Association between Policy Changes for Oxygen Saturation Alarm Settings and Neonatal Morbidity and Mortality in Infants Born Very Preterm

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Objective To determine the impact of policy changes for pulse oximetry oxygen saturation (SpO_2) alarm limits on neonatal mortality and morbidity among infants born very preterm.

Study design This was a retrospective cohort study of infants born very preterm in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network. Infants were classified based on treatment at a hospital with an SpO_2 alarm policy change and study epoch (before vs after policy change). We used a generalized linear mixed model to determine the effect of hospital group and epoch on the primary outcomes of mortality and severe retinopathy of prematurity (ROP) and secondary outcomes of necrotizing enterocolitis, bronchopulmonary dysplasia, and any ROP.

Results There were 3809 infants in 10 hospitals with an SpO_2 alarm policy change and 3685 infants in 9 hospitals without a policy change. The nature of most policy changes was to narrow the SpO_2 alarm settings. Mortality was lower in hospitals without a policy change (aOR 0.63; 95% CI 0.50-0.80) but did not differ between epochs in policy change hospitals. The odds of bronchopulmonary dysplasia were greater for hospitals with a policy change (aOR 1.65; 95% CI 1.36-2.00) but did not differ for hospitals without a policy change. Severe ROP and necrotizing enterocolitis did not differ between epochs for either group. The adjusted odds of any ROP were lower in recent years in both hospital groups.

Conclusions Changing SpO_2 alarm policies was not associated with reduced mortality or increased severe ROP among infants born very preterm. *(J Pediatr 2019;209:17-22)*.

Oxygen is commonly used in the treatment of infants born preterm. Like many interventions, oxygen has a therapeutic window. Clinicians must titrate supplemental oxygen to provide adequate oxygen delivery to tissues while avoiding oxygen-related injury to developing organs. The optimal target pulse oximetry oxygen saturation (SpO_2) range to achieve this balance remains undefined.

Five large international randomized trials were undertaken to determine the impact of lower (85%-89%) vs higher (91%-95%) SpO_2 target ranges on mortality and morbidity in infants born extremely preterm.[1-3] None of these individual trials demonstrated superiority for either SpO_2 target with respect to the composite primary outcome of death or neurodevelopmental disability. However, the individual trials and pooled analysis of these trials suggest that there is a tradeoff in secondary outcomes for either SpO_2 target.[4,5] Assignment to the greater SpO_2 target reduced the incidence of death and necrotizing enterocolitis and assignment to the lower SpO_2 target reduced the incidence of severe retinopathy of prematurity (ROP).

These findings have led to continued debate regarding optimal SpO_2 targets in infants born extremely preterm,[6] with many neonatal intensive care units implementing changes to their SpO_2 targets.[7] Previous authors have reported greater rates of ROP following an increase in SpO_2 targets,[8] but this finding is not consistent.[9] Furthermore, secular trends in infant demographics and clinical practice

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
GDB	Generic Database
NRN	Neonatal Research Network
ROP	Retinopathy of prematurity
SpO_2	Pulse oximetry oxygen saturation
SUPPORT	Surfactant Positive Pressure and Pulse Oximetry Randomized Trial

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Supported by the National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (K23HD084727 to E.F.). In addition, the National Institutes of Health, the NICHD, the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study through cooperative agreements (U10 HD27904, U10 HD21364, M01 RR80, U10 HD27853, M01 RR8084, U10 HD40492, UL1 TR1117, M01 RR30, UL1 TR1111, U10 HD27851, M01 RR39, U10 HD27856, M01 RR750, U10 HD21373, U10 HD36790, U10 HD27880, M01 RR70, U10 HD34216, M01 RR32, U10 HD53109, M01 RR59, U10 HD53089, M01 RR997, U10 HD40689, M01 RR633, U10 HD21385). Although the NICHD staff did have input into the study design, conduct, analysis, and manuscript drafting, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflicts of interest.

Portions of this study were presented as an abstract at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California.

https://doi.org/10.1016/j.jpeds.2019.01.048

may influence clinical outcomes in a before/after study design, particularly in a single-site setting.

