Randomized Trial of Occlusive Wrap for Heat Loss Prevention in Preterm Infants

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Objective To determine whether the application of occlusive wrap applied immediately after birth will reduce mortality in very preterm infants.

Study design This was a prospective randomized controlled trial of infants born 24 0/7 to 27 6/7 weeks' gestation who were assigned randomly to occlusive wrap or no wrap. The primary outcome was all cause mortality at discharge or 6 months' corrected age. Secondary outcomes included temperature, Apgar scores, pH, base deficit, blood pressure and glucose, respiratory distress syndrome, bronchopulmonary dysplasia, seizures, patent ductus arteriosus, necrotizing enterocolitis, gastrointestinal perforation, intraventricular hemorrhage, cystic periventricular leukomalacia, pulmonary hemorrhage, retinopathy of prematurity, sepsis, hearing screen, and pneumothorax.

Results Eight hundred one infants were enrolled. There was no difference in baseline population characteristics. There were no significant differences in mortality (OR 1.0, 95% CI 0.7-1.5). Wrap infants had statistically significant greater baseline temperatures (36.3°C wrap vs 35.7°C no wrap, $P < .0001$) and poststabilization temperatures (36.6°C vs 36.2°C, $P < .001$) than nonwrap infants. For the secondary outcomes, there was a significant decrease in pulmonary hemorrhage (OR 0.6, 95% CI 0.3-0.9) in the wrap group and a significant lower mean one minute Apgar score ($P = .007$) in the wrap group. The study was stopped early because continued enrollment would not result in the attainment of a significant difference in the primary outcome.

Conclusion Application of occlusive wrap to very preterm infants immediately after birth results in greater mean body temperature but does not reduce mortality. *(J Pediatr 2015;166:262-8)*.

For more than 40 years, hypothermia has been recognized as an independent risk factor for death in newborn infants.[1-11] Despite modern resuscitation techniques, 40%-65% of premature newborns still experience hypothermia, and it remains an independent risk factor for death in this population.[2,12,13] Very preterm infants are particularly vulnerable to heat loss because of immature, keratin-deficient skin without subcutaneous fat, poor vasomotor control, and increased surface area to body weight ratio.[11,14-16] Besides an increased risk of mortality, other complications associated with neonatal hypothermia include morbidity from acidosis, delayed transition from fetal to newborn circulation, abnormal coagulation, infection, and respiratory distress syndrome.[2]

The application of occlusive wrap immediately after birth can reduce immediate postnatal evaporative heat loss. In a systematic review, Cramer et al[17] evaluated 3 small, randomized controlled trials and 5 trials using historical controls that studied the use of occlusive wrap immediately after birth in infants born at less than 33 weeks' gestation. They concluded that infants wrapped immediately after birth had significantly greater admission temperatures compared with nonwrapped infants and that wrapping significantly reduced the incidence of hypothermia. The systematic review did not show a significant difference in mortality between wrapped and unwrapped infants. An adequately powered, randomized controlled trial (RCT), therefore, was needed to determine whether

DR	Delivery room
GA	Gestational age
HeLP	Heat Loss Prevention
PDA	Patent ductus arteriosus
RCT	Randomized controlled trial
VON	Vermont Oxford Network

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the use of wrapping immediately after delivery would result in a difference in mortality.

Methods

We hypothesized that polyethylene occlusive wrap applied immediately after delivery to infants born at 24 0/7 to 27 6/7 weeks' gestation would result in decreased mortality compared with the conventional method of drying and thermal management.

We conducted a multicenter RCT at 39 participating Vermont Oxford Network (VON) centers. All participating centers received a training package and participated in a teleconference to ensure familiarity with the study protocol and procedures before patients were enrolled. Detailed methods have been published previously.[18]

Primary Outcome and Secondary Outcomes

The primary outcome was all-cause mortality occurring before discharge from the hospital or 6 months' corrected age, whichever came first. We attempted to collect primary outcome data on infants transferred to other institutions. Trial infants who remained hospitalized at 6 months' corrected age were coded as being alive.

