Dry Care Versus Antiseptics for Umbilical Cord Care: A Cluster Randomized Trial

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abstract

BACKGROUND AND OBJECTIVES: In developed countries, where omphalitis has become rare and related mortality nil, benefits of antiseptic use in umbilical cord care have not been demonstrated. We aimed to assess the noninferiority of dry care compared with antiseptics in France where antiseptic use is widespread.

METHODS: We conducted a noninferiority, cluster-randomized, 2-period crossover trial, in 6 French university maternity units including all infants born after 36 weeks' gestation. Maternity units were randomly assigned to provide either their usual antiseptic care or a dry care umbilical cord method for a 4-month period, and then units switched to the alternate cord cleansing method for a 4-month period. The primary outcome was neonatal omphalitis, adjudicated by an independent blinded committee based on all available photographs, clinical, and bacteriological data. We used a noninferiority margin of 0.4%. Analysis was performed per protocol and by intention to treat.

RESULTS: Among 8698 participants, omphalitis occurred in 3 of 4293 (0.07%) newborns in the dry care group and in none of the 4404 newborns in the antiseptic care group (crude difference: 0.07; 95% confidence interval: −0.03 to 0.21). Late neonatal infection, parental appreciation of difficulty in care, and time to separation of the cord were not significantly different between the 2 groups.

CONCLUSIONS: Dry cord was noninferior to the use of antiseptics in preventing omphalitis in full-term newborns in a developed country. Antiseptic use in umbilical cord care is therefore unnecessary, constraining, and expensive in high-income countries and may be replaced by dry care.

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WHAT'S KNOWN ON THIS SUBJECT: Although the World Health Organization recommends umbilical cord dry care in developing countries, it has been proven that antiseptic treatment reduces omphalitis-associated mortality. However, in some developed countries where omphalitis has become rare, antiseptic treatment is still used despite no demonstrated benefit.

WHAT THIS STUDY ADDS: In France, where antiseptics are commonly used, we demonstrated that dry cord care was noninferior to the use of antiseptics in preventing omphalitis in full-term newborn babies. The use of antiseptics in umbilical cord care is therefore unnecessary in high-income countries.

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Omphalitis is defined as infection of the umbilical cord stump and is characterized by the presence of pus, abdominal erythema, or swelling. It is considered a key entry point for invasive pathogens and is associated with a high mortality rate if left untreated.[1,2] In a large, community-based, cluster-randomized trial in Nepal, Mullany et al reported high neonatal mortality (17.7 in 1000) and severe omphalitis rates (13 in 4930) in dry cord care clusters; in the chlorhexidine-treated group, the occurrence of severe omphalitis was reduced by 75%, and neonatal mortality was 24% lower than in the dry cord care group.[3] Several meta-analyses of randomized controlled trials have shown a statistically significant benefit in the use of an antiseptic cord care regimen in developing countries in terms of reducing both omphalitis and neonatal mortality.[4–6] However, in developed countries, which offer better sanitary conditions and aseptic perinatal care, omphalitis and omphalitis-related mortality have become rare.[7] Two meta-analyses of randomized controlled trials performed in hospital settings in developed countries concluded no demonstrated benefit to the use of antiseptic cord care in preventing omphalitis.[4,5] These findings may be biased due to a lack of high-quality, empirical evidence in this context. The dry care method ("keep clean and dry") using only soap and water for umbilical cord care is currently recommended by the World Health Organization[8–10] and may be as effective and practical as antiseptics. Furthermore, dry care would be less expensive for healthy newborns in hospital settings in high-income countries. In this context, we designed a pragmatic, noninferiority, cluster-randomized crossover trial to compare, the use of dry care with antiseptics for cord cleansing to prevent omphalitis in newborns in France where antiseptic cord care is still systematically used.