We designed the current multisite study within the National Institute of Child Health and Human Development Neonatal Research Network (NRN) to investigate the interaction between changes in SpO_2 alarm limit policies in NRN hospitals and time (before/after policy changes). Our objective was to identify the association between changes in SpO_2 alarm limit policies on neonatal mortality and morbidity and supplemental oxygen exposure among infants born very preterm.

Methods

This was a retrospective cohort study using prospectively collected data in the NRN Generic Database (GDB). We included infants in the GDB who were born between January 1, 2006, to December 31, 2014, with birth weight 401-1000 g or gestational age <29 weeks and who were treated at a hospital that participated in the NRN continuously from 2006 to 2014. We excluded infants who were born during the study washout period (see Study Epoch Definition, to follow), infants who died within the first 12 hours of life (as they were not included in the GDB), infants with major congenital anomalies, infants who were born at referring hospitals and transferred to an NRN hospital (as these infants were not consistently enrolled in the GDB throughout the study period), and infants who had been identified as likely to be eligible for enrollment in Surfactant Postive Pressure and Pulse Oximetry Randomized Trial (SUPPORT).[1]

Each enrolled infant was classified on the basis of 2 exposures: treatment at a hospital with an SpO_2 alarm policy change during the study period and the study epoch in which they were born (before or after policy change).

Policy Change Definition

We administered a questionnaire to NRN site principal investigators in October 2016 to identify hospitals that changed their SpO_2 alarm setting policy between 2006 and 2014. SpO_2 policies, including alarm settings, had to be clearly documented (such as within a practice standard). Because SpO_2 alarm settings may match or slightly exceed the extremes of the desired SpO_2 targets,[6] we characterized policies based on the presence of change in the SpO_2 alarm settings, not the specified SpO_2 targets. Hospitals with an SpO_2 alarm setting policy change during the study period were designated "policy change." Hospitals without a policy change during the study period were classified "no policy change."

Study Epoch Definition

For hospitals with a policy change, we defined the study epochs based on the date of the policy change for each individual hospital. We designated a 6-month period before and after the policy change as the "washout" period. For each of these hospitals, Epoch 1 was defined as January 1, 2006, until 6 months before that hospital's policy change, and Epoch 2 was defined as the interval starting 6 months after the hospital's policy change until December 31, 2014. Infants born during the 1-year washout period were not included in this analysis.

For hospitals without a policy change, we designated the calendar year 2010 (the year SUPPORT results became available) as the transition between Epoch 1 and 2. For those hospitals, we defined Epoch 1 as January 1, 2006, to December 31, 2009, and Epoch 2 as January 1, 2011, to December 31, 2014. Infants born during the 1-year washout period January 1, 2010, to December 31, 2010 were not included in this analysis.

Clinical Outcomes

The primary outcomes were (1) mortality before hospital discharge, transfer, or 120 days of life for infants with longer hospitalization; (2) severe ROP, defined as ROP treatment or retinal detachment in either eye. These were selected because of the observed tradeoff in the risks of these outcomes in the oxygen targeting randomized trials. Infants who were diagnosed with severe ROP before death were considered to have both primary outcomes. Each primary outcome was reported separately. Secondary outcomes included necrotizing enterocolitis stage ≥2,[10] any ROP, moderate/severe bronchopulmonary dysplasia (BPD) (National Institutes of Health consensus definition[11]), supplemental oxygen use after discharge, and cumulative days on supplemental oxygen during the hospitalization among infants who survived to discharge.

Information on the greatest fraction of inspired oxygen (FiO_2) level at prespecified time points is recorded in the GDB. We examined the greatest FiO_2 recorded on the following days: 24 hours, 3 days, 7 days, 14 days, and 28 days. We also assessed the greatest FiO_2 across these time points; this analysis was restricted to infants who survived to 28 days to reduce bias introduced by early death.

Statistical Analyses

Our first objective was to assess the relationship between changes in SpO_2 alarm setting policies and changes in the primary and secondary outcomes between the study epochs. We used a generalized linear mixed model to explore the effect of instituting a change in hospital policy on the proportion of infants with each outcome between Epoch 1 and 2. Models included the hospital-level effect of policy change (yes/no), epoch, and the interaction between policy change and epoch. A significant interaction term would indicate that the difference in outcomes between Epoch 1 and 2 varied based on the hospital group (policy change or no policy change). We adjusted this analysis for the following infant-level characteristics: gestational age, birth weight, multiple gestation, antenatal steroid exposure, sex, race, ethnicity, intubation for resuscitation, small for gestational age status,[12] and admission temperature.[13] Although different infants were present during the 2 epochs, a random effect for hospital was included in the models to account for the fact that infants treated at the same hospital may have more similar outcomes.