Secondary outcomes included baseline temperature taken after cardiorespiratory stabilization if admitted directly to the neonatal intensive care unit or after arrival in the neonatal intensive care unit if immediate resuscitation took place in the delivery room (DR), and poststabilization temperature taken after admission procedures were completed and the infant was left to rest in a stable thermoneutral environment. Other secondary outcomes included Apgar scores, pH, base deficit, and blood pressure and blood glucose. The incidence of common complications of prematurity, including respiratory distress syndrome, bronchopulmonary dysplasia, seizures, patent ductus arteriosus (PDA), necrotizing enterocolitis, gastrointestinal perforation, intraventricular hemorrhage, cystic periventricular leukomalacia, pulmonary hemorrhage, retinopathy of prematurity, sepsis, failed hearing screen, and pneumothorax were compared.[19]

All temperatures were axillary and taken with a standardized thermometer (Medline Digital Thermometer, Mundelein, Illinois). Rectal temperatures were optional and only taken when infants were not wrapped. Axillary temperature on wrapped infants was taken over the wrap to prevent opening the wrap and potential cooling of the infant.

Statistical Analyses

Analysis was performed on an intention-to-treat basis. Baseline mortality data from VON for inborn infants 24 0/7 to 27 6/7 weeks' gestation in the calendar year 2002 was 22.7%. To detect a 25% relative risk reduction from 22.7% to 17% at 80% power and alpha of 0.05, enrollment of 802 infants in each group was planned.

Permuted variable block randomization lists using random-number generating software were produced. Separate independent randomization lists were created for each site and each gestational age (GA) stratum (stratum 1: 24 0/7 weeks to 25 6/7 weeks; stratum 2: 26 0/7 weeks to 27 6/7 weeks). Group allocation was 1:1.

Descriptive statistics were calculated for all variables of interest. Continuous measures were summarized via mean and SD, whereas categorical measures were summarized by the use of the count and percentage. The primary outcome of mortality was assessed between groups using a logistic model adjusting for the correlation among observations taken at the same site. Results were reported with OR and their associated 95% CI. Secondary outcomes were compared between groups using χ^2 analyses or t tests, depending on whether the outcome measure was categorical or continuous. A logistic regression model was run to assess differences in mortality between groups adjusting for predictors of interest (GA, sex, method of delivery, antenatal steroids, race, and birth weight) as well as the correlation among observations taken at the same site. All analyses were run across the entire sample as well as separately by stratum. All analyses used SAS Version 9.2 (SAS Institute, Cary, North Carolina). A trend of test analysis was run to compare the distribution of baseline and poststabilization temperatures in wrap and no wrap infants in predetermined temperature ranges.

Results

Infants from 39 VON centers were enrolled between November 2004 and June 2010. The number of eligible infants and the number assigned to each group are in Figure 1. Stratum 1 (24 0/7 to 25 6/7 weeks' gestation) included 366 infants and stratum 2 (26 0/7 to 27 6/7 weeks' gestation) included 435 infants.

All sites were offered the option to apply to their local institutional research board for permission to use a waiver of consent or delayed consent. Four sites, 1 Canadian and 3 US, applied and received approval. The Canadian site allowed any infant who was born within the first 24 hours of maternal admission to the hospital to be enrolled under delayed consent. When appropriate, consent then had to be obtained to submit data collected during the study period and to continue with the study. All other infants had to be enrolled under informed consent. The US sites were approved to use a waiver of consent or delayed consent at any time. The families of all infants enrolled in the study under a delay/waiver of consent were informed of the study, and any infant enrolled at any time (under informed, waiver or delayed consent) was allowed to be removed from the study if the parent(s) wished. Eighty-three percent (668) of the infants were enrolled under informed consent, and 17% (133) were enrolled under delayed/waiver of consent.