METHODS

Study Design and Population

We conducted this noninferiority, cluster-randomized, 2-period crossover and unmasked study in maternity units at 6 university hospitals in Western France (Hopitaux Universitaires du Grand Ouest). Two 4-month study periods (4-month recruitment and 1 month follow-up) were separated by a 3-month washout period. The choice of a cluster design was driven by logistical considerations because we needed to recruit a large number of newborns. Moreover, individual randomization would have resulted in a high risk of contamination by both caregivers and mothers between the intervention and control groups. Given that only 6 maternity units were involved in this study, we chose a crossover design to ensure the comparability of baseline cluster characteristics and to increase statistical power. All infants born after 36 weeks' gestation were eligible for enrollment into the study, corresponding to a maternity hospital newborn population. Exclusion criteria were as follows: serious congenital malformation, early admission to the NICU, and any barriers to dry cord cleansing adherence or follow-up (eg, homelessness, substandard housing). Even though both cord care cleaning strategies are considered standard methods of hospital care by French regulatory authorities, families were nevertheless clearly informed and asked to consent to their child's participation in the trial and to permit the research team full access to neonatal clinical data. The study was approved by the Research Ethics Review Committee of Angers (France). The trial is registered with ClinicalTrials.gov (identifier NCT01556867).

Randomization and Masking

Each maternity unit was allocated to conduct the control and intervention cord care methods in a random order. Maternity units were randomized all at once. Random allocation sequences (ie, 1 block of 6) were independently generated by the study methodologist, who had no further involvement in the patient's inclusion in the study. Because of the nature of the intervention, caregivers and mothers were aware of the assignment during the study.

Procedures

During the antiseptic cord care (control) period, the cord was cleansed with an antiseptic according to the maternity unit's routine practice, that is, 1, 2, or 3, daily applications of antiseptic solution. In 3 centers, the usual antiseptic used was a combination of benzyl alcohol, benzalkonium chloride, and chlorhexidine gluconate (Biseptine); chlorhexidine gluconate solution (Diaseptyl) in 2 centers; and 70% modified alcohol in the sixth centers. During the period of dry care, the cord was cleansed with water and the nonantiseptic liquid soap usually used in each maternity, and carefully dried twice a day.[8–10]

One week before the start of the study, each maternity team was informed of its allocation for the first period and received information about the study procedures. The study staff in each participating maternity hospital consisted of 1 pediatrician, 1 nursery nurse, 1 midwife, and 1 clinical research associate. Two weeks before the start of the study, the study staff was educated alongside caregivers on the specifics of the study and the umbilical soap care procedure during repeated in situ teaching sessions. Written information was distributed by post to all caregivers (eg, general practitioners, midwives, and pediatricians) working in the area who may be in contact with the mothers and newborns enrolled in the study. The information included details about the study objectives

and the necessity to contact the investigation team in case of any umbilical pathology. During maternity stay, parents were shown how to administer the appropriate umbilical care method (according to the cluster randomization period) and asked to continue this care until cord separation was obtained. At maternity discharge, a written reminder of the cord care strategy to be used was given to parents, and a copy was added to the health book for any caregiver (eg nurse, pharmacist, midwife, and general practitioner) likely to be involved in the newborn's health care within the first 28 days of life. An information form explaining the study objectives was given to the parents that also asked caregivers to inform the investigators and to contact their maternity unit in any case of adverse umbilical cord healing. For cases in which umbilical cord symptoms required additional consultation, the maternity pediatrician completed a special form with clinical data, took photographs, and sent bacteriological cultures to the laboratory. All families included in the study were contacted by telephone at the end of the first postnatal month and asked for specific information concerning this period, such as time to separation of the cord, parental satisfaction regarding umbilical cord care and healing, hospitalization, late-onset bacterial infection, and any antibiotic treatment.

End Points

The primary outcome was omphalitis within 28 days after birth. Omphalitis was defined as occurrence of at least 1 of the following signs: purulent or malodorous discharge from the umbilical stump, periumbilical erythema, edema, or tenderness. All these signs were explained to the parents before the newborn's discharge from hospital. Suspected cases of omphalitis were evaluated during appointments made with the maternity pediatrician when parents were concerned. Data were reviewed by an independent, blinded committee composed of 1 pediatrician, 1 dermatologist, and 1 infantile surgeon not otherwise involved in this trial. Omphalitis cases were adjudicated on the basis of all available photographs and clinical and bacteriological data. The committee also classified omphalitis cases into 3 categories as follows: grade I, purulent discharge from the umbilical stump; grade II, abdominal cellulitis or lymphangitis; and grade III, inflammation extending into the subcutaneous fat and deep fasciae.[11]

Secondary outcomes were time to separation of the cord, parental satisfaction regarding umbilical cord care and healing, hospitalization, early- and late-onset bacterial infection and antibiotic treatment within the first 28 postnatal days.