Our second objective was to examine the relationship between instituting a change in SpO_2 alarm settings, epoch, and

supplemental oxygen exposure in infants born very preterm. Because the greatest FiO_2 variable was highly skewed, with a large number of infants whose greatest FiO_2 was 0.21, we modeled a dichotomous variable, greatest FiO_2 >0.21, based on hospital groupings and epochs. This analysis used a similar generalized linear mixed model and adjusted for the same covariates. *P* values <.05 were considered statistically significant, and hospital policy change (yes/no) and epoch interaction terms with *P* values <.05 were considered evidence of an epoch effect that differed between the 2 hospital groupings. No adjustment was made for multiple comparisons. Only nonmissing data were included in analysis; statistical modeling methods assumed missing data were missing at random. All analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, North Carolina).

Results

There were 19 NRN hospitals with continuous participation in the GDB between 2006 and 2014. Of these, 10 changed the policy for SpO_2 alarm settings, and 9 did not change the policy during the study period. Among hospitals with a SpO_2 policy change, the median SpO_2 alarm limits transitioned from 85% (lower) and 96% (upper) to revised median limits of 89% (lower) and 95% (upper) (**Figure 1**). Among hospitals without a SpO_2 alarm policy change, the median SpO_2 alarm limits were 88% (lower) and 95% (upper).

Of 7494 infants included in this study (**Figure 2**; available at www.jpeds.com), there were 3809 infants in hospitals with a SpO_2 alarm policy change and 3685 infants in hospitals without a policy change. Differences in demographic characteristics between epochs for each group of hospitals are shown in **Table I**. Mortality did not significantly differ between epochs for infants in hospitals with a SpO_2 alarm policy change, and mortality was significantly lower in Epoch 2 for infants in hospitals without a SpO_2 alarm policy change (**Table II**). Severe ROP did not significantly differ between epochs for either group.

For infants in hospitals with a SpO_2 alarm policy change, the adjusted odds of BPD were significantly greater in Epoch 2. There was no difference in BPD between epochs among infants in hospitals without a SpO_2 alarm policy change. Necrotizing enterocolitis did not differ between epochs for either group. There was a reduction in the adjusted odds of any ROP in Epoch 2 for both groups of hospitals. The interaction term between epoch and hospital group was not significant for this outcome, indicating that the reduction in ROP between study epochs did not vary based on hospital group.

There was no significant interaction between hospital group and epoch for the outcomes of cumulative oxygen exposure or supplemental oxygen use after discharge. Averaged across both groups of hospitals, infants born in Epoch 2 who survived to discharge had longer exposure to supplemental oxygen (mean difference 2.79 days; 95% CI 1.30-4.28; $P < .001$) and were more likely to be discharged home on supplemental oxygen (aOR 1.28; 95% CI 1.05-1.57; $P = .02$).

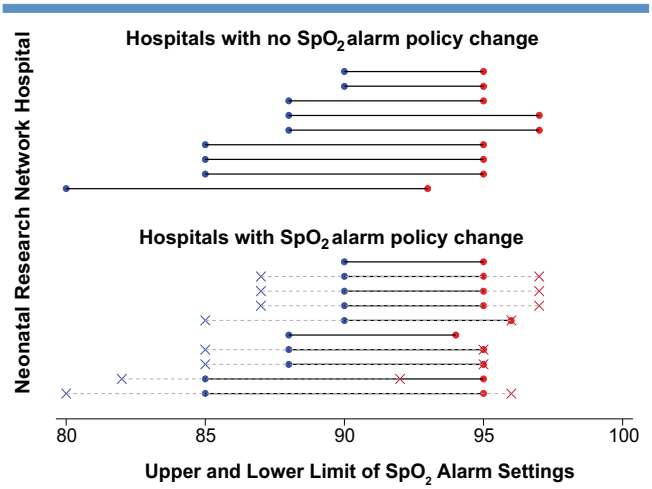

Figure 1. SpO_2 alarm settings for hospitals with and without a policy change. For hospitals without a SpO_2 alarm policy change, median alarm limits were 88% (lower limit) and 95% (upper limit). For hospitals with a policy change, original alarm settings, shown in *X marks*, had median values of 85% (lower limit) and 96% (upper limit). The revised alarm settings, shown in *circles*, had median values of 89% (lower limit) and 95% (upper limit). Original alarm settings are not shown for 2 hospitals in the SpO_2 alarm policy change group: 1 hospital transitioned from no policy to an SpO_2 alarm policy, and 1 hospital did not have record of the original SpO_2 alarm settings.