Interim analyses for safety were performed at 25% enrollment, and for safety and futility at 50% enrollment of the projected sample size. The futility analysis determined that even if the full sample size were enrolled, the study would not achieve its goal of demonstrating a 25% relative risk

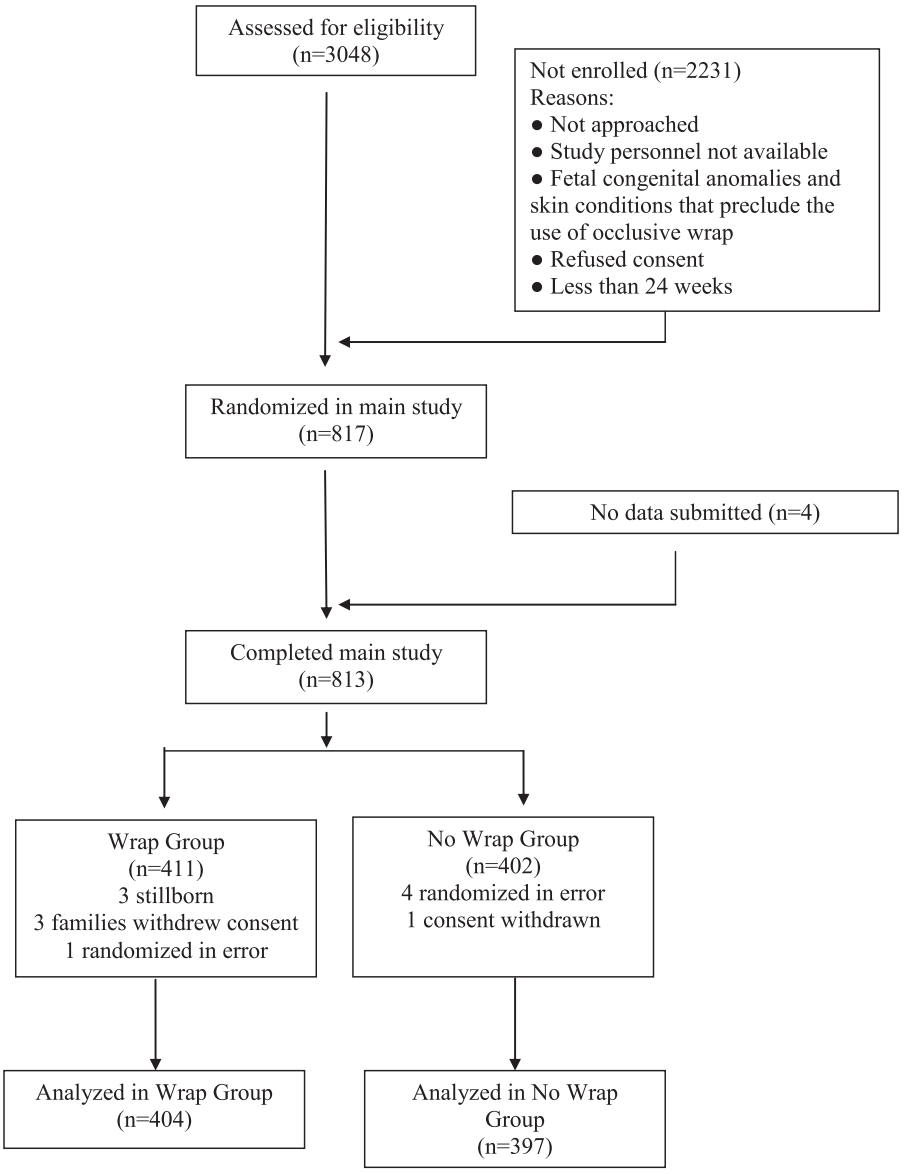

Figure 1. Number of infants who were eligible for the study and randomly assigned to the wrap or no-wrap group.

reduction in the primary outcome. Consequently, the Data and Safety Monitoring Board recommended halting enrollment, and the Heat Loss Prevention (HeLP) Trial Steering Committee closed enrollment June 30, 2010.