Statistical Analysis

All statistical analyses were performed using SAS (version 9.3, SAS Institute Inc, Cary, NC).

Assuming an omphalitis proportion at day 28 of 0.2% in both groups and a noninferiority margin of 0.4%, a standard sample size calculation to achieve 90% power based on a 2-sided 95% confidence interval approach (corresponding to an α set at 2.5% for the noninferiority hypothesis) would have required 3400 newborns per study group. Given that the study design was a cluster crossover randomized trial, the sample size calculation had to take into account both the intraclass correlation coefficient, ρ (correlation between responses of any 2 newborns in the same maternity unit during a given period) and the interclass correlation coefficient, η (correlation between responses of any 2 newborns in the same maternity unit at different periods). η was expected to be lower than ρ. Six maternity units were available to be randomized, so assuming $\rho = 0.001$ and $\eta = 0.0005$, we aimed to enroll 9480 newborns (4740 per group).[12]

We performed 3 analyses for the primary outcome. The intention-to-treat (or imputed) analysis was performed on all randomized newborns, except those whose parents withdrew consent to participate, imputing missing primary outcomes with a best case scenario (ie, a missing outcome equals no omphalitis, whatever the group). We also performed a completers analysis taking into account only newborns with available data for the primary outcome. Finally, in the per-protocol analysis, we excluded infants with a major protocol violation, which was defined as either no antiseptic cord care received for a newborn in the antiseptic cord care group or antiseptic cord care received for a newborn in the soap cord care group. The exception to this was if antiseptics were received after a visit for cord infection symptoms for a newborn in the dry care group. Other outcomes were not imputed. We concluded noninferiority if the upper limit of the 2-sided 95% confidence interval of the difference in omphalitis rate between the 2 cord care strategies (calculated according to Wilson score confidence limits)[13] was lower than the a priori defined margin of 0.4%. Because of the rare event rate and small number of clusters, the cluster crossover design could not be taken into account for the primary outcome analysis.

For descriptive statistics, categorical data are presented with numbers and proportions, and continuous data with means and SDs, or medians and interquartile ranges for skewed distributions. For secondary outcomes, we used an unweighted estimator of the intervention effect, which is a method based on the crossover difference calculation at the cluster level.[14] Intraclass correlation coefficients were

