Antenatal Risk Factors Associated with Spontaneous Intestinal Perforation in Preterm Infants Receiving Postnatal Indomethacin

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Objective To determine if antenatal variables affect the risk of spontaneous intestinal perforation (SIP) among preterm infants when prophylactic indomethacin is used.

Study design Retrospective case-control study of infants <29 weeks of gestational age between January 2010 and June 2018 at one hospital. SIP was defined as acute abdominal distension and pneumoperitoneum without signs of necrotizing enterocolitis at <14 days of life. Each case (n = 57) was matched with 2 controls (n = 114) for gestational age and birth year. Maternal and infant data were abstracted until the SIP or equivalent day for controls. Univariate analyses were followed by adjusted conditional logistic regressions and reported as OR and 95% CI.

Results Mothers of cases were younger, more often delivering multiples (31% vs 14%, $P = .007$), and less abruptions (15% vs 29%, $P = .045$) but did not differ in intra-partum betamethasone, magnesium, or indomethacin use. Prophylactic indomethacin was given on day 1 to 99% of infants. SIP was associated with a shorter interval from last betamethasone dose to delivery (46 hours vs 96 hours, $P = .01$). Dopamine use (14% vs 4%, $P = .02$), volume expansion (23% vs 8%, $P = .003$), and high grade intraventricular hemorrhage (28% vs 8%, $P = .0008$) were related postnatal factors. The adjusted odds of SIP increased by 1% for each hour decrease between the last dose of betamethasone and delivery (OR 1.01, 95% CI 1.002-1.019) and with multiple births (OR 2.66, 95% CI 1.05-6.77).

Conclusions Antenatal betamethasone given shortly before delivery is associated with an increased risk of SIP. Potential interaction with medications such as postnatal indomethacin needs study. *(J Pediatr 2021;232:59-64)*.

Spontaneous intestinal perforation (SIP) occurs in approximately 4% of preterm infants <28 weeks of gestation[1] and is associated with an increase in mortality[2] and poor neurodevelopmental outcome.[3] Multiple randomized trials have reported associations between early postnatal steroid administration and SIP[4,5] and an interaction between early postnatal steroids and indomethacin administration shortly after birth.[6,7] Animal models suggest that steroid administration may mediate a skewed trophism in the ileum whereby a thinning of the submucosa is associated with a simultaneous hyperplasia of the mucosa, which predisposes to perforation in the presence of altered bowel motility.[8] In contrast, there has been no association reported between antenatal steroids and SIP.[9]

Since 2012, the frequency of SIP has increased at Women and Infants Hospital of Rhode Island (WIH) with rates as high as 14.5% among infants born at 23 and 24 weeks of gestation. Prophylactic indomethacin has been used at WIH since 1995 based on randomized trials for infants <29 weeks and/or <1250 g birth weight.[10,11] Observational data of the benefits of antenatal steroids at gestations of <25 weeks[12] and increases in survival of periviable births[13] may provide rationale for a more aggressive ante-partum approach including maternal medication administration closer to birth. The latter may provide an opportunity for antenatal medication to influence postnatal events. Alternatively, periviable infants may be more susceptible to medications effects found to be safe in more mature preterm infants. Therefore, the objective of this study was to estimate if antenatal variables affect the risk of developing SIP among preterm infants. It was hypothesized that antenatal steroid administration close to the time of delivery may increase the risk of SIP among extremely preterm infants in a neonatal intensive care unit (NICU) where postnatal indomethacin is used prophylactically.

IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PROPHET	PROPHylaxis of adrenal insufficiency in the Tiny baby
SIP	Spontaneous intestinal perforation
WIH	Women and Infants Hospital of Rhode Island

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Methods

This was a retrospective case-control study and was performed after institutional approval for a waiver of consent. WIH is a regional perinatal center with approximately 8500 deliveries/year. The NICU has 1200-1300 admissions/year and 10%-15% are out-born.

Inclusion/Exclusion Criteria

Inclusion criteria were a gestational age of <29 weeks, born between January 1, 2010 and June 30, 2018, outborn or inborn, and admitted to the NICU at <72 hours of age. Inclusion began in 2010 prior to the increase in SIP. Exclusion criteria were congenital intestinal malformations, other major anomalies, chromosomal abnormality, hydrops, or necrotizing enterocolitis (NEC). The case definition for SIP was recognition <14 days after birth, development of acute abdominal distension, with or without discoloration of the abdominal wall and groin, evidence of radiographic or sonographic intra-abdominal free air, and absence of signs of NEC. Cases were identified by trained personnel who reviewed records with a diagnosis of SIP in a divisional database and confirmed via an independent chart review.