There were no statistically significant differences in the maternal or neonatal characteristics between groups (**Table I**). The mean temperature of the DR for the wrap group was 23.5°C (range 16.1°C to 36°C) compared with 23.3°C for the no-wrap group (range 15°C to 32.2°C).

Mortality data were available for 799 of the 801 infants. There was no significant difference in mortality between the 2 groups with 83 deaths (20.5%) in the wrap group and 79 deaths (20%) in the no-wrap group (OR 1.0, 95% CI 0.7-1.5, **Table II**; available at www.jpeds.com). After adjustment for variables that could impact on the risk of death (GA, sex, method of delivery, birth weight, race, antenatal steroids), logistic regression analysis revealed that the difference between groups remained nonsignificant (OR 0.9, 95% CI 0.6-1.3).

In infants 24 0/7 to 25 6/7 weeks' gestation (stratum 1), 26.1% of the wrap group died compared with 33.2% of the no-wrap group (OR 0.7, 95% CI 0.5-1.1; **Table II**). In infants 26 0/7 to 27 6/7 weeks' gestation (stratum 2), 15.7% of the wrap group died compared with 9.2% of the no-wrap group (OR 1.8, 95% CI 1.0-3.3). After adjustment for variables that could impact the risk of death, logistic regression analysis revealed that the difference between groups was no longer statistically significant (stratum 1: OR 0.66, 95% CI 0.40-1.1 and stratum 2: OR 1.6, 95% CI 0.8-3.0).

Table I. Baseline characteristics of infants at randomization

	Wrap	No wrap
Maternal characteristics		
Prenatal care	390/403 (97%)	382/397 (96%)
Any antenatal steroids	375/403 (93%)	370/395 (94%)
Vaginal delivery	123/404 (30%)	129/397 (33%)
Rupture of membranes >24 h	113/399 (28%)	130/391 (33%)
Chorioamnionitis	79/380 (21%)	75/374 (20%)
Mean maternal temperature before delivery, °C (range)	36.9 (33.7-39.7)	36.9 (34.6-39.5)
Neonatal characteristics		
Birth weight	800 ± 205 (SD)	821 ± 199 (SD)
GA in weeks, mean	25.6	26.0
Sex		
Male	208/404 (51%)	219/397 (55%)
Race		
Asian	48/402 (12%)	41/396 (10%)
Black	106/402 (26%)	112/396 (28%)
Native American	0/402 (0%)	2/396 (<1%)
White	230/402 (57%)	226/396 (57%)
Other	18/402 (5%)	15/396 (4%)
Hispanic	47/404 (12%)	42/397 (11%)
Maternal education: less than high school	76/368 (21%)	71/367 (19%)
Multiple birth	75/404 (19%)	84/397 (21%)

For the secondary outcomes, there was a significantly lower mean 1-minute Apgar score ($P = .007$) in the wrap group but no differences in the 5- or 10-minute Apgar scores. The median one minute Apgar score was 5 with a lower and upper quartile range of 3-7 for both wrap and no-wrap groups. There was also a statistically significant decrease in pulmonary hemorrhage (OR 0.6, 95% CI 0.3-0.9) in the wrap group (**Table III**; available at www.jpeds.com). In the lower GA stratum there was a statistically significant decrease in the risk of treated PDA (OR 0.6, 95% CI 0.4-0.99) and pulmonary hemorrhage (OR 0.4, 95% CI 0.2-0.8) in the wrap group. This difference was not seen in the infants randomized to stratum two. There were no other differences between the groups.

Infants randomized to the wrap group were wrapped at a mean time of 24 seconds after birth with the wrap being removed at a mean time of 84 minutes after birth. There was no difference between groups in the length of time spent in the DR (wrapped infants, 16 minutes; no-wrap infants, 16 minutes).