For both groups of hospitals, the adjusted odds of greatest FiO_2 >0.21 at 14 and 28 days of life were greater in Epoch 2. There was no significant interaction between epoch and hospital group for those individual time points. However, there was a significant interaction between hospital and epoch for the combined variable of greatest FiO_2 >0.21 across the first 28 days of life (**Table III**).

Discussion

The target SpO_2 values to optimize outcomes for infants born preterm remains a topic of active debate, with some authors uniformly advocating a greater SpO_2 target range.[14] Given the wide variation in SpO_2 targets employed across neonatal intensive care units,[15] reflexively implementing these greater targets would imply a change in oxygen targeting policies for many hospitals. We sought to determine the impact of changing SpO_2 alarm settings for infants born very preterm on neonatal mortality and morbidity. In the post SUPPORT era, one-half of hospitals in the NRN revised their policy for SpO_2 alarm settings and the other one-half made no changes. Among hospitals in the NRN that revised their oxygen saturation policy, the nature of most of these changes was to narrow the range of SpO_2 alarm settings, consistent with other reports.[7] We found no evidence that modifying the SpO_2

Table I. Baseline maternal and infant characteristics

Characteristics	Infants in hospitals with SpO_2 alarm policy change (n = 3809)			Infants in hospitals with no SpO_2 alarm policy change (n = 3685)		
	Epoch 1 n = 1981	Epoch 2 n = 1828	*P* value	Epoch 1 n = 1620	Epoch 2 n = 2065	*P* value
Antenatal steroids	1599/1977 (80.9%)	1676/1826 (91.8%)	<.001	1387/1605 (86.4%)	1892/2063 (91.7%)	<.001
Race			.002			.13
Black	816/1949 (41.9%)	816/1756 (46.5%)		724/1598 (45.3%)	867/2053 (42.2%)	
White	1046/1949 (53.7%)	830/1756 (47.3%)		746/1598 (46.7%)	1043/2053 (50.8%)	
Other	87/1949 (4.5%)	110/1756 (6.3%)		128/1598 (8.0%)	143/2053 (7.0%)	
Hispanic	424/1959 (21.6%)	276/1823 (15.1%)	<.001	195/1464 (13.3%)	266/2035 (13.1%)	.83
Multiple gestation	451/1981 (22.8%)	442/1828 (24.2%)	.30	445/1620 (27.5%)	576/2065 (27.9%)	.78
Gestational age, wk, mean (SD)	26.7 (2.1)	26.2 (2.0)	<.001	26.8 (2.0)	26.3 (1.9)	<.001
Birth weight, g, mean (SD)	891 (245)	840 (237)	<.001	906 (240)	870 (233)	<.001
Male sex	995/1981 (50.2%)	944/1828 (51.6%)	.38	811/1620 (50.1%)	1064/2065 (51.5%)	.38
SGA	337/1981 (17.0%)	294/1828 (16.1%)	.44	246/1620 (15.2%)	282/2065 (13.7%)	.19
Delivery room intubation	1158/1981 (58.5%)	1040/1827 (56.9%)	.34	997/1620 (61.5%)	1286/2065 (62.3%)	.65
Admission temperature, °F, mean (SD)	97.5 (1.6)	97.7 (1.3)	<.001	96.9 (1.9)	97.6 (1.6)	<.001

SGA, small for gestational age.

alarm setting policy reduced mortality or increased severe ROP. Supplemental oxygen exposure was greater in Epoch 2 in both groups of hospitals, but this finding was not significantly associated with a policy change in SpO_2 alarm settings.

