

ORIGINAL ARTICLE

Fever in healthy asymptomatic newborns during the first days of life

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Objective: To determine the characteristics of febrile full term infants during the first days of life, and to discover the rate of serious bacterial infections among low risk neonates with systemic fever.**Design:** A retrospective case-control study of 122 cases and 122 controls in a single institution.**Results:** Weight loss, breast feeding, caesarean section delivery, and high birth weight were found to be the most significant predictors of developing fever during the first days of life. Of the 122 patients in the study group, only one had a serious bacterial infection (a positive urine culture for group B streptococcus).**Conclusions:** In low risk full term infants, fever with no other symptoms during the first days of life (but after the first day) is related primarily to dehydration, breast feeding, caesarean section, and high birth weight. Infection is the least common explanation.

Fever during the neonatal period is considered an alarming sign of systemic infection. Affected babies are usually admitted to hospital after a complete sepsis work up and treated with antibiotics for three to five days. Only a few studies have tried to identify infants with fever yet have a low risk of serious bacterial infection.^{1–6} In these studies, normal physical examination and laboratory tests were correlated with low risk for serious bacterial infection. In some of the studies, low risk babies were treated on an ambulatory basis, and no antibiotic treatment was given. However, in babies under the age of 1 month presenting with fever, the same definition of low risk failed to predict serious bacterial infection.^{7–8} To the best of our knowledge, only one study⁹ has attempted to identify low risk babies with fever during the first days of life. Appleton and Foo¹⁰ described the phenomenon of dehydration fever in large breast fed babies on days 3–4 of life. They stated that much of the current neonatal literature makes little or no reference to dehydration fever. Singh *et al*¹¹ discussed the possible pathogenesis of this phenomenon, suggesting that fever may be caused by environmental temperature rather than dehydration.

In our nursery, healthy full term babies often develop fever during the first days of life but have no other clinical manifestation and no pathological finding on physical examination. In such cases, suspicion of dehydration fever rises. Most febrile infants in our nursery are investigated for evidence of infection and treated with intravenous antibiotics for five days. Our objectives in this study were to: (a) determine the risk factors in healthy full term infants for developing fever during the first days of life; (b) discover the rate of serious bacterial infection among low risk neonates with systemic fever.

METHODS

Medical charts were reviewed for all term newborn infants born at the Sheba Medical Center between 1 January 1997 and 31 December 2001 who subsequently developed fever during their stay in our nursery. Body temperature is not routinely measured in full term healthy newborn babies during their stay in the nursery unless they feel warm to the caregiver or there are other clinical signs. Fever was defined as rectal or axillary temperature equal to or exceeding 37.8°C. The standard work up for febrile infants includes blood, cerebrospinal

fluid, and urine cultures, blood count, and analysis of serum electrolytes.

The policy of our hospital is to weigh infants on a daily basis. Weight loss of more than 3% of birth weight a day is considered abnormal.

In order to include low risk babies only, we excluded infants who had developed fever on the first day of age. The inclusion criteria were babies who, other than systemic fever, did not show any clinical manifestations, such as respiratory distress, bloody stools, or apathy, and whose physical examination was normal when fever was diagnosed (we included infants with signs of dehydration, such as low turgor or dry mucous membranes). Exclusion criteria were babies with major congenital malformations and infants who had received special medical treatment before or during the onset of fever—that is, maternal or infant antibiotic treatment, exchange transfusion, intravenous fluids, etc.

Details such as gestational age, birth weight, maternal age and parity, mode of delivery, feeding mode, weight loss, laboratory data, and medical treatment given to the baby were taken from the medical charts.

“Day of age” in our department is defined according to the baby’s age by hours (0–23 hours is considered “day 0”, 24–47 hours is “1 day old”, 48–72 hours is “2 days old”, etc). Breast feeding was considered to be the primary form of feeding when it constituted more than 80% of feeds. The policy of our hospital is to encourage breast feeding, and no formula milk supplementation is given unless clinically indicated. Most (70–80%) of our discharged newborns are exclusively breast fed.

A total of 185 medical records were reviewed. Seventeen were excluded because fever onset was during the first 23 hours of life (eight babies) or after the fifth day (nine babies). Twenty babies were treated with antibiotics from 1 day old (17 because of maternal fever during labour), nine exhibited additional clinical manifestations other than fever (bloody stool, apathy, respiratory distress, etc), and three had congenital malformations. In 10 of the medical charts, the data were not informative, and another four were excluded for other reasons (born at another hospital, thrombophilia, exchange transfusion before fever onset). The remaining 122 babies met the inclusion criteria and were enrolled in the study.