Infants randomized to the wrap group had significantly greater mean baseline temperature (36.3°C) compared with the no-wrap group (35.7°C) ($P < .0001$) as well as significantly greater mean poststabilization temperature for the wrap group (36.6°C) compared with the no-wrap group (36.2°C) ($P < .0001$).

Figure 2 shows the distributions of baseline and poststabilization temperatures for wrap and no wrap infants. With regard to severe hypothermia, 51 infants (7.2%) had a baseline temperature <34.5°C. The majority of these infants (42, or 82%) were in the no-wrap group; 35 infants (4.6%) had a poststabilization temperature <34.5°C, and the majority of these infants (23, or 66%) were also in the no-wrap group.

With regard to hyperthermia, 32 infants (4.5%) had a baseline temperature ≥37.5°C; the majority of these infants (28, or 88%) were in the wrap group. Sixty-one infants (8%) had a poststabilization temperature ≥37.5°C; the majority of these infants (43, or 70%) also were in the wrap group. DR temperature did not seem to contribute to the risk of hyperthermia. Wrapped infants resuscitated in a DR with a temperature >25°C were as likely to have a baseline temperature >38.0°C as wrapped infants resuscitated in a DR with a temperature <25°C ($P = .10$).

A trend of test analysis of the temperature distributions in both groups indicated a highly significant difference over temperature categories between groups ($P < .0001$) for both baseline and poststabilization temperatures, with no-wrap infants trending to be colder and wrap infants trending to be warmer in all temperature categories. There was a marginally significant difference in mortality favoring the no-wrap group in infants who had a baseline temperature between 35.5°C and 36.4°C (19.4% for the wrap group and 11.3% for the no-wrap group, $P = .05$). There were no statistically significant differences in mortality between the wrap and no-wrap groups for all other baseline and poststabilization temperature ranges.

Forty-three protocol violations were recorded for 37 infants in the no-wrap group, with the most common being the use of an adjunct heat source when the temperature was not known to be less than 35.5°C (n = 17), randomization card pulled out of sequence (n = 9), or infant wrapped after birth (n = 10). One hundred eighty-five protocol violations were recorded for 114 infants in the wrap group, including delayed application of wrap (n = 43), wrap opened (n = 42), wrap removed early (n = 18), use of adjunct heat source when the temperature was not known to be less than 35.5°C (n = 12), randomization card pulled out of sequence or lost (n = 14), and infant dried before wrap applied (n = 1).

Discussion

Even though the application of occlusive wrap to very preterm infants improved baseline and poststabilization body temperatures compared with standard management, there was no associated improvement in all-cause mortality. There were also no differences in the secondary outcomes except for the 1-minute Apgar score and pulmonary hemorrhage. In stratum 1 (24 0/7 to 25 6/7), there was a significant increase in both pulmonary hemorrhage and treated PDA in the no-wrap group. It is plausible that the increase in pulmonary hemorrhage in the no-wrap group could have been directly related to the increase in hypothermia, mediated via hemodynamic, metabolic, and/or hematologic effects. However,[20] this association must be considered speculative because this was one of many secondary outcomes.

The differences in mortality in both strata were lost after logistic regression. Because this study was not powered to detect a difference in mortality within strata, we cannot be sure that