The surgical approach to SIP was largely bedside placement of an intra-abdominal drain. Because of the use of drains, SIP cases were classified as either certain, reasonably certain, or uncertain. Certain SIP required confirmation by a subsequent laparotomy or a postmortem examination. Reasonably certain SIP cases were not confirmed by a subsequent surgery, but the hospital course was consistent with an uncomplicated SIP (treated with a drain, no further surgery, remained clinically stable, no contrast study, or unremarkable contrast study if performed). Uncertain SIP were infants with an initial diagnosis of SIP but review raised concerns and the diagnoses was without confirmation. Uncertain cases were adjudicated by 2 co-authors and led to either exclusion of infants or inclusion with a preplanned sensitivity analysis. WIH participated in a randomized trial of laparotomy vs abdominal drain for intestinal perforation for suspected SIP or NEC from January 2010 through March 2017 (NEC Surgery Trial, NCT 01029353). Five infants were randomized to laparotomy, 9 were randomized to drain and are part of this case-control study.

Data Collection

Each SIP case was matched with 2 control infants for gestational age (±1 week) and year of birth. Predefined data variables were abstracted from the medical record and were collected to the time of SIP recognition or the equivalent time point for matched controls. Chart review also included surgical pathology if available. Maternal variables included age, gravida, parity, multiples, medical problems during pregnancy, and medication use. Labor and delivery variables included chorioamnionitis (clinical or histologic), placental problems (abruption, previa), cord accident, rupture of membranes >24 hours, spontaneous labor, medications (betamethasone, magnesium, indomethacin, nifedipine, antibiotics), total dose of medication and the time interval from last dose to delivery, and delivery mode. Infant data included gestational age, birth weight, and growth measures, small for gestational age status, sex, out-born, intubation at birth, chest compression, and Apgar scores. Neonatal morbidities included respiratory distress syndrome, pneumothorax, patent ductus arteriosus (PDA, confirmed by echocardiogram), and early and late onset sepsis (positive blood culture and antibiotic treatment at ≤3 days and >3 days, respectively). Intraventricular hemorrhage (IVH) was collected from cranial ultrasounds performed prior to the diagnosis of SIP. Clinical practices included umbilical catheters, surfactant, caffeine, volume expansion, pressor support, postnatal dexamethasone or hydrocortisone, indomethacin (prophylactically or for PDA treatment), blood transfusions (number and day of life closest to the SIP), and feeding history. Also recorded were the admission temperature, maximum serum blood urea nitrogen, and creatinine.

Prophylactic indomethacin (0.1 mg/kg/day, 3 doses) was used shortly after birth. The approach to enteral feeds was to encourage use of mothers own milk, colostrum for mouth care during indomethacin treatment, and initiate feeds after indomethacin treatment.

Statistical Analyses

Initial group comparisons were made using *t* tests and Wilcoxon tests for continuous variables, as appropriate for the distributions. Categorical variables were compared using the χ^2 test. Exploratory analyses to examine a possible inflection point in the relationship between time of antenatal medications relative to birth and SIP were carried out with time prior to delivery classified into tertiles and quartiles.

Conditional multivariate logistic regression adjusting for matching was used to test the relationships of antenatal variables with SIP. Covariates were limited to 5 variables given the number of cases and were either associated with SIP on univariate testing or considered clinically important. Variables reporting the interval from the last dose of medication to delivery were assigned a value of zero if the medication was not administered. Effects are shown as ORs and 95% CIs. Possible interactions among medications were also tested, initially with 2 × 2 tables to test for co-occurrence, followed by testing in the logistic models when appropriate. Interactions that were not significant were removed. After the final model was selected, a sensitivity analysis was conducted by re-estimating the model without previously adjudicated uncertain cases. We explored whether postnatal variables associated with SIP on univariate testing would alter associations between antenatal variables and SIP in the multivariate logistic regression. Postnatal variables of interest were tested individually by addition to the logistic regression to ensure that models converged.

Additional data were extracted following the results of the logistic regression including the duration of intubation prior

to SIP, the interval from last dose of volume expansion until SIP or its equivalent day for controls, and the interval from maternal hospital admission to delivery.

