Original Paper

Neonatology

Neonatology 2018;113:146–151
DOI: 10.1159/000480538

Received: June 23, 2017
Accepted after revision: August 22, 2017
Published online: December 1, 2017

Topical Coconut Oil in Very Preterm Infants: An Open-Label Randomised Controlled Trial

Tobias Strunk[a–c] Sameer Pupala[a] Julie Hibbert[b] Dorota Doherty[c]
Sanjay Patole[a–c]

[a]Neonatal Directorate, King Edward Memorial Hospital for Women, Subiaco, WA, and [b]Centre for Neonatal Research and Education and [c]Faculty of Health and Medical Sciences, University of Western Australia, Perth, WA, Australia

Keywords
Coconut oil · Preterm infant · Skin condition

Abstract
Background: The immature fragile skin of preterm infants represents an inadequate protective barrier. The emollient and anti-infective properties of coconut oil make it a potentially beneficial topical agent for this population. ***Objectives:*** Our aim was to evaluate feasibility, safety, and the effects of topical coconut oil on skin condition in very preterm infants. ***Methods:*** An open-label randomised controlled trial in preterm infants <30 weeks' gestation was conducted. Enrolled infants were randomised to receive either routine care or topical coconut oil (5 mL/kg) twice daily for 21 days, starting within 24 h of birth. The neonatal skin condition was the primary outcome, and was assessed using the Neonatal Skin Condition Score (NSCS) on days 1, 7, 14, and 21. The number of coconut oil applications was recorded to assess clinical feasibility and all enrolled infants were monitored for adverse effects of topical coconut application, such as skin irritation. ***Results:*** A total of 72 infants born <30 weeks' gestation were enrolled (36 infants per arm), with comparable demographic characteristics. Topical application of coconut oil was feasible and without adverse effects. The NSCS was maintained in the coconut oil group throughout the intervention period, but deteriorated from a median (IQR) of 3 (3–4) on day 1 to 4 (4–4) on day 21 in the control group (p = 0.01). There were no differences in common neonatal outcomes, including sepsis, necrotising enterocolitis, retinopathy of prematurity, chronic lung disease, and mortality. ***Conclusions:*** Topical coconut oil maintained a better skin condition in very preterm infants without adverse effects. This simple, safe, and affordable intervention warrants further investigation.

Introduction

Advances in neonatal intensive care have improved the survival of very preterm infants (gestation <30 weeks) [1]. The immature fragile skin of very preterm infants represents an inadequate protective barrier, and a poor skin condition may contribute to the risk of nosocomial infections [2–4]. Topical emollients have the potential to improve skin condition, enhance the skin barrier function, reduce water loss, and prevent topical and neonatal sepsis [5–8]. In many Asian and African low- and middle-income settings (LMIC), newborn and infant massage

E-Mail karger@karger.com
www.karger.com/neo

Assoc. Prof. Tobias Strunk
Neonatal Directorate, King Edward Memorial Hospital for Women
374 Bagot Road
Subiaco, WA 6008 (Australia)
E-Mail tobias.strunk@health.wa.gov.au

with natural oils has been used for centuries, with beneficial effects reported, including an improved skin barrier function, reduced transepidermal water loss, and lower energy expenditure for temperature maintenance [7, 9–12]. A systematic review of 8 randomised controlled trials (RCTs) of preterm infants (<37 weeks) in LMIC settings assessed the effects of topical emollients, predominantly vegetable oils [7]. The review concludes that topical emollients significantly improved weight gain, and reduced the risk of infection and mortality. In contrast, a recent Cochrane review of topical emollient application in preterm infants in LMIC and high-income settings concluded that there was insufficient quality data on infection or mortality, but that topical application of vegetable oils may improve weight gain and that more studies are needed [13]. The varying results may be partially explained by the predominant use of natural oils in more mature infants in LMICs, whereas mineral oil-based emollients are commonly used in high-resource neonatal intensive care units (NICUs) in extremely immature and vulnerable preterm infants.