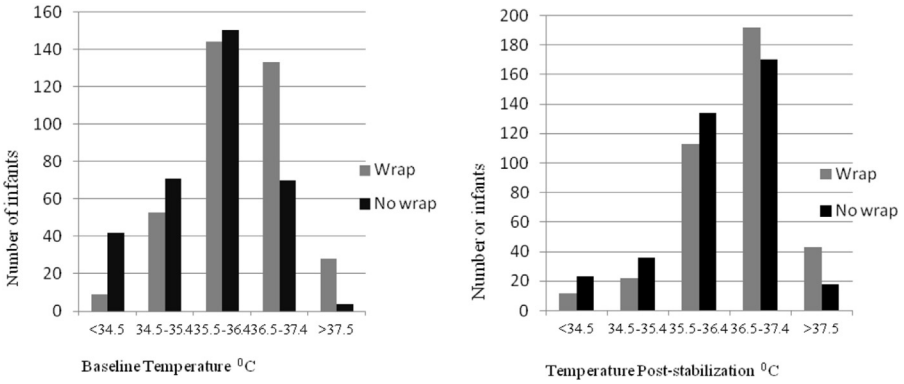

Figure 2. Distribution of baseline and poststabilization temperature in infants assigned to wrap and no-wrap groups.

there is no lifesaving benefit accrued by wrapping infants born at less than 25 6/7 weeks' gestation. The results indicate that such benefits may be greatest in the smallest, most premature infants. Similarly, we cannot be sure that there is not a potential lifesaving benefit in not wrapping infants born 26 0/7 to 27 6/7 weeks' gestation although this would seem unlikely.

Knobel et al[21] found that warmer DRs were associated with greater admission temperatures and that only the subgroup of infants who were both delivered in a warm DR and wrapped had a mean admission temperature >36.4°C. The World Health Organization[22] guidelines recommend that the minimum temperature in the DR be 25°C. This was rarely achieved in this study. Our data show that 86% of the infants enrolled received their initial resuscitation in a room with a temperature ≤25°C. Eleven percent of the no-wrap infants received their initial resuscitation in a room with a temperature >25°C compared with 17% of the infants randomized to the wrap group. There was no difference in mortality noted in these infants resuscitated in a warmer DR environment.

The possible association between duration of the wrap placement and mortality was analyzed, and there was no difference in the duration of wrap between those infants who survived and those who died ($P = .64$). Similar results were obtained for both age strata (stratum 1, $P = .59$; stratum 2, $P = .79$).

With regard to hyperthermia, the majority of infants who had a baseline and post stabilization temperature ≥37.5°C were in the wrap group (28/32 baseline and 43/61 poststabilization). The risk of hyperthermia was unrelated to the DR temperature. The number of participants in these hyperthermia analyses was quite small; therefore, it is impossible to speculate on any potential adverse effects of postnatal hyperthermia for wrapped infants.

Figure 3 shows the mortality rates for each temperature range for baseline and poststabilization temperatures. The greatest mortality rates were in the severely hypothermic infants with the rates steadily decreasing as temperatures increased. Mortality rates for infants who are hypothermic at poststabilization are greater, suggesting that hypothermic infants who remain hypothermic during the course of their resuscitation have increased odds of dying.

This study had several limitations. The study was stopped at 50% enrollment. Early closure may be recommended and

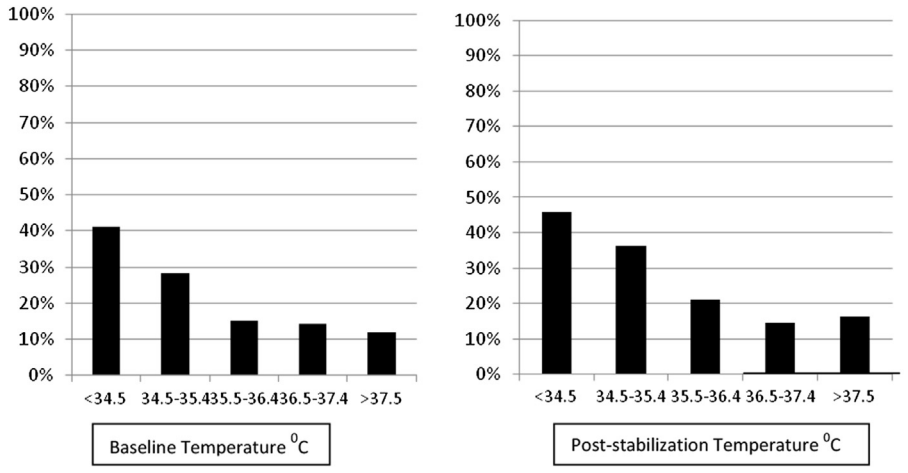

Figure 3. Mortality rates of all infants according to baseline and poststabilization temperature.