Results

A total of 62 infants met the inclusion criteria for SIP. Five infants were excluded after adjudication. After matching for gestational age and year of birth, there were no differences between cases (n = 57) or controls (n = 114) in infant characteristics or delivery room interventions (Table I). SIPs occurred at 6 ± 2 days (mean ± SD, range 2-11 days) (Figure 1; available at www.jpeds.com).

Infants with SIP were born to 54 mothers and control infants were born to 110 mothers (Table I). Mothers of infants with SIP were younger, were more often delivering multiples, and less abruptions but did not differ in the percent with hypertension, diabetes, use of medications, or mode of delivery. Although hypertension did not differ, chronic hypertension occurred in 9% of mothers of control infants and in none of mothers of infants with SIP (P = .025). There was no difference between groups in histologic chorioamnionitis. The use of medications during labor and delivery did not differ between groups (type, total dosage). In contrast, the mean (±SD) number of hours from the last dose of betamethasone until delivery was 46 ± 58 hours and 96 ± 108 hours for mothers of SIP and control infants, respectively (P = .01, Figure 2). The time from the last dose of indomethacin until delivery was 69 ± 156 hours and 75 ± 107 hours for mothers of SIP and control infants, respectively (P = .02). Exploratory analyses by tertile and quartile of time from last dose to delivery did not reveal a clear inflection point to separate SIP and control infants. Rescue steroids were administered to mothers of 1 case and 1 control.

Table I. Characteristics of infants and mothers

Infant data	SIP (n = 57)	Control (n = 114)	*P* value
Gestational age (wk)	24.8 ± 1.4*	24.9 ± 1.4	.48
Birth weight (g)	749 ± 209	770 ± 195	.53
Small for gestational age	4 (7%)	7 (6.4%)	.83
Male	33 (58%)	56 (49%)	.28
Number of multiple infants	20 (35%)	19 (17%)	.007
Outborn	2 (4%)	6 (5%)	.61
Intubation at birth	46 (81%)	95 (83%)	.67
Chest compressions	2 (4%)	6 (5%)	.61
Apgar scores – 5 min	6 (5-8)†	6 (5-7)	.36
Maternal data	**SIP (n = 54)**	**Control (n = 110)**	***P* value**
Age (y)	26.7 ± 5.3*	29.1 ± 6.7	.02
Gravida	2, 1-3†	2, 1-3	.63
Hypertension (chronic, gestational, pre-eclampsia)	8 (15%)	25 (23%)	.23
Diabetes (insulin, diet controlled)	6 (11%)	9 (8%)	.54
Medication (SSRI, labetalol, methadone, buprenorphine, illicit)	12 (22%)	28 (25%)	.65
Multiple delivery	17 (31%)	15 (14%)	.007
Spontaneous labor	42 (78%)	81 (74%)	.56
Rupture of membranes >24 h	6 (11%)	36 (33%)	.003
Chorioamnionitis (histologic)	38 (70%)	82 (75%)	.57
Placental abruption	8 (15%)	32 (29%)	.045
Placental previa	0 (0%)	2 (2%)	.32
Cesarean delivery	37 (69%)	61 (55%)	.11
Medication			
Betamethasone (any)	47 (87%)	103 (94%)	.16
Last dose to delivery (h)	46 ± 58	96 ± 108	.01
Magnesium (any)	45 (83%)	98 (89%)	.30
Last dose to delivery (h)	2 ± 7	6 ± 30	.23
Indomethacin (any)	23 (43%)	40 (36%)	.44
Last dose to delivery (h)	69 ± 156	75 ± 107	.02
Nifedipine (any)	4 (7%)	10 (9%)	.72
Last dose to delivery (h)	20 ± 26	11 ± 24	.11

SSRI, selective serotonin reuptake inhibitor.
*Mean ± SD.
†Median, IQR.

Neonatal morbidities prior to the day of SIP did not differ between groups for respiratory distress syndrome, pneumothorax, PDA, and culture proven sepsis (Table II). In contrast, grade III and IV IVH occurred more frequently among infants with SIP. Initial cranial ultrasounds were performed between days 1 and 3, and 10 infants did not have an ultrasound prior to recognition of the SIP (n = 7) or the comparable day among controls (n = 3). Nearly all infants received prophylactic indomethacin, and all infants received caffeine on day 1. Volume expansion and dopamine use were more frequent prior to the SIP among cases. Postnatal hydrocortisone and dexamethasone were infrequently used. Receipt of any enteral feeds prior to the SIP was less frequent among cases (51%) compared with control infants (89%, P = .0001).