There are no evidence-based recommendations for routine emollient therapy for newborn infants in high-resource settings, especially for the most immature preterm infants with the highest burden of poor skin integrity, acquired infections, and poor weight gain. Some of the frequently used natural oils, including mustard seed oil and olive oil, have potentially deleterious effects on the newborn skin condition and barrier function [7]. In contrast, coconut oil has no such effects and, importantly, contains high amounts of lauric acid and its ester, monolaurin, both of which have well-documented and potentially clinically relevant antimicrobial properties [14–18]. Furthermore, a recent RCT of topical coconut oil in preterm infants (>26 to <37 weeks) in Pakistan resulted in better weight gain and a substantially reduced incidence of late-onset sepsis (LOS) [6]. While current evidence indicates potential benefits of topical coconut oil application in preterm infants, data on its efficacy in very preterm infants in high-income settings are lacking. Here, we report the results of an open-label RCT of topical coconut oil in very preterm infants (<30 weeks) from a large, tertiary NICU in Western Australia.

Subjects and Methods

Design and Setting

An open-label RCT was conducted at the NICU at Edward Memorial Hospital, Perth, the only perinatal referral centre in Western Australia. Recruitment took place between March and October 2016. The eligibility criteria were: gestation <30 weeks, postnatal age <24 h, and informed consent. Exclusion criteria were: the presence of major congenital malformations, congenital skin abnormality or signs of pre-existing skin infection, and the infant being critically unwell and not expected to survive.

Ethics

The RCT was approved by the institutional human research ethics committee (HREC2015191EW) and registered with the Australian Clinical Trial Registry (ACTRN12616000042448). Infants were enrolled once written informed consent was obtained from the parents or guardians.

Outcomes

The primary outcomes were: (1) the feasibility of the coconut oil application to enrolled infants as per the study protocol, (2) safety – the incidence of skin irritation or local infection, and (3) efficacy – skin condition as assessed by the Neonatal Skin Condition Score (NSCS). Secondary outcomes included the incidence of temperature instability, weight gain, intraventricular haemorrhage, LOS, necrotising enterocolitis, retinopathy of prematurity, chronic lung disease, and mortality.

Assessment of Skin Integrity

The NSCS is a validated tool for the assessment of neonatal skin condition and is routinely used at the trial centre [19]. Two independent assessors applied the NSCS to enrolled infants prior to starting the study intervention and on days 7, 14, and 21.

Adverse Events

All adverse events, especially skin irritation and/or inflammation leading to the cessation of the intervention, were monitored.

Randomisation, Allocation Concealment, and Blinding

Computer-generated random numbers (variable blocks of 4) were used for randomisation stratified by gestation (<28 weeks and ≥28 to <30 weeks) to ensure an equal distribution between the 2 arms of the trial. Randomisation was performed by a statistician not involved in the RCT. Random numbers were contained in sealed, coded, opaque, and serially numbered envelopes stored at the NICU. Allocation concealment was optimised by opening the randomisation envelopes only after informed consent and basic demographic data were obtained. Infants not treated with topical coconut oil served as controls. Considering that blinding was not achievable, parents, all investigators, and healthcare team members could not be masked to the allocation status of the enrolled infants. The internal validity of the trial was optimised by ensuring that the biostatistician responsible for analysing the data was unaware of the allocation status.

Intervention

Virgin coconut oil was sourced from a single manufacturer (Nature Pacific, Varsity Lakes, QLD, Australia) and distributed to study participants in individually sealed 5-mL sachets for each application. Regulatory approval was obtained from the Therapeutic Goods Administration, Australia (Clinical Trial notification CT-2015-CTN-03227-1).

The coconut oil (5 mL/kg every 12 h for 21 days) was applied by trained nursing staff and commenced within 24 h of birth. A routine hand hygiene protocol was followed. The coconut oil was