acceptable in large neonatal clinical trials due to futility,[23] safety,[24] or slow enrollment.[25,26] Regardless, this is the largest RCT evaluating the short-term effects of wrapping infants born between 24 0/7 and 27 6/7 weeks' gestation immediately after birth and offers a significant addition to the body of knowledge on this subject. Even if the trial had progressed beyond 50% enrollment, futility analysis revealed that we would not have achieved our 25% relative risk reduction goal for mortality.

Another limitation is the number of reported protocol violations. This was a large pragmatic trial with 39 participating centers. Not surprisingly, the majority of the protocol violations occurred in the treatment group rather than in the standard of care group. The most common protocol violations in the wrap group that could have affected the temperature of the infants were delayed application of the wrap, wrap opened during the study period, and early removal of the wrap. Despite these violations, infants in the wrap group still demonstrated significantly greater baseline and poststabilization temperatures than the no-wrap infants, suggesting that the wrap violations may not have greatly affected heat loss. Another common protocol violation was the use of an adjunct heat source when the temperature was not known to be less than 35.5°C. These infants could have been hypothermic, normothermic, or hyperthermic at the time of the application of the heat source. Only 12 infants in the wrap group experienced this violation, and 17 infants in the no-wrap group experience this violation. The numbers are small and occurred in both groups, suggesting that any distortion of the significance of the secondary outcome of temperature and the primary outcome of mortality is unlikely.

Another limitation may be the method of consent and enrollment. Informed consent for resuscitation trials is problematic and may result in selection bias and nongeneralizability of the results.[27,28] Ethical options for enrolling participants without individual informed consent, such as a waiver approved by the institutional review board or delay of consent, were used within some centers participating in the HeLP Trial and may pose a solution for this research barrier.

The application of occlusive wrap in infants born 24 0/7 to 27 6/7 weeks' gestation reduced the overall incidence of hypothermia but did not reduce mortality or other selected complications of prematurity. Our data show that hypothermia remains a problem for infants born 24 0/7 to 27 6/7 weeks' gestation, that mortality rates increase with the severity of hypothermia, and that wrapping had no strong significant benefit on reducing mortality. We speculate that hypothermia may be a marker for increased risk of death but wrapping is not an effective intervention to reduce hypothermia associated death. This may be especially true in infants who continue to lose heat during the stabilization period despite adequate environmental thermal care. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Enteric Disease Due to Enteropathogenic *Escherichia coli* in Hospitalized Infants in Kotzebue, Alaska

McAlister R, Brody JA, Overfield TM. J Pediatr 1965;66:343-8

It was known in the 1960s that diarrheal diseases were prevalent and were associated with substantial morbidity and mortality in rural Alaska. Identified etiologies primarily were *Shigella* and *Salmonella* species. High burden of disease was attributed to multiple factors, most importantly vulnerable clean water sources, lack of running water in homes, and poor handling of septic waste. The role of *Escherichia coli* was not documented. McAlister et al performed serotyping on stool isolates of *E coli* to identify enteropathogenic strains (EPEC) from 91 patients admitted to the Alaska Native Hospital in Kotzebue for diarrhea over a 12-month period from 1962-1963. A striking 44% had EPEC as the only pathogen identified; EPEC was the predominant pathogen identified in infants <1 year of age. The authors acknowledge inability to definitively ascribe illness to the *E coli* isolate (which predominantly was *E coli* 0111:B4); carriage rate in another study of healthy individuals was 6%. This study was the first to describe a substantial potential pathogenic role for EPEC in the Far North. Water and sewage handling in Kotzebue at the time of the study was delineated. Clean water sources were from melted ice or hauling of river water (in summer). Human waste was disposed of by use of "honey buckets," which were emptied into a garbage truck and dumped into the sea or adjacent rivers.

There is renewed interest in *E coli* as a pathogen of diarrheal disease because modern molecular assays can identify organisms containing a variety of virulence factors. Undoubtedly, the pathogenic role of *E coli* has been underestimated to date. Fifty years later, lack of piped clean water into homes and waste disposal out continue to be identified as underpinnings of the excessive burden of respiratory and gastrointestinal infections in indigenous Alaskan populations.

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Table II. Primary outcome for infants assigned to the wrap and no wrap groups

Mortality	Wrap	No wrap	OR (95% CI)	*P* value
All infants	83/404 (20.5%)	79/395 (20.0%)	1.0 (0.7-1.5)	.85
Stratum 1: 24 0/7 to 25 6/7	49/188 (26.1%)	59/178 (33.2%)	0.7 (0.5-1.1)	.14
Stratum 2: 26 0/7 to 27 6/7	34/216 (15.7%)	20/217 (9.2%)	1.8 (1.0-3.3)	.04

Table III. Secondary outcomes of infants assigned to the wrap and no-wrap groups

Secondary outcomes	Wrap	No wrap	*P* value	OR (95% CI)
Apgar scores (mean)				
1 min	4.68 ± 2.3	5.12 ± 2.3	**.007**	
5 min	7.05 ± 2.0	7.30 ± 1.8	.11	
10 min	7.31 ± 2.3	7.33 ± 2.2	.67	
RDS	373/404 (92%)	363/396 (92%)	.73	1.09 (0.7-1.08)
Treated PDA	192/401 (48%)	209/394 (53%)	.14	0.8 (0.6-1.1)
IVH				
Any	143/378 (38%)	148/375 (40%)	.97	0.95 (0.6-1.45)
Severe (3 and 4)	45/378 (12%)	45/375 (12%)		0.97 (0.5-1.8)
Cystic PVL	17/376 (5%)	21/375 (6%)	.50	0.78 (0.41-1.50)
Pulmonary hemorrhage	27/403 (7%)	44/393 (11%*)	**.03**	0.6 (0.3-0.9)
GI perforation	23/402 (6%)	18/393 (5%)	.47	1.3 (0.7-2.4)
NEC (stage 2 or more)	34/403 (8%)	35/394 (9%)	.82	0.9 (0.6-1.5)
ROP, severe (stage 3 or greater)	58/305 (19%)	57/301 (19%)	.98	1.0 (0.7-1.5)
Bacterial sepsis (early)	16/401 (4%)	22/394 (6%)	.29	0.7 (0.4-1.4)
Sepsis and/or meningitis late (any bacterial)	78/373 (21%)	93/369 (25%)	.16	0.8 (0.5-1.1)
Sepsis and/or meningitis late (coagulase negative staphylococcus only)	86/373 (23%)	80/367 (22%)	.68	1.1 (0.8-1.5)
Sepsis and/or meningitis late (fungal)	25/372 (7%)	20/367 (6%)	.47	1.3 (0.7-2.3)
BPD (collapsed category analysis)	184/354 (52%)	182/348 (52%)	.93	1.0 (0.7-1.3)
Steroids for BPD	75/403 (19%)	78/393 (20%)	.66	0.9 (0.6-1.3)
Pneumothorax	24/403 (6%)	24/393 (6%)	.93	1.0 (0.5-1.7)

BPD, bronchopulmonary dysplasia; *GI*, gastrointestinal; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *PVL*, periventricular leukomalacia; *RDS*, respiratory distress syndrome; *ROP*, retinopathy of prematurity.
Bolded values are statistically significant.