Multivariate conditional logistic regression indicated that multiple births during the current pregnancy had the strongest association with SIP (Table III). The association of betamethasone with SIP was based on the time interval between last exposure and birth. The odds of SIP were increased by 1% for each hour decrease between the last dose of betamethasone and delivery from 72 hours before delivery to progressively shorter intervals prior to birth. There was no interaction between antenatal betamethasone and indomethacin administration and the risk of SIP. The analysis was unchanged after removing 5 uncertain SIP cases and their respective control infants (data not shown). Addition of postnatal variables associated with SIP on univariate testing (Table II) to the multivariate logistic regression did not change the odds ratios for the association between antenatal steroids and SIP. The OR of SIP remained associated with a decrease in the interval between the last betamethasone dose and birth with the inclusion of receipt of enteral feeds (OR 1.010, 95% CI 1.001-1.019, P = .022), volume expansion (OR 1.010, 95% CI 1.001-1.018, P = .026), or high grade IVH (OR 1.009, 95% CI 1.000-1.019, P = .061). The P value for the association between betamethasone and SIP did change when IVH was added to the regression, but the full cohort could not be analyzed (head ultrasounds absent in 10 infants). This resulted in exclusion of 8 matched sets to maintain a balanced sample, but the OR and 95% CI were minimally changed. The interval of last betamethasone dose to delivery was not correlated with age at SIP (r = 0.06).

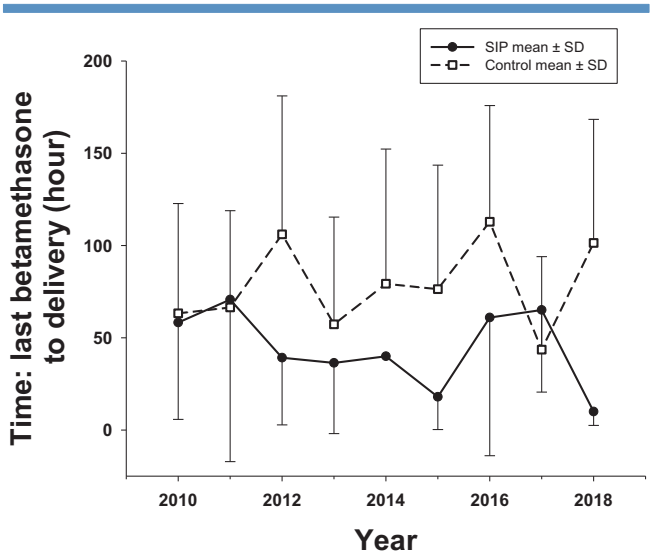

Figure 2. The time from last betamethasone dose to delivery in hours (Y axis) is plotted by the year of the study. The values are mean ± SD, and the SIP cases are represented by the solid symbols and lines, while the controls are open symbols and dashed lines.

Surgical pathology was available for 24 of 29 infants who underwent a laparotomy upon diagnosis (n = 9) or who underwent a drain followed by a laparotomy (n = 15); all specimens indicated focal intestinal perforation. Among the remaining 28 infants, 25 were managed with an abdominal drain only, 2 infants did not receive an operative intervention (1 confirmed on autopsy, 1 with a transient pneumoperitoneum) and the operative approach could not be discerned for 1 infant. Post-hoc analyses indicated no differences between groups for the number intubated at the time of SIP recognition (91% vs 94%), the days intubated prior to SIP recognition (5.3 ± 3.0 vs 4.6 ± 2.7 days) and the interval between the last volume expansion and SIP recognition (60 ± 59 vs 54 ± 42 hours) for SIP and controls, respectively. In contrast, the interval from maternal hospital admission to delivery was shorter for cases (60 ± 85, median 42 hours) vs controls (105 ± 120, median 69 hours, $P = .019$).