Manley et al reported their single-center experience of 346 infants born preterm after increasing SpO_2 targets from 88%-92% to 91%-95%. ROP was significantly more frequent among infants born after the SpO_2 target change, and mortality rates did not significantly differ.[8] Other authors have not observed significant differences in neonatal morbidity following changes to SpO_2 target policies.[9] The impact of changing SpO_2 alarm limits on clinical outcomes in a given setting likely depends on many factors, such as local baseline outcome rates.

Secular trends in infant demographics and clinical practice make it difficult to isolate the impact of a given change in practice on clinical outcomes in a single site before/after study. Because of our multisite study design, we were able to assess the interaction between epochs and hospital grouping to better account for concurrent secular trends. Previous authors have described decreasing mortality over time among infants born extremely preterm.[16-18] Similarly, we observed a reduction in mortality in Epoch 2 among hospitals without a hospital policy change—where a wider range of acceptable SpO_2 alarm limits was retained. Conversely, the adjusted odds of BPD were significantly greater in Epoch 2 for hospitals in which SpO_2 alarm settings were revised. The interaction between instituting a policy change and epoch was significant for both of these outcomes. We speculate that additional unmeasured differences in infant demographics and hospital practice may have contributed to these study findings. Nonetheless, our results do not suggest that changing SpO_2 alarm settings alone led to a significant benefit in neonatal outcomes.

Use of supplemental oxygen was assessed in multiple ways. More infants were exposed to FiO_2 >0.21 at 14 and 28 days of life in Epoch 2 in both hospital groups. In addition, the cumulative duration of oxygen exposure and use of supplemental oxygen after discharge were both increased in Epoch 2 for both groups of hospitals. Although we adjusted for changes in important baseline characteristics, other unmeasured differences in patient demographics may have contributed to increased oxygen use in Epoch 2. In addition, we speculate that the lower mortality rate in Epoch 2 within hospitals without an SpO_2 alarm policy change may have led

Table II. Changes in outcomes between epochs for infants in hospitals with and without a SpO_2 alarm policy change

Outcomes	Infants in hospitals with SpO_2 alarm policy change (n = 3809)			Infants in hospitals with no SpO_2 alarm policy change (n = 3685)			
	Epoch 1 n = 1981	Epoch 2 n = 1828	aOR or mean difference (95% CI)*	Epoch 1 n = 1620	Epoch 2 n = 2065	aOR or mean difference (95% CI)*	Adjusted interaction *P* value
Mortality	297/1979 (15.0%)	324/1828 (17.7%)	0.94 (0.75-1.18)	269/1615 (16.7%)	280/2061 (13.6%)	0.63 (0.50-0.80)	.01
Severe ROP	127/1703 (7.5%)	126/1535 (8.2%)	1.09 (0.78-1.52)	88/1300 (6.8%)	127/1746 (7.3%)	0.91 (0.64-1.29)	.46
Necrotizing enterocolitis	245/1980 (12.4%)	250/1827 (13.7%)	0.96 (0.78-1.20)	210/1620 (13.0%)	250/2065 (12.1%)	0.83 (0.67-1.04)	.35
BPD	592/1722 (34.4%)	700/1541 (45.4%)	1.65 (1.36-2.00)	443/1343 (33.0%)	794/1797 (44.2%)	1.21 (0.99-1.48)	.03
Any ROP	829/1703 (48.7%)	655/1535 (42.7%)	0.71 (0.59-0.86)	706/1300 (54.3%)	935/1746 (53.6%)	0.57 (0.47-0.69)	.11
Cumulative days on supplemental O_2, d, mean (SD)†	43.5 (39.8)	53.2 (42.5)	3.87 (1.80-5.94)	39.5 (37.2)	49.8 (40.3)	1.70 (–0.038 to 3.79)	.14
Discharged home on O_2†	161/1395 (11.5%)	201/1113 (18.1%)	1.47 (1.09-1.99)	223/1183 (18.9%)	331/1357 (24.4%)	1.12 (0.86-1.45)	.17

*Analyses adjusted for gestational age, birth weight, multiple gestation, antenatal steroids, sex, race, ethnicity, delivery room intubation, small for gestational age status, and admission temperature.
†Among infants who survived to discharge.