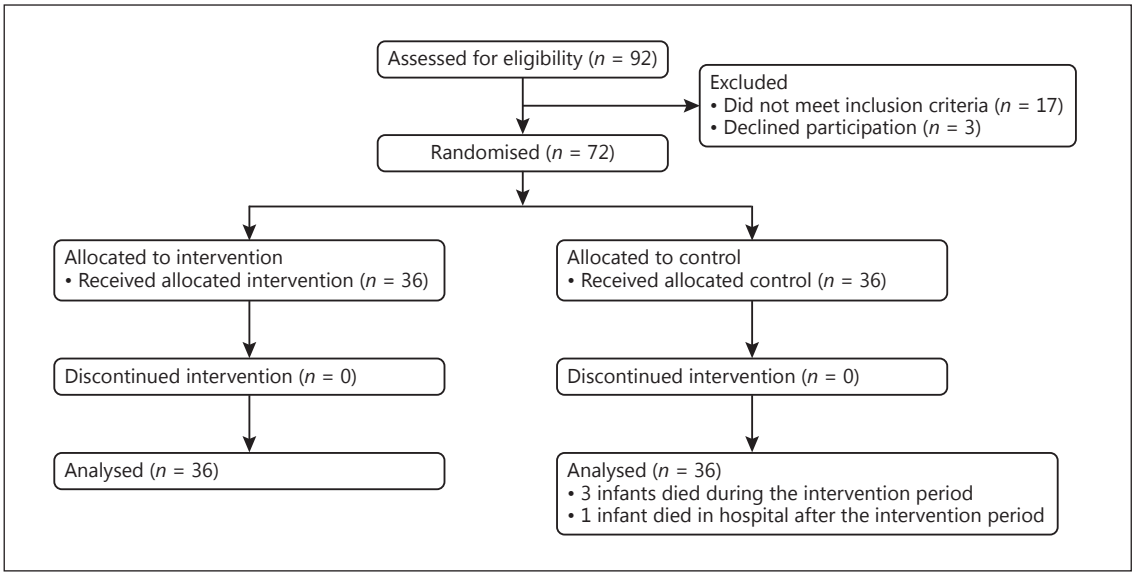

Fig. 1. Trial flow chart.

applied to the entire skin, excluding the face, scalp, and sites of any catheters or drains, and involved gentle strokes without massage. The application was completed in 2–3 min. To avoid excessive handling, the oil application was performed with routine cares.

The control group received routine neonatal care as per current NICU guidelines without topical coconut oil application. The study intervention could not be blinded as: (a) there is currently no topical emollient recommended for routine neonatal skin care, and (b) coconut oil is readily distinguishable by its fragrance.

Sample Size Estimation

Based on published data, recruitment of 60 very preterm infants (30 each in the intervention and control arms) assured 80% power to detect a 1 – standard deviation difference in the skin integrity score in the intervention versus control infants in this pilot RCT [20]. An additional 12 infants were recruited to cover for a potential 20% loss to follow-up. Therefore, a total of 72 preterm infants were enrolled (36 in each arm).

Statistical Analysis

The analysis was based on the intention-to-treat principle. The Australian National Health and Medical Research Council guidelines were followed for protecting confidentiality and data storage [21]. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools [22].

Continuous data were summarised using medians and interquartile ranges (IQR), and categorical data were summarised using frequency distributions. Univariate group comparisons were performed using the χ^2 and Fisher exact tests, as appropriate. Linear regression analysis on log-transformed repeated NSCS scores over a period of 3 weeks was performed with individual neonates modelled as random effects. The interaction between group and time was modelled to evaluate changes in NSCS scores over time. The pairwise comparisons between the groups and pairwise contrasts within each group at each time point were tested at an overall significance level 0.05 with Bonferroni correction for multiple comparisons. Data analyses were performed using SPSS version 20 (IBM, Armonk, New York, NY, USA). All hypothesis tests were 2-sided, and p values <0.05 were considered significant.

Results

There were 92 eligible infants delivered during the study period and 72 preterm infants were enrolled. Parents of 3 participants declined consent, while 17 did not meet the inclusion criteria (Fig. 1). The neonatal demographic characteristics were comparable between the 2 arms of the trial (Table 1). The gestational age ranges were 23.7–29.9 weeks for the intervention and 23.0–29.9 weeks for the control groups. Three participants died during the study intervention period as a result of necrotising enterocolitis, intestinal perforation, and severe pulmonary hypertension, and all 3 were in the control arm. One infant, also in the control arm, died after the intervention period from respiratory failure.

Primary Outcomes

Skin Condition. The median (IQR) NSCS deteriorated from 3 (3–4) on day 1 to 4 (4–4) on day 21 in the control group, but remained stable from birth throughout the intervention period in the coconut oil group infants (p = 0.01; Fig. 2).