Table II. Morbidities/medications/practices prior to SIP or equivalent day for controls

Morbidities, medications, and practices	SIP (n = 57)	Control (n = 114)	*P* value
Morbidities			
Respiratory distress syndrome	57 (100%)	112 (98%)	.32
Pneumothorax	3 (5%)	9 (8%)	.53
PDA (echocardiogram confirmed)	8 (14%)	13 (11%)	.62
Indomethacin treatment	1 (2%)	6 (5%)	.28
IVH-grade III/IV*	14 (28%)	9 (8.1%)	.0008
Late onset sepsis	3 (5%)	1 (1%)	.07
NEC	0	0	N/A
Medications			
Surfactant (any)	50 (88%)	102 (89%)	.73
Caffeine	56 (98%)	109 (96%)	.38
Dopamine	8 (14%)	5 (4%)	.02
Hydrocortisone	2 (4%)	0	.044
Dexamethasone	2 (4%)	1 (1%)	.22
Indomethacin (IVH prophylaxis)	56 (98%)	113 (99%)	.62
Practices			
Admission temperature	36.3 ± 0.8†	36.4 ± 0.8	.31
Umbilical artery catheter	40 (70%)	88 (77%)	.32
Umbilical venous catheter	48 (84%)	97 (85%)	.88
Red cell transfusions	40 (70%)	74 (65%)	.49
Volume expansion	13 (23%)	8 (7%)	.003
Any feeding	29 (51%)	101 (89%)	.0001
Day of life feeds initiated	3.5 ± 1.6†	3.0 ± 1.2	.20
Breastmilk - % of feeds	24 (83%)	80 (79%)	.67

*Because of missing data, the sample size for IVH was 50 for SIP and 111 for control.
†Mean ± SD.

Table III. Associations with SIP (logistic regression)

Maternal variables	OR	95% CI	
Betamethasone*	1.010†	1.002	1.019
Indomethacin*	0.999	0.988	1.009
Abruption	0.388	0.137	1.099
Hypertension	0.677	0.255	1.800
Multiple births	2.662	1.046	6.770

*Hours between last dose of drug and delivery.
†The odds of SIP increased by 1% for each hour decrease between the last dose of betamethasone and delivery.

Discussion

The interest in antenatal steroids is an extension of prior associations of early postnatal steroid exposure and SIP.[6,7] Antenatal indomethacin was also of interest given the postnatal practice at WIH to initiate prophylactic indomethacin on the day of birth and known interactions with steroids. Adjusted analysis indicated that the interval between the last dose of betamethasone and delivery, and multiple births during the current pregnancy were associated with SIP. The case definition of SIP, review of cases, and adjudication process were used to attain as high a certainty as possible of the correct diagnosis. Occurrence in the first 14 days was used to minimize overlap with NEC. Surgical and autopsy findings confirmed the diagnosis of SIP in 25 of the 57 cases. A sensitivity analysis excluding cases with an uncertain diagnosis of SIP did not indicate any change in the multivariable analysis.

A retrospective case-control study reported an association between early postnatal dexamethasone administration to prevent lung injury and the occurrence of focal small bowel perforation now termed SIP.[14] Multiple randomized trials and a meta-analysis have also reported an increased frequency of SIP associated with early use of postnatal steroids (dexamethasone and hydrocortisone) with varying predefined surveillance for SIP.[4,5,15] Associations between postnatal steroids and SIP have been supported by a mouse model where steroid administration promoted mucosal hyperplasia at the expense of the submucosa in the ileum and may predispose the bowel to perforation in the presence of other conditions (eg, poor intestinal motility, abdominal distension).[15]

There has been speculation that antenatal steroids may increase the risk for SIP secondary to high cortisol levels.[16] A randomized trial of postnatal hydrocortisone to prevent early adrenal insufficiency and bronchopulmonary dysplasia was stopped due to an increase in SIP (PROPHylaxis of adrenal insufficiency in the Tiny baby [PROPHET] study); higher cortisol values were observed over the first week among infants with vs without SIP.[7] However, antenatal steroids suppress fetal endogenous cortisol production and the latter returns to normal over 7 days.[17,18] In the PROPHET study, lower cortisol values were reported among infants born to mothers given antenatal steroids in a time dependent manner from the last dose of steroids.[19] Thus, the relationship between cortisol values and SIP in the PROPHET trial remains unclear, but the results supported an interaction between hydrocortisone and indomethacin. In the present report, a shorter interval between the last dose of betamethasone and delivery was associated with an increased adjusted risk of SIP. This observation was not altered by the addition of selected postnatal variables to the model. The results raise the possibility that antenatal steroids may affect the intestine similarly to postnatal steroids, but caution is needed because interactions with drugs (eg, indomethacin) administered postnatally could not be studied. An interaction between antenatal betamethasone and postnatal indomethacin appears plausible and needs to be confirmed in a cohort with and without indomethacin use shortly after birth among mothers with varying time of last administration of antenatal steroids prior to delivery.