Table III. Change in supplemental oxygen exposure at specified time points between epochs for infants in hospitals with and without an oxygen saturation alarm policy change

FiO_2 >0.21 at time points	Infants in hospitals with SpO_2 alarm policy change (n = 3809)			Infants in hospitals with no SpO_2 alarm policy change (n = 3685)			Adjusted interaction *P* value
	Epoch 1 n = 1981	Epoch 2 n = 1828	aOR (95% CI)*	Epoch 1 n = 1620	Epoch 2 n = 2065	aOR (95% CI)*	
24 h	1193/1952 (61.1%)	1199/1802 (66.5%)	1.00 (0.85-1.17)	845/1582 (53.4%)	1133/2031 (55.8%)	1.08 (0.92-1.27)	.48
Day 3	1381/1923 (71.8%)	1403/1788 (78.5%)	1.15 (0.96-1.39)	1010/1553 (65.0%)	1410/2020 (69.8%)	1.17 (0.99-1.40)	.88
Day 7	1010/1835 (55.0%)	1103/1718 (64.2%)	1.16 (0.96-1.40)	694/1454 (47.7%)	1061/1956 (54.2%)	0.98 (0.81-1.18)	.22
Day 14	1005/1681 (59.8%)	1131/1647 (68.7%)	1.25 (1.01-1.54)	697/1313 (53.1%)	1282/1889 (67.9%)	1.60 (1.30-1.96)	.10
Day 28	878/1570 (55.9%)	1042/1577 (66.1%)	1.28 (1.04-1.59)	556/1165 (47.7%)	1163/1819 (63.9%)	1.68 (1.35-2.09)	.08
Across the first 28 days†	1408/1767 (79.7%)	1380/1593 (86.6%)	1.29 (1.02-1.63)	1051/1416 (74.2%)	1584/1850 (85.6%)	1.79 (1.44-2.23)	.045

*Analyses adjusted for gestational age, birth weight, multiple gestation, antenatal steroids, sex, race, ethnicity, delivery room intubation, small for gestational age status, and admission temperature.
†Among infants who survived to 28 days of life.

to increased supplemental oxygen use among survivors. Despite the fact that supplemental oxygen use increased, we did not find any evidence of increased rates of severe ROP in Epoch 2 for infants born in either group of hospitals, and rates of any ROP were lower in Epoch 2 for both groups.

This analysis was restricted to SpO_2 policies in the neonatal intensive care unit setting. We did not account for changes in delivery room oxygen management following changes to neonatal resuscitation treatment recommendations in 2010.[19] Reassuringly, a meta-analysis of randomized trials comparing high vs low initial FiO_2 for delivery room resuscitation of infants <29 weeks of gestation found no significant differences in clinical outcomes of death, ROP, or BPD.[20]

Study limitations include the observational study design. Although we accounted for important baseline demographic characteristics and interventions that changed between epochs, it is possible that other secular trends in practice at participating hospitals influenced the study results. In addition, we recognize that hospitals may vary in terms of how strictly the alarm policies were followed[15] or how strictly infants' SpO_2 levels were maintained within set alarm limits.[21] Finally, we classified hospitals based on a change to the SpO_2 alarm settings and not the absolute values of the alarm limits. Our objective was not to determine the impact of specific SpO_2 targets on patient outcomes. This question, addressed in the pooled analysis of 5 RCTs in the Neonatal Oxygenation Prospective Meta-analysis collaboration, is unlikely to be answered in an observational study.

In conclusion, we did not find evidence that narrowing SpO_2 alarm limits had a significant impact on neonatal mortality or severe ROP among more than 7000 infants born very preterm in the NICHD NRN. These results suggest that changing policies for oxygen saturation alarm settings alone may not confer a significant benefit on the outcomes of infants born preterm. ■

Data collected at participating sites of the NICHD NRN were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr Abhik Das (DCC Principal Investigator), Dr Marie Gantz (DCC Statistician), and Mr Benjamin Carper (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

Submitted for publication Nov 21, 2018; last revision received Jan 8, 2019; accepted Jan 29, 2019.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Intestinal Obstruction Complicating Familial Mediterranean Fever

Schrager G. J Pediatr 1969;74:966-8.