Table 1. Neonatal demographic characteristics

Characteristics	Coconut oil (n = 36)	Control (n = 36)	p value
Gestation, weeks	27.9 (26.3–29.3)	27.9 (25.4–29.1)	0.77
Birth weight, g	1,070 (879–1,202)	950 (726–1,155)	0.2
Birth weight z-score	0.1237 (–0.3954 to 0.5281)	–0.606 (–0.8846 to 0.3737)	0.31
Caesarean section	20 (55.6)	25 (69.4)	0.22
Male	13 (36.1)	19 (52.8)	0.16
Multiple births	9 (25)	6 (16.7)	0.58
PPROM >24 h	7 (19.4)	6 (16.7)	0.76
Antenatal glucocorticoid exposure	25 (69.4)	26 (72.2)	0.78
APGAR <7 at 5 min	9 (25)	5 (13.8)	0.37
CRIB II score	9 (6.3–11)	9 (7–13.8)	0.408

Data are expressed as the median (IQR) or n (%). PPROM, preterm premature rupture of membranes.

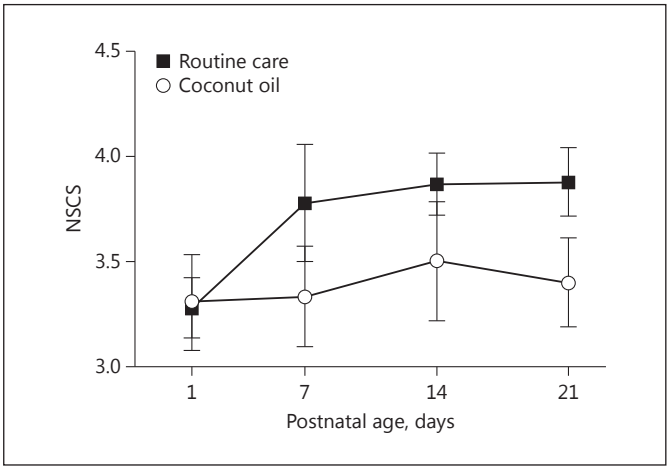

Fig. 2. The NSCS during the intervention period (median, 95% CI).

Feasibility. Twice-daily coconut oil application was highly feasible, with all infants in the treatment arm completing 100% of the scheduled coconut oil applications. All infants in both study arms completed all NSCS assessments until death or day 21.

Safety. There were no adverse events attributed to coconut oil. The incidence of skin irritation was comparable (coconut oil group, n = 9 [25%] vs. control group, n = 8 [22.2%]; p = 0.779). The incidence of temperature instability was similar in the coconut oil versus control group infants. There were 10 (27.8%) infants in the control group and 14 (38.9%) infants in the coconut oil group without any adverse outcomes. No statistical hypothesis tests were performed on secondary outcomes due to the sample size of this pilot RCT (Table 2).

Discussion

This is the first RCT to assess the feasibility, safety, and effect on skin condition of topical coconut oil in very preterm infants in a high-resource setting, and the data indicate that prophylactic topical coconut oil results in significantly better skin integrity without adverse effects. The neonatal skin is colonised with microorganisms, including potential pathogens, within days of birth, and poor skin integrity is a frequent problem in the NICU and likely associated with an increased risk of LOS. Despite this, there are currently no emollient products recommended for routine skin care in this high-risk population. Published data, predominantly from LMIC settings and utilising natural oils in relatively mature preterm infants, suggest that this practice improves skin integrity, weight gain, and may reduce neonatal sepsis. Beneficial effects were also observed for the topical use of the mineral oil-derived emollient, namely Aquaphor ointment. In contrast, a large RCT of Aquaphor ointment in very preterm infants in high-resource NICUs found that, while it improved skin condition, there was the possibility of an increased LOS incidence in the smallest infants [23].