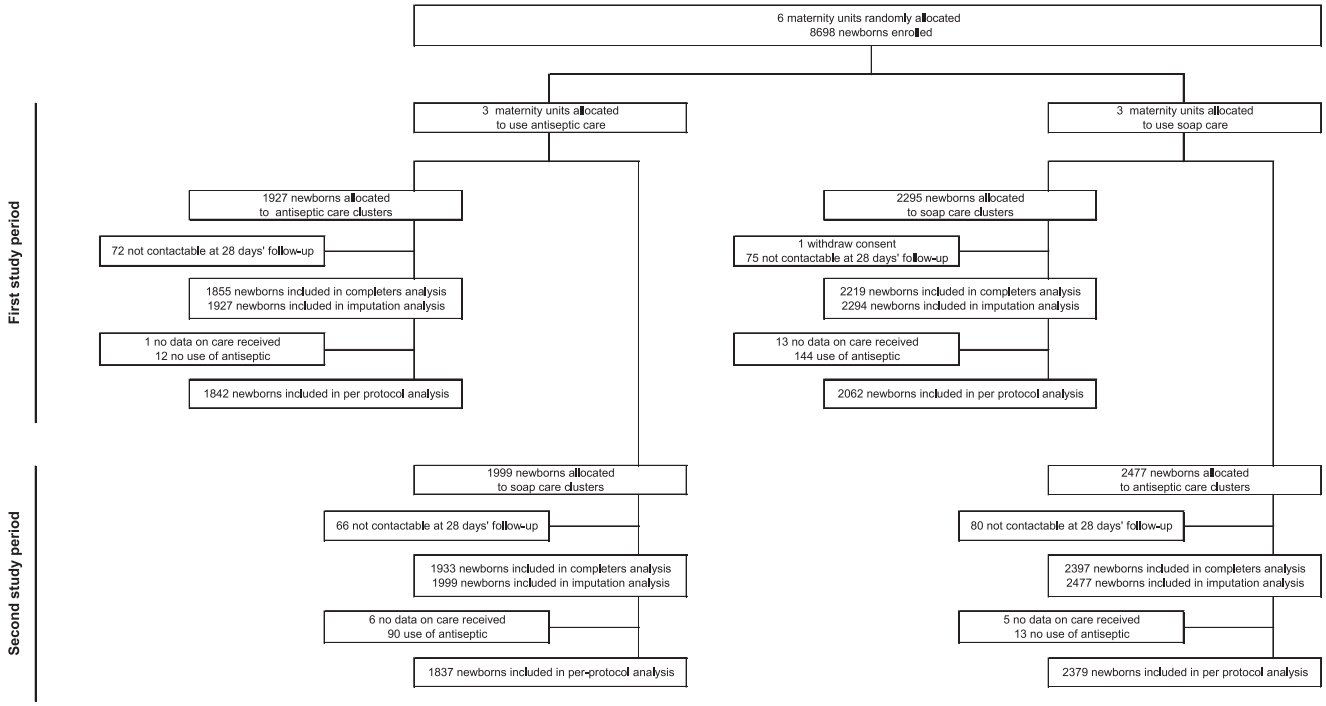

FIGURE 1
Trial profile.

estimated by treatment group using the Fleiss and Cuzick estimator.[15]

$P < .05$ was considered statistically significant.

Role of the Funding Source

The sponsor of the study had no role in the study design, data collection, data analysis, writing of the report, or in the decision to submit this report for publication. The corresponding author had full access to the data and final responsibility for the decision to submit for publication.

RESULTS

In participating maternity units, the median annual number of deliveries was 3694 (interquartile range, 2762–3858) and median number of beds was 48 (38–50). The first period of recruitment was from March 1, 2011, to June 31, 2011 (follow-up period until July 31, 2011). The washout period was from June 1, to September 31, 2011, and the final period was from October 1, 2011, to January 31, 2012 (follow-up period until March 1, 2012).

A total of 8593 mothers gave birth to 8698 newborns enrolled in the study. Of these, 4294 were in the dry cord care group and 4404 in the antiseptic cord care group (Fig 1). The parents of 1 newborn in the dry care group objected to the study after initial inclusion. Thus, the intention-to-treat imputation analysis comprised 8697 newborns (n = 4293 in the dry care group and n = 4404 in the antiseptic care group). The primary outcome was missing for 293 (3.4%) infants (141 infants in the dry care group and 152 infants in the antiseptics care group) because parents could not be contacted after 28 days of life. Protocol violations were reported in 253 infants in the dry care group (19 with no data on the type of cord care received and 234 who received antiseptic care) and 31 infants in the antiseptic group (6 with no data on the method of care received and 25 who did not receive antiseptic care). Thus, 8120 infants were included in the per-protocol analysis (n = 3899 in the dry care group and n = 4221 in the antiseptic care group). Mother and newborn characteristics were balanced between study periods (Table 1).

We observed 3 cases of omphalitis in the dry care group; these are described in Box 1. In the per-protocol population, omphalitis was observed in 3 (0.08%) infants of 3899 in the dry care group and in none (0%) of the 4221 newborns in the antiseptic care group. The risk difference was well within the noninferiority margin (crude risk difference 0.08, 95% confidence interval –0.03% to 0.23%) (Table 2). The corresponding risk difference was 0.07 (95% confidence interval –0.03% to 0.21%) in both the intention-to-treat analyses with imputation and completers analysis.

Median time until to separation of the cord was 10 days (interquartile range, 8–12) with dry cord care, and 11 days[8–14] with the antiseptic cord care regimen. The proportion of newborn babies with a time to

separation of the cord longer than 21 days did not significantly differ according to the cord care strategy (Table 3). Parental dissatisfaction with umbilical cord healing was rare and did not differ between the study groups. We observed no statistically significant difference for the rate of hospitalization or antibiotic treatment within the first 28 days of life in either group. No late neonatal infection was observed. Appointments made to visit the maternity pediatrician for umbilical cord symptoms were more frequent; although not significantly different between the 2 groups, we recorded 34 pediatrician visits made by 4213 infants in the dry care group and 7 of 4307 in the antiseptic care group (adjusted risk difference 0.72, 95% confidence interval −0.01 to 1.45, $P = .052$). Intraclass correlation coefficients varied between 0 and 0.08 (Supplemental Table 4). During the study, 1 male infant born at 39 weeks, who was included in the antiseptic cord care group, died at 34 days of life. A viral myocardiopathy was diagnosed after autopsy.