Each patient included in the study was matched with a control—a baby born at the same gestational age and at a time

Table 1 Characteristics of study and control groups

	Study (n=122)	Controls (n=122)	p Value	Odds ratio
Mean (SD) birth weight (g)	3604 (381)	3411 (416)	<0.001	3.39*
Range	2585–4510	2390–4655		
Mean (SD) gestational age (weeks)	40.35 (0.9)	40.34 (0.9)	NS	
Male/female (%)	47.1/52.9	51.2/48.8	NS	
Mean (SD) maternal age (years)	30.1 (4.9)	28.35 (4.4)	<0.01	
No of primipara	52 (43%)	51 (41.8%)	NS	
Mean (SD) weight loss (%)	7.8 (2.1)	4.8 (7.1)	<0.001	1.73†
No of patients with weight loss >10%	16 (13.3%)	2 (1.8%)	=0.001	
Labour mode				
Partum spontaneous	83 (68%)	100 (83.3%)		
Caesarean section	31 (25.4%)	10 (8.3%)	<0.005	1.74‡
Instrument	8 (6.6%)	10 (8.3%)		
Feeding mode				
Breast fed primarily	94 (78.3%)	43 (35.8%)		
Formula only	1 (0.8%)	20 (16.7%)	<0.001	6.47§
Combined	25 (20.8%)	57 (47.5%)		

*For each 1 kg increase in birth weight.

†For each 1% of weight lost.

‡Caesarean section v partum spontaneous and instrumental delivery.

§Breast v formula and combined feeding.

Table 2 Results of stepwise logistic regression for parameters predicting fever in newborn infants

Parameter	Odds ratio	95% CI	p Value
% weight loss*	1.67	1.36 to 2.04	<0.001
Feeding: primarily breast v other†	5.33	2.63 to 10.8	<0.001
Type of birth: CS v other‡	4.86	1.71 to 13.8	=0.001
Birth weight (kg)§	3.38	1.4 to 8.16	=0.006

*For each 1% of weight loss.

†Breast v formula and combined feeding.

‡Caesarean section v partum spontaneous and instrumental delivery.

§For each 1 kg increase in birth weight.

CI, Confidence interval.

closest to the birth time of the baby in the study group. The medical charts of the control babies were reviewed for birth weight, maternal age and parity, mode of delivery, feeding mode, and weight loss.

The study was approved by the research ethics committee of our institution.

Statistical analysis

The data were analysed using BMDP.¹² To determine associations between categorical variables and the study variable, we used Pearson's χ^2 test and Fisher's exact test as appropriate. Continuous variables were analysed by analysis of variance. Logistic regression was used to determine variables that significantly predict fever in the first days of life. $p = 0.05$ was considered significant.

RESULTS

Of 42 312 infants born in our hospital during the study period, 185 (0.43%) exhibited early fever. Complete blood counts and blood cultures were taken from all 122 infants included in the study. Cerebral spinal fluid cultures were taken from 109 infants in the study group. Table 1 gives the characteristics of the study and control group. Table 2 gives the results of the logistic regression for parameters predicting fever in the study group.

The mean (SD) age at fever onset was 54.5 (15.5) hours. The mean (SD) duration of fever was 2.9 (1.6) hours. In 13 of the 122 babies in the study, temperature returned to the normal range (<37.5°C) more than four hours after the first onset of fever. About half (52.5%) had lost 3% or more of their body weight in the day before the day of fever onset, and of these babies, 18.6% had lost 5% or more in one day. No infant in the

study had an abnormal white cell count, platelet count, or glucose level. Mean (SD) serum sodium level was 145 (3.9) mmol/l in 100 babies for whom sodium levels were obtained, and equal to or higher than 150 mmol/l in 11. The mean (SD) serum urea level was 12.6 (6.3) mmol/l in the study group.

A total of 108 of the 122 study infants received intravenous antibiotic treatment for five days, and 38 were also treated with intravenous fluids.

Cultures were positive in eight babies. Of these, seven blood cultures were positive for coagulase negative staphylococci and were considered to be contaminated on a clinical basis and negative after repeated blood culture.