The positive effects on skin condition observed in this trial are in line with previous neonatal RCTs of coconut oil from LMIC settings. Maintaining skin integrity may reduce the incidence of LOS, with a high proportion of LOS organisms recovered from blood cultures originating from the skin, even in the absence of indwelling vascular catheters. In addition to better skin integrity, and based on its antimicrobial properties, coconut oil might modulate the epidermal microbiome during the time of

Table 2. Secondary outcomes

Outcomes	Coconut oil (n = 36)	Controls (n = 36)
Maximum weight loss[1], % of birth weight	5 (0.9–8.3)	2 (0–8.2)
Time to regain birth weight, days	5 (2–8)	5 (2–10)
Time to full enteral feeds (150 mL/kg/day), days	8 (6–14)	10 (6–15)
Weight day 7, g	1,100 (939–1,257)	1,007 (751–1,210)
Weight day 14, g	1,180 (1,051–1,345)	1,056 (921–1,348)
Weight day 21, g	1,312 (1,085–1,502)	1,296 (1,066–1,492)
Weight at discharge, g	3,042 (2,528–3,693)	2,988 (2,728–3,441)
Time to grade out of incubator, days	32 (23–46)	31 (24–44)
Episodes of abnormal temperature[2]	3 (2–4)	3 (2–3)
Age at discharge home, days	77 (63–110)	77 (69–90)
Mortality	0 (0)	4 (11.1)
Respiratory support		
CPAP	36 (100)	34 (94.4)
Duration, h	606.5 (118–970.3)	514.5 (134.3–1102.8)
Endotracheal ventilation	27 (75.0)	27 (75.0)
Duration, h	39 (11–275)	45 (20–654)
Surfactant therapy	29 (80.6)	27 (75.0)
EOS	0 (0)	0 (0)
LOS overall	2 (5.6)	5 (13.9)
During study intervention	1 (2.8)	3 (8.3)
After study intervention	1 (2.8)	2 (5.6)
LOS organisms	*S. marcescens*, *E. faecalis*, *S. warneri*	*E. cloacae* and *E. faecalis*, *S. capitis*, *S. epidermidis*, *S. aureus*
NEC	0 (0)	2 (5.6)
Chronic lung disease	14 (38.9)	15 (41.7)
PDA	19 (52.8)	20 (61.1)
Any ROP	9 (25)	16 (44.4)
ROP requiring treatment[3]	4 (44.4)	4 (25)

Data are expressed as the median (IQR) or n (%). CPAP, continuous positive airway pressure; EOS, early-onset sepsis; LOS, late-onset sepsis; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.
[1] From birth to day 7. [2] Defined as <36.5° C or >37.5° C; median number per baby. [3] % based on neonates with any ROP.

highest LOS risk, but such data are not yet available. In this RCT, fewer LOS cases occurred in the control compared to the intervention arm, but it was not powered for LOS as a primary outcome. In contrast to findings from LMIC settings, we did not observe weight gain differences between the groups. This may be due to the recruitment of a significantly more immature cohort of preterm infants than previous studies, and because the application of coconut oil involved only a few gentle strokes rather than massage.

The strengths of this RCT include its prospective controlled design that was powered to detect differences in skin condition during the first critical weeks of life. Furthermore, all enrolled infants received the complete study intervention until death or the end of the intervention period, and there were no withdrawals from the study. One unavoidable limitation of our study was the lack of an appropriate placebo as there currently are no topical emollients recommended for routine neonatal skin care in Australia, and therefore the trial could not be blinded.

In conclusion, this RCT demonstrates that the topical application of coconut oil, starting within 24 h from birth, in very preterm infants is feasible, safe, and effective in maintaining skin integrity. Adequately powered RCTs are required to assess whether this simple, affordable, and safe intervention may also reduce the burden of LOS in high-resource settings.

Acknowledgements

This study was supported by a grant from the Channel 7 Telethon Trust and Women and Infants Research Foundation. We thank the families, participants, and all staff that contributed to this study and made it possible.

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz ID 3rd, Watterberg KL, Saha S, Das A, Higgins RD: Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443–456.

2 Kalia YN, Nonato LB, Lund CH, Guy RH: Development of skin barrier function in premature infants. J Invest Dermatol 1998;111:320–326.

3 Lund C, Kuller J, Lane A, Lott JW, Raines DA: Neonatal skin care: the scientific basis for practice. J Obstet Gynecol Neonatal Nurs 1999;28:241–254.