DISCUSSION

The results of our study of >8600 healthy, full-term newborns in a high-income country with systematic use of antiseptic cord care practices showed that dry umbilical cord care was not inferior in preventing omphalitis compared with care with antiseptics. Moreover, we did not find any difference in neonatal infection and parental satisfaction rates. The only 3 cases of omphalitis we observed (caused by *Staphylococcus aureus*) were in the dry care group, but they were easily managed, including the case that presented with Panton-Valentine Leukocidin toxin, which is usually associated with serious bacterial infection.[16] The most frequent bacterium cultured from the umbilical cord was *S aureus*, as previously described in high-income countries.[4,17,18] In all isolated bacteria, no resistance to usual antibiotic treatment was observed. However, it is not clear that these were true cases of omphalitis as opposed to funisitis because parenteral antibiotics treatment is generally necessary for true omphalitis. Our interpretation would be that neither group had any cases of real omphalitis.

TABLE 1 Baseline Maternal and Neonatal Characteristics

	Dry Cord Care	Antiseptic Cord Care
Maternal characteristics	*n* = 4241	*n* = 4352
Education		
Middle or primary school	1138 (27.2)	1168 (27.0)
High school	1482 (35.4)	1471 (34.0)
University	1563 (37.4)	1692 (39.1)
Parity		
First child	1891 (44.6)	1898 (43.6)
Second or third child	2089 (49.3)	2223 (51.1)
Fourth or higher	259 (6.1)	231 (5.3)
Neonatal characteristics	*n* = 4293	*n* = 4404
Singleton	4176 (97.3)	4294 (97.5)
Gestational age (wk), mean (SD)	39.3 (1.3)	39.4 (1.3)
Birth wt (g), mean (SD)	3324.1 (452.2)	3327.7 (456.0)
Sex		
Male	2179 (50.8)	2227 (50.6)
Female	2114 (49.2)	2177 (49.4)

Data are *n* (%) unless otherwise stated.

TABLE 2 Primary Outcome Results: Omphalitis

	Dry Cord Care, *n*/*N* (%)	Antiseptic Cord Care, *n*/*N* (%)	Risk Difference in Percentage[a] (95% CI)
Per-protocol	3/3899 (0.08)	0/4221 (0.00)	0.08% (−0.03% to 0.23%)
ITT imputation analysis	3/4293 (0.07)	0/4404 (0.00)	0.07% (−0.03% to 0.21%)
Completers analysis	3/4152 (0.07)	0/4252 (0.00)	0.07% (−0.03% to 0.21%)

CI, confidence interval; ITT, intention to treat.
[a] %dry cord care − %antiseptics cord care.

TABLE 3 Secondary Outcomes Results Adjusted and Unadjusted for Cluster Crossover Design

	Dry Cord Care *n*/*N* (%)	Antiseptic Cord Care, *n*/*N* (%)	Unadjusted Risk Difference in Percentage[a]	Adjusted[b] Risk Difference in Percentage[c] (95% CI)	*P*
Parental dissatisfaction with umbilical healing	204/4141 (4.93%)	184/4237 (4.34%)	0.58%	0.19% (−1.68% to 2.06%)	.790
Ease of care: difficult or very difficult	83/4145 (2.00%)	90/4245 (2.12%)	−0.12%	−0.42% (−2.43% to 1.58%)	.591
Time to separation of the cord >21 d, *n* (%)	61/4128 (1.5%)	371/4202 (8.8%)	−7.35%	−8.01% (−19.76% to 3.75%)	.132
Visit for umbilical cord symptoms	34/4213 (0.81%)	7/4307 (0.16%)	0.64%	0.72% (−0.01% to 1.45%)	.052
Antibiotics prescription: yes	48/4293 (1.12%)	24/4404 (0.54%)	0.57%	0.60% (−0.43% to 1.63%)	.181
Hospitalization, whatever the reason: yes	159/4150 (3.83%)	122/4249 (2.87%)	0.96%	1.30% (−0.48% to 3.07%)	.112

[a] %dry cord care − %antiseptics cord care.
[b] Adjusted for cluster cross over design.
[c] %dry cord care − %antiseptics cord care.