Associations between postnatal prophylactic indomethacin and SIP remain controversial.[20-22] There is biologic plausibility for antenatal indomethacin as a risk factor for postnatal SIP reflecting ready passage across the placenta[23] and reductions in regional blood flow to the intestine, kidneys, and cerebrum.[24,25] There are limited data on associations of antenatal indomethacin exposure with SIP because the latter was not analyzed in meta-analyses.[26,27] After covariate adjustment in the current report, antenatal indomethacin was not associated with SIP. Associations between antenatal magnesium and postnatal SIP are unclear.[28,29] Magnesium was administered at WIH per a randomized trial[30] and was not associated with SIP.

The variable most strongly correlated with SIP was multiple births during the current pregnancy. Multiple reports have observed an unadjusted association between multiple gestations and SIP.[31-33] Cohorts of SIP cases were small, ranging from 16 to 24 patients from single centers. Some reports have suggested that twin-twin transfusion syndrome may be associated with SIP.[34,35] Details of the type of twinning is not available in the current report. A large multicenter database (739 infants) reported no differences in the frequency of multiple gestations among SIP cases and controls.[21]

Although not the objective of this study, it may be difficult to understand whether postnatal variables associated with SIP are in the causal path or reflect a higher acuity among infants destined to develop SIP because of the uncertainty of when an SIP occurred. For example, the delay in receipt of enteral feeds among infants with SIP could result in intestinal mucosal atrophy[36] and potentially increase the risk of SIP. Alternatively, lack of enteral feeds may indicate that clinicians were unwilling to feed infants because they may have been sicker. Matching for gestational age and year of birth were to avoid confounding by differences in the risk of mortality and morbidities, and changes in obstetric and neonatal practices over time. However, the reason mothers of infants with SIP were admitted to the hospital closer to delivery could not be obtained. In spite of the association between antenatal betamethasone and postnatal SIP, confounding by indication and/or severity cannot be excluded.

The strengths of this study are a contemporary cohort, detailed information on the timing of medications administered to the mother, data abstraction from matched controls until the same day as the SIP, and the use of predefined variables. Limitations include the retrospective design, a limited number of SIP cases, and uncertainty of the SIP diagnosis for some cases. Because of the sample size, the number of matched variables and covariates for regressions were limited.

This study is consistent with the known associations between early postnatal steroids and the development of SIP among extremely preterm neonates. It provides biological plausibility that the time interval from betamethasone exposure may be important in the development of SIP. Whether this association would occur in NICUs that do not administer prophylactic indomethacin cannot be determined. There is, however, biological plausibility for an interaction between antenatal steroids and postnatal indomethacin given the effects when both drugs are used postnatally. There may also be important differences in the susceptibility of infants at the borderline of viability to therapies previously found to be safe and effective in preterm infants of more advanced gestational age. However, we cannot exclude confounding and caution is needed before changing clinical management. Further investigation is needed to replicate these observations and examine interactions between maternal antenatal steroids and postnatal therapies. ■

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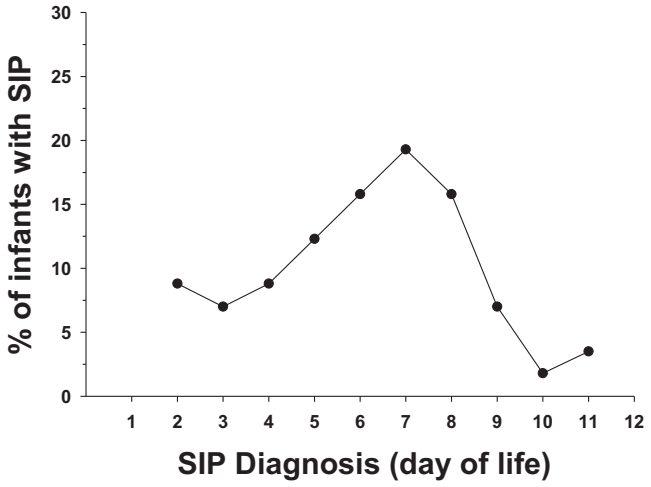

Figure 1. The percent of infants with SIP among cases (Y axis) is plotted by the age in days of SIP diagnosis on the x axis. The average age at SIP was 6.1 $\pm$ 2.3 days (x $\pm$ SD).