4 Hammarlund K, Nilsson GE, Oberg PA, Sedin G: Transepidermal water loss in newborn infants. II. Relation to activity and body temperature. Acta Paediatr Scand 1979;68:371–376.

5 Zutavern A, von Klot S, Gehring U, Krauss-Etschmann S, Heinrich J: Pre-natal and post-natal exposure to respiratory infection and atopic diseases development: a historical cohort study. Respir Res 2006;7:81.

6 Salam RA, Darmstadt GL, Bhutta ZA: Effect of emollient therapy on clinical outcomes in preterm neonates in Pakistan: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2015;100:F210–F215.

7 Salam RA, Das JK, Darmstadt GL, Bhutta ZA: Emollient therapy for preterm newborn infants – evidence from the developing world. BMC Public Health 2013;13(suppl 3):S31.

8 Darmstadt GL, Ahmed S, Ahmed AS, Saha SK: Mechanism for prevention of infection in preterm neonates by topical emollients: a randomized, controlled clinical trial. Pediatr Infect Dis J 2014;33:1124–1127.

9 Darmstadt GL, Saha SK: Traditional practice of oil massage of neonates in Bangladesh. J Health Popul Nutr 2002;20:184–188.

10 Fernandez A, Patkar S, Chawla C, Taskar T, Prabhu SV: Oil application in preterm babies – a source of warmth and nutrition. Indian Pediatr 1987;24:1111–1116.

11 Duffy JL, Ferguson RM, Darmstadt GL: Opportunities for improving, adapting and introducing emollient therapy and improved newborn skin care practices in Africa. J Trop Pediatr 2012;58:88–95.

12 Yurdakok M, Yurdakok K: Topical vegetable oil therapy for premature infants. J Pediatr 1997;130:330–332.

13 Cleminson J, McGuire W: Topical emollient for prevention of infection in preterm infants: a systematic review. Lancet 2015;385(suppl 1):S31.

14 Carpo BG, Verallo-Rowell VM, Kabara J: Novel antibacterial activity of monolaurin compared with conventional antibiotics against organisms from skin infections: an in vitro study. J Drugs Dermatol 2007;6:991–998.

15 Batovska DI, Todorova IT, Tsvetkova IV, Najdenski HM: Antibacterial study of the medium chain fatty acids and their 1-monoglycerides: individual effects and synergistic relationships. Pol J Microbiol 2009;58:43–47.

16 Fischer CL, Blanchette DR, Brogden KA, Dawson DV, Drake DR, Hill JR, Wertz PW: The roles of cutaneous lipids in host defense. Biochim Biophys Acta 2014;1841:319–322.

17 Ogbolu DO, Oni AA, Daini OA, Oloko AP: In vitro antimicrobial properties of coconut oil on *Candida* species in Ibadan, Nigeria. J Med Food 2007;10:384–387.

18 Nakatsuji T, Kao MC, Fang JY, Zouboulis CC, Zhang L, Gallo RL, Huang CM: Antimicrobial property of lauric acid against *Propionibacterium acnes*: its therapeutic potential for inflammatory acne vulgaris. J Invest Dermatol 2009;129:2480–2488.

19 Lund CH, Osborne JW: Validity and reliability of the Neonatal Skin Condition Score. J Obstet Gynecol Neonatal Nurs 2004;33:320–327.

20 Darmstadt GL, Badrawi N, Law PA, Ahmed S, Bashir M, Iskander I, Al Said D, El Kholy A, Husein MH, Alam A, Winch PJ, Gipson R, Santosham M: Topically applied sunflower seed oil prevents invasive bacterial infections in preterm infants in Egypt: a randomized, controlled clinical trial. Pediatr Infect Dis J 2004;23:719–725.

21 Australian Government National Health and Medical Research Council: Joint NHMRC/AVCC statement and guidelines on research practice. Canberra, NHMRC, 2015.

22 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–381.

23 Edwards WH, Conner JM, Soll RF; Vermont Oxford Network Neonatal Skin Care Study Group: The effect of prophylactic ointment therapy on nosocomial sepsis rates and skin integrity in infants with birth weights of 501 to 1000 g. Pediatrics 2004;113:1195–1203.