Our results differ from those observed in community or primary care settings in developing countries where antiseptic use should be recommended.[5,6] However, the situation is completely different between these 2 settings; whereas the omphalitis rate in developed countries is low (3 in 8698 or 0.34 in 1000 births in our study, 0.6 to 1 in 1000 in a cohort of 1470 Italian newborns, and 0% in a cohort of 1811 Canadian newborns),[7,19] the rate is much higher in developing countries (475 of 9741 or 48 of 1000 in Pakistan, with a mortality rate of 90 per 1000 live births,[20] and 4.2 to 155.7 of 1000 in rural Bangladesh depending on the infection severity[21] with a mortality rate of 28.3 of 1000 live births). The underlying risk of omphalitis and omphalitis-related mortality is so high in these countries that the strategies for umbilical cord care could not be extrapolated to high-income countries. The objective of the current study, which focused on a low-risk population (omphalitis prevalence <1 in 1000 births) in full-term French newborns was to provide missing complementary data from a developed country.

We conclude that the dry care strategy is noninferior to usual antiseptic care. However, we did not focus on a specific antiseptic strategy, as others have previously published.[4] We deliberately chose to group together the usual antiseptic care regimens used in hospitals in a large area of France because, as expected, we observed many different practices in umbilical cord care.[22] The pragmatic methodology of this study, which takes usual daily antiseptic practices into account, constitutes a strength of this study and increases the external validity of our results. However, our results are restricted to a specific population of full-term newborns with no health problems, who stayed with their mothers in a maternity unit but who are the most common cases of newborns requiring umbilical care. In light of this, our results cannot be generalized to include newborns with a higher risk of infection, such as those who are born preterm or those hospitalized in ICUs. The microbiota is different in these cases and the possibility of virulent bacteria and or antibiotic resistance is increased in these contexts.[23]

We found no difference in parental satisfaction regarding umbilical care and, regardless of study group, there were few reported difficulties. Allocation to the dry care group did not induce any specific problems except a high revisit rate for umbilical cord symptoms, probably related to parents and caregivers worried about the possibility of infection due to a change in the normally recommended care practice. Despite a large difference in extended time to cord separation, the strength of evidence for this difference was modest, and this difference was expected based on previous studies describing a shorter cord separation time with dry care compared with antiseptic care because of the bacterial colonization responsible for the cicatrization and separation of the cord stump.[24] In this study, we still practiced total bathing during the initial postnatal days instead of the sponge bath recommended by the American Academy of Pediatrics and National Institute of Health Care and Excellence[8,9] which probably explains why the time to cord separation is not significantly different between the 2 groups.[25]

We believe that these findings have significant implications for public health in developed countries. Our results suggest that dry care is an easy, and likely money-saving, approach; we estimate that antiseptics and dressings cost ~15 euro (~17 US dollars) per newborn, which should be multiplied by ~600 000 full-term newborns per year in France. In this domain, traditional practices should give way to evidence-based ones. Future studies should investigate the precise savings that may be obtained with this new umbilical care strategy. Ideally, resources should be directed to provide antiseptics for umbilical cord care in those developing countries that would benefit most from it.[5,6]

BOX 1 DESCRIPTION OF OMPHALITIS CASES

Case 1 was a female singleton newborn (38 wk of gestational age, birth wt 3280 g). Omphalitis was diagnosed in the maternity unit at 4 d of life. Symptoms were fever, periumbilical redness, and vesicles on the groin and side. Bacteriological culture isolated *Staphylococcus aureus* that was positive for Panton-Valentine leukocidin (PVL) toxin. This grade 1 omphalitis was managed with antiseptics and oral oxacillin syrup.

Case 2 was a male singleton newborn (41 wk of gestational age, birth wt 3534 g). Omphalitis was diagnosed at 12 d of life. Symptoms were periumbilical redness and purulent discharge with *Staphylococcus aureus* and *Proteus mirabilis* isolated on microbiological cultures. He was managed with antiseptics and oral amoxicillin and clavulanic acid treatment.

Case 3 was a male singleton newborn (40 wk of gestational age, birth wt 4090 g). Omphalitis was diagnosed at 6 d of life. Symptoms were periumbilical redness and purulent discharge. Bacteriological culture isolated *Staphylococcus aureus*, which was managed with antiseptics and an increased frequency of umbilical cord care.

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the manuscript; Drs Caillon and Barbarot designed the study and analyzed the omphalitis cases and revised the manuscript; and all authors approved the final manuscript as submitted.

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