377	3791	
Cord infection	15	119	
Infection 3: severe redness with pus			2.31 (0.66–8.10)
No cord infection	389	3897	
Cord infection	3	13	
Sepsis specific mortality			
Infection 1: redness extending onto the abdominal skin			1.43 (0.94–2.18)
No cord infection	188	2190	
Cord infection	29	213	
Infection 2: redness with pus, or severe redness			1.18 (0.58–2.40)
No cord infection	208	2113	
Cord infection	9	77	
Infection 3: severe redness with pus			3.52 (0.67–18.4)
No cord infection	215	2184	
Cord infection	2	6	

* AOR indicates odds ratio adjusted for trial treatment, sex, and number of cord assessments.

TABLE 2

Association of Umbilical Cord Infections With All Cause Mortality by Time of Onset of Infection

Cord Infection Definition [†]	Exposure Occurring After 1 Day	Exposure Occurring After 2 Days	Exposure Occurring After 3 Days
	AOR* (95% CI)	AOR* (95% CI)	AOR* (95% CI)
All cause mortality			
Infection 1 (most broad)	1.38 (1.00–1.92)	2.04 (1.27–3.27)	3.11 (1.68–5.74)
Infection 2	1.34 (0.77–2.33)	1.94 (1.00–3.76)	2.02 (0.94–4.36)
Infection 3 (most severe)	2.31 (0.66–8.10)	3.33 (0.90–12.3)	5.00 (1.25–20.0)
Sepsis mortality			
Infection 1 (most broad)	1.46 (0.94–2.28)	3.18 (1.76–5.73)	4.63 (2.15–9.96)
Infection 2	1.29 (0.63–2.63)	1.95 (0.85–4.47)	3.26 (1.28–8.31)
Infection 3 (most severe)	3.52 (0.67–18.4)	5.00 (0.92–27.3)	6.67 (1.11–39.9)

* Adjusted for trial treatment, sex, and number of cord assessments.

[†] Infection 1, redness extending onto the abdominal skin; Infection 2, redness with pus, or severe redness; Infection 3, severe redness with pus.