The author presented the case of a mixed Sephardic/Ashkenazi Jewish female patient with weekly episodes of fever and abdominal pain lasting 48 hours since the age of 8 years. Acute phase reactants were elevated, particularly fibrinogen, without proteinuria. After 4 years of disease, the patient developed intestinal obstruction secondary to fibrinous adhesions of the serosal surface causing obstruction of the distal ileum. Surgical treatment was successful.

This case description is classic for familial Mediterranean fever (FMF). FMF is a genetic (usually, but not always, autosomal recessive) disease manifest with recurrent episodes of fever, severe abdominal pain (representing peritonitis), chest pain (representing pleuritis and/or pericarditis), and arthritis. Untreated patients frequently develop AA amyloidosis, usually presenting with proteinuria that can lead to renal failure. Other complications include chronic arthritis (~5%), growth failure, anemia, splenomegaly, and rarely vasculitis. Adhesions, causing intestinal obstruction as described herein or infertility (male and female) are a result of frequent episodes of peritoneal inflammation.

FMF is caused by mutations in the *MEFV* gene on chromosome 16 encoding pyrin ("fire"), an important protein in the activation pathway of interleukin-1, a crucial mediator of inflammation. The 1997 discovery of the gene responsible for FMF was the first among the monogenic diseases causing periodic fever. FMF is considered the prototype of the rapidly developing field of autoinflammatory diseases, related primarily to dysregulation of the innate immune system, as opposed to autoimmune diseases related to autoreactivity of the adaptive immune system.

FMF affects primarily, but not exclusively, populations surrounding the Mediterranean, especially Sephardic Jews, Turks, Armenians, and Arabs. Although considered an orphan disease in the US, many of the historical milestones of FMF occurred there. These include description of the first series (1945), discovery of the causative gene (in collaboration with Israeli researchers from the Sheba Medical Center), understanding of the role of pyrin in causing inflammation (2016) and treatment breakthroughs, colchicine in 1972, and the first controlled trial of an interleukin-1 inhibitor for patients not responsive to colchicine in 2012.

Early diagnosis is crucial to initiate timely colchicine treatment, not used for FMF at the time of this publication. Colchicine completely prevents inflammatory episodes in ~2 out of 3 patients, is partially effective in ~25%, and not effective in ~5%, while preventing amyloidosis in nearly all patients.

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Appendix

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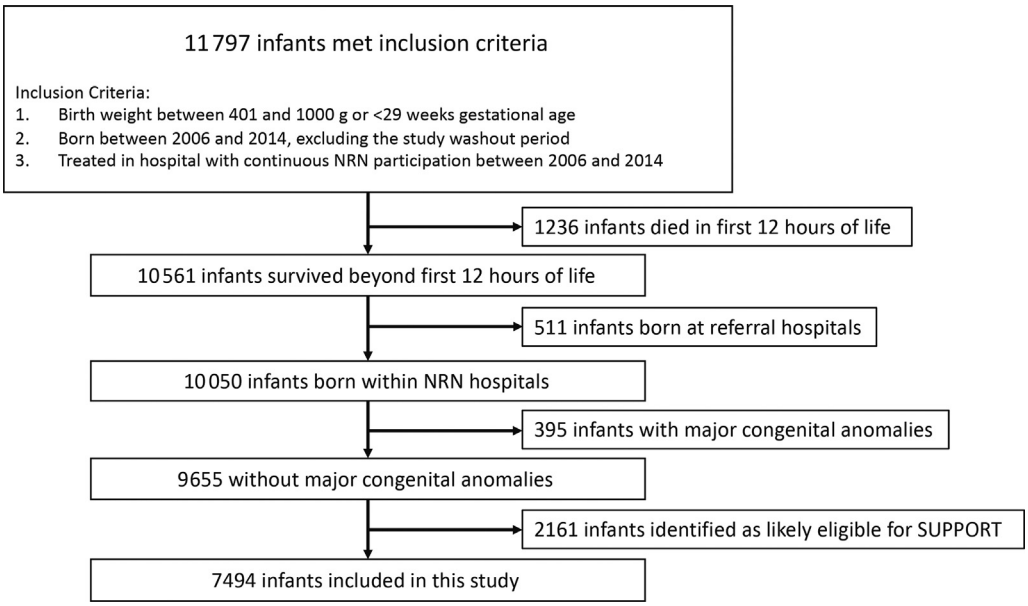

Figure 2. Study flow diagram.