In one infant, urine culture by suprapubic aspiration was positive for group B streptococcus. His blood count was normal (white blood cells $12.84 \times 10^3/\mu\text{l}$; platelets $262 \times 10^3/\mu\text{l}$), and he developed fever up to 38°C on the third day of life which lasted five hours. A diagnosis of vesiculoureter reflux was later confirmed. Blood and cerebrospinal fluid cultures were sterile.

No differences in fever onset were noted over the course of the year, although a peak increase was recorded during March.

Table 3 shows the characteristics of the high fever (equal to or greater than 38.5°C) subgroup. No differences were recorded in blood count parameters. Sodium and urea levels were higher in the high fever group, although percentages of weight loss from birth and on the day before fever onset were similar.

More infants in the high fever group were born to primipara and younger mothers than those with fever less than 38.5°C. Fewer babies were delivered by caesarean section and more using vacuum or forceps in the high fever group.

Table 3 Characteristics of babies who developed high fever ($\geq 38.5^{\circ}\text{C}$) compared with lower fever

	$\geq 38.5^{\circ}\text{C}$ (n=25)	$< 38.5^{\circ}\text{C}$ (n=97)	p Value
Gestational age (weeks)	40.4	40.3	
Range	38–42	37–42	NS
Birth weight (g)	3590	3690	
Range	2585–4295	2728–4510	NS
Caesarean section	3 (12%)	28 (28.9%)	<0.05
Breast fed primarily	21 (84%)	73 (76.8%)	NS
Weight loss (%)			
From birth	8.2 (2.2)	7.7 (2.1)	NS
Laboratory results			
Sodium (mmol/l)	147.2 (4.6)	144.2 (3.4)	<0.005
Urea (mmol/l)	16.1 (8.7)	11.6 (5.1)	<0.005

Values are mean (SD) unless otherwise indicated.

DISCUSSION

Our results indicate that the main risk factor for developing neonatal fever after the first day of life is excessive weight loss. Other risk factors include breast feeding (suggesting difficulties in initiating breast feeding), delivery by caesarean section, and high birth weight.

Our low risk asymptomatic study group presented with fever that was not related to serious bacterial infection. Only one patient had serious bacterial infection, with a urine culture testing positive for group B streptococcus, but with negative blood and cerebrospinal fluid cultures. Bilateral urinary tract reflux was later diagnosed in this case. Such infections are very rare,¹³ and the presence of negative blood cultures, normal blood count, and a short period of fever makes this diagnosis questionable.

Although delivery caesarean section appeared to be a risk factor for fever, the extremely low rate (0.3%) of fever combined with today's high rate of caesarean section means that the actual risk for developing fever in this group is still very low.

Hypernatraemic dehydration in infants who are exclusively breast fed has been described,^{14,15} including cases of mortality¹⁶ and some in which fever was involved.¹⁷ Indeed, sodium levels were higher in the babies with high fever ($\geq 38.4^{\circ}\text{C}$), and in 11% even exceeded 149 meq/l. Although in this subgroup, weight loss was not higher than in the group with lower fever, the high sodium and urea levels point to considerable dehydration in this subgroup.

Our results do not agree with those of Voora *et al.*,¹⁸ who found 10% positive blood cultures on the first days of life among febrile newborns. However, their study included symptomatic infants as well as babies on the first day of life, and these accounted for most of the cases of serious bacterial infection.

Philip and Hewitt⁹ determined the laboratory factors that correlate with serious bacterial infection and found that combined white blood cell and neutrophil count serves as the best indicator of serious bacterial infection. In our study, total white blood cell count was in the normal range ($> 5 \times 10^3/\mu\text{l}$) for all patients in the study group, and for those whose white blood cell differential was obtained (data not shown in the study), total neutrophil count exceeded $1.5 \times 10^3/\mu\text{l}$.

It has been shown that hepatitis B vaccination increases the incidence of fever in the first days of life,¹⁹ and a few of the babies in the study group may have had fever for this reason. All infants in the study group and controls were vaccinated on the first day of life.

The results of our study provide support for the hypothesis that the main cause of fever during the first days of life is dehydration resulting from difficulties at the beginning of breast feeding. We believe there is a need for early intervention to teach and instruct new mothers about breast feeding, particularly those who have given birth to large infants by caesarean section. Shortening the course of antibiotic treatment for infants in the low risk group should also be